DECEMBER 2025

THE JOURNAL OF ARTHROPLASTY

International Consensus Meeting 2025

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James Cashman, Seyed Mohammad Javad Mortazavi, Pier Francesco Indelli, Siddharth Rele, Carl Haasper, Fatih Yildiz, Christopher T. Holland, Juan D. Lizcano, Álvaro Auñón-Rubio, Don Bambino Geno Tai, Bartolome Allende, Abtin Alvand, Claudia Arias, Armin Arshi, Vasily Artyukh, George C. Babis, Jose Baeza-Oliete, Nicolaas Budhiparama, Frank Buttacavoli, Pedro Ivo Carvalho, Felix C. Vilchez Cavazos, Cheng-Fong Chen, Pawel Chodór, Peter F.M. Choong, Osman Çiloglu, David Dewar, Fundación Jiménez Díaz, Goksel Dikmen, Ayman Ebied, Sina Esmaeili, Jonathan T. Evans, Guilherme Falotico, Pedro Foguet, Massimo Franceschini, Peter Gold, Enrique Gómez-Barrena, Joan Gómez-Junyent, Daniel Gould, Akram A. Hammad, Hyuk-Soo Han, Christian Hipfl, Catriona Hunter, Mustafa Alper Incesoy, Nathan B. Kaplan, Kayahan Karaytug, Huiwu Li, Francisco Arguelles Linares, Jorge Manrique-Succar, Oliver Marín-Peña, Paul McCarroll, Robert McCulloch, Rene Mihalič, Laura Morata, Seyed Amirsadegh Mortazavi, Sumon Nandi, Elise Naufal, Julio César Palacios, Juan Carlos Martinez Pastor, Tim Petheram, Alaina Ritter, Ola Rolfson, Javier Martinez Ros, Marisa Sanchez, Ignacio Sancho, Jay D. Shah, Puyi Sheng, Alex Soriano, Mark J. Spangehl, Jeffery B. Stambough, Saad Tarabichi, Daniel Taupin, Satit Thiengwittayaporn, I. Remzi Tözün, Rihard Trebše, Shang-Wen Tsai, Ibrahim Tuncay, Ewout S. Veltman, Felix Vilchez-Cavazos, Marianne Westberg, Haobo Wu, Piers J. Yates, Mehmet Kursat Yilmaz, and Je-Hyun Yoo

(continued)

S326 2025 ICM: One-Stage Exchange
Erik Hansen, Baochao Ji, Matthew J. Dietz, Amir Human Hoveidaei, Akos Zahar, Wenbo Mu, Alisina Shahi, Svetlana A. Bozhkova, Mansour Abolghasemian, Chikodi Angad, Jose Baeza-Oliete, Nicholas A. Bedard, Martí Bernaus, Scot A. Brown, Timothy S. Brown, László Bucsi, David Campbell, Li Cao, James Cashman, Osman Çiloğlu, Mustafa Citak, Julian Costantini, Joshua S. Davis, Daniele De Meo, Ayman Ebied, Abhay Elhence, Jonathan T. Evans, Andrew Fraval, Mathias Glehr, Peter Gold, Luiz S. Marcelino Gomes, Johannes Goosen, Carl Herndon, Thomas L. Hilton, Bálint L. Horváth, Plamen S. Kinov, Shivaprasad Kolur, Carolyn D. Kramer, Jesse W.P. Kuiper, Fabiano Kupczik, Jeppe Lange, Allison Lastinger, Yicheng Li, Federico Llobet, Rajesh Malhorta, Seyedarad Mosalamiaghili, James Nace, Jesse E. Otero, Peter M. Preobrazhensky, Yanguo Qin, Jakub Ratkowski, Markus Rupp, Jose Ignacio Sanchez, Ricardo Sousa, Róbert Sződy, Seyed Pouya Taghavi, Daniel Taupin, Staffan Tevell, Rosalba Tortia, Hamed Vahedi, Artyukh Vasily, Ewout Veltman, Willaim.W. Wang, and Xiaogang Zhang

S341 2025 ICM: Spacers
Bernd Fink, Mehmet Kürşat Yılmaz, Hamidreza Yazdi, Ewout S. Veltman, Daniele De Meo, Ashley Castan, Matthew Squire, David Rodriguez, Paolo Adravanti, İbrahim Azboy, Ireneusz Babiak, Nicholas A. Bedard, Joseph Benevenia, Federico José Burgo, Henrique B. Cabrita, Giorgio Cacciola, Dipak Dave, Federico De Meo, Guilherme Guadagnini Falotico, Conor George, Ismail Ghadi, Gabriel Baron Girgulsky, Mohammadamin Haghbin, Minna Hassaballa, Thomas Hilton, Tomislav Mađjarević, Dirk Jan F. Moojen, Temiloluwa Olufemi, Antonio Russo, Andrea Sambri, Jonathan Sauer, Roger Rojas Sayol, Rajeev K. Sharma, Jeffrey B. Stambough, Marijn H. Stelwagen, Rolando Suárez, T. David Tarity, Kevin D. Tetsworth, Hua Tian, Shang-Wen Tsai, Hiroyuki Tsuchiya, and Jesse Wolfstadt

S362 2025 ICM: Antibiotic Prophylaxis in Primary Joint Arthroplasty
Alexus M. Cooper, Ana Lucia Munhoz Lima, T. David Luo, Armin Arshi, Mark J. Spangehl, Ibrahim Elganzoury, Seyed Mohammad Javad Mortazavi, Abdelhak Adjel, Keivan Ahadi, Khaleel Albatran, Hazem M. Alkhawashki, Bolarinwa Akinola, Lucas A. Anderson, Sina Babazadeh, Barry Brause, Antea Buterin, Li Cao, André Dias Carvalho, Laura Certain, John Cordero, Nicolás Cortés-Penfield, Aydin Gahramanov, Raúl García-Bógalo, Erik N. Hansen, Angela L. Hewlett, Amir Human Hoveidaei, Ayaz M. Humbatov, Sofiene Kallel, James Kigera, Kang-il Kim, Allison Lastinger, Fernando A. Lopreite, Jose G. Luque, Sébastien Lustig, Tomislav Madjarevic, Ilda Molloy, Calin S. Moucha, David Novikov, Lazaros Poultsides, Mohammad Poursalehian, Ashok Rajgopal, Julie E. Reznice, Talha Riaz, Dolors Rodriguez-Pardo, Cecile Ronde-Oustau, Meredith Schade, Poorani Sekar, Linda Suleiman, Darko Talevski, Saad Tarabichi, Jorge A. Villafuerte, Bill Walter, Koji Yamada, Simon W. Young, and Ahmed Saeed Younis

S376 2025 ICM: Antibiotic Prophylaxis in Revision Arthroplasty
Joost T.P. Kortlever, Joshua P. Rainey, Paulo Alencar, Lucas A. Anderson, Raul Bogola, Thiago Busato, Luis B. Chirveches, Serban Dragosloveanu, Jon H.M. Goosen, Julian Guerra Perez, Carlos A. Higuera-Rueda, Harriet Hughes, Amir Khoshbin, Fabiano Kupczik, Zachary C. Lum, Anders Odgaard, Elido A. Perez-Gonzalez, David Rodriquez-Quintana, Cristian Scheau, Karin Veerman, Dace Vigante, and Meghan A. Whitmarsh-Brown

S381 2025 ICM: Abbreviated Two- and 1.5-Stage
James Cashman, Guilherme Falotico, Vasily Artyukh, Vaibhav Bagaria, Giovanni Balato, Gabriel Baron, David Deckey, Thomas Hilton, Christian Hipfl, Christopher Jones, Scott Matthews, James Nace, Bryan Springer, Tobias Winkler, and Piers Yates

S385 2025 ICM: Two-Stage
Abhay Elhence, Christoph Böhler, Frank Kolhoff, Andrew Fraval, Rajeev K. Sharma, Katherine Belden, Vinay K. Aggarwal, Derek Amanatullah, Tiziana Ascione, Bülent Atilla, Svetlana A. Bozhkova, Armen Daniliyants, Federico De Meo, Jose Luis Del Pozo, Lopreite Fernando, Bernd Fink, Elizabeth Gancher, Daniel Gould, Michael W. Henry, Bryan Hess, Ashraf Jamal, Jason M. Jennings, Jay Lieberman, Ramneek Mahajan, Dominic Meek, Oscar Murillo, Valeri Murylev, Michael Neufeld, Anders Odgaard, Martin Pietsch, James Powell, Jakrapun Pupaibool, Ashok Rajgopal, Rajesh Kumar Rajnish, Rostagno Roberto, Poorani Sekar, Jong-Keun Seon, Jay D. Shah, Jennifer Straub, Darko Talevski, Daniel H. Taupin, Darren Tay, Udit Vinayak, Koji Yamada, and Bernadette Young

(continued)

S399 2025 ICM: End-Stage or Intractable Cases
Andrea Sambri, Andrea Montanari, Mohammad Mahdi Sarzaeem, Martin Sarungi, Jiri Gallo, and Michael Held

S402 2025 ICM: Diagnostic Techniques: Histology
Irene K. Sigmund, Mansour Abolghasemian, Mathias Bostrom, Mats Bue, Rebecca Burr, Louise Kruse Jensen, James Nace, Pietro S. Randelli, Federica Rosso, Marta Sabater-Martos, Rafael J. Sierra, Anna Stefánsdóttir, Kamolsak Sukhonthamarn, and Zeng Yirong

S407 2025 ICM: Diagnostic Techniques: Molecular Tests
Brandon J. Martinazzi, Pier Francesco Indelli, Ibrahim Azboy, Geroge Babis, Goksel Dikmen, Henry Flores, Massimo Franceschini, Karan Goswami, Hyuk-Soo Han, James Huddleston, Pier Francesco Indelli, Naomi Kobayashi, Martin Krsak, Jacek Kruczyński, Mel Lee, Ana Lucia Munhoz Lima, Barend C. Mitton, Rajkumar Natesan, Jeroen GV. Neyt, and Maria Eugenia Portillo

S412 2025 ICM: Diagnostic Techniques—Serological and Point-Of-Care
Dariusz Grzelecki, Dina Raafat, Rares-Mircea Birlutiu, Katherine A. Belden, Giovanni Balato, Vittorio Bellotti, Razvan-Silviu Cismasiu, Osamu de Sandes Kimura, Elizabeth Gancher, Yasuhiro Homma, Kaisa Huotari, Jason M. Jennings, Michael M. Kheir, Feng-Chih Kuo, Priscila Rosalba Oliveira, Vahit Emre Ozden, Javad Parvizi, F. Johannes Plate, Maryam Salimi, Meredith Schade, Janosch Schoon, AliSina Shahi, Sebastian Sujeesh, Piotr Sypień, Majd Tarabichi, Kevin Tetsworth, Rüdiger von Eisenhart-Rothe, Bill Walter, and Marjan Wouthuyzen-Bakker

S423 2025 ICM: Surgical Strategy and Approach
Saad Tarabichi, Pablo Sanz-Ruiz, Adolph V. Lombardi Jr, Guilherme Falotico, Abtin Alvand, Ireneusz Babiak, Joshua S. Bingham, Pawel Chodór, H. John Cooper, Pedro Dantas, Mohamed Elkabbani, Ismet Gavrankapetanović, Thorsten Gehrke, Julian Guerra-Perez, Erik N. Hansen, Christian Hipfl, Victor M. Ilizaliturri, Baochao Ji, José M. Lamo-Espinosa, Stergios Lazarinis, Óliver Marín-Peña, Seyed Mohammad Javad Mortazavi, Ernesto Muñoz-Mahamud, Douglas E. Padgett, Antony Palmer, Ali Parsa, Juan Carlos Martinez Pastor, Vito Pavone, Walter Ricioli Jr, Victor M. Ilizaliturri Sánchez, Mohammadmahdi Sarzaeem, Lais Sales Seriacopi, Rami Sorial, Mark J. Spangehl, Jens T. Verhey, and Shang-Wen Tsai

S432 2025 ICM: Special Cases of Infected Implants
Dikmen Goksel, Simon Garceau, Jason M. Jennings, Muzaffer Ağır, Abtin Alvand, Nicholas C. Arpey, George Babis, Seung-Hoon Baek, Gabriel Baron, Brent Benavides, Claudia Arias Calderón, Abhay Elbence, Christopher W. Jones, Sherif A. Khaled, Georgios Komnos, Arthur Malkani, Tim Petheram, Camilo Restrepo, Benjamin Ricciardi, Antonio Russo, Rajeev K. Sharma, Anna Stefánsdóttir, Edward Vasarhelyi, Udit Vinayak, and Marianne Westberg

S437 2025 ICM: Monitoring and Declaring Success
Laurens Manning, Pablo A. Slullitel, Martin A. Buttaro, Theofilos Karachalios, Richard Kuehl, Dominic Meek, Roberto Olivetto, Nicolás S. Piuzzi, Daniel Rienzi, Antonio Russo, Antonio Solano, Danguole Vaznaisiene, and Jesse Wolfstadt

S443 2025 ICM: Antimicrobial Therapy Options in Special Circumstances
Mahmoud Abdel Karim, Wenbo Mu, Claudia Arias, Craig Aboltins, Keivan Ahadi, Murat Birinci, Stanislav Bondarenko, David Campbell, Li Cao, José Luis del Pozo, Mohamed Gobba, Abdullah Hammad, Michael Henry, Bryan Hess, Wei Huang, Daisuke Inoue, Carolyn Kramer, Oscar Murillo, Rajeev Sharma, Toshibumi Taniguchi, Koji Yamada, and Ahmed S. Younis

The Journal of Arthroplasty 41 (2025) S1–S3

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Editorial

Another International Consensus Meeting Concludes: We Are Here for the Patients

Check for updates

The third International Consensus Meeting (ICM) on Infection was held in Istanbul, Türkiye, from May 8 to 10, 2025. Dr Javad Parvizi, chair of the meeting, along with Dr Thorsten Gehrke, opened the meeting with an important message that resonated throughout the meeting: "…there is one reason above all that we are gathered here…PATIENTS." This message set the tone of the meeting and was a North Star throughout the meeting to help guide discussion and voting. This important mandate, along with the unique format of the meeting, generated a level of engagement and investment among the delegates and attendees of the meeting, which has led to the creation of a set of important documents and slide decks with the potential to impact patient care for years to come.

To understand the impact of the documents, it is critical to understand the format of the ICM. While the details of the process will be published as a separate document, a brief outline provides important context for the remainder of this editorial. The entirety of the ICM process lasted over two years and began with the Executive Committee selecting delegates based on predetermined criteria and soliciting questions from the group. A Delphi process was then used to select the most important questions, numbering over 300 in total. These questions were then divided among the delegates, with each delegate contributing to one or more questions. The delegates in each group worked together to find the best evidence to answer each question and prepared a two-page document and a slide deck summarizing these findings. Thus, by the time the in-person portion of the meeting began, each delegate had already invested substantial time and effort into the success of the meeting. Furthermore, each delegate had the opportunity to vote on each question's recommendations by voting "agree," "disagree," or "abstain." Thus, more so than at many scientific meetings, there was excellent attendance at all sessions throughout the meeting, despite early morning starts and evening finishes.

The documents generated from the ICM, and the ICM process in general, can help to guide and improve patient care through four main mechanisms: (1) direct impact on clinical practice; (2) a unified and global understanding of musculoskeletal infection; (3) hypothesis generation for future research; and (4) fostering international collaboration with a shared purpose. Each document may fit into one or more of these categories, and the impacts may vary by surgeon, region, and clinical pathology. Given that each question was answered using the best available evidence and that each document contains a level of evidence and a level of consensus based on the in-person vote, we can imagine a hypothetical X-Y axis with level of evidence on the X-axis and level of consensus on the Y-axis. We can then divide the grid into four quadrants based on combinations of high or low evidence and consensus (Figure 1)

Direct Impact on Clinical Practice

A subset of questions posed during the ICM was able to be answered with high-quality evidence and reached a high consensus on the delegate vote. It should thus follow that these documents should serve as guidelines for practice wherever possible. Surgeons, infectious disease physicians, and other providers whose practices diverge substantially from these documents should closely review them and evaluate whether there is a good reason for their practice to continue to be divergent from these recommendations. Barring any convincing, evidence-based, or context-specific reason, it is likely that practice patterns should be modified to follow these ICM recommendations.

Questions with high evidence but low levels of consensus present a unique challenge. Despite high levels of evidence, the recommendations did not achieve high levels of consensus at the ICM. Thus, it is important for the musculoskeletal infection community to carefully review the evidence for these questions, as it is of high quality; however, the conclusions drawn from the evidence may be different from the recommendations made by the group of delegates working on a given question. Nevertheless, questions in this category contain high-quality evidence that merits review and understanding by surgeons and other providers and researchers.

A Unified and Global Understanding of Musculoskeletal Infection

The definition of periprosthetic joint infection (PJI) produced by each ICM is well-disseminated and forms an important part of orthopaedic and infectious disease education and clinical practice. Nevertheless, in previous years, a number of different societies with a focus on musculoskeletal infection had each released differing definitions of PJI. The different definitions, including those from the European Bone and Joint Infection Society and the Infectious Diseases Society of America, were found to have

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.035.

https://doi.org/10.1016/j.arth.2025.10.035
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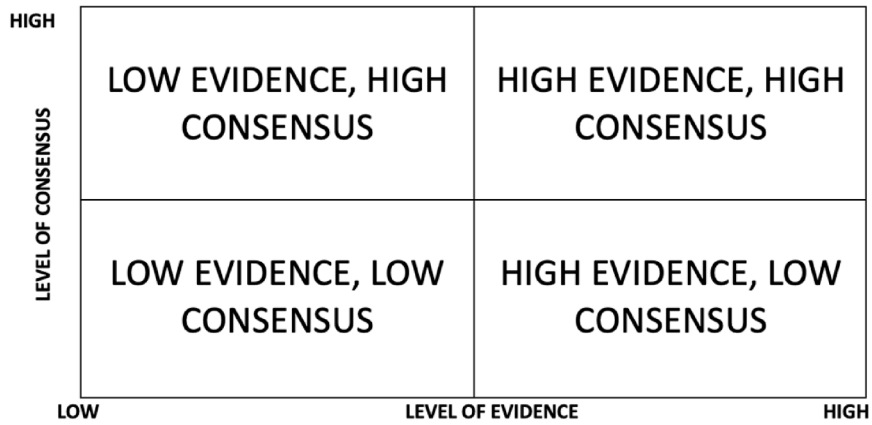

Figure 1. Hypothetical evidence versus consensus plot, divided into four quadrants.

differing diagnostic capabilities, creating the potential for both academic and clinical uncertainty [1].

By contrast, the 2025 version of the PJI definition is a unified definition, approved and endorsed by the ICM, European Bone and Joint Infection Society, Infectious Diseases Society of America, the Musculoskeletal Infection Society, and the European Society of Clinical Microbiology and Infectious Diseases. The entirety of the definition, including the process used to reach it, will also be published in a separate document. However, the fact that the definition is now unified will allow for simpler clinical and academic applications of the definition. Furthermore, the new definition more closely mirrors clinical practice and is applicable in nearly all clinical settings, regardless of the availability (or lack thereof) of specific tests. Also, the definition draws a clear distinction between different types of PJI, including those based on source of infection and chronicity. Given the fact that over 100 countries were represented at the ICM, this definition and the rest of the documents produced by the ICM can have a truly global impact, including in areas of the world that are traditionally underrepresented in the orthopaedic literature.

Hypothesis Generation for Future Research

Returning to Figure 1, questions that fall into the "low level of evidence" half of the graph also serve an important function. These represent areas that are ripe for future research, some of which can hopefully be answered in the coming years. In a way, the ICM serves not only as a platform to answer questions related to musculoskeletal infection, but also to identify those that cannot yet be answered based on the available evidence. This is an important function of most academic meetings and conferences; however, the ICM is unique in that for each question, a group of experts has already retrieved and presented the best available evidence. Thus, it serves an important role as a launching pad for future studies.

Fostering International Collaboration

The ICM, since its inception, has been committed to bringing together a truly global group of experts and attendees. Given that many orthopaedic meetings and conferences are organized by regional or national societies, this puts the ICM in a unique position. At the ICM, surgeons, infectious disease doctors, and other musculoskeletal infection surgeons from around the world have the opportunity to connect and discuss ideas for collaboration. Despite a busy meeting schedule, the coffee breaks and social events were rife with discussions of research ideas and a clear appetite for future international collaborative research. Dr Mohit Bhandari, in his keynote speech to wrap up the meeting, spoke about the importance of this type of collaboration and, in particular, the importance of sustaining the momentum of the meeting into the coming months and years. The ICM also provided a platform for collaborative research initiatives to be presented in order to garner substantial interest, including the ROADMAP trial, the Orthopaedic Device Infection Network, and an effort to update the ICM PJI Risk Calculator.

Overall, the ICM was a truly global and collaborative effort, which would not have been possible without the hard work and dedication of the delegates, administrative team, and event staff, including the local team in Istanbul. Over two years of hard work culminated in a brief, but intense in-person meeting. The documents generated from the meeting will be publicly available with no paywall, in addition to publication in *the Journal of Arthroplasty*. These documents can help to inform clinical practice, unify the global understanding of musculoskeletal infection, generate hypotheses for future research, and foster international collaboration. As Dr Parvizi made clear at the start of the third ICM, improving patient care for those experiencing these devastating infections will always be the most important goal of the ICM.

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Mark Spangehl
Saad Tarabichi
Marco Teloken
Eleftherios Tsiridis
Ibrahim Tuncay
Qiaojie Wang
Marjan Wouthuyzen-Bakker
Koji Yamada

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The Journal of Arthroplasty 41 (2025) S4–S5

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Editorial

International Consensus Meeting 2025: Did We Need Another One?

Check for updates

"Telling an orthopaedic patient that they have an infection is like giving them a diagnosis of cancer." Late Richard Rothman, MD, PhD (1999).

This statement continues to be true even three decades later. Why? We believe the answer can be captured by the acronym IDEA-FAD—seven interlocking reasons why our patients continue to endure the devastating consequences of orthopaedic infections.

(1) Innovations: Orthopaedic surgery has witnessed some groundbreaking innovations that have transformed the lives of our patients. However, management of orthopaedic infections has seen little to no innovations. We are hard-pressed to name a single innovation that has been transformative in this field.
(2) Dogma: The orthopaedic community continues to pass down dogma after dogma to the next generation. Some of the original, and some may argue brilliant, ideas and assumptions by our forefathers have not undergone the scrutiny of science, and we continue to accept them as the world of gospel. The six weeks of antibiotic therapy for those undergoing resection arthroplasty for periprosthetic joint infection (PJI), the use of space suits, the need for intravenous (as opposed to oral) antibiotics for all patients who have PJIs, the need for two-stage exchange for (all) patients who have PJIs, the use of antibiotic-impregnated polymethyl methacrylate cement in patients undergoing primary joint arthroplasty, the need for a 2-week antibiotic holiday before reimplantation, and so on, are some of these assumptions we have made without searching for concrete science.
(3) Evidence: With the incidence of PJI (fortunately) being low at around 1 to 2% after primary arthroplasty, it is extremely difficult to generate level 1 evidence for some of the issues and problems that we face. An immense investment of time, resources, and energy is needed to complete clinical trials related to orthopaedic infections. The dedicated surgeons, infectious disease specialists, and scientists around the globe continue to engage in scientific discoveries, and despite all challenges, have concluded numerous groundbreaking clinical trials in recent years.
(4) Abstinence: Despite the colossal and immeasurable effort to generate level 1 evidence in this field, it appears that some of our colleagues either fail to familiarize themselves with evidence or simply choose to exercise self-restraint from embracing it. Instead, and sadly, some of our community appear to be more comfortable being mesmerized by the "experts" who may not be reading off the script and may not actually be familiar with evidence themselves.
(5) Fragmentation: Orthopaedic infection care is inherently multidisciplinary, requiring collaboration across surgery, infectious disease, microbiology, pharmacy, and sometimes plastic surgery. Too often, this results in fragmented care, inconsistent protocols, and diffusion of responsibility. This leaves patients caught between specialties.
(6) Accuracy of Diagnostics: Despite advances, we still lack a universally reliable, rapid, inexpensive diagnostic test. Biomarkers and sequencing technologies show promise, but remain imperfect, costly, or inaccessible. Persistent diagnostic uncertainty fuels both overtreatment and undertreatment.
(7) Disparity in Economics: The economic burden of orthopaedic infections is staggering, yet funding and research support lag far behind oncology, cardiology, or other high-profile fields. This mismatch perpetuates stagnation and limits progress in prevention and treatment.

So, what can we do to start marching forward? Simple: we need to build consensus. We need to know what the issues are, what solutions (evidence) we have for each issue, and then agree on the issues for which we do not have much evidence (or any solution). We can then allocate our energy to generate evidence (future studies) for those issues or engage in innovation to solve the problem.

The International Consensus Meeting, a nonprofit organization, delivers on the above principles. Its members (delegates) are experts who have published expertise or are high-volume clinicians/surgeons dealing with patients who have orthopaedic infections. The delegates are asked to propose issues (questions) that we (or our patients) face. The literature related to the issues is then explored using comprehensive systematic reviews. The delegates then meet in person to discuss the literature and propose a solution (recommendation) to the problem. After discussions and deliberations, the delegates then vote on the recommendations. The International Consensus Meeting 2025 Istanbul meeting undertook reviewing over 360 questions in the field of biofilm, hip, knee, shoulder, and spine surgery. The proceedings are available on the website (www.ICMortho.org), and hip- and knee-related

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.034.

https://doi.org/10.1016/j.arth.2025.10.034
0883-5403/© 2025 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

documents are published in this issue of *the Journal of Arthroplasty.* The meeting brought together over 1,200 delegates from 100 countries around the globe. The delegates traveled to the meeting at their own cost and spent eight hours a day over three days to deliberate on these issues. The dedication and commitment of the delegates to patient care were on full display during the meeting. Our industry partners, also recognizing the gravity of orthopaedic infections, were there in full support to observe and identify opportunities for innovations to address this devastating problem.

Of course, everyone desires to see as many level 1 studies as possible on every issue. However, while we strive for the upper ground, we should be aware of the current science or evidence on every issue and the deficiencies that exist as we move forward as a community that has one and only one mission in mind: to enhance patient care.

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Michael A. Mont

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The Journal of Arthroplasty 41 (2025) S6–S18

Contents lists available at ScienceDirect

The Journal of Arthroplasty

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General Topics

2025 ICM: Risk Factors for Surgical Site Infection (SSI)/ Periprosthetic Joint Infection (PJI)

Nathanael Heckmann, Amir Human Hoveidaei, Seyed Mohammad Javad Mortazavi, Sayid Omar Ahmed, Mohammadali Enayatollahi, Arash Aali Rezaie, Mauro J. Salles, Azlina Amir Abbas, Vinay K. Aggarwal, Derek F. Amanatullah, Bülent Atilla, Wael Barsoum, Natividad Benito, Joshua S. Bingham, Cara A. Cipriano, Janet D. Conway, McKenzie Culler, Raquel B. da Silva, Juliana Arruda de Matos, Daniel Dieg, Eduardo C. dos Santos, Margarita Veloso Duran, Ali Soltani Farsani, Jeremy M. Gililland, Carl Herndon, Carlos A. Higuera-Rueda, Meeri P. Honkanen, Yutaka Inaba, Jason M. Jennings, Nathan Kaplan, Eustathios Kenanidis, Keita Morikane, Wayne E. Moschetti, Michael E. Neufeld, Javad Parvizi, Vito Pavone, Joris JW. Ploegmakers, Mohamed B. Rashed, Moein Rast, A.V. Gurava Reddy, Ola Rolfson, Marta Sabater-Martos, Mitchell J. Schwaber, Lais S. Seriacopi, Neil P. Sheth, Paul N. Smith, Toshiyuki Tateiwa, Eleftherios Tsiridis, Danguole Vaznaisiene, Weijun Wang, Derek T. Ward, Matthias D. Wimmer

Question 1: Is there a genetic predisposition to developing surgical site infection (SSI)/periprosthetic joint infection (PJI) after major orthopaedic procedures?[1]

Response/Recommendation

Yes. There may be a genetic predisposition to developing SSI/PJI following major orthopaedic procedures.

Level of Evidence: Limited

Delegate Vote: Agree 79.6%, Disagree 8.2%, Abstain 12.2% (Strong Majority, Moderate Consensus)

Rationale

Periprosthetic joint infection (PJI) and deep surgical site infection (SSI) following both total joint arthroplasty and other major orthopaedic surgical interventions are multifactorial processes that involve a complex interplay between host and environmental factors. The contribution of genetic factors in the development of PJI and SSI is the subject of ongoing investigations in an attempt to address several unanswered questions, including a more thorough understanding of the specific role of epigenetics and various single-nucleotide polymorphisms (SNPs) on the risk of developing PJI. Furthermore, while it has become increasingly clear that there may be genetic factors associated with an increased risk of PJI and SSI, the role of genetics in the context of other known risk factors has yet to be determined.

Large population-wide studies have shed light on the heritable nature of both PJI and SSI and have helped identify genes and SNPs associated with an increased risk of infection [1–3]. Anderson et al. assessed 66,985 patients who underwent either total hip arthroplasty (THA) or total knee arthroplasty (TKA), of whom 1,530 (2.3%) developed a subsequent PJI [1]. First-degree relatives of patients who developed a PJI were approximately twice as likely to also develop a PJI (hazard ratio [HR] 2.16; 95% CI 1.29 to 3.59). Furthermore, these authors identified 116 high-risk familial pedigrees that had greater than twice the likelihood of developing a PJI compared to the population average. However, these authors did not identify any specific genes associated with the increased risk they observed. Chen and Wen assessed 19,767 TKA patients, of whom 269 (1.4%) developed a subsequent SSI, and performed a genome-wide association study (GWAS) to identify SNPs associated with SSI [2]. The authors identified four SNP genotypes associated with an increased risk of postoperative infection involving four genes: PLCB1 (OR 2.67; 95% CI 1.83 to 3.89), EXD3 (OR 2.42; 95% CI 1.71 to 3.42), SAMD4B (OR 3.50; 95% CI 2.14 to 5.73), and STAG1 (OR 1.86; 95% CI 1.45 to 2.38). Guo et al. performed an extensive genome-wide association study analysis comparing 957 PJI patients to 398,708 controls and identified two high-risk SNPs and one high-risk gene (i.e., RBM26) [3]. However, the two SNPs were

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.101.

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https://doi.org/10.1016/j.arth.2025.10.101

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not associated with any specific genes, and the authors did not report an odds ratio or hazard ratio associated with RBM26. Population-wide data to date suggest that the risk of PJI and SSI is heritable, at least in certain subpopulations, and that there are certain SNPs associated with the development of both PJI and SSI.

Case-control studies have also elucidated specific genetic risk factors for both PJI and SSI [4–10]. However, many of these studies suffer from critical limitations, including non-generalizable patient populations, small sample sizes, and other methodological flaws such as the absence of a unified definition of PJI. Malik et al. compared 71 THA patients who developed a deep infection to 150 controls who had a well-functioning THA and found an increased frequency of the OPG-163 SNP among infected patients, suggesting that "deep infection [following] THA may be under the influence of susceptibility genes." [4] Malik et al., in a separate study, compared 71 infected THA patients to 150 controls and assessed four SNPs in the mannose-binding lectin gene and found one of the SNPs to be more prevalent in the infection group [5]. Navratilova et al. compared 112 TJA patients who had a PJI to 245 TJA patients who did not have a PJI and 196 control patients who did not have a TJA [6]. The authors found an SNP in the promoter region of the MBL2 gene associated with an increased risk of PJI. Stahelova et al. compared 89 PJI patients to 214 patients who did not have a PJI and 168 controls who did not have a TJA and found an SNP associated with the IL-1β gene to have an increased frequency among PJI patients, implicating this genetic variant as a potential risk factor for PJI [7]. Neufeld et al. assessed 23 THA patients with a PJI to 26 control patients matched by age, sex, body mass index, and comorbidities [10]. The authors identified three HLA genotypes associated with the development of PJI and a fourth HLA genotype that may be protective of PJI. While case-control studies have identified several genetic factors associated with an increased risk of PJI, these findings require further validation in large-scale prospective studies using standardized definitions of PJI to establish correlations and confirm their clinical relevance.

Conclusion

Based on the available literature to date, there is evidence to suggest a genetic predisposition to developing SSI and PJI following major orthopaedic procedures. However, conclusive evidence is lacking, as studies are critically limited by heterogeneity, small sample sizes, methodological flaws, and poor-quality data. Furthermore, the contribution of genetics, in the context of other known risk factors, has not been conclusively established.

Question 2: Does air travel just before surgery influence the rate of surgical site infection (SSI) in patients undergoing major orthopaedic procedures?[2]

Response/Recommendation

There is no definitive link between immediate air travel before surgery and increased risk of subsequent site infections (SSI) or periprosthetic joint infection (PJI).

Level of Evidence: Limited

Delegate Vote: 79.9% Agree; 17.0% Disagree; 3.1% Abstain

Rationale

The effect of preoperative travel, particularly long-distance travel, on surgical complications such as surgical site infections (SSIs) and periprosthetic joint infections (PJI) in major orthopaedic surgeries has not been definitively studied. While studies have evaluated the impact of travel on postoperative outcomes such as deep vein thrombosis [11], no clear evidence currently exists linking travel distance to an increased risk of infection-related complications.

Our analysis suggests that long distances between a patient's hometown and the surgery location, typically involving air travel within the United States (U.S.), do not show any significant differences in SSI or PJI rates for elective total hip, knee, and/or shoulder arthroplasty procedures. This conclusion is supported by a review of three relevant studies examining the role of travel distance on Injury Severity Score and PJI in total hip arthroplasty (THA) [12], total knee arthroplasty (TKA) [13], and shoulder arthroplasty (SA) [14].

All three of these studies used the PearlDiver database to perform a retrospective cohort analysis of patients undergoing elective primary THA, TKA, and SA, identified via CPT codes. Propensity score matching was performed to adjust for confounding factors—such as age, sex, obesity, diabetes, alcohol abuse, tobacco use, and drug abuse—when these differed between the baseline groups. Outcomes of interest included 30- and 90-days SSI and 90-days and 2-years PJI, compared between the air and land travel groups. Each group included 7,723 patients for THA, 11,866 for TKA, and 1,414 (air) versus 1,429 (land) for SA. There were no significant differences in complication rates observed.

In this analysis of postoperative infections by mode of travel, no statistically significant differences were observed. For 30-days SSI, rates were similar between air and land travelers: THA (0.7 versus 0.7%, $P = 0.923$), TKA (1.3 versus 1.4%, $P = 0.260$), and SA (0.4 versus 0.0%, $P = 0.072$) (Figure 1). The 90-days SSI rates were likewise comparable: THA (1.1 versus 1.2%, $P = 0.452$), TKA (1.8 versus 2.0%, $P = 0.200$), and SA (0.6 versus 0.3%, $P = 0.258$) (Figure 2). For 90-days PJI, infection rates remained low with no significant difference: THA (0.4 versus 0.5%, $P = 0.175$), TKA (0.5 versus 0.5%, $P = 0.642$), and SA (0.6 versus 0.1%, $P = 0.110$) (Figure 3). At two years, PJI rates were still similar: THA (0.71 versus 0.85%, $P = 0.362$), TKA (0.97 versus 0.98%, $P = 1.000$), and SA (1.5 versus 1.1%, $P = 0.384$) (Figure 4). Overall, air travel did not appear to increase the risk of postoperative infections compared to land travel.

While these findings indicate no clear association between travel distance and infection rates, the current body of literature is limited and fragmented. Further research, especially involving different surgical procedures and international travel, is necessary to provide a more definitive answer and establish clear guidelines for managing patients traveling long distances for surgery.

Question 3: Does asymptomatic urinary bacteriuria increase the risk of surgical site infection (SSI)/periprosthetic joint infection (PJI) in patients undergoing major orthopaedic surgery?[3]

Response/Recommendation

Although there seems to be an association between asymptomatic bacteriuria (ASB) and an elevated risk of periprosthetic joint infections (PJI)/deep surgical site infections (SSI) in patients undergoing major orthopaedic surgeries, the microorganism

[2] These authors contributed to Question 2: Amir Human Hoveidaei, Joshua S. Bingham, Cara A. Cipriano, Matthias D Wimmer, Wayne E Moschetti, Neil P. Sheth, Janet D. Conway

[3] These authors contributed to Question 3: Seyed Mohammad Javad Mortazavi, Ali Soltani Farsani, Juliana Arruda de Matos, Meeri P Honkanen, Eustathios Kenanidis, Eleftherios, A.V. Gurava Reddy, Tsiridis, Daniel Diego, Carl Herndon, Vito Pavone

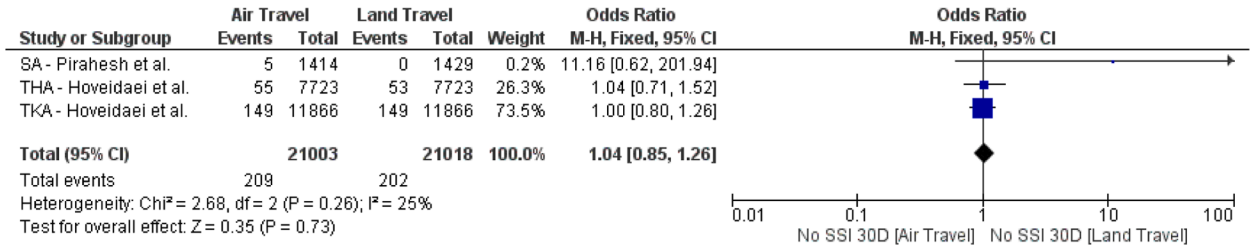

Figure 1. 30-days surgical site infection (SSI) outcomes.

causing SSI/PJI is almost always different from that identified in ASB.

Level of Evidence: Moderate

Delegate Vote: Agree 66.1%, Disagree 28.8%, Abstain 5.1% (Strong Majority, Moderate Consensus)

Rationale

Recent studies have indicated a potential link between asymptomatic bacteriuria (ASB) and an elevated risk of PJI and wound infections [15,16]. They suggest that ASB may lead to bacterial colonization of the genitourinary tract, which can cause infections in prostheses due to hematogenous seeding or skin contamination through continuity [17]. The Infectious Diseases Society of America defines ASB as being diagnosed with isolation levels of at least 10^5 colony-forming units (CFUs)/mL in urine cultures (UCs), without any indications or symptoms of a urinary tract infection (UTI) [18]. The Infectious Diseases Society of America, the American Society of Anesthesiologists, and the International Consensus Meeting (ICM) in 2018 do not recommend routine preoperative urine screening, including UC and urinalysis, before nonurologic surgeries for ASB patients [19–23]. Conversely, the British Orthopedic Association recommends conducting preoperative urine screening [24].

We performed a comprehensive systematic review and meta-analysis of the literature to address the relationship between the ASB and postoperative SSI/PJI. A comprehensive database search, including PubMed, Embase, Web of Science, and Scopus, yielded 602 papers. After two screening steps, 14 papers met the inclusion criteria [16,17,25–36], which focused on studies comparing the rates of SSI or PJI in adult patients and have ASB who underwent major orthopedic surgeries.

Among the included studies, nine reported data on the incidence of PJI in patients who have ASB and underwent major orthopaedic surgeries, in comparison to non-ASB patients [16,17,25,27–29,33,35,36]. In total, there were 27,410 patients in the non-ASB group and 2,159 patients in the ASB group. A random-effects meta-analysis indicated that patients who have ASB undergoing major orthopaedic surgeries had a significantly higher relative risk of PJI than those who do not have ASB, with a relative risk (RR) of 3.14 (95% confidence interval [CI]: [1.22 to 8.10], $P = 0.0244$). Three studies reported data on the incidence of superficial wound infections [16,25,35]. The non-ASB group comprised 20,227 patients, while the ASB group included 1,512 patients. A random-effects meta-analysis revealed no significant difference in the incidence of superficial wound infections between ASB patients and the control group (RR: 2.24, 95% CI: [0.20 to 25.76], $P = 0.2906$).

Also, we conducted a comprehensive meta-analysis of all studies for the incidence of SSI, including superficial wound infections, deep incision infections, and PJI. The analysis encompassed 43,292 patients, with 40,596 individuals in the control group and 2,696 patients in the ASB group. All studies employed UC for the preoperative examination of ASB in patients, except the study by Peng et al., which utilized an automated urine analyzer to quantify bacteriuria [16]. The prevalence of ASB among patients varied significantly, ranging from 3 to 31%, depending on the inclusion criteria. A random-effects meta-analysis indicated that patients who have ASB undergoing major orthopedic surgeries face a markedly higher relative risk of SSI compared to those who do not have ASB (RR = 2.99, 95% CI: [1.62 to 5.51], $P = 0.0019$) (Figure 5). Similarly, a meta-analysis conducted by Wang et al. (2018) examined whether ASB increases the risk of PJI in patients undergoing TJA [37]. By analyzing data from five studies that included 3,588 joint arthroplasties and 441 ASB cases (with a 12.3% incidence), the researchers found that the ASB group exhibited a significantly higher risk of PJI compared to the control group (RR = 2.87, 95% CI: 1.65 to 5.00, $P < 0.005$). Additionally, seven of the included studies reported the organisms isolated in the perioperative UC of ASB patients and the pathogens identified in subsequent SSI [27–29,33–36]. All of these seven studies examined PJI in patients. Notably, none of the studies found a concordance between the organisms responsible for ASB and the pathogens isolated during the subsequent PJI. *Escherichia coli* was identified as the most prevalent microorganism in the UCs of the ASB group before surgery, while coagulase-negative staphylococci emerged as the most commonly isolated pathogens in PJIs after surgery.

Question 4: What are the modifiable risk factors for postoperative infection in patients undergoing major orthopaedic surgery?[4]

Response/Recommendation

Evidence suggests that more than 25 modifiable risk factors are associated with an increased risk of surgical site infection (SSI) and periprosthetic joint infection (PJI) in patients undergoing major orthopaedic surgery. Common modifiable risk factors include smoking, obesity, diabetes, anemia, and malnutrition, while others such as alcoholism, vitamin D deficiency, preoperative antibiotic prophylaxis, rheumatoid arthritis, corticosteroid use, anticoagulants, poor dental hygiene, HIV infection, urinary tract infection, surgical site preparation, operation room environment, operative time, depression, history of proton pump inhibitors (PPI) use, opioids, frailty, and medical comorbidities like congestive heart failure and chronic pulmonary, renal, and liver diseases also contribute to infection risk.

Level of Evidence: Strong

Delegate Vote: Agree 77.0%, Disagree 13.8%, Abstain 9.2% (Strong Majority, Moderate Consensus)

Rationale

Surgical site infection (SSI) and periprosthetic joint infection (PJI) after major orthopaedic surgeries are devastating and impose

[4] These authors contributed to Question 4: Sayid Omar Ahmed, Margarita Veloso Duran, Marta Sabater-Martos, Joris Ploegmakers, Jason M. Jennings, Nathan Kaplan, Derek T Ward, Keita Morikane, Javad Parvizi

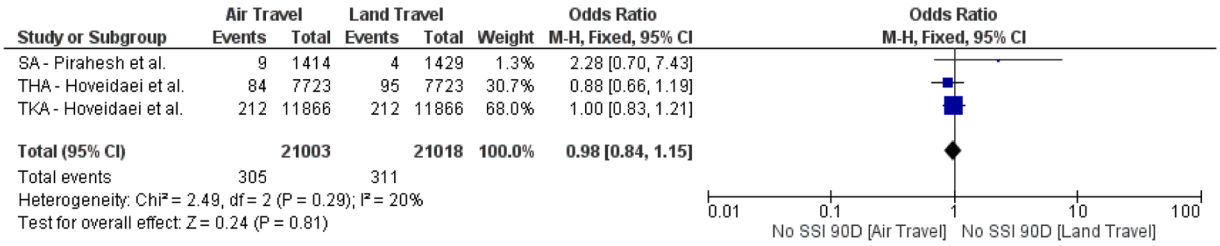

Figure 2. 90-days surgical site infections (SSI) outcomes.

major societal, healthcare system, and economic burden. The risk for developing SSI or PJI following major orthopedic surgeries is multifactorial. Notably, 80% of patients undergoing arthroplasty have at least one modifiable infection risk factor, primarily related to patient characteristics or surgical factors [38–43].

Identification and optimization of these modifiable risk factors preoperatively could potentially reduce the risk of SSI and PJI [44–47]. We conducted a systematic review to identify modifiable risk factors associated with surgical site infections and periprosthetic joint infections in the existing literature. A comprehensive search was performed in PubMed and Embase using specific MeSH terms developed by librarians. The search yielded 475 studies, of which 79 were included in the final analysis after a two-stage screening process conducted independently by two different authors.

Several major modifiable risk factors have been extensively studied in the literature, and they are summarized in Table 1 [48–53].

Conclusions

Several modifiable factors have a correlation with the contribution of SSI and PJI in patients undergoing major orthopedic surgeries. Strong evidence in the literature supports the importance of preoperative optimization to reduce these risks. Key strategies include smoking cessation, preoperative weight reduction, strict glycemic control, nutritional optimization, and anemia correction. Medical optimization of patients who have comorbidities such as renal failure, liver failure, congestive heart failure, chronic pulmonary diseases, and HIV, as well as optimization of oral and nasal hygiene and control of any urinary or cutaneous infections, has also been shown to be important in reducing the risk of SSI [43,62,73,77].

Optimization of all other patient, surgeon, and operating room-related factors is crucial for reducing the risk of surgical site infection (SSI) and periprosthetic joint infections (PJI), as some evidence suggests that they contribute to infection prevention.

Question 5: What is the optimal marker of glycemic control for patients undergoing major orthopaedic surgery?[5]

Response/Recommendation

This workgroup recommends that any or all available markers, namely HbA1c, fructosamine, or blood glucose variability, should be used to determine glycemic control.

Level of Evidence: Moderate

Delegate Vote: Agree 85.7%, Disagree 12.2%, Abstain 2.1%

Rationale

Diabetes mellitus is one of the most prevalent diseases, affecting millions of people worldwide [78]. Dysregulated blood glucose levels are commonly observed in patients undergoing orthopaedic surgeries [79,80]. This condition has been linked to both short- and long-term complications, such as infections, readmission, and overall mortality [79,81–83]. As a result, it has been recommended that all patients be screened for glycemic control before surgery [84]. Currently, the American Diabetes Association has endorsed HbA1c as a reliable marker for assessing blood glucose levels before surgery. In recent years, there has been growing uncertainty regarding the ability of HbA1c to predict complications after orthopedic surgeries, as well as debate over the optimal cutoff values for this marker [85,86]. At the same time, increasing research is exploring other markers, such as fructosamine, which may offer potential in reducing postoperative complications in orthopedic patients [87,88].

A systematic review and meta-analysis were conducted. After the initial and full-text screening, 67 papers were included in the final review [89–155]. Currently, three main markers are used to assess glycemic status in patients undergoing major orthopedic surgeries: HbA1c, fructosamine, and glucose variability. It should be noted that the included papers vary with regard to the inclusion of these three markers for comparison, use differing cutoffs to study significance, and involve inconsistent times of marker obtainment (preoperative, intra-operative, or postoperative). Nevertheless, three primary outcomes were evaluated in these studies for major orthopedic surgeries: infections (including surgical site infections [SSIs] and periprosthetic joint infections [PJI]), readmissions, and reoperations. The meta-analysis revealed that HbA1c has a strong predictive value for infection and readmission following major orthopedic surgeries, but not for reoperation. However, the heterogeneity across all analyses ranged from moderate to high, which limits the interpretability of the results. A commonly used cutoff value for HbA1c is 7%; however, this threshold has recently been called into question [156–158]. A subgroup analysis was conducted to evaluate the association between different HbA1c cutoff levels and infection rates following orthopedic surgery. However, the analysis revealed that the differences between the cutoff values were not statistically significant. Fructosamine was also evaluated as a predictive marker for outcomes following major orthopedic surgeries, demonstrating promising results. The most commonly used cutoff for fructosamine was 292 to 293 μmol/L [159,160]. It exhibited significant predictive value for infections, readmissions, and reoperations. Although the heterogeneity among studies was low, the limited number of studies investigating this marker reduces the robustness of the conclusions that can be drawn from these findings. Glucose variability was evaluated and reported in studies using the

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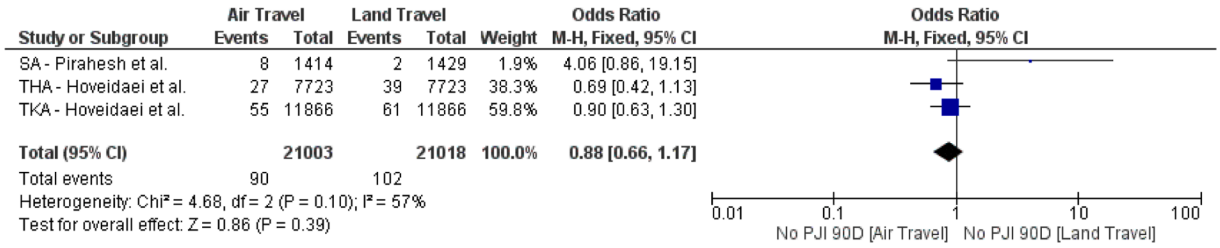

Figure 3. 90-days periprosthetic joint infections (PJI) outcomes.

coefficient of variation (CV), with most studies stratifying CV into three tertiles. A subgroup analysis was conducted to evaluate high and medium CV levels in comparison to low CV for predicting infection rates following orthopedic surgeries. Significant results were observed for high glucose variability compared to low, but not for medium glucose variability.

Comparative research aimed at identifying the optimal glycemic marker remains limited. A 2019 study by Shohat et al. on fructosamine demonstrated that it provides superior predictive value, responds more rapidly to treatment, and can identify patients who have postoperative complications and have normal HbA1c levels but whose fructosamine levels exceed the established cutoff [159]. Additionally, a 2017 study by Shohat et al. reported that while HbA1c levels above 7% were not able to predict or show a significant association with infection, reoperation, or readmission, fructosamine demonstrated greater predictive value [160]. These results highlight the need for better-controlled comparisons between these two markers in the literature to obtain more meaningful findings.

A variety of other markers, such as single assessments of blood glucose, the HbA1c/albumin ratio, and albumin-corrected fructosamine, have been studied. Some research has demonstrated good predictive value for these markers; however, due to the limited number of studies and variations in evaluation methods, further research is required to establish their clinical relevance [88,161–163].

Conclusions

Based on the current evidence, three main markers are used for assessing glycemic control in patients undergoing major orthopedic surgeries: HbA1c, fructosamine, and blood glucose variability. Hemoglobin A1c is the most widely adopted method of assessment; however, it has been shown to be less reliable in recent investigations. Fructosamine, an emerging marker, may offer greater predictive value compared to HbA1c. Nevertheless, further research is needed to compare these two markers using more controlled and comprehensive methods to determine the optimal glycemic marker for predicting outcomes following orthopedic surgeries.

Question 6: Are former COVID-19 patients undergoing major orthopaedic procedures at risk for subsequent periprosthetic joint infection (PJI) and surgical site infection (SSI)?[6]

Response/Recommendation

A recent (within 90 days) history of COVID-19 infection appears to increase the risk of SSI/PJI in patients undergoing major orthopaedic procedures.

Strength of Recommendation: Level II

Delegate Vote: Agree 76.9%, Disagree 15.4%, Abstain 7.7% (moderate consensus)

Rationale

The COVID-19 pandemic is one of the greatest health challenges of the 21st century, imposing a major social and economic burden, particularly on vulnerable populations such as the elderly, those who have chronic diseases, and those requiring urgent medical interventions, including trauma care [164–167]. Despite several articles having highlighted the negative impact of the pandemic on the outcomes of orthopedic surgeries, including a high mortality rate [168–172], the effect of COVID-19 on the incidence of PJI and SSI is still unclear, and no comprehensive review has investigated the effect of COVID-19 on PJI and SSI after orthopedic surgeries [170,173–180]. We conducted a systematic review and meta-analysis to investigate the effect of COVID-19 based on the time of infection (preoperative, during, and postoperative) on the outcomes of PJI and SSI after orthopaedic surgeries. The inclusion criteria consisted of observational studies examining the effect of patients presenting with COVID-19 on PJI and SSI complications following major orthopedic surgeries, including all fractures and joint replacements with at least one month of follow-up. Preoperative, intraoperative, and postoperative COVID-19 were defined based on a positive test within 90 days before surgery, on the day of surgery, and within 90 days after surgery, respectively. There were 17 studies that met the inclusion criteria for analysis. There were 19,157 (2.1%) of the patients who had a positive perioperative COVID-19 test. The pooled prevalence of PJI and SSI in COVID-19-positive patients who underwent orthopedic surgery was 1.8% (95% confidence interval (CI): 1.2 to 2.5%) and 2% (95% CI: 1.5 to 2.5%), regardless of the timing of COVID-19 positivity. Pooled estimation of 13 studies showed that, regardless of the time of infection, COVID-19 positivity was associated with an increased probability of PJI (OR: 2.25, 95% CI: 2.68 to 2.83, I^2: 93.7%) and SSI (OR: 2.01, 95% CI: 1.74 to 2.28, I^2: 73.6%) in major orthopaedic surgeries. The probability of PJI occurrence was significantly higher in patients who tested positive for COVID-19 preoperatively and intraoperatively compared to those who did not have COVID-19. However, the probability of PJI was not significantly associated with postoperative COVID-19 positivity (OR: 1.5, 95% CI: 0.67 to 2.33, I^2: 76.3%). The probability of SSI in patients who have COVID-19 preoperatively, intra-operatively, and postoperatively was significantly higher compared to those who do not have COVID-19.

Several studies provide insights into the potential risks and mechanisms by which a history of COVID-19 infection impacts SSI and PJI in orthopedic patients. Having COVID-19 leads to prolonged immune system dysregulation, including hyperinflammation, T-cell dysfunction, and increased prothrombotic states. These factors collectively impair wound healing and increase infection susceptibility [181,182]. A recent study

[6] These authors contributed to Question 6: Arash Aali Rezaie, Bülent Atilla

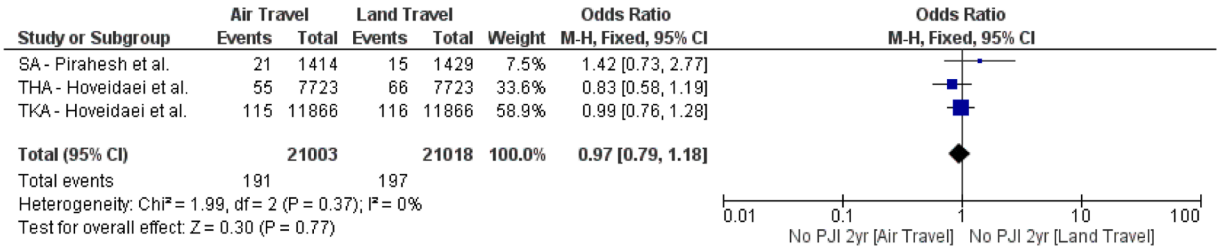

Figure 4. 2-years periprosthetic joint infections (PJI) outcomes.

showed significantly elevated risks for venous thromboembolism (VTE), sepsis, and 30-days mortality in patients undergoing spinal surgery within two weeks of a COVID-19 diagnosis. However, patients operated on beyond six weeks showed no significant differences in complications, highlighting the importance of delaying surgery [182]. The COVID-19-associated systemic inflammation and vascular damage may predispose patients to SSI and PJI. For example, one study reported a 4.65-fold increase in PJI risk after total joint arthroplasty in patients who have a postoperative COVID-19 diagnosis [181]. An analysis of Japan's national surgical database found that heightened hygiene protocols during the pandemic had no significant effect on overall SSI rates in orthopaedic surgeries, suggesting the need for targeted infection prevention strategies [183]. Studies recommend postponing elective orthopedic procedures for at least six to 12 weeks post-COVID-19 diagnosis to allow for immune recovery and stabilization. Another study evaluating trauma patients undergoing surgery demonstrated that the presence of COVID-19 significantly increases the likelihood of perioperative complications, including infections, due to systemic inflammation [184]. Also, COVID-19 protocols implemented during primary and revision total hip arthroplasties highlighted the importance of institutional infection control measures and their role in mitigating the risk [184,185]. These findings emphasize the need for a cautious approach in managing former COVID-19 patients undergoing major orthopaedic procedures, balancing surgical urgency with the risks of postoperative complications.

Meta-analyses show that COVID-19 significantly increases postoperative mortality and complications in orthopedic trauma patients. Wang et al. [170] reported a 32.6% early mortality rate in hip fracture patients, 5.66 times higher than in non-COVID-19 patients, while another study found a 7.72-fold increase in mortality [171]. Tripathy et al. [172] and Jain et al. [186] confirmed higher risks of mortality, pneumonia, severe complications, and prolonged hospitalization in COVID-19-positive patients. These outcomes are linked to advanced age, immunosuppression, inactivity, and limited rehabilitation, increasing risks of PE, deep vein thrombosis, PJI, and SSI [187–194].

Conclusions

This meta-analysis revealed a higher prevalence of PJI and SSI in COVID-19-infected patients undergoing orthopedic surgery compared to those who do not have COVID-19. Infection during preoperative and perioperative periods increased the risk of PJI in major orthopaedic procedures by over twofold, while postoperative infection showed no significant association. Additionally, COVID-19 increased the likelihood of SSI across all periods. Future research should explore the optimal timing for elective surgeries after COVID-19 and develop preventive strategies to reduce PJI and SSI risks.

Question 7: What are the risk factors for infection with multiresistant microorganisms for patients undergoing major orthopaedic procedures?[7]

Response/Recommendation

Risk factors for infection with multiresistant microorganisms (MDRO) in patients undergoing major orthopaedic procedures are multifactorial, including severe illness, older age, malnutrition, immunosuppression, need for multiple procedures for open fractures or early PJI, previous orthopaedic infection, postoperative infected hematoma, previous and inappropriate use of systemic antibiotics, and prolonged hospital and ICU stay. The MDR/XDR infections are linked to poor outcomes and mortality, with hospital-specific practices, such as surgical preventive measures, surveillance, and strict infection control, being critical for improving patient outcomes.

Level of Evidence: Moderate

Delegate Vote: Agree 86%, Disagree 9.3%, Abstain 4.7% (Super Majority, Strong Consensus)

Rationale

Major orthopedic-associated infections (OAIs), including prosthetic joint infections (PJIs), fracture-related infections (FRIs), spinal implant-associated infections (SIAIs), and chronic osteomyelitis (COM), are predominantly caused by biofilm-forming staphylococci, despite the increasing identification of Gram-negative bacteria (GNB) [195,196]. Trauma and implant-associated infections (IAIs), such as PJI, FRI, and SIAI, are leading causes of osteomyelitis, often involving polymicrobial pathogens including staphylococci, aerobic GNB, and anaerobes [196,197]. The rise of multidrug-resistant organisms (MDROs) presents significant therapeutic challenges, requiring prolonged antibiotic regimens and multiple surgeries [198–200]. International consensus defines MDROs as resistant to at least one agent in three antibiotic classes, while extensively drug-resistant (XDR) microbes are susceptible to two or fewer agents, and pandrug-resistant (PDR) organisms are resistant to all available antibiotics [201]. Methicillin-resistant *S. aureus* (MRSA), methicillin-resistant *S. epidermidis* (MRSE), and multidrug-resistant Gram-negative organisms (MDR-GNB), such as *Pseudomonas aeruginosa*, *Enterobacter spp*., *Klebsiella pneumoniae*, *E. coli*, and *Acinetobacter baumannii*, are major challenges in MDR-OAIs [202]. A thorough understanding of microbial profiles and associated risk factors is crucial for developing effective prevention and treatment strategies.

Studies on the microbial epidemiology of and predisposing factors for MDR-OAIs are limited, with most being single-center retrospective cohorts with few exceptions [197,199,207,208]. A large multicenter study of PJI conducted across 19 Spanish centers

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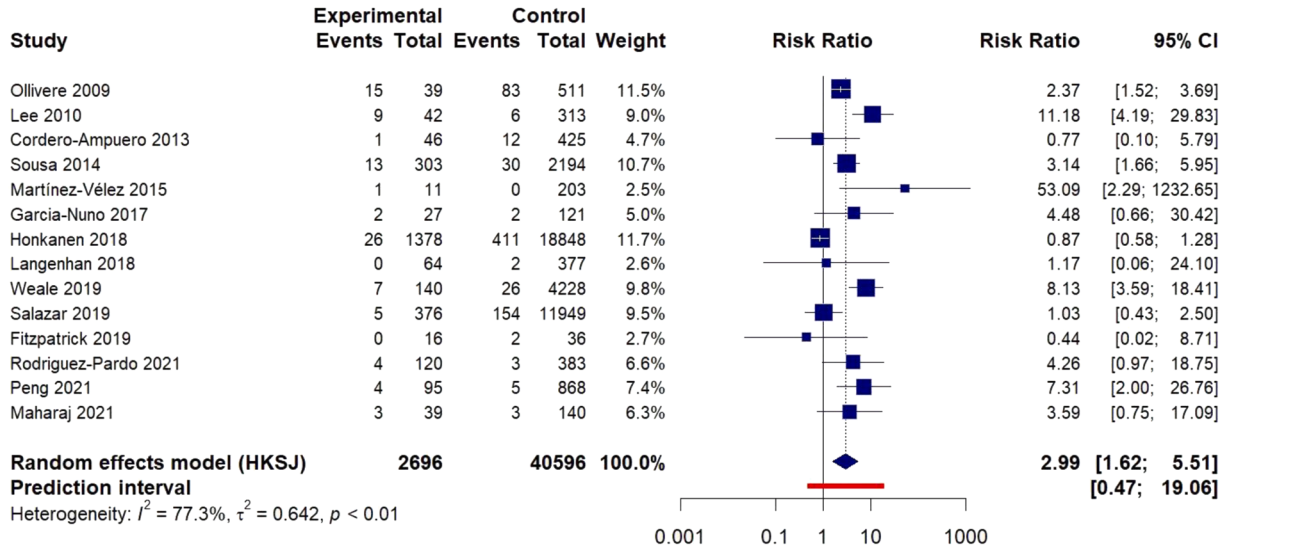

Figure 5. Random-effects meta-analysis using the Hartung-Knapp method of included studies. All statistical analyses were conducted using R software (version 4.0.0) with the 'meta' package.

over a 9-year period demonstrated that *Staphylococcus aureus* accounted for a significant proportion of infections, with MRSA associated with longer hospital stays and higher reoperation rates ($P = 0.015$). The MDROs were more prevalent in early postoperative PJI (24%) according to Tsukayama's classification, compared to late PJI (7.8%) and acute-late PJI (10.9%) [197]. Logistic regression analyses revealed that polymicrobial infections were associated with an increased risk of complications compared to monomicrobial infections (odds ratio (OR) 2.74, $P < 0.001$) [197]. A retrospective review in Brazil of 98 patients with hip and knee PJI identified revision arthroplasty (prevalence ratio (PR) 1.7; $P = 0.002$), previous orthopaedic infection (PR 1.5; $P = 0.002$), postoperative hematoma (PR 2.6; $P < 0.001$), and early infection (PR 2.2; $P = 0.001$) as independent risk factors for PJIs caused by MDR/XDR-GNB. XDR-GNB infections (PR 2.3; $P = 0.044$) and comorbidities (PR 2.9; $P = 0.044$) strongly predict treatment failure, with a 4.6-fold higher risk of mortality compared to infections caused by other pathogens (OR 4.6; $P = 0.010$) [198]. McCulloch et al. conducted a retrospective review of 118 patients undergoing two-stage revision surgery (n = 74) for knee PJI and compared patients who had undergone lower-limb two-stage revision of oncology knee endoprostheses (n = 44). The MDROs were significantly more prevalent in endoprosthesis (36%) compared to TKA (17%; $P = 0.01$) [202].

Additionally, high infection rates with MDROs have been reported in orthopedic trauma units, particularly in developing countries, due to factors such as the severity of open injuries, need for multiple surgical procedures, prolonged hospital stays, and overuse of systemic antibiotics [196,200]. Recent single-center studies from China and Brazil further assessed these issues. Sun et al. reported that polymicrobial infections accounted for a major proportion of limb FRIs, with key pathogens including MRSA and extended-spectrum beta-lactamase (ESBL)-producing GNB. Risk factors for MDROs included bedridden status (OR 2.66; $P = 0.037$), repeated infections (OR 4.00; $P = 0.005$), and longer operative times (≥ three hours; OR 2.28; $P = 0.023$) [203]. Liang et al. analyzed 239 patients with open wound infection, while MDR-FRI accounted for 37.2%. Cultures yielded 178 strains, and 29.8% were MDROs. MDR-GNB, ESBLs, XDR/PDR-*Pseudomonas aeruginosa*, carbapenem-resistant *A. baumannii* (CRAB), and MRSA predominated. Logistic multivariate analyses showed that the length of hospital stays (OR 1.17; $P < 0.05$), antibiotic use time (OR 1.60; $P < 0.05$), open injury (OR 3.66; $P = 0.05$), and serum albumin levels < 1.96 g/dL (OR 1.96; $P < 0.05$) were independent predictors of MDRO infection in orthopedic trauma patients [200]. A similar Brazilian single-center study assessed 132 cases of limb FRIs over a 1-year period and identified *Klebsiella pneumoniae* as a leading pathogen, with prior antibiotic use (PR 7.0; $P = 0.001$) and cancer (PR 9.8; $P = 0.005$) as significant risk factors [204]. In pediatric patients, improper timing of prophylactic antibiotics, administered outside the recommended preoperative window and ignificantly increased the risk of infection (OR: 8.4, $P < 0.001$). Independent risk factors for MDROs included younger age (≤ one year, OR 0.45, $P < 0.001$), contaminated surgical incision types (dirty incision, OR 16.38, $P = 0.001$), admission during winter (OR 2.939, $P < 0.001$), preoperative infection (OR 2.817, $P < 0.001$), and catheter drainage > three days (OR 3.712, $P < 0.001$) [205]. A Chinese retrospective surveillance study in the orthopaedic unit has identified 358 (25.7%) MDROs yielded from various sources (e.g., tissue, skin secretion, blood, and urine). The ESBL-positive *E. coli*, MDR-*Acinetobacter baumannii*, and MDR-Pseudomonas aeruginosa were predominant pathogens, with resistance patterns strongly influenced by age ≥ 60 years (OR = 1.838, $P < 0.05$), open injuries (OR = 1.737, $P < 0.05$), and central lesions (OR = 2.821, $P < 0.05$) [206].

The epidemiology of MDR-OAIs in orthopedic trauma units varies between developed and developing regions. Dudareva et al. conducted a single-center cohort study in Oxford of COM cases undergoing internal fixation devices and compared microbiological results from 2001 to 2004 to 2013 to 2017. Polymicrobial infection was present in 21.5%. Only metalwork was associated with MDR infection (unadjusted OR 5.0). The proportion of MDR infections was similar in both cohorts (15.2 versus 17.2%). MRSA (10.5%) was associated with a higher risk of reoperation (OR 2.85; $P = 0.009$) [196]. In a German/Swiss study of trauma patients presenting Injury Severity Score ≥ 9 and admitted to intensive care units (ICUs), MDRO was significantly associated with severe cases of worse Glasgow Outcome Scores (GOS; $P < 0.001$), ICU stays > 48 hours (OR 4.01; $P < 0.001$), and men (OR 1.73; $P = 0.037$) [13]. A multicenter study in northern Australia found significantly higher rates of MRSA and MDR nonfermenters like *Pseudomonas aeruginosa* and *Acinetobacter*

Table 1
Modifiable Risk Factors for Periprosthetic Joint Infection.

Risk Factor	Relation to PJI	Intervention
Smoking [54,55]	Wound tissue hypoxia, endothelial dysfunction, decreased immune response, and poor wound healing	Preoperative counseling and smoking cessation at least 4 weeks before surgery
Obesity [56–58]	Longer operative time, decreased vascularization of fatty tissue, risk of poor wound healing, and presence of other medical comorbidities	Preoperative weight loss intervention, including exercise, diet, or bariatric surgery
Uncontrolled diabetes and hyperglycemia [44,53,59,60]	impairs neutrophil function and delays wound healing	Preoperative glycemic control using diet, exercise, and medications
Anemia [52,61–63]	Tissue hypoxia, risk of allogenic blood transfusion, and possible underlying chronic kidney diseases	Preoperative correction of anemia, administration of erythropoietin in cases of chronic kidney disease
Malnutrition [51,64,65]	impairs immune function and delays tissue repair	Nutrition optimization (proteins, vitamins, and minerals)
Low Vitamin D [66–68]	May increase susceptibility to infection	Preoperative optimization of vitamin D and overall nutritional status
Alcoholism [69]	Weakens immune function and impairs wound healing	Preoperative screening, counseling, and alcohol cessation
Preoperative antibiotic prophylaxis [49,70]	Delayed or inappropriate use increases PJI risk	Strict adherence to antibiotic protocols
Rheumatoid arthritis and immunosuppressive drugs [71]	Causes immunosuppression, delays healing, and increases risk of infection	Preoperative cessation of immunosuppressive medication
Surgical and operating room environment factors [40,49,72]	Longer operative time, increased OR traffic, and inappropriate surgical site preparation increase infection risk	Proper surgical site preparation, minimizing OR traffic, and procedure duration
Cardiovascular diseases [62]	Atherosclerosis and microvascular complications, anticoagulant therapy, and immune dysfunction lead to poor blood supply and hematoma formation, which may lead to a higher risk of PJI	Preoperative optimization of blood pressure and lipid levels, bridging of anticoagulants, and screening for congestive heart failure
Chronic renal diseases [62]	Anemia, impaired protein metabolism, and uremic-induced immune suppression all contribute to an increased risk of PJI	Preoperative correction of anemia and fluid, and electrolyte imbalance
Chronic liver diseases [62]	Malnutrition, hypoalbuminemia, coagulopathy, and reduced synthesis of complement proteins contribute to the risk of delayed wound healing and the risk of infection	Optimize nutrition, correct coagulopathy and assess overall liver function test
Chronic pulmonary diseases [62,73]	Hypoxia and poor tissue oxygenation from atelectasis and respiratory failure lead to prolonged hospitalization, delayed wound healing, and subsequent risk of PJI	Preoperative optimization, pulmonary rehabilitation, oxygen therapy, and smoking cessation
Opioid use [74,75]	Alterations in immune function and impact on collagen synthesis lead to poor wound healing and risk of PJI	Screen for dependence, discuss and reduce opioid usage, and involve pain management specialists
Depression [62]	Poor nutrition, anemia, subsequent risk of allogeneic blood transfusion, and poor adherence to postoperative instructions	Screen for depression, counsel preoperatively, optimize therapy, and encourage psychosocial support
PPI use [76]	Decreases neutrophil activity and disrupts absorption of essential nutrients, leading to malnutrition, which further suppresses immune function and increases risk of infection	Temporary cessation of PPI and/or switching to other medications

baumannii in tropical hospitals compared to subtropical ones [208]. Similarly, a 10-years multicenter study by the European Study Group on Implant-Associated Infection (ESGIAI-ESCMID) found that XDR infections required longer treatment durations and were associated with worse clinical outcomes compared to MDR infections, emphasizing the challenges in managing these cases. The remission rate after combined therapy was only 50.9%, while treatment failure was statistically associated with age > 60 years (hazard ratio (HR) 3.8; $P = 0.004$) and multiple surgeries (HR 2.8; $P = 0.024$) [199].

Conclusion

Most studies highlight modifiable and nonmodifiable independent significant causes of MDRO in OAI (1) Advanced age (> 60 years) and comorbidities, notably obesity, are consistently associated with an increased risk of MDRO infections [196]. Open fractures, particularly Gustilo III B and III C types, significantly increase the risk of infection with resistant organisms, with studies from China and Europe highlighting their strong association with MRSA infections. Degenerative diseases were similarly linked to ESBL-*E. coli* infections; [197] Low serum albumin levels (< 1.96 g/dL) predict MDRO acquisition, while immunosuppression from diseases or treatments further increases susceptibility; [198] Procedure-related risk factors such as type of surgical interventions and prolonged operative duration (≥ three hours) are established contributors to the risk of MDRO infections. Evidence from studies on limb fracture infections reported that longer procedures increased the likelihood of MDRO infections. Patients requiring multiple revision surgeries are particularly vulnerable. [199] Open injuries and trauma-related fractures significantly elevate the risk of MDR infections, with studies showing that open injuries are associated with a threefold higher risk of MDRO acquisition compared to closed injuries. In certain cases, including road traffic accidents and falls, the mechanism of injury influences infection outcomes as well by increasing vulnerability to contamination and subsequent infection [200]. Microbial and antibiotic-related factors play a pivotal role, with MDROs such as MRSA, ESBL-producing *Escherichia coli*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* being major contributors to infection risk and adverse clinical outcomes. Prolonged or inappropriate antibiotic use serves as a significant contributor to antimicrobial resistance. Research focusing on open wound infections has demonstrated that extended antibiotic administration markedly elevates the MDRO risk. Additionally, delayed or suboptimal prophylaxis further contributes to infections, with a pediatric study revealing that improper timing of antibiotic administration is associated with an eightfold increase in the likelihood of developing infections [201]. Clinical and environmental factors, such as ICU stays exceeding 48 hours, are associated with a fourfold increase in the risk of MDRO colonization. Furthermore, hospital-specific practices, including surgical volume and strict adherence to infection control protocols, are critical determinants of patient outcomes [202]. Geographic variability significantly influences

pathogen prevalence, with regional differences playing a critical role. For instance, tropical hospitals in Australia report higher multidrug resistance prevalence in *Pseudomonas aeruginosa* compared to those in subtropical regions, highlighting the necessity for tailored, location-specific strategies to address these challenges.

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The Journal of Arthroplasty 41 (2025) S19–S29

Contents lists available at ScienceDirect

The Journal of Arthroplasty

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General Topics

2025 ICM: Anemia, Blood-Saving, and Thromboprophylaxis

Seyed Mohammad Javad Mortazavi, Antony Palmer, Fatih Yildiz, Ibrahim Elganzoury, Waleed A. Al-Saadan, Udo E. Anyaehie, Jamal Ashraf, Pawel Bartosz, Kerem Başarir, Jerzy K. Bialecki, Marcus Crestani, Mohammadali Enayatollahi, Sana Eybpoosh, Matteo Carlo Ferrari, George Grammatopoulos, Sina Hajiaghajani, Seung Beom Han, Nathanael Heckmann, Yutaka Inaba, Mustafa Alper Incesoy, Ben Kendrick, Mercelo Lizarraga, Geert Meermans, Amin Moradi, Nikolai Nikolaev, Antony Palmer, Mohammadreza Razzaghof, A.V. Gurava Reddy, Mustafa Şenyurt, Yasuhito Tanaka, Gabriele Tucci, Michael Whitehouse, Mark Wu, Ahmed Saeed Younis

Question 1: Is preoperative anemia a risk factor for surgical site infection (SSI) and periprosthetic joint infection (PJI) for patients undergoing major orthopaedic surgery?[1]

Response/Recommendation

Yes. Preoperative anemia is a risk factor for surgical site infection (SSI) and periprosthetic joint infection (PJI) in patients undergoing major orthopaedic surgeries.

Level of Evidence: Moderate

Delegate Vote: Agree 91.4%, Disagree 5.7%, Abstain 2.9% (total consensus, unanimity)

Rationale

To address the question posed above, we conducted a comprehensive systematic review using the MeSH terms created by librarians. A literature search of four databases (PubMed, Scopus, Web of Science, and Embase) was conducted to identify 908 potential articles. After screening the identified literature, 872 were excluded, leaving 36 studies that were eligible for inclusion in the final analysis. Inclusion criteria required studies addressing preoperative anemia as a risk factor for surgical site infection (SSI)/periprosthetic joint infection (PJI) in major orthopaedic surgeries, including joint arthroplasties, spine surgeries, complex lower limb fractures, and limb salvage procedures. A meta-analysis was conducted on all included studies, followed by subgroup analyses based on the type of major orthopaedic surgery: hip and knee arthroplasties (20 studies), spine surgeries (11 studies), and shoulder arthroplasty (five studies). Additionally, nine studies (three hip/knee, five spine, and one shoulder) reported separate results for superficial and deep SSI. Consequently, additional subgroup meta-analyses were performed specifically for superficial and deep SSI outcomes in spine surgeries.

The meta-analysis of all studies demonstrated a significant association between preoperative anemia and the risk of SSI/PJI, with a pooled odds ratio (OR) of 1.712 (95% CI [confidence interval]: 1.566 to 1.870, $P = 0.0001$). Subgroup analyses revealed similar significant associations for hip and knee arthroplasties (OR: 1.732, 95% CI: 1.564 to 1.917, $P = 0.0001$), spine surgeries (OR: 1.520, 95% CI: 1.283 to 1.799, $P = 0.0001$), and shoulder arthroplasty (OR: 2.038, 95% CI: 1.514 to 2.744, $P = 0.0001$). In spine surgeries, separate meta-analyses for superficial and deep SSI outcomes also showed significant associations, with pooled ORs of 1.286 (95% CI: 1.117 to 1.479, $P = 0.0001$) and 1.847 (95% CI: 1.634 to 2.086, $P = 0.0001$), respectively (Figure 1).

Several potential limitations were encountered in this study. The definition of anemia varied across studies. Some studies classified anemia by severity (e.g., mild versus moderate to severe). In these cases, data were extracted by grouping all anemia cases together and comparing them with nonanemia cases. Second, many studies were not exclusively focused on anemia as a risk factor but also examined various other factors using both univariate and multivariate analyses. Due to the wide variety of risk factors assessed across studies, including them in the meta-analyses would have introduced excessive complexity, making the study impractical. Therefore, only data related to anemia prevalence in SSI/PJI versus non-SSI/PJI groups were extracted. Third, some studies provided both unmatched and matched analyses. Although unmatched analyses included more patients, data from matched cohorts were prioritized for the meta-analysis due to their greater accuracy. Also, the definition of infection outcomes varied between studies (e.g., SSI, PJI, or wound infection). For consistency, different infection outcomes were pooled under the category of SSI/PJI.

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to doi: 10.1016/j.arth.2025.10.082.

[1] These authors contributed to Question 1: Seyed Mohammad Javad Mortazavi, Mohammadreza Razzaghof, George Grammatopoulos, Yutaka Inaba, Mercelo Lizarraga, Geert Meermans, Matteo Ferrari

https://doi.org/10.1016/j.arth.2025.10.082
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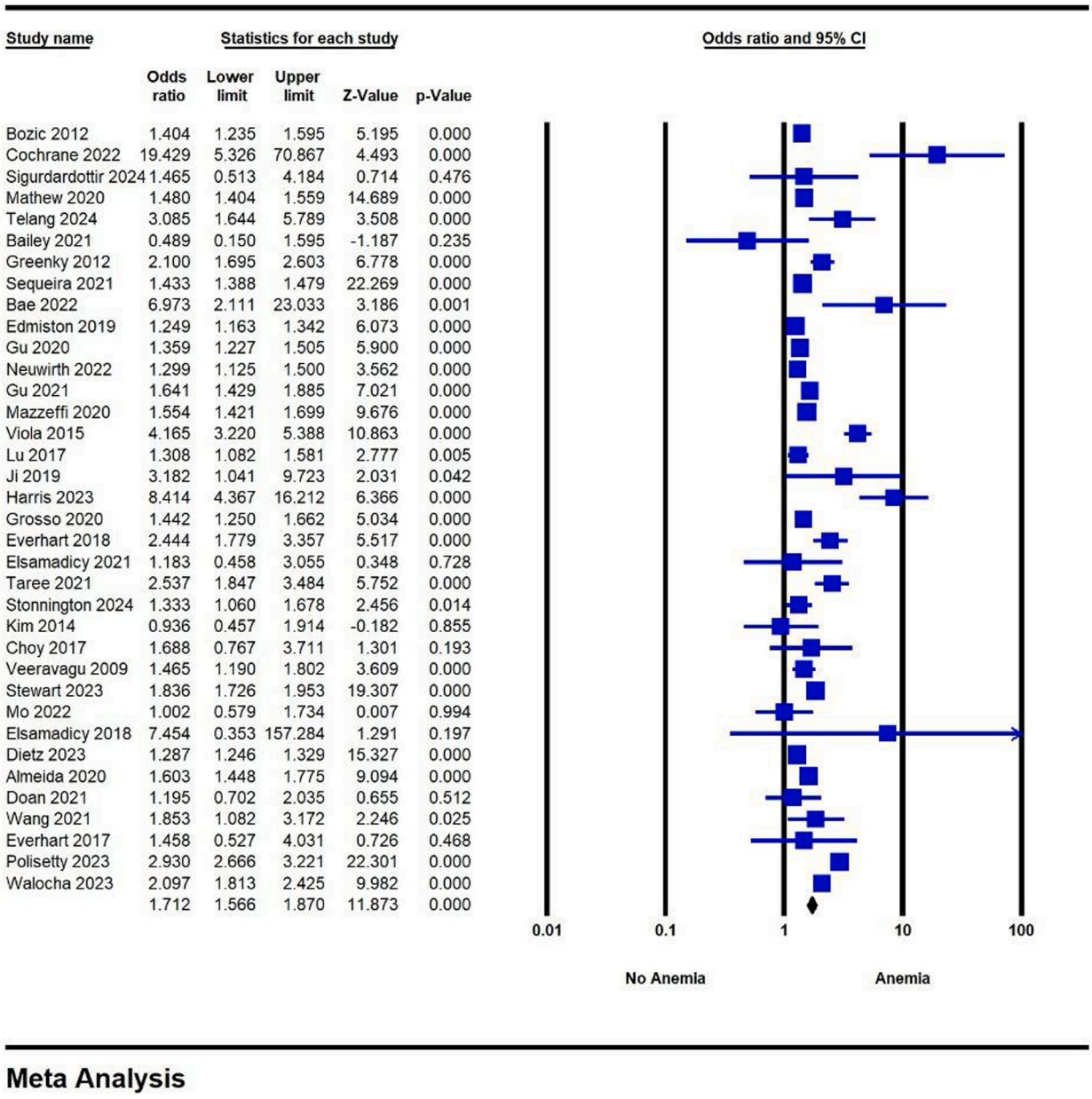

Figure 1. Meta-analysis of all included studies [1–33].

Additionally, subgroup analyses for superficial and deep SSI outcomes were performed specifically in spine surgery studies.

Thus, the meta-analyses were conducted under the following conditions:

- Cases of anemia were included irrespective of the heterogeneity in definitions across studies.
- Infection outcomes were pooled as SSI/PJI, regardless of variations in definitions among studies.
- Other potential risk factors were not considered in the meta-analyses. However, in studies providing both matched and unmatched analyses, data from the matched cohorts were used.

In conclusion, based on the current literature, preoperative anemia appears to be a significant risk factor forSSI and PJI) in patients undergoing major orthopaedic surgeries. Despite several potential limitations in this systematic review, the findings underscore that preoperative anemia is a modifiable risk factor that should be carefully managed to improve surgical outcomes. Further research is needed to establish standardized definitions and protocols for managing anemia in this patient population.

Question 2: Does the use of tranexamic acid reduce the incidence of infection in patients undergoing major orthopaedic surgery?[2]

Response/Recommendations

The administration of tranexamic acid (TXA) is associated with a reduced incidence of infection.

Level of Evidence: Moderate

[2] These authors contributed to Question 2: Palmer AJR, Moradi A, Kendrick BJL, Tanaka Y, Crestani M, Wu M, Ashraf J, Hajiaghajani S, Eybpoosh S, Enayatollahi M

Delegate Vote: Agree 63%, Disagree 13%, Abstain 24% (simple majority, low/no consensus)

Rationale

Infection following major orthopedic surgery results in patient morbidity and increased health care costs [34]. Strategies are sought to minimize the risk of infection, particularly PJI, which represents a catastrophic complication [35,36]. Tranexamic acid (TXA) is an antifibrinolytic agent that reduces perioperative blood loss and has shown potential in decreasing surgical complications [37–39]. However, whether TXA can reduce the risk of infection remains uncertain.

We conducted a meta-analysis of studies that compared TXA administration with no TXA administration for all major orthopedic surgeries, with or without metalwork. The primary outcome measure was any SSI within 90 days of surgery [40–98]. Since periprosthetic joint infection (PJI) can take more than 90 days to present following surgery, we also included joint arthroplasty studies with up to two years of follow-up [88–97]. After screening 1,326 articles, 58 studies were included [40–98] consisting of 19 randomized controlled trials and 39 cohort studies. A total of 2,510,982 patients were included, with 1,503,126 receiving TXA and 1,007,856 not receiving TXA as controls.

Surgical Site Infection

A meta-analysis was performed of 36 studies [40–45,47–50,52–56,58–60,62–68,70,72–80,83,86] reporting at least one SSI within 90 days of surgery. Superficial and deep infections were grouped together. There was no difference in infection rates between TXA and controls (OR = 0.93; 95% confidence interval (CI) [0.73 to 1.18]; $P = 0.54$; $I^2 = 83\%$). There was also no difference in infection rates when restricting the analysis to studies [40,42,43,47,48,70,75,77,84], where only topical TXA was administered (OR = 0.74; 95% CI [0.30 to 1.82]; $P = 0.51$; $I^2 = 0$).

We then explored the effect of TXA on superficial and deep infections separately. A meta-analysis was performed of 29 studies [41,43,44,47,49,51–53,56,58–60,63–68,70,73–80,84,86] reporting at least one superficial infection within 90 days of surgery. There was no difference in superficial infection rates between TXA and controls (OR = 0.91; 95% CI [0.65 to 1.28]; $P = 0.58$; $I^2 = 80\%$). A meta-analysis was performed of 15 studies [40–42,48,49,52–55,62,66,72,74,75,78] reporting at least one deep infection within 90 days of surgery. There was no difference in deep infection rates between TXA and controls (OR = 0.95; 95% CI [0.72 to 1.25]; $P = 0.69$; $I^2 = 82\%$).

Periprosthetic Joint Infection

A meta-analysis was performed of 20 studies [32,40–42,49,53–55,62,66,74,75,78,90–95,97] that reported at least one PJI within two years of surgery. The TXA administration reduced the incidence of PJI (OR = 0.69; 95% CI [0.53 to 0.90]; $P = 0.01$; $I^2 = 88\%$). There was no difference in the incidence of PJI between TXA and controls in studies (42-47, 66, 53-55, 62, 66, 72, 74, 75, 78, 65), reporting outcomes within 90 days of surgery (OR = 0.91; 95% CI [0.69 to 1.19]; $P = 0.48$; $I^2 = 83\%$). There was a reduction in the incidence of PJI with TXA over controls in studies (56-61, 63), reporting outcomes between 90 days and two years of surgery (OR = 0.50; 95% CI [0.38 to 0.66]; $P < 0.001$; $I^2 = 47\%$).

Conclusions

Tranexamic acid is associated with a reduction in the incidence of PJI but has not been shown to reduce the incidence of overall SSI within 90 days. There may be inadequate statistical power, and most larger studies were retrospective cohort studies or registry data with potential selection bias. The mechanism of reducing the incidence of PJI is not known, but it could represent a reduction in transfusion rates or hematoma formation, which are associated with periprosthetic joint infection [98–100]. TXA has also demonstrated immunomodulatory properties [101,102]. The optimal route of TXA administration also remains unknown [103]. Therefore, TXA is recommended for all joint arthroplasties for optimal patient blood management and may also reduce the risk of PJI.

Question 3: Does allogeneic blood transfusion increase the risk of postoperative infections in patients undergoing major orthopaedic surgery?[3]

Response/Recommendation

Yes. Allogeneic blood transfusion is associated with an increased risk of postoperative infections, including SSI/PJI and systemic infections in patients undergoing major orthopaedic surgery.

Level of Evidence: Strong

Delegate Vote: Agree 88.2%, Disagree 5.9%, Abstain 5.9% (super majority, strong consensus)

Rationale

The risk of postoperative infections after major orthopaedic surgeries is influenced by various factors, including patient-related, surgeon-related, and perioperative factors [104]. Allogeneic blood transfusion has been associated with potential adverse effects on the recipient's immune system, termed transfusion-related immunomodulation [105]. The transfusion-related immunomodulation is thought to involve both cellular and humoral immune suppression, which could potentially increase the recipient's susceptibility to infection. For this reason, in recent years, patient blood management strategies include preoperative optimization of anemia, minimizing intraoperative blood loss and adopting restrictive transfusion triggers.

Conflicting results have been reported regarding the association between ABT and infection [106,107]. Some studies found an increased risk of infection with ABT [108,109], while others have not [110–112]. The International Consensus Meeting in 2018 recognized an increased risk of SSI associated with ABT compared to no transfusion or autologous transfusion but concluded that there is no data to support withholding ABT in patients who have symptomatic anemia as a strategy to prevent SSIs [113].

The relationship between ABT and infection risk in spinal surgery has been a subject of considerable investigation, yielding mixed results. Many studies have identified ABT as a significant risk factor for postoperative infection after instrumented spinal fusion [114–119]. Woods et al. found a significant association between the volume of ABT and SSI in lumbar spine surgery [120], and Zhang et al. further identified a dose-response relationship with an inflection point of three units [121]. These findings underscore the complexity of the relationship between ABT and infection risk in spinal surgery, highlighting the need to consider potential confounding factors such as patient comorbidities and surgical complexity when interpreting the study results [122].

In patients undergoing joint arthroplasty surgery, the relationship between ABT and infection has been extensively studied, with results indicating that ABT may be associated with an increased risk of infection [109]. A meta-analysis by Kim et al. showed a mean risk ratio for infection after ABT of 1.71 (range, 1.23 to 2.40) in patients undergoing total hip or knee arthroplasty [123]. Berríos-Torres et al. conducted a meta-analysis according to the Centers for Disease Control and Prevention (CDC) guidelines for the prevention of SSI, which examined the association between allogeneic and autologous blood transfusions and the risk

[3] These authors contributed to Question 3: Fatih Yildiz, Mustafa Alper Incesoy, Mustafa Şenyurt, Waleed A. Al-Saadan, Nathanael Heckmann, Gabriele Tucci, Udo E. Anyaehie, Kerem Başarir, Antony Palmer

of infection [124]. The study found that ABT was associated with increased odds of infection compared to no transfusion (odds ratio [OR]: 1.96, 95% confidence interval [CI] 1.46 to 2.63, $P < 0.01$, $I2 = 0$).

For the current systematic review and meta-analysis, we searched PubMed, Embase, and Scopus databases. There were 34 studies included after reviewing 497 articles by at least two independent reviewers. There were 14 of those studies that investigated the relation between ABT and SSI or PJI. The remaining 20 studies have results of mixed data, including SSI/PJI and systemic infections such as urinary tract infection and lower respiratory tract infection. A meta-analysis of those 34 articles showed that ABT is associated with an increased risk of infection compared to non-ABT (risk ratio [RR] = 1.94, 95% confidence interval [CI]: 1.59 to 2.37, $P < 0.01$, Figure 2) [105,107–109,111,112,114–119,122,125–145]. Both arthroplasty and spine surgery showed a trend of increased infection risk with ABT [105,107–109,111,112,114–119,122,125–145]. The analysis was further stratified by subgroups with different transfusion exposure, with one group having received no previous transfusion and the other having received autologous blood. ABT was associated with a higher risk of infection in both nontransfused and allogeneic nonexposed subgroups (Figure 3) [105,107–109,111,112,114–119,122,125–145]. Subgroup analysis examining isolated SSI/PJI (RR = 2.23, 95% CI: 1.66 to 2.99, $P < 0.01$) and general infection (RR = 1.83, 95% CI: 1.41 to 2.36,

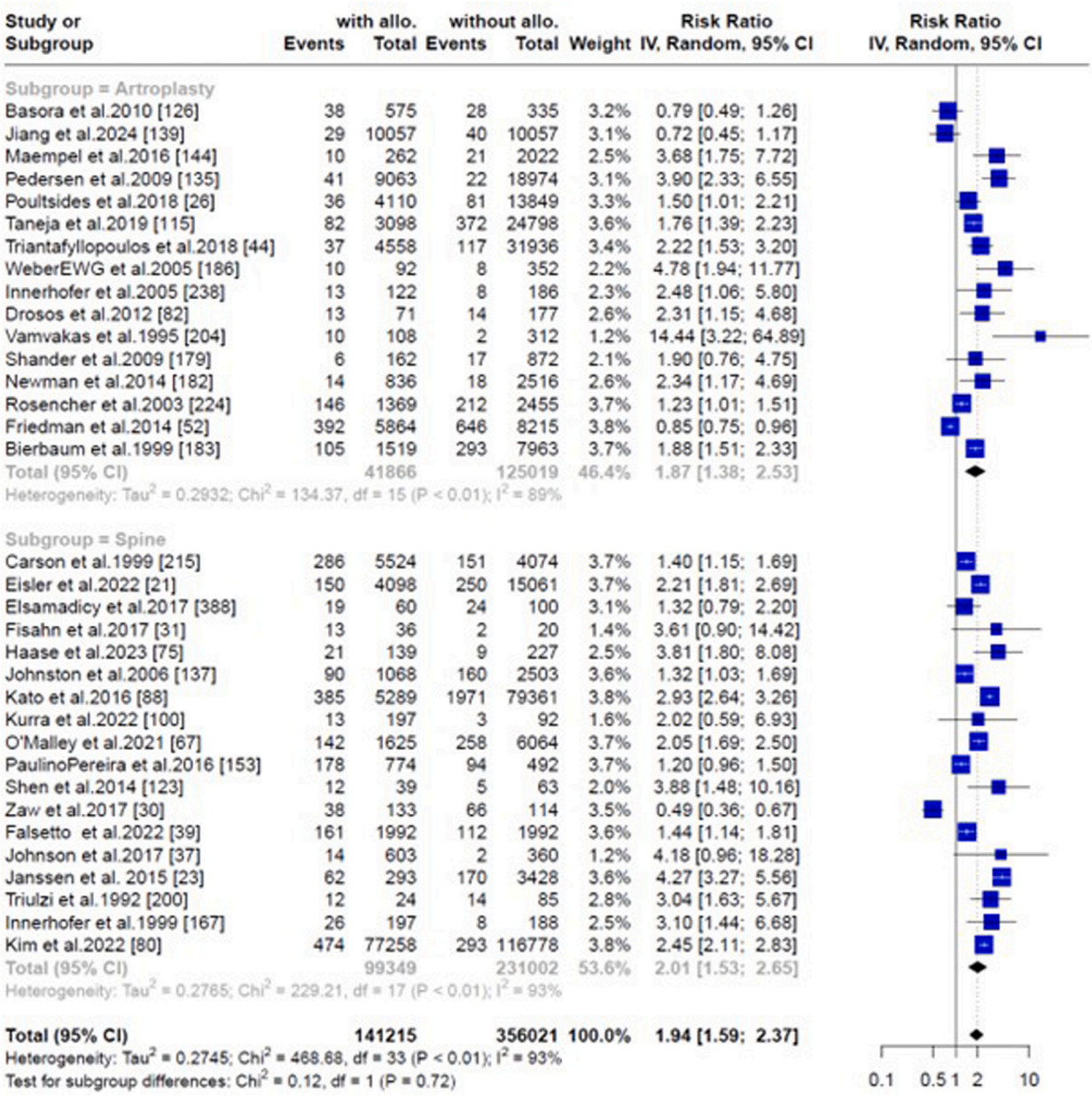

Figure 2. The forest plot presents the risk ratio of infection in patients receiving allogeneic blood transfusion (ABT), stratified to compare outcomes between those undergoing arthroplasty and spine surgery.

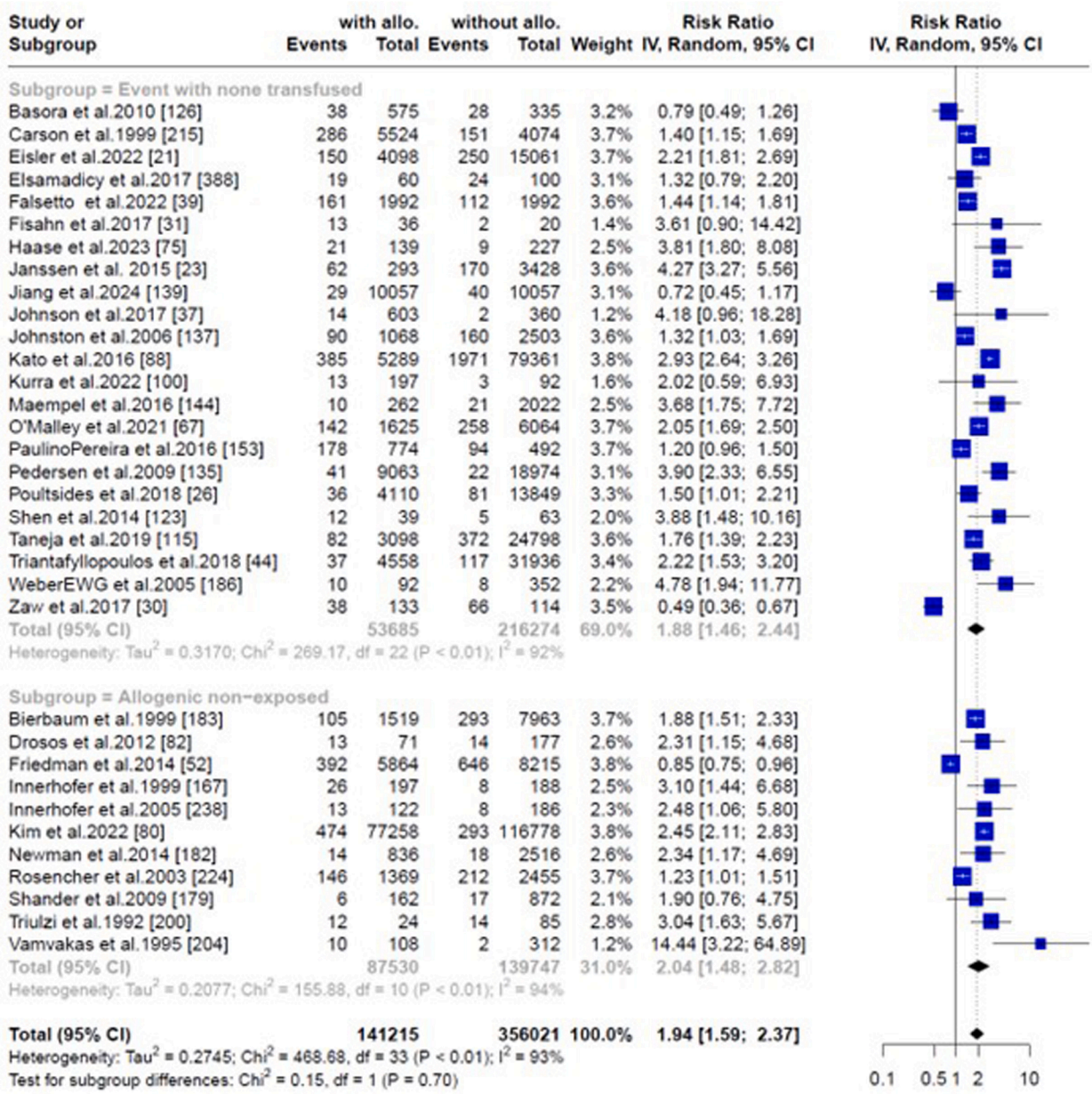

Figure 3. The forest plot showing the stratified risk ratio of infection associated with allogeneic blood transfusion (ABT) in subgroups based on prior transfusion exposure.

$P < 0.01$) revealed a consistent association between ABT and increased risk (Figure 4). A separate meta-analysis evaluating the mean difference in the number of allogeneic blood units transfused between patients with and without infection revealed that patients with infection received a significantly higher number of units (mean difference [MD] = 1.02, 95% CI: 0.58 to 1.45, $I^2 = 64\%$, Figure 5) [120,121,146–148]. This finding further supports the association between ABT and an increased risk of infection.

In conclusion, the present systematic review and meta-analysis demonstrated a significant association between ABT and increased risks of SSI/PJI and systemic infections in the context of major orthopaedic surgery. This observation remained consistent across various subgroups and surgical categories, including arthroplasty and spine surgery. Patients with infection received a higher number of allogeneic blood units, suggesting a possible dose-response relationship.

Question 4: Does the type of venous thromboprophylaxis affect the incidence of surgical site infection (SSI)/ periprosthetic joint infection (PJI) in patients undergoing major orthopaedic surgery?[4]

Response/Recommendations

[4] These authors contributed to Question 4: Ibrahim Elganzoury, Pawel Bartosz, Jerzy K. Bialecki, Michael Whitehouse, Nikolai Nikolaev, Seung Beom Han, Ahmed Saeed Younis

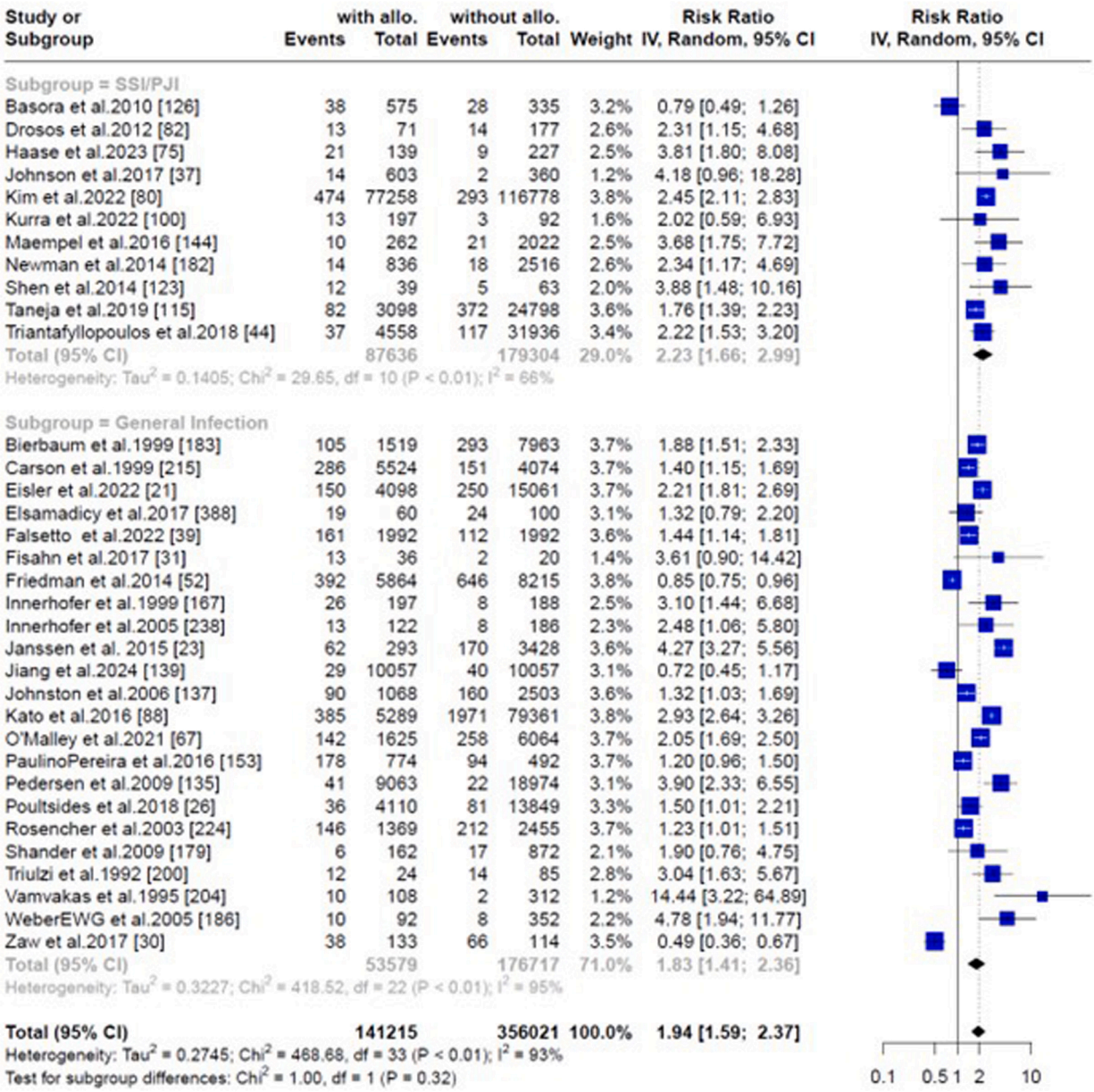

Figure 4. The forest plot presenting the subgroup analysis of the risk ratio of isolated surgical site infection/periprosthetic joint infection (SSI/PJI) and general infection associated with allogeneic blood transfusion (ABT).

Yes. The type of venous thromboprophylaxis appears to affect the incidence of SSI/PJI. Warfarin is associated with the highest risk of infection, while aspirin shows the lowest risk.

Level of Evidence: Limited

Delegate Vote: Agree (91.3%) Disagree (4.4%) Abstain (4.4%) (total consensus, unanimity)

Rationale

Venous thromboprophylaxis is crucial in postoperative management after total joint and lower-limb fracture surgery [149]. The risk of symptomatic venous thromboembolic (VTE) complications after major lower limb surgery ranges from 1 to 4% [150,151]. Wound complications and PJI are among the devastating complications and a main cause of morbidity after total joint arthroplasty and trauma surgery [152,153]. Studies have shown that there is a relationship between the use of anticoagulation in orthopedic surgery and the occurrence of infection-related complications. The association with postoperative wound complications and administration of anticoagulation is also well known [154,155]. Prolonged wound discharge is a concerning issue, as it is one of the major risk factors for SSI and PJI [156]. Postoperative hematoma formation and other bleeding complications, which may occur after anticoagulation therapy, are also risk factors for infections [157,158].

To answer the above question, we conducted a comprehensive search of PubMed and Scopus databases using the MeSH terms that were developed by librarians. Our initial search yielded 3,266 potential articles. After screening by two independent reviewers, 3,024 studies were excluded, and 45 randomized controlled trials (RCTs) were added in our final meta-analysis. We also decided to provide evidence from non-RCT trials, as the outcome PJI may

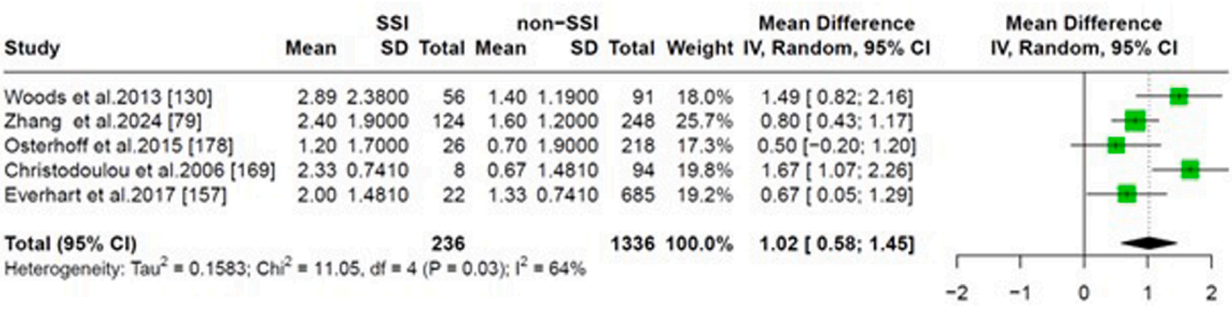

Figure 5. The forest plot displaying the mean difference in the number of allogeneic blood units transfused between patients with and without infection.

require large sample studies for long follow-up periods, and due to the small number of reported events of PJI in RCTs. We decided to answer two questions: Q1: Does the incidence of SSI/PJI differ in patients receiving venous thromboprophylaxis versus no prophylaxis? and Q2: Does the incidence of SSI/PJI differ with different agents of venous thromboprophylaxis?

Our meta-analysis results showed that eight studies [159–166] reported the outcome of infection with no statistically significant difference between patients who received thromboprophylaxis (18 of 954) and the control group (11 of 972) (relative risk (RR): 1.25 confidence interval (CI): 0.66 to 2.37). There were 11 studies [159,165–173] that reported the outcome of hematoma formation with no statistically significant difference between patients who received thromboprophylaxis treatment (14 of 904) and the control group (10 of 916).

[165,166,169–173] There were three studies [159–161] that reported the outcome wound discharge with no statistically significant difference between the venous thromboprophylaxis group (24 of 407) and the placebo group (10 of 417) (RR 2.53, CI: 1.28 to 5.00). There was one study [166] that reported the outcome of PJI with no cases of PJI during the period of follow-up. We also compared the risk of infection, hematoma formation, wound drainage, and PJI between different agents of venous thromboprophylaxis.

Our meta-analysis showed no difference in outcomes between patients who received venous thromboprophylaxis and placebo groups regarding the risk of SSI/PJI, wound hematoma, and wound drainage. Also, there was no difference between different thromboprophylaxis agents with regard to risk of SSI/PJI, wound hematoma, and wound drainage. However, we have downgraded the evidence of our meta-analysis to two levels due to imprecision, as all studies had a small sample size. Also, there was little data available about the risk of PJI in the included RCTs, with weak reporting of the PJI outcome.

The retrospective studies alternatively demonstrated significant associations between the administration of VTE prophylaxis and subsequent SSI/PJI. Pai et al. reported a higher 90-day readmission risk in patients who received pharmacological VTE prophylaxis with low molecular weight heparin (LMWH) for 3 days and postoperative low-dose aspirin compared to the control group. They reported a 90-day risk of PJI of 0.4% (eight of 1,957) in patients who received pharmacological prophylaxis compared to 0.1% (eight of 5,554) in the control group [174]. Parvizi et al. reported that the rate of PJI was higher in patients who received anticoagulation therapy with LMWH and warfarin, especially when the International Normalized Ratio (INR) level was more than 1.5 [175]. Sachs et al. (2003) in their cohort reported a double infection-related complication rate in patients who received warfarin treatment after total joint arthroplasty [176]. Recent studies showed an increased rate of infection with the use of aggressive protocols of VTE prophylaxis such as warfarin, LMWH, fondaparinux, and factor X inhibitors. These studies recommended the use of less aggressive modalities, such as low-dose aspirin and sequential pneumatic devices, as they observed no increased risk of thrombosis with their use [177,178]. Data from most retrospective reports showed that the risk of PJI is higher with the use of warfarin and lowest with the use of aspirin [179–182]. Anil et al. reported that aspirin may have the lowest risk of PJI among all VTE prophylaxis agents and is reported to be as effective as other agents in preventing VTE-related complications [181]. Najafi et al. recommended the use of low-dose aspirin, as it has a protective effect against staphylococcal infection and has a synergistic action with antibiotics compared to high-dose aspirin [183]. The potential limitations of these reports are that they provide a conflicting relation between the type of venous thromboprophylaxis agent and the risk of PJI, a lack of clear definitions of infection, and are nonrandomized retrospective studies, which make their results affected by many confounders.

Conclusions

Based on the available data, the majority of which emanates from retrospective cohort studies, there is some evidence that the type of VTE prophylaxis given to patients undergoing orthopedic procedures does influence the subsequent risk of SSI/PJI. Because of the low rate of SSI/PJI, a few available randomized studies were not powered to be able to examine the possible correlation between the type of VTE prophylaxis and subsequent infections in orthopedic patients. However, data from most retrospective cohorts showed that warfarin is associated with the highest risk of SSI/PJI and, to varying extents, enoxaparin, fondaparinux, and rivaroxaban. Studies are in favor of low-dose aspirin as the VTE prophylaxis of choice for orthopaedic patients, as aspirin is least associated with infection-related complications. Large-scale randomized studies are needed to determine the exact association between the type of VTE prophylaxis and SSI/PJI risk and investigate the applicability of both the aggressive and less aggressive regimens on high-risk patients who are at increased risk for either SSI/PJI or VTE events.

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The Journal of Arthroplasty 41 (2025) S30–S52

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General Topics

2025 ICM: Antibiotic Prophylaxis

Alisina Shahi, T. David Luo, Michael Yayac, Jason M. Jennings, Mauro Jose Salles, Natsumi Saka, Thananjeyen Srirangarajan, Renjy Nelson, Zachary K. Christopher, Samuel Parra Aguilera, Matthew S. Austin, Kristen I. Barton, Pawel Bartosz, Natividad Benito, Sebastian Braun, Laura E. Damioli, Raquel B. da Silva, Fabio Stucchi Devito, Eduardo C. dos Santos, Margarita Veloso Duran, Panayiotis J. Papagelopoulos, Nicolás Enviado, David Figueroa, Raul Garcia-Bógalo, Nicholas J. Giori, George Guild, Abdullah S. Hammad, Hitoshi Honda, Meeri Honkanen, Amir Human Hoveidaei, Christopher Kandel, Ben Kendrick, Ianiv Klaber, Tyler Konen, Gwo-Chin Lee, Bingyun Li, Óliver Marín-Peña, Kenneth Mathis, Panayiotis D. Megaloikonomos, Piret Mitt, J Robert Molloy, Keita Morikane, Javad Parvizi, Trisha N. Peel, Christopher E. Pelt, Daniel Ramírez, Daniel Schweitzer, Lais S. Seriacopi, Randi Silibovsky, Justinas Stucinskas, Jonatan Tillander, Katsufumi Uchiyama, Ilker Uçkay, Edward M. Vasarhelyi, Dace Vigante, Koji Yamada, Chun Hoi Yan, Fatih Yildiz

Question 1: Should the administration of prophylactic antibiotics be weight-based?[1]

Response/Recommendation

Yes. Administration of all prophylactic antibiotics needs to be weight based.

Level of Evidence: Strong

Delegate Vote: Agree 97.0%, disagree: 3.0%, abstain: 0%

Rationale

Obesity is a well-established major risk factor for surgical site infection (SSI) and periprosthetic joint infection (PJI), contributing to higher infection rates through multiple physiological and pharmacokinetic mechanisms [1–4]. A major way in which obesity increases the risk of SSI/PJI is by making it more challenging to achieve adequate therapeutic tissue and serum concentrations with standard antibiotic dosing. Obese patients have an increased volume of distribution and altered drug metabolism, which can result in subtherapeutic antibiotic levels when fixed dosing regimens are used. Studies have demonstrated that patients who have a body mass index (BMI) of $\geq$ 35 or who weigh $\geq$ 120 kg face a markedly higher risk of PJI. A retrospective cohort study found that underdosed patients in this weight category had a 1-year PJI rate of 3.25%, whereas those who received weight-adjusted dosing experienced a substantially lower rate of 0.83% [5,6].

Beyond pharmacokinetic challenges, obesity predisposes patients to infection through poor vascular perfusion, which limits antibiotic penetration to the surgical site, and increased subcutaneous tissue, which creates a favorable environment for bacterial colonization [7,8]. Additionally, obesity is associated with higher rates of wound complications, delayed healing, and chronic systemic inflammation, further compounding the risk of PJI [9–11]. Given these multifaceted challenges, weight-based antibiotic dosing is essential to ensure effective prophylaxis and improve surgical outcomes in obese patients.

Weight-based dosing ensures adequate drug levels in both serum and bone tissue, which is critical for effective infection prophylaxis in total hip and knee arthroplasties. Antibiotics such as cefazolin must reach sufficient concentrations not only in the bloodstream but also in the bone and soft tissues surrounding the surgical site to prevent bacterial colonization and subsequent PJI [12,13]. Studies evaluating the trabecular

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.087.

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https://doi.org/10.1016/j.arth.2025.10.087

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bone concentrations of cefazolin have demonstrated that fixed dosing frequently results in subtherapeutic levels, particularly in obese patients. This is attributed to the increased volume of distribution in individuals who have higher body weights, which dilutes the antibiotic concentration in both serum and tissue compartments [14]. For example, one study found that fixed-dose cefazolin failed to achieve the minimum inhibitory concentration (MIC) for common pathogens such as methicillin-sensitive *Staphylococcus aureus* in a significant proportion of obese patients. Conversely, weight-adjusted dosing protocols, such as administering two grams of cefazolin for patients weighing 60 to 120 kg and three grams for those over 120 kg, have been shown to maintain adequate serum and tissue levels, effectively reducing the risk of PJI [15].

Moreover, adequate antibiotic penetration into bone tissue is particularly important for combating low-virulence organisms that can persist in the avascular or poorly perfused areas surrounding prosthetic implants. A weight-based approach ensures that therapeutic concentrations are achieved uniformly across patient populations, mitigating the risk of underdosing in heavier individuals and the associated complications. This strategy not only improves prophylactic efficacy but also reduces the likelihood of bacterial resistance arising from subtherapeutic dosing [6,9,14].

Weight-based antibiotic dosing is endorsed by professional organizations such as the American Academy of Orthopedic Surgeons, the International Consensus Meeting (ICM) (2018), and the Centers for Disease Control (CDC), which recommend adjusting cefazolin and vancomycin doses based on body weight to optimize efficacy [16]. Beyond clinical benefits, this approach is also cost-effective. By reducing the incidence of PJIs, weight-adjusted dosing minimizes the need for costly revision surgeries and extended hospital stays, with PJI treatment costs often exceeding $50,000 per case. Implementing these evidence-based dosing strategies enhances both patient outcomes and health care resource utilization [15].

Conclusion

Weight-based antibiotic administration is a crucial component of effective surgical prophylaxis in orthopaedic surgery. By ensuring optimal drug concentrations in serum, bone, and periarticular soft tissues, this approach significantly reduces the risk of SSI/PJI, particularly in obese and high-risk patients. Evidence from clinical studies supports its role in improving infection prevention, surgical outcomes, and overall patient safety. Furthermore, adopting weight-adjusted dosing protocols aligns with evidence-based best practices and professional guidelines, reinforcing their necessity in modern orthopaedic surgery.

Practical considerations

- Weight-adjusted dosing protocols should be implemented as standard practice for antibiotic prophylaxis in arthroplasty.
- Dosing adjustments should account for patient-specific factors such as body mass index and comorbidities.

To achieve optimal prophylaxis, the following dosing guidelines are recommended:

Cefazolin: two grams for patients < 120 kg and three grams for patients ≥ 120 kg

Vancomycin: 15 mg/kg, timed to ensure peak levels at incision

Intraoperative redosing: Additional doses for procedures exceeding three to four hours or with major blood loss

Question 2: Should prophylactic antibiotics be altered for patients who are carriers of methicillin-resistant *Staphylococcus aureus*?[2]

Response/Recommendation

Yes. Patients who are carriers of methicillin-resistant *Staphylococcus aureus* (MRSA) should receive an additional antibiotic with activity against MRSA in addition to cephalosporin.

Level of Evidence: Limited

Delegate Vote: Agree 96%, disagree 2%, abstain 2%

Rationale

Perioperative antibiotic prophylaxis is critical for reducing the risk of periprosthetic joint infections and surgical site infections (SSI) in orthopaedic and spinal surgeries [17]. Studies have explored the efficacy of combining vancomycin and cefazolin, particularly for preventing methicillin-resistant *Staphylococcus aureus* (MRSA) infections [18]. While the addition of vancomycin to cefazolin was not superior to cefazolin and placebo in the prevention of SSI in a population with low prevalence of MRSA colonization [19], the optimal antibiotic regimen that balances efficacy and potential adverse effects in MRSA carriers remains an active area of research.

This systematic review began with an initial screening of 482 article titles and abstracts from PubMed and Web of Science, resulting in 117 relevant studies. After full-text evaluation, 52 studies met the inclusion criteria, with 14 studies selected for data extraction and detailed analysis [20–33] (Table 1). There was no study that definitively assessed outcomes in confirmed MRSA carrier patients. Our meta-analysis found that cefazolin alone significantly reduces MRSA infections compared to noncefazolin regimens ($P < 0.001$; Figure 1). The combination of vancomycin and cefazolin provides superior protection, significantly lowering MRSA infection rates compared to cefazolin alone ($P = 0.002$; Figure 2).

Three studies were not included in our meta-analysis:

1. Takeuchi et al. [15]: Compared topical vancomycin versus ampicillin in patients undergoing thoracic and/or lumbar fusions. Infection with MRSA occurred in one patient (out of 114) in the ampicillin group, with no MRSA cases reported in the vancomycin group.
2. Choi et al. [34]: Compared sulfamethoxazole/trimethoprim plus cefazolin or vancomycin (84 patients) versus cefazolin or vancomycin alone (511 patients) in spinal surgery. MRSA infection occurred in one patient in each group.
3. Kanellakopoulou et al. [35]: Compared teicoplanin (278 patients) versus second-generation cephalosporins, β-lactam/β-lactamase inhibitors, or ciprofloxacin (338 patients) in total hip/knee arthroplasty. MRSA infection was identified in one patient in the teicoplanin group and two in the comparison group (Table 1).

Conclusion

Currently, no definitive studies have evaluated outcomes in confirmed MRSA carriers; however, our literature review indicates that while cefazolin alone is effective at reducing MRSA infections compared to cases in which noncefazolin, nonvancomycin antibiotics were used, the combination of cefazolin and vancomycin results in significantly lower MRSA infection rates. The combination of vancomycin and cefazolin appears to offer superior

[2] These authors contributed to Question 2: T. David Luo, Piret Mitt, Christopher E. Pelt, Keita Morikane, Bingyun Li, Robert Molloy, Hitoshi Honda, Randi Silibovsky, Panayiotis D. Megaloikonomos, Amir Human Hoveidaei

Table 1
Included Studies.

Author	Year	Country	Type of Procedure	Case	Control	Sample Size		Mean Age (SD)		Gender(M%)		MRSA	
						Case	Control	Case	Control	Case	Control	Case	Control
Heller	2015	USA	Posterior instrumented spinal arthrodesis	Vancomycin + cefazolin	Cefazolin	342	341	55.3 (19.1)	49.1 (20.9)	45.3	49.3	0	5 (1.5)
Burger	2018	USA	THA, TKA	Vancomycin + cefazolin	Cefazolin	914	957	59.10 (11.55)	60.31 (11.49)	43.04	41.8	1	4
Kanellakopoulou	2008	Greece	THA, TKA	Teicoplanin	Second-generation cephalosporin B lactams/B lactamase inhibitors ciprofloxacin	278	338	67.40 (10.74)	70.69 (8.01)	25.17	21.79	1	2
Ortiz	2014	USA	THA	Vancomycin or clindamycin	Cefazolin	882	9,028			294 (33)	4,071 (45.1)	2	8
Choi	2021	USA	Spinal surgery	Sulfamethoxazole/ trimethoprim + cefazolin or vancomycin	Cefazolin or vancomycin	84	511	62	60.8	44.5	43.4	1	1
Sewick	2012	USA	TJA	Vancomycin + Cefazolin	Cefazolin	1,328	500	60.6 (12.5)	59.6 (12.0)	36	44	1	4
Bains	2024	USA	TJA	Vancomycin + cefazolin	Cefazolin	1,437	1,470	62	62	44	46	1	2
Takeuchi	2018	Japan	Thoracic and/or lumbar fusions	Vancomycin	Ampicillin	116	114	66 (14)	68 (14)	52.58	38.59	0	1
Saveli	2013	USA	Open Fracture Surgery	Vancomycin + cefazolin	Cefazolin	65	65	40 (16)	42 (18)	78	66	1	1
Hofmann	2017	USA	THA, TKA	Vancomycin + cefazolin	Cefazolin	538	496	61.5 (11.6)	60.6 (12.3)	43.75	39.77	1	6
Marigi	2024	USA	TSA	Vancomycin	Cefazolin	298	6,879	69.5 (11.4)	68.6 (11.5)	41.6	49.2	1	1
Tafish	2017	USA	Spinal surgery	Vancomycin	Non vancomycin	81	375	50	45	58	66.4	2	2
Garofalo	2023	Italy	TSA	Vancomycin + cefazolin	Cefazolin	420	405	73 (7)	71 (7)	31.4	28.6	0	4
Buchalter	2022	USA	TKA	Clindamycin and/or vancomycin	Cefazolin	1,066	10,484	65.14 (10.2)	65.6 (9.6)	22.8	32.8	4	3

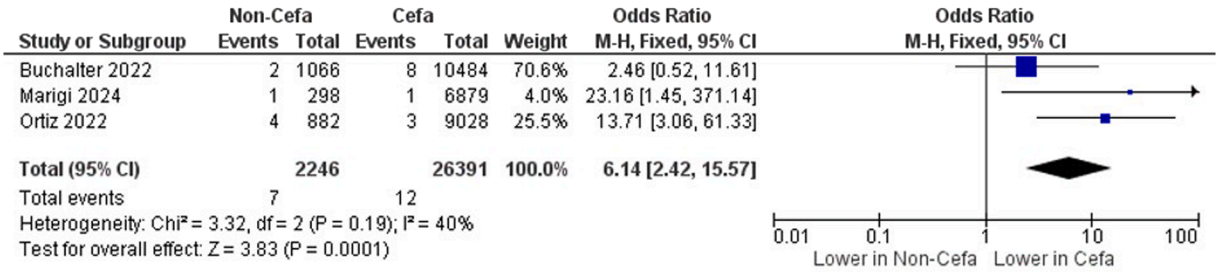

Figure 1. Comparison of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in cefazolin and noncefazolin prophylaxis cohorts across three studies.

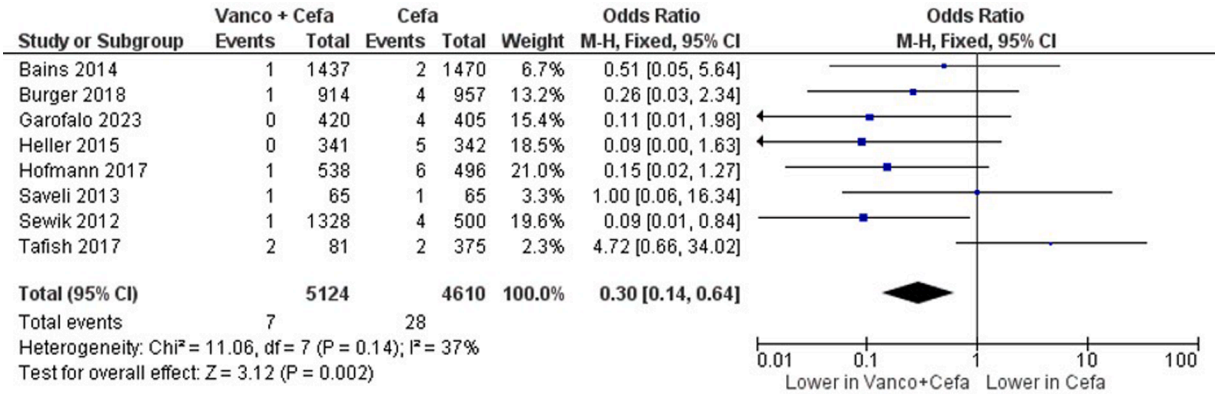

Figure 2. Comparison of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in vancomycin plus cefazolin versus cefazolin alone for preoperative prophylaxis.

protection against MRSA infections in orthopaedic and spinal surgeries compared to cefazolin alone. It is worth noting that most included studies were retrospective cohort studies, and only a few randomized controlled trials were conducted. Moreover, as there are major variations in the patient population, interventions, types of orthopaedic procedures, and outcomes among included studies, it is hard to conclude that the routine addition of anti-MRSA agents or switching to anti-MRSA agents would be better than a traditional regimen of surgical antimicrobial prophylaxis (i.e., cefazolin) for all patients (MRSA carriers and noncarriers) undergoing orthopaedic procedures. The potential risks of dual prophylaxis, such as increased antibiotic resistance and nephrotoxicity, must also be carefully considered. Given the absence of studies specifically addressing confirmed MRSA carriers, further high-quality research is essential to develop definitive guidelines for antibiotic prophylaxis in this patient population.

Question 3: Is there a role for skin testing in patients reporting penicillin allergy who are undergoing major orthopaedic procedures?[3]

Response/Recommendation

Routine skin testing for patients reporting penicillin allergy is not required, as the majority of these patients can safely receive cephalosporins.

Level of Evidence: Level III

Delegate Vote: Agree 82%, disagree 14%, abstain 4% (super majority, strong consensus)

Rationale

The first- or second-generation cephalosporins are typically recommended as the optimal preoperative systemic antibiotic prophylaxis in patients undergoing major orthopaedic procedures, with alternatives, such as vancomycin or clindamycin, reserved for patients who have severe allergic reactions to cephalosporins or penicillins (PCN) [36–39]. The 2018 ICM recommended that routine skin testing is not necessary for the majority of patients who have a reported PCN allergy, as they can safely tolerate cephalosporins due to the low cross-reactivity rate, and for those who have nonanaphylactic reactions, a test dose can be administered in the operating room [4]. More recent guidelines from the American Academy of Allergy, Asthma, and Immunology recommend direct oral challenge without any skin testing for low-risk patients, as well as no testing required for cephalosporin use in patients who have an unverified nonanaphylactic PCN allergy [40].

The percentage of patients reporting an allergy to PCN is considerably higher than the estimated true prevalence of these allergies [41]. Most reported PCN allergies are not severe IgE-mediated reactions but rather intolerances to the medication, such as gastrointestinal discomfort, or mild reactions, such as pruritus without a rash, which are considered low risk, and where it may be safe to administer a cephalosporin [42–47]. Moderate risk includes a pruritic rash or urticaria, and high risk includes anaphylaxis, positive skin testing, recurrent reactions to PCN, or hypersensitivities to multiple β-lactam antibiotics [47]. Early studies suggested that cross-reactivity between PCNs and cephalosporins was relatively high, reported at approximately

[3] These authors contributed to Question 3: Michael Yayac, Tyler Konen, Meeri Honkanen, Ianiv Klaber, Matthew S. Austin, Christopher Kandel, Margarita Veloso, Laura E. Damioli, Chun Hoi Yan

10%, but more recent data have shown that the actual rate may be less than one percent [41]. Nevertheless, a documented history of a PCN allergy has a substantial impact on perioperative care, as it greatly reduces the likelihood of receiving a first-line cephalosporin for antibiotic prophylaxis [48–54]. Across 12 studies, including 12,321 patients who have a reported PCN allergy, only 7,832 (67.3%, 95% confidence interval [CI] 66.7 to 67.9) received a first-line cephalosporin [43,44,48–57]. In contrast, 93.7% (95% CI 93.6 to 94.0%) of 58,700 patients across seven studies without a reported allergy received a first-line cephalosporin [42–45,49,50,52,55].

Several studies have demonstrated that patients who have a reported PCN allergy are at a 56% higher risk of SSI (pooled odds ratio: 1.56, 95% CI: 1.02 to 2.37) [44,48,49,52,54,58,59]. This is because patients who have a reported allergy are more likely to receive an alternative antibiotic, such as clindamycin or vancomycin, which are associated with a higher risk of SSI [44,47,48,48,49,49,50,52–64]. Across nine studies, patients who received an alternative antibiotic were at a 74% (pooled odds ratio: 1.74, 95% CI: 1.18 to 2.56) higher risk of developing SSI compared to those who received a first-line cephalosporin [44,48,53–55,57,60,63,64].

Allergy skin testing may be used to determine which patients are not truly allergic to cephalosporins, but Savic et al. demonstrated that low-risk patients may be delabeled of their PCN allergy quickly through a direct oral challenge [65]. Furthermore, several studies have demonstrated that patients who have a reported PCN allergy and low risk of a severe reaction can safely receive a cephalosporin without any prior testing [42–44,48,50,66,67]. There were no patients across any study who had a reported PCN allergy who received a cephalosporin and developed a severe allergic reaction, and all reactions resolved promptly with discontinuation of the antibiotic and appropriate medical treatment [42–44,48,50,67]. Therefore, the additional cost, inconvenience, and potential delay in care incurred by allergy skin testing can be avoided in patients who have a low risk of a severe reaction.

For patients who have a potentially severe allergic reaction, referral to an allergist for skin testing and/or an oral challenge can be effective in removing erroneous allergies from patient records and increasing the number of patients who receive a first-line cephalosporin for antibiotic prophylaxis [51,55,56,68,69]. Of 416 patients across five studies, 389 (94.9%; 95% CI 92.3 to 96.6%) had PCN allergy removed from their medical history following completion of allergy testing [51,55,56,68,69].

From an economic standpoint, routine skin allergy testing can be cost-effective, as the savings from preventing periprosthetic joint infections (PJIs) through first-line antibiotic prophylaxis would exceed the relatively low cost of routine skin testing. A break-even analysis in total shoulder arthroplasty found that only an absolute risk reduction of 0.45% would be required for skin testing to be cost-effective, which is lower than the reported reduction in PJI rate of 1.99% using first-line antibiotic prophylaxis over alternatives [59,70]. A similar break-even analysis regarding total knee arthroplasty (TKA) or total hip arthroplasty (THA) concluded that an absolute risk reduction of 0.81% for TKA and 0.655% for THA would be needed for allergy testing to be considered cost-effective, which is considerably lower than the reported differences in infection rates between first-line and alternative antibiotics [64,71]. A similar economic analysis among TKA and THA estimated a nearly $1.2 billion cost savings over a 20-year period with implementation of routine skin testing, assuming that 90% of reported allergic reactions are not true allergies [72].

Conclusion

Penicillin allergy labels should be routinely evaluated preoperatively. Many reported allergies are not true IgE-mediated reactions or are considered low risk, and these patients can safely receive cephalosporins without testing. There may be a limited role for skin testing in patients reporting a severe PCN allergy (severe IgE-mediated reactions such as anaphylaxis or severe urticarial reactions) undergoing major orthopaedic procedures, as it helps identify those who can safely tolerate first-line cephalosporins, thereby reducing administration of alternative antibiotics associated with higher risks of SSIs and PJIs.

Question 4: What is the optimal antibiotic prophylaxis for patients who have a penicillin allergy?[4]

Response/Recommendation

It is safe and appropriate to administer a first-generation cephalosporin (cefazolin) as first-line antibiotic prophylaxis in the operating room setting for patients who have a documented penicillin allergy.

Level of Evidence: Strong

Delegates Vote: Agree 88.2%, disagree 11.8%, abstain 0% (super majority, strong consensus)

Rationale

Selection of preoperative antibiotic prophylaxis can be challenging in patients who have a history of penicillin allergy [73]. For patients who have an IgE-mediated hypersensitivity reaction, previous guidelines recommend the use of alternative agents. However, those alternative agents are associated with worse outcomes, including an increased risk of surgical site infection (SSI) and higher cost [73]. Approximately 10% of the population will report a penicillin allergy [74], yet few have clinically relevant reactions [75]. Over-reporting of penicillin allergies and the safety of cephalosporins in patients who have reported penicillin allergies have been well established throughout the evidence [76]. The overall cross-reactivity rate between penicillins and cephalosporins is low at approximately 1 to 2% when using first-generation cephalosporins or cephalosporins with similar R1 side chains [76,77]. Moreover, the use of third- or fourth-generation cephalosporins or cephalosporins with dissimilar side chains to the offending penicillin carries a negligible risk of cross-allergy in penicillin-allergic patients [76]. Evaluation of penicillin allergy before prophylactic antibiotics is crucial for antimicrobial stewardship [75]. A recent systematic review [78] demonstrated that penicillin allergy screening and testing markedly increase the use of first-line antibiotics. Porto et al. [78] showed low rates of true penicillin allergy (0.7 to 3%), and the allergic reaction frequency for patients who have reported penicillin allergy receiving cephalosporins was between 0 and 2%.

Reported penicillin allergy and adverse reactions

From the systematic review (Figure 3), in the six studies [79–84] that reported the adverse reactions related to penicillin allergy, the majority were nonsevere allergic reactions (rash, hives, pruritus, gastrointestinal upset, local swelling, intolerance, or remote history/unknown). All but one study [85] used cefazolin for prophylactic antibiotics in their nonpenicillin allergy patients, and they used cefuroxime. In all the reviewed studies, alternatives to cefazolin for penicillin allergy included clindamycin or vancomycin (Tables 2-4).

[4] These authors contributed to Question 4: Jason M. Jennings, Hitoshi Honda, Michael Yayac, Meeri Honkanen, Christopher E. Pelt, Piret Mitt, Nicholas J. Giori, Daniel Schweitzer, Kristen I. Barton

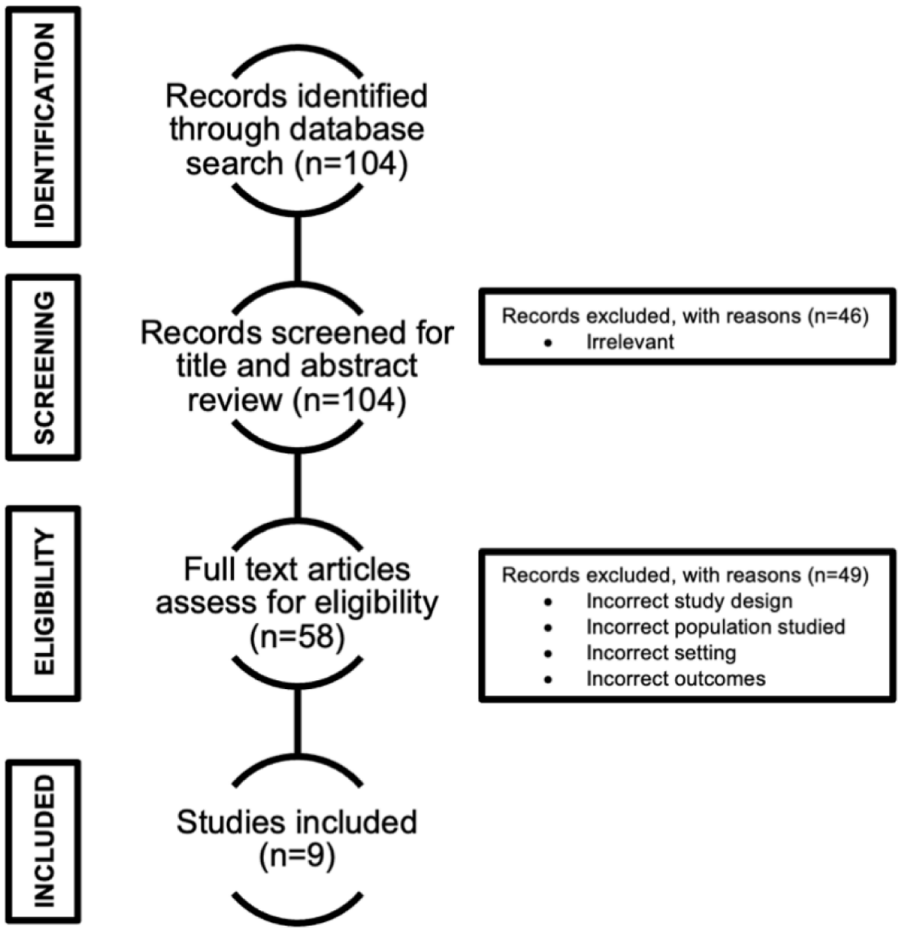

Figure 3. Systematic review approach.

Risk of allergic reaction

The risk of allergic reactions in patients who have a reported penicillin allergy and are given cephalosporin prophylaxis is that allergic reactions occurred in 0 to 1.5% of patients (Table 5). In all the patients who received cefazolin who previously had a severe penicillin allergy, no patients had severe adverse reactions, and cefazolin was well tolerated.

All symptoms resolved promptly with antibiotic discontinuation and administration of antihistamines and/or corticosteroids [79]. Bukowski et al. [79] demonstrated that perioperative prophylaxis with cefazolin resulted in a 0.1% incidence of allergic reactions that were clinically indolent. Jones et al. [81] reported that no patients had signs of an allergic reaction related to cefazolin, including eight patients who had severe penicillin allergies. Similarly, Michaud and Yen [82] reported that among those with non-IgE-mediated reactions to penicillin who received cefazolin, there were no adverse reactions. Furthermore, Stone et al. [84] also reported that no patient who had a penicillin allergy and was given cefazolin prophylaxis experienced a reaction. Also, Goh et al. [80] reported that there were no differences in total allergic reactions or severity between cephalosporin and noncephalosporin antibiotics. In addition, one study reported that the frequency of intraoperative hypersensitivity reactions was not different between groups (cefazolin = 0.2 versus clindamycin/vancomycin = 1.3%; $P = 0.06$) [83].

Postoperative infections

The incidence of postoperative infections when using alternative antibiotic prophylaxis has been reported in six studies (Table 5) [79,80,83–86]. Bukowski et al. [79] observed no differences in the rates of superficial infections (0.1 versus 0.2%; $P = 0.58$), deep infections (0.3 versus 0.4%; $P = 0.68$), or *Clostridioides difficile* (*C. difficile*) infections (0.04 versus 0%; $P = 0.99$) within 90 days of surgery in reported penicillin allergy patients who received cefazolin versus alternative preoperative antibiotics. Similarly, Goh et al. [80] found there were no differences in the rates of superficial wound, periprosthetic joint infection (PJI), or *C. difficile* infections between the protocol and control groups. Stevoska et al. [85] demonstrated there was no difference in the presence of PJI (2.1 versus 2.9%; $P = 0.440$), presence of culture-positive PJI (2.0 versus 2.9%; $P = 0.309$), presence of polymicrobial infection (19.7 versus 16.7%; $P = 0.860$), or number of pathogens isolated between cefuroxime-administered cases and noncefuroxime-administered cases. Also, Stone et al. [84] concluded that there was no difference in the incidence of postoperative infection by reported penicillin allergy (0.6 versus 0.4%; $P = 0.473$) or antibiotic prescribed (0.5 versus 0.6%; $P = 0.4817$). However, Norvell et al. [83] found that there were fewer SSIs in the cefazolin group compared with the clindamycin and/or vancomycin group (0.9 versus 3.8%; $P = <0.001$), including fewer PJIs (0.1 versus 1.9%). Wyles et al. [87] reported that after allergy-tested patients ($n = 2,576$ of 22,705), 97% ($n = 2,493$) were cleared to use cephalosporins. For the cohort

Table 2
Demographics Information for the Reviewed Manuscripts.

Authors	Study Participants	Single-Center Study	Mean Age (years)	Body Mass Index	Women (%)
Bukowski et al. JOA 2024	THA: $n = 25,759$ TKA: $n = 24,304$	Yes	No rPCNA + cefazolin: 65 ± 10.3 rPCNA + cefazolin: 66 ± 9.9 rPCNA + alternative: 66 ± 9.9	No rPCNA + cefazolin: 30.0 ± 6.2 rPCNA + cefazolin: 30.1 ± 6.5 rPCNA + alternative: 30.4 ± 6.3	No rPCNA + cefazolin: $n = 25,059$ (57.8%) rPCNA + cefazolin: $n = 3,397$ (68.8%) rPCNA + alternative: $n = 435$ (76.3%)
Goh et al. JBJS 2021	Control: $n = 2,078$ Protocol: $n = 2,078$	Yes	Control: 64.5 ± 9.4 Protocol: 64.4 ± 9.5	Control: 30.3 ± 5.3 Protocol: 30.2 ± 5.5	Control: $n = 1,210$ (58.2%) Protocol: $n = 1,185$ (57.0%)
Jones et al. CORR 2021	Preintervention: $n = 90$ Postintervention: $n = 90$	Yes	Preintervention: 67 (range 61 to 74) Postintervention: 68 (range 62 to 73)	Preintervention: 31 (range 27 to 34) Postintervention: 30 (range 27 to 36)	Preintervention: $n = 63$ (70%) Postintervention: $n = 74$ (83%)
Marigi et al. JSES 2024	Cefazolin: $n = 6,879$ Vancomycin: $n = 298$	Yes	Cefazolin: 68.6 ± 11.5 Vancomycin: 69.5 ± 11.4	Cefazolin: 30.6 ± 6.6 Vancomycin: 31.0 ± 7.2	Cefazolin: $n = 3,498$ (50.9%) Vancomycin: $n = 174$ (58.9%)
Michaud et al. COP 2017	$n = 801$	Yes	Not reported	Not reported	Not reported
Norvell et al. OFID 2023	Cefazolin: $n = 809$ Clindamycin and/or vancomycin: $n = 319$	Yes	Cefazolin: 68.1 ± 9.6 Clindamycin and/or vancomycin: 67.2 ± 10.4	Cefazolin: 30.2 ± 6.5 Clindamycin and/or vancomycin: 30.6 ± 6.4	Cefazolin: $n = 571$ (70.6%) Clindamycin and/or vancomycin: $n = 218$ (68.3%)
Stevoksa et al. JOA 2024	Cefuroxime: $n = 5,578$ Noncefuroxime: $n = 417$	Yes	Not reported	Not reported	Not reported
Stone et al. JAAOS 2019	No penicillin allergy: $n = 4,107$ (83.8%) Penicillin allergy: $n = 796$ (16.2%)	Yes	No penicillin allergy: 66.3 ± 9.7 Penicillin allergy: 67.7 ± 9.5	No penicillin allergy: 30.6 ± 6.6 Penicillin allergy: 31.0 ± 7.2	No penicillin allergy: $n = 2,332$ (56.8%) Penicillin allergy: $n = 556$ (69.8%)
Wyles et al. BJJ 2019	Cefazolin: $n = 28,174$ No cefazolin: $n = 1,521$	Yes	Cefazolin: 67.1 ± 11.4 No cefazolin: 67.5 ± 11.2	Cefazolin: 31.4 ± 6.6 No cefazolin: 32.7 ± 7.7	Cefazolin: $n = 15,299$ (54.3%) No cefazolin: $n = 1,053$ (69.2%)

rPCNA, reported penicillin allergy; THA, total hip arthroplasty; TKA, total knee arthroplasty; TSA, total shoulder arthroplasty.

Table 3
Reported Study Purpose, Procedure, and Level of Evidence for Reviewed Manuscripts.

Authors	Purpose	Surgical Procedure	Level of Evidence
Bukowski et al. JOA 2024	Determine safety of perioperative antibiotic prophylaxis with cefazolin in reported penicillin allergy patients undergoing TJA without routine preoperative allergy testing	THA Control: $n = 1,112$ (53.6%) Protocol: $n = 1,144$ (55.2%) TKA Control: $n = 966$ (46.4%) Protocol: $n = 934$ (44.8%)	III
Goh et al., JBJS 2021	Assess the effectiveness of a protocol-driven penicillin allergy screening program without the need for additional work-up	THA Control: $n = 1,112$ (53.6%) Protocol: $n = 1,144$ (55.2%) TKA Control: $n = 966$ (46.4%) Protocol: $n = 934$ (44.8%)	II
Jones et al., CORR 2021	Understand if antibiotic stewardship interventions improve adherence to appropriate prophylactic antibiotic usage in patients with a documented penicillin allergy undergoing primary TJA Understand the risk of allergic or adverse reactions secondary to cefazolin use in patients with a documented penicillin allergy	THA Preintervention: $n = 18$ (20%) Postintervention: $n = 19$ (21%) THA (anterior approach) Preintervention: $n = 28$ (31%) Postintervention: $n = 33$ (37%) TKA Preintervention: $n = 44$ (49%) Postintervention: $n = 38$ (42%)	III
Marigi et al., JSES 2024	Comparative efficacy of cefazolin and complete vancomycin administration for surgical prophylaxis in primary TSA with respect to infectious complications	TSA All patients ($n = 7,177$)	III
Michaud et al., COP 2017	Determine the various reactions that are reported as a penicillin allergy and the rate of cefazolin cross-reactivity in patients having only non-IgE reactions to penicillin	All orthopaedic surgeries $n = 801$	II
Norvell et al., OFID 2023	Compare cefazolin with second-line antibiotics to evaluate the incidence of SSIs within 90 d following joint replacement surgery and interoperative HSRs among patients labeled allergic to a penicillin or cephalosporin	THA Cefazolin: $n = 375$ (46.5%) Clindamycin and/or vancomycin: $n = 148$ (46.4%) TKA Cefazolin: $n = 433$ (53.5%) Clindamycin and/or vancomycin: $n = 171$ (53.6%)	II
Stevoksa et al., JOA 2024	Compare causative bacteria and their antibiotic resistance profiles in patients developing a PJI based on preoperative prophylactic antibiotic regimens in primary THA and primary TKA/UKA	THA Cefuroxime: $n = 3,123$ Noncefuroxime: $n = 206$	II

(*continued on next page*)

Table 3 (*continued*)

Authors	Purpose	Surgical Procedure	Level of Evidence
Stone et al., JAAOS 2019	Analyze the effect of penicillin allergy on antibiotic type prescribed and surgical site infection in our TJA population	TKA Cefuroxime: $n = 2,455$ Noncefuroxime: $n = 211$ TKA: $n = 3,126$ Posterior approach THA: $n = 516$ patients Lateral and anterior approach THA: $n = 1,261$	II
Wyles et al., BJJ 2019	Characterize antibiotic choices for perioperative TKA and THA prophylaxis, assess antibiotic allergy testing efficacy, and determine rates of PJI based on perioperative antibiotic regimen	THA Cefazolin: $n = 12,068$ (42.8%) No cefazolin: $n = 601$ (39.5%) TKA Cefazolin: $n = 16,106$ (57.2%) No cefazolin: $n = 902$ (60.5%)	III

rPCNA, reported penicillin allergy; GI, gastrointestinal; PJI, prosthetic joint infection; THA, total hip arthroplasty; TKA, total knee arthroplasty; UKA, unicompartmental knee arthroplasty; TJA, total joint arthroplasty (TJA).

Table 4
Reported Penicillin Allergies, Reported Adverse Reactions, and Prophylactic Antibiotic Used for Reviewed Manuscripts.

Authors	Reported Penicillin Allergy Label	Reported Penicillin Allergy Adverse Reactions	Prophylactic Antibiotic Used
Bukowski et al., JOA 2024	rPCNA + cefazolin: $n = 4,938$ rPCNA + alternative: $n = 570$	rPCNA + cefazolin: Anaphylaxis: $n = 1,529$ (31%) Dermatologic: $n = 1,674$ (33.9%) GI intolerance: $n = 105$ (2.1%) Dyspnea: $n = 23$ (0.5%) Swelling: $n = 215$ (4.4%) Other (headache, dizziness, anxiety, palpitations): $n = 164$ (3.3%) Unspecified: $n = 1,228$ (24.9%) rPCNA + alternative Anaphylaxis: $n = 347$ (60.9%) Dermatologic: $n = 71$ (12.5%) GI intolerance: $n = 3$ (0.5%) Dyspnea: $n = 8$ (1.4%) Swelling: $n = 40$ (7.0%) Other (headache, dizziness, anxiety, palpitations): $n = 24$ (4.2%) Unspecified: $n = 77$ (13.5%)	No rPCNA + cefazolin: $n = 43,359$ rPCNA + cefazolin: $n = 4,938$ rPCNA + alternative (vancomycin or clindamycin): $n = 570$
Goh et al., JBJS 2021	Control: $n = 310$ (14.9%) Protocol: $n = 357$ (17.2%)	Protocol group: Gastrointestinal upset $n = 19$ (5.3%) Unknown history $n = 69$ (19.3%) Non-generalized rash $n = 133$ (37.3%) Itching $n = 18$ (5.0%) Generalized rash or hives $n = 84$ (23.5%) Angioedema $n = 19$ (5.3%) Anaphylaxis $n = 15$ (4.2%)	Cefazolin Control: $n = 1,762$ (84.8%) Protocol: $n = 1,960$ (94.3%) Vancomycin Control: $n = 290$ (14.0%) Protocol: $n = 101$ (4.9%) Clindamycin Control: $n = 26$ (1.2%) Protocol: $n = 17$ (0.8%)
Jones et al., CORR 2021	All patients in study (n = 180)	Preintervention (n = 90): Nonsevere allergy (n = 76) Rash: n = 37 (49%) Pruritus: n = 4 (5%) Hives: n = 27 (36%) Local swelling: n = 7 (9%) Intolerance: n = 12 (16%) Remote history and unknown: n = 8 (11%) *Severe Allergy (n = 14)* Anaphylaxis: $n = 14$ (100%) Laryngeal edema: $n = 0$ (0%) Postintervention ($n = 90$): *Nonsevere allergy* ($n = 79$) Rash: $n = 29$ (37%) Pruritus: $n = 4$ (5%) Hives: $n = 29$ (37%) Local swelling: $n = 3$ (4%) Intolerance: $n = 16$ (20%) Remote history and unknown: $n = 7$ (9%)	Cefazolin: patients with a reported nonsevere penicillin allergy without MRSA risk factors ($n = 75$) Cefazolin + vancomycin: patients with a nonsevere penicillin allergy with MRSA risks factors ($n = 1$) Vancomycin: patients with a severe penicillin allergy regardless of MRSA risk factors ($n = 14$)

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Table 4 (*continued*)

Authors	Reported Penicillin Allergy Label	Reported Penicillin Allergy Adverse Reactions	Prophylactic Antibiotic Used
		Severe allergy ($n = 11$) Anaphylaxis: $n = 10$ (91%) Laryngeal edema: $n = 1$ (9%)	
Marigi et al. JSES 2024	Cefazolin: not reported Vancomycin: $n = 282/289$	Not reported	Cefazolin: $n = 6,879$ Vancomycin: $n = 298$
Michaud et al. COP 2017	$n = 113$ (14%)	Urticaria: $n = 10$ (8.8%) Immediate airway compromise: $n = 8$ (7.1%) Anaphylaxis: $n = 7$ (6.2%) Angioedema: $n = 5$ (4.4%) Rash: $n = 49$ (43.4%) Unknown/can't remember: $n = 28$ (24.8%) GI Upset: $n = 2$ (1.8%) Confusion: $n = 1$ (0.9%) Yeast infection: $n = 2$ (1.8%) Agitation: $n = 1$ (0.9%)	Cefazolin, clindamycin, vancomycin (numbers not reported)
Norvell et al., OFID 2023	All patients had a labeled beta-lactam allergy Penicillin allergy Cefazolin: $n = 743$ (91.8%) Clindamycin and/or vancomycin: $n = 267$ (83.7%) Cephalosporin allergy Cefazolin: $n = 91$ (11.2%) Clindamycin and/or vancomycin: $n = 117$ (36.7%) Multiple beta-lactam allergies Cefazolin: $n = 59$ (7.3%) Clindamycin and/or vancomycin: $n = 88$ (27.6)	Immediate reaction Cefazolin: $n = 290$ (35.8%) Clindamycin and/or vancomycin: $n = 190$ (59.6%) Delayed reaction Cefazolin: $n = 279$ (34.5%) Clindamycin and/or vancomycin: $n = 87$ (27.3%) Intermediate timing of reaction Cefazolin: $n = 241$ (29.8%) Clindamycin and/or vancomycin: $n = 44$ (13.8%)	Cefazolin: $n = 809$ Clindamycin: $n = 146$ Vancomycin: $n = 79$ Clindamycin + vancomycin: $n = 94$
Stevoksa et al., JOA 2024	Not reported	Not reported	Cefuroxime: $n = 3,123$ Noncefuroxme: $n = 206$
Stone et al JAAOS 2019	$n = 796$ patients	Tier 1—Severe reactions and hypersensitivities: $n = 615$ (77.2%) Hives: $n = 208$ (26.1%) Rash: $n = 199$ (25.0%) Swelling/angioedema: $n = 65$ (8.2%) Anaphylaxis: $n = 60$ (7.5%) Respiratory distress, stridor, palpitations: $n = 32$ (4.0%) Itching: $n = 31$ (3.9%) Syncope/hypotension: $n = 7$ (0.9%) Blisters: boils, sores, Stevens Johnson syndrome: $n = 5$ (0.6%) Flushing, burning: $n = 5$ (0.6%) Convulsions: $n = 2$ (0.3%) Paralysis: $n = 1$ (0.1%) Tier 2—Side effects and intolerances: $n = 89$ (11.2%) Diarrhea, nausea/vomiting/GI symptoms: $n = 70$ (8.8%) Musculoskeletal symptoms: $n = 8$ (1.0%) Mental status change, headache: $n = 5$ (0.6%) Oral thrush, yeast infection: $n = 3$ (0.4%) Clostridioides difficile: $n = 2$ (0.3%) Exacerbation of existing condition: $n = 1$ (0.1%) Tier 3—Unknown or unspecified: $n = 92$ (11.6%) Unknown: $n = 58$ (7.3%) Childhood reaction: $n = 29$ (3.6%) Family reaction: $n = 5$ (0.6%)	Cefazolin: $n = 3,953$ (80.6%) Clindamycin: $n = 686$ patients (14.0%) Vancomycin: $n = 264$ patients (5.4%)
Wyles et al., BJJ 2019	$n = 2,576$ allergy tested before surgery for patient-reported possible penicillin or cephalosporin allergy	Not reported	Cefazolin: $n = 28,174$ No cefazolin: $n = 1,521$

rPCNA, reported penicillin allergy; *GI*, *gastrointestinal*.

Table 5
Allergic Reactions, Adverse Reactions by Group and Severity, and Postoperative Infections for Reviewed Manuscripts.

Authors	Allergic Reactions	Allergic Reactions by Study Group	Adverse Reactions by Severity	Postoperative Infections
Bukowski et al., JOA 2024	Total: $n = 17$ (0%) No rPCNA + cefazolin: $n = 11$ (0%) rPCNA + cefazolin: $n = 5$ (0.1%) rPCNA + alternative: $n = 1$ (0.2%)	No rPCNA + cefazolin: $n = 224$ (0.5%) rPCNA + cefazolin: $n = 23$ (0.5%) rPCNA + alternative: $n = 3$ (0.5%)	Grade 1: No rPCNA + cefazolin: $n = 11$ (0%), rPCNA + cefazolin: $n = 4$ (0.1%), rPCNA + alternative: n = 1 (0.2%) Grade 2: No rPCNA + cefazolin: $n = 0$ (0%), rPCNA + cefazolin: $n = 1$ (0%), rPCNA + alternative: $n = 0$ (0%)	Superficial infection No rPCNA + cefazolin: $n = 50$ (0.1%) rPCNA + cefazolin: $n = 7$ (0.1%) rPCNA + alternative: $n = 1$ (0.2%) Deep infection No rPCNA + cefazolin: $n = 154$ (0.4%) rPCNA + cefazolin: $n = 14$ (0.3%) rPCNA + alternative: $n = 2$ (0.4%) C. Difficile infection No rPCNA + cefazolin: $n = 20$ (0%) rPCNA + cefazolin: $n = 2$ (0%) rPCNA + alternative: $n = 0$ (0%)
Goh et al., JBJS 2021	Total: $n = 31$ (0.7%) Protocol: $n = 16$ (0.8%)	Cefazolin Control: $n = 13$ (86.7%) Protocol: $n = 15$ (93.8%) Vancomycin Control: $n = 1$ (6.7%) Protocol: $n = 1$ (6.2%) Clindamycin Control: $n = 1$ (6.7%) Protocol: $n = 0$ (0.0%)	Grade 1: control $n = 15$ (0.7%), $n = 16$ (0.8%) Grade 2: Control $n = 0$ (0.0%), protocol $n = 0$ (0.0%) Grade 3: Control $n = 0$ (0.0%), Protocol $n = 0$ (0.0%) Grade 4: Control $n = 0$ (0.0%), Protocol $n = 0$ (0.0%)	Superficial infection Control $n = 25$ (1.2%), Protocol $n = 16$ (0.8%) Deep infection Control $n = 8$ (0.4%), Protocol $n = 10$ (0.5%) *C. Difficile* infection Control $n = 4$ (0.2%), Protocol $n = 3$ (0.1%)
Jones et al. CORR 2021	Itching: $n = 2/130$ $n = 8$ patients with reported severe penicillin allergy, no patients experienced an allergic reaction to cefazolin	Not reported	Not reported	Not reported
Marigi et al., JSES 2024	Not reported	Not reported	Not reported	C. acnes–related infection Cefazolin: $n = 31$ (40.8%) Vancomycin infusion >30 min: $n = 2$ (66.7%) *S. aureus*–related Infection Cefazolin: $n = 16$ (21.1%) Vancomycin infusion >30 min: $n = 1$ (33.3%) *S. coagulase*–negative related infection Cefazolin: $n = 7$ (9.2%) Vancomycin infusion >30 min: $n = 1$ (33.3%) Streptococcus-related infection Cefazolin: $n = 4$ (5.3%) Vancomycin infusion >30 min: $n = 0$ (0%) Other infection Cefazolin: $n = 12$ (15.8%) Vancomycin infusion >30 min: $n = 0$ (0%)
Michaud et al.,COP 2017	Of the $n = 81$ non-IgE mediated penicillin allergic patients who received cefazolin, no adverse reactions were reported	Not reported	Not reported	Not reported
Norvell et al., OFID 2023	Cefazolin: $n = 4$ Clindamycin and/or vancomycin: $n = 8$	Interoperative hypersensitivity reaction Cefazolin: $n = 2$ Clindamycin and/or vancomycin: $n = 4$ Airway involvement Cefazolin: $n = 0$ Clindamycin and/or vancomycin: $n = 0$ Skin involvement Cefazolin: $n = 1$ Clindamycin and/or vancomycin: $n = 2$ Facial/throat swelling Cefazolin: $n = 0$ Clindamycin and/or vancomycin: $n = 0$ Hemodynamic instability Cefazolin: $n = 10$ Clindamycin and/or vancomycin: $n = 2$	Not reported	Surgical site infection Cefazolin: $n = 7$ (0.9%) Clindamycin and/or vancomycin: $n = 12$ (3.8%) PJI Cefazolin: $n = 1$ (0.1%) Clindamycin and/or vancomycin: $n = 6$ (1.9%) Polymicrobial infection Cefazolin: $n = 1$ Clindamycin and/or vancomycin: $n = 4$ Staphylococcus spp. Cefazolin: $n = 2$ Clindamycin and/or vancomycin: $n = 8$ MSSA Cefazolin: $n = 1$ Clindamycin and/or vancomycin: $n = 5$ *S. pseudointermedius*

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Table 5 (*continued*)

Authors	Allergic Reactions	Allergic Reactions by Study Group	Adverse Reactions by Severity	Postoperative Infections
				Cefazolin: $n = 0$ Clindamycin and/or vancomycin: $n = 1$ *S. epidermis* Cefazolin: $n = 1$ Clindamycin and/or vancomycin: $n = 1$ *E. faecalis* Cefazolin: $n = 0$ Clindamycin and/or vancomycin: $n = 3$ *E. avium* Cefazolin: $n = 0$ Clindamycin and/or vancomycin: $n = 1$ *Streptococcus canis* Cefazolin: $n = 1$ Clindamycin and/or vancomycin: $n = 0$ Cutibacterium avidum Cefazolin: $n = 1$ Clindamycin and/or vancomycin: $n = 0$ Klebsiella pneumoniae Cefazolin: $n = 0$ Clindamycin and/or vancomycin: $n = 3$ Enterbacter cloacae Cefazolin: $n = 0$ Clindamycin and/or vancomycin: $n = 1$ Proteus mirabilis Cefazolin: $n = 1$ Clindamycin and/or vancomycin: $n = 0$
Stevoksa et al., JOA 2024	Not reported	Not reported	Not reported	Gram positive Cefuroxime: $n = 66/76$ (86.8%) Noncefuroxme: $n = 8/8$ Coagulase-positive staphylococci Cefuroxime: $n = 15/76$ (19.7%) Noncefuroxme: $n = 0/8$ Coagulase−negative staphylococci Cefuroxime: $n = 32/76$ (42.1%) Noncefuroxme: $n = 3/8$ Streptococcus spp. Cefuroxime: $n = 4/76$ (5.3%) Noncefuroxme: $n = 1/8$ Anaerobes Cefuroxime: $n = 8/76$ (10.5%) Noncefuroxme: $n = 2/8$ Enterococcus spp. Cefuroxime: n = 6/76 (7.9%) Noncefuroxme: $n = 2/8$ Gram negative Cefuroxime: $n = 10/76$ (13.1%) Noncefuroxme: $n = 0/8$
Stone et al., JAAOS 2019	No patient with a penicillin allergy and given cefazolin experienced an adverse reaction	Not reported	Not reported	Cefazolin: $n = 18$ (0.5%) Clindamycin: $n = 4$ (0.6%) Vancomycin: $n = 0$ (0%)
Wyles et al., BJJ 2019	Not reported	Not reported	Not reported	Not reported

rPCNA, reported penicillin allergy.

($n = 28{,}174$ total joint arthroplasties [TJA]), 94.9% went on to receive cefazolin, and 5.1% received noncefazolin antibiotics. The authors found that infection-free survival was significantly higher among patients receiving cefazolin compared with those with noncefazolin antibiotics. Although the results were mixed, there may be a higher rate of SSI in penicillin allergy patients when noncefazolin antibiotics are used for perioperative TJA prophylaxis.

Antibiotic stewardship

The studies were all in agreement that evaluation of severe penicillin allergy before prophylactic antibiotics is crucial from an antimicrobial stewardship perspective. In a study by Jones et al. [81], a multifaceted antibiotic stewardship intervention increased the appropriateness of antibiotic prophylaxis in elective primary TJA. In this study, patients who have nonsevere penicillin allergies, even those reporting hives or local swelling, tolerated cefazolin. In another study, a simple screening protocol allowed two-thirds of patients who had a self-reported allergy to receive cefazolin without the need for additional consultations or testing. The authors concluded that this protocol could be safely implemented to increase the rate of cefazolin usage without a corresponding increase in the number of allergic reactions [80]. Furthermore, prophylaxis protocols should promote appropriate indications for the use of cephalosporins and alternative prophylactic antibiotics to mitigate infectious risks after TJA [86]. Antibiotic stewardship interventions and protocols [84,86] can be used in patients who have a reported penicillin allergy.

Table 6
Key Study Conclusions for the Reviewed Manuscripts.

Authors	Study Conclusions
Bukowski et al.	• In patients who had an rPCNA undergoing primary TJA, perioperative prophylaxis with cefazolin resulted in a 0.1% incidence of allergic reactions that were clinically indolent
JOA 2024	• Cefazolin can be safely administered to most patients, independent of rPCNA severity
Goh et al. JBJS 2021	• Using a penicillin allergy screening protocol, two-third of patients with a self-reported allergy were able to receive cefazolin safely, and the overall rate of cefazolin usage increased by 9% to 94%, without an increase in adverse reactions
Jones et al. CORR 2021	• Patients with nonsevere penicillin allergies, even those reporting hives or local swelling, can tolerate cefazolin • Antibiotic stewardship interventions can be implemented across institutions to expand cephalosporin use in patients with a reported penicillin allergy within orthopaedic TJA patients
Marigi et al.	• In comparison to cefazolin, complete administration of vancomycin (infusion to incision time greater than 30 min) as the primary prophylactic agent does not adversely increase the rates of infectious complications and PJI
JSES 2024	• Prophylaxis protocols should promote appropriate indications for the use of cefazolin or vancomycin, and when necessary, ensure complete administration of vancomycin to mitigate infectious risks after primary TSA
Michaud et al.	• It is important to obtain the specific reaction in patients reporting that they are allergic to penicillin to guide the choice of antibiotics
COP 2017	• In patients who report a non-IgE reaction to penicillin, it is safe to administer cefazolin
Norvell et al. OFID 2023	• The use of cefazolin as a perioperative antibiotic for infection prophylaxis in total joint arthroplasty in patients labeled beta-lactam allergic is associated with decreased postoperative surgical site infections without an increase in interoperative hypersensitive reactions
Stevoksa et al.	• The use of the second-line antibiotic did not influence the pathogen spectrum or antibiotic resistance
JOA 2024	• A high proportion of coagulase negative staphylococci strains was resistant to clindamycin
Stone et al. JAAOS 2019	• No patient with a penicillin allergy and given cefazolin experienced an adverse reaction; based on reported reactions, most patients with a penicillin allergy can safely receive first-line antibiotic therapy • In this population, penicillin allergy and second-line antibiotic therapy did not influence rate of surgical site infections
Wyles et al. BJJ 2019	• PJI rates are significantly higher when noncefazolin antibiotics are used for perioperative TKA and THA prophylaxis, highlighting the positive impact of preoperative antibiotic allergy testing to increase cefazolin usage • Given the low rate of true penicillin allergy positivity, and the readily modifiable risk factor that antibiotic choice provides, we recommend perioperative testing and clearance for all patients presenting with penicillin and cephalosporin allergies

rPCNA, reported penicillin allergy; PJI, prosthetic joint infection; THA, total hip arthroplasty; TKA, total knee arthroplasty; TJA, total joint arthroplasty ; TSA, total shoulder arthroplasty.

Conclusion

Based on the current systematic review, we found that there are very low rates of cross-reactivity between penicillins and cephalosporins. The reviewed studies concluded that it is appropriate to administer a first-generation cephalosporin (cefazolin) as the first choice for antibiotic prophylaxis for patients who have a documented penicillin allergy (Table 6). When cefazolin is not available, a second-generation cephalosporin (cefuroxime) can be used. Most patients who have a penicillin allergy can safely receive first-line antibiotic therapy [86] without experiencing adverse reactions. Allergy to first- or second-generation cephalosporins is exceedingly rare, and if it does occur, it is most often mild and can be easily treated.

Question 5: Should prophylactic antibiotics be altered for patients undergoing major orthopaedic procedures based on their comorbidity profile?[5]

Response/Recommendation

Although tailored antibiotic prophylaxis may be considered for high-risk populations, and based on regional microbial epidemiology, altering antibiotic prophylaxis based on patient comorbidity profile does not seem to make a difference in infection rate.

Level of Evidence: Moderate

Delegate Vote: Agree 79%, disagree 12.9%, abstain 8.1% (strong majority, moderate consensus)

Rationale

Prophylactic use of systemic antibiotics remains a crucial part of the infection prevention bundle in orthopaedic surgery. Yet, in major instrumented orthopaedic procedures with implants, surgical site infections (SSIs), prosthetic joint infections (PJIs), and osteomyelitis do occur, which can be disabling, costly, and sometimes lethal [88]. Failure of prophylactic antibiotics can occur and is multifactorial, especially impacted by higher rates of β-lactam-resistant bacteria present as part of the patient's skin microbiome [89].

Some patients, including those who have comorbidities, are at an increased risk of infection after orthopaedic implant procedures [90]. The most cited comorbidities associated with postoperative infections are uncontrolled diabetes (fasting blood glucose > 180 mg/dL, hemoglobin A1c > 7%), malnutrition (serum albumin levels < 3.50 g/dL), cardiovascular disease, chronic kidney insufficiency, obesity (BMI ≥30), active smoking (tobacco use), immunosuppressive state (untreated HIV-positive patients, malignancy, autoimmune diseases, consumption of immunosuppressants), and prior joint surgery [90–96]. Moreover, an increased score on validated risk stratification instruments, such as the American Society of Anesthesiologists (ASA) score and Charlson Comorbidity Index, correlates well with increased rates of infection after orthopaedic procedures [89–91].

Standardized antibiotic prophylaxis with cephalosporins is effective in preventing SSIs and PJIs in most patients [92]. We assessed whether perioperative optimization of antibiotic prophylaxis according to patient comorbidity profile was needed to reduce postoperative infections in patients undergoing major orthopaedic surgeries. Optimal antibiotic selection and dosages for prophylaxis, including local antibiotic therapy, extension of antibiotic use after discharge, and combination of drugs to cover cephalosporin-resistant bacteria, were evaluated. Open fracture surgeries were excluded from the analysis.

Tailoring antibiotic prophylaxis toward comorbidities and site-relevant microbial susceptibility patterns shows promise for specific populations. A retrospective Spanish study of 657 patients showed that adding teicoplanin prophylaxis in hip fracture surgery for MRSA prevention reduced SSI rates.

[5] These authors contributed to Question 5: Mauro Jose Salles, Eduardo C. dos Santos, Raquel B. da Silva, Lais S. Seriacopi, Jonatan Tillander

Protracted surgeries (> 120 minutes, odds ratio [OR] 4.5, $P = 0.02$), red blood cell transfusions (OR 11.6, $P = 0.002$), and urinary tract infections (OR 4.28, $P = 0.02$) were significant risk factors for orthopaedic infections [7]. A recent European study switched antibiotic prophylaxis from cefuroxime to teicoplanin plus gentamicin in primary TJA, targeting resistant pathogens, particularly coagulase-negative staphylococci and cefuroxime-resistant *Enterobacteriaceae*. Early and delayed PJI rates were reduced by 75.2% (0.57 versus 2.24%, HR: 0.25, $P = 0.004$). Increased reversible stage-1 acute kidney injury (AKI) rates (3.3 versus 0.8%, $P = 0.001$) were noted [8]. Conversely, Tan et al. analyzed 8,575 TJAs and found no significant impact on PJI rates when comparing standardized cefazolin or vancomycin prophylaxis (1.1 versus 1.3%, $P = 0.33$). The incidence of PJI did not significantly differ between the cefazolin and vancomycin prophylaxis groups when stratified by comorbidities such as diabetes (1.7 versus 2.1%, $P = 0.28$), rheumatoid arthritis (1.8 versus 2.2%, $P = 0.47$), liver disease (2.1 versus 2.3%, $P = 0.59$), or hypothyroidism (1.2 versus 1.5%, $P = 0.34$). The authors concluded that tailoring antibiotics based on patient comorbidities does not significantly reduce the risk of PJI [9]. Tailoring antibiotic prophylaxis protocol toward high-risk patients was effective in a pediatric population undergoing spine surgery, as cefazolin alone was insufficient for specific high-risk pediatric patients (ASA > 2, sacrum/pelvic instrumentation, greater number of fused levels, surgery duration longer than 5.6 h, nonambulatory status, lack of sphincter control, cognitive impairment, and postoperative intensive care unit admission). Culture yielded 72% of Gram-negative bacilli, 85.5% of which were susceptible to gentamicin. The authors concluded that adding gentamicin improved Gram-negative bacilli coverage, reducing SSIs ($P < 0.001$) [97].

Innovative approaches are also effective in specific contexts. Additional evidence underscores the importance of procedure and patient-specific considerations. Successfully tailored systemic and local antibiotic prophylaxis has been used for PJI prevention after hip hemiarthroplasty surgery for patients who have proximal femoral fractures, in which rates of infection of up to 9% are expected [98,99]. Most hip fracture patients are at high risk of infection because of their underlying comorbidities, old age, frequent hospitalization, and colonization by multidrug-resistant Gram-negative bacteria [98–100]. In a quasi-randomized controlled clinical study of 848 patients, the rate of deep SSI was 3.5% in the standard-of-care group (cement with 0.5 gram of gentamicin) and 1.1% in the intervention group (one gram of clindamycin and one gram of gentamicin; $P = 0.041$; logistic regression adjusting for age and sex). Systemic antibiotic prophylaxis with single doses of gentamicin (three mg/kg) and teicoplanin (400 mg) was used for all patients. The number needed to treat to prevent one infection was approximately 42 [100].

Conclusion

Standardized antibiotic prophylaxis with cephalosporins is effective in reducing infections after orthopaedic procedures. However, innovative approaches show promise for specific populations and epidemiological patterns. Tailoring antibiotic prophylaxis by local microbial resistance patterns may reduce the risk of subsequent infections. Meanwhile, correctly tailored systemic antibiotic prophylaxis in pediatric spine surgery and for patients who have hip fractures shows promise. Future randomized controlled trials with sufficient follow-up should explore these strategies to refine antibiotic prophylaxis protocols without driving antimicrobial resistance.

Question 6: Does the use of vancomycin powder in the wound reduce the incidence of surgical site infection/periprosthetic joint infection in patients undergoing major orthopaedic procedures?[6]

Response/Recommendation

Due to the insufficient high-level evidence, we recommend against the routine use of topical vancomycin powder to reduce surgical site infection/periprosthetic joint infection in major orthopaedic surgeries.

Strength of Recommendation: Limited

Delegate Vote: Agree 89.1%, disagree 9.1%, abstain 1.8%

Rationale

For this document, we conducted a systematic review and meta-analysis to clarify the efficacy of topical vancomycin (VCM) powder over control to reduce the incidence of SSI/PJI in patients undergoing major orthopaedic procedures. We used a random effect model to pool the results and used the Cochrane risk of bias tool 2.0 to evaluate the risk of bias in each outcome. We used Grading of Recommendations Assessment, Development and Evaluation to evaluate the certainty of the evidence and create a summary of findings table to describe the results [101]. Trial sequential analysis (TSA) was conducted to evaluate the robustness of the result.

The previous ICM consensus in 2018 concluded that there was insufficient evidence for topical VCM powder in reducing SSI, with only one randomized controlled trial (RCT) published at that time. After this consensus, several RCTs have been published, which enable a meta-analysis on this topic.

After searching PubMed and Embase, 13 RCTs with 5,041 participants were included [102–113]. All studies were published from 2013 to 2024. There were three studies from India [101,106,110], two studies were from Iran [102], two studies were from China (109,112), and other studies were from Thailand, Iraq, the United States, Canada, Pakistan, and Nigeria [103,104,107,108,111,113]. There were eight studies focused on spine surgery [101–103,110,113–115,116], two studies focused on total knee arthroplasty (TKA) [106,107], one study focused on both TKA and total hip arthroplasty (THA) [101–103], and two studies focused on fracture surgery [104,110]. There were two studies in spine surgery that did not use an implant [111,113]. Sample size ranged from 42 to 1,022, and the follow-up period ranged from 30 to 182 days. The amount of the VCM powder used was either 0.5 g [113], one gram [101,104,107–111], or two grams [102,103,105,106,110]. All studies used routine intravenous preoperative antibiotics, and no studies used alternative topical antibiotics or a placebo as their comparative intervention. For the definition of infection, four studies used the Centers for Disease Control definition [103–106,109], one study used the fracture-related consensus definition [110], two studies used the Musculoskeletal Infection Society Criteria [106,107], one study used their own definition [113], and the remaining five studies did not provide any clear definition [101,102,108,111,112]. Risk of bias varied from some concern to high across studies.

Among 13 studies, only one study, which focused on patients undergoing open or microscopic discectomy, demonstrated a significantly favorable result of VCM powder in reducing overall SSI (relative risk [RR] 0.19; 95% confidence interval [CI] 0.04 to 0.83) [113]. Other studies failed to show the significant efficacy of VCM powder in reducing SSI, and one trial in TKA was suspended due to the increase in SSI in the VCM powder group [107]. There

[6] These authors contributed to Question 6: Natsumi Saka, Koji Yamada, Abdullah S Hammad, Fatih Yildiz, Fabio Stucchi Devito, Pawel Bartosz, George N Guild III

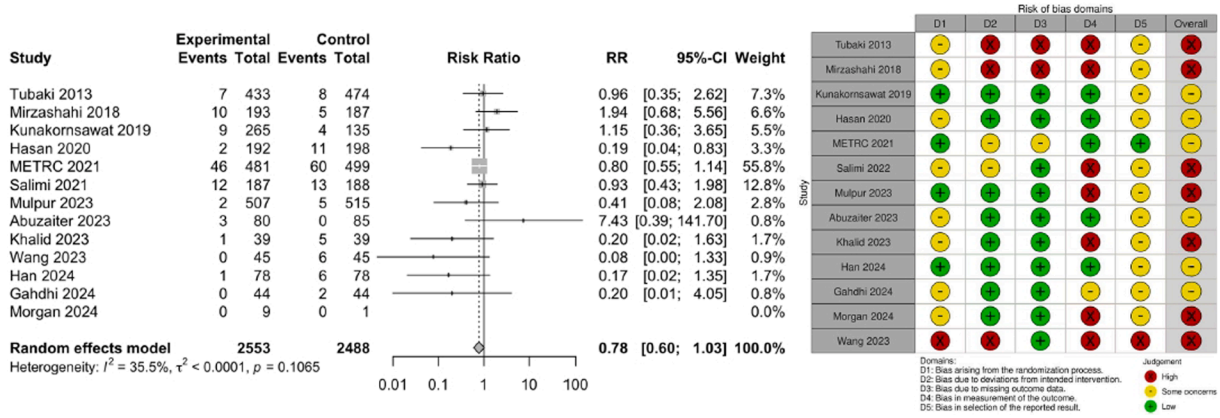

Figure 4. Forest plot and RoB of overall SSI.

was one large study in high-risk tibial plateau or pilon fractures that failed to show a decrease in overall SSI but demonstrated the reduction of Gram-positive cocci (GPC) infection [104]. However, this outcome was not prespecified.

In terms of meta-analytic results, VCM powder failed to show a significant reduction of SSI in major orthopaedic surgeries (RR 0.78; 95% CI 0.60 to 1.03; $I^2 = 35.5\%$; very low certainty of the evidence; Figure 4). Although there was a chance of asymmetry in the funnel plot, asymmetry was not significant by Egger's test ($P = 0.25$). This result was consistent in our sensitivity analysis, such as the analysis excluding studies with a high risk of bias and the leave-one-out sensitivity analysis. In our subgroup analysis, there was no subgroup difference between implant surgery versus nonimplant surgery (test for subgroup difference; $P = 0.46$) and between surgery types, such as spine versus fracture versus TKA versus TKA and THA (test for subgroup difference; $P = 0.44$). From the TSA, the total sample size did not reach the required information size of 20,629, and the *Z*-curves did not cross the trial sequential monitoring or futility boundary, suggesting the inconclusive result of this meta-analysis.

From further analysis of our secondary outcomes, VCM powder showed a significant reduction in preventing GPC SSI compared to the control (RR 0.51; 95% CI 0.32 to 0.81; $I^2 = 0\%$; low certainty of the evidence). However, in leave-one-out sensitivity analysis, this result became insignificant when we omitted a large study on tibial fracture [104]. For other outcomes, VCM powder failed to demonstrate statistically significant efficacy with very low certainty of the evidence (Table 7). There were five studies that reported no adverse event [101,103,109–111]. There were four studies that did not report the adverse event [102,105,108,113]. There were four studies that reported adverse events [104,106,107,112], with one study reporting renal dysfunction and rash in the VCM powder group [112]. However, the overall association between VCM powder and adverse events was not clear.

Although VCM powder showed significant SSI reduction for GPC SSI in our analysis, its efficacy for overall SSI was not

Table 7
Summary of Findings: VCM Provider Compared to Control for SSI.

Outcomes	Nº of Participants (Studies) Follow-Up	Certainty of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk with Control	Risk Difference With VCM Powder
Overall SSI	5,041 (13 RCTs)	Very low[a,b,c]	RR 0.78 (0.60 to 1.03)	50 per 1,000	11 fewer per 1,000 (20 fewer to 2 more)
Reoperation	2,002 (2 RCTs)	Very low[a,b,c]	RR 0.77 (0.44 to 1.35)	28 per 1,000	6 fewer per 1,000 (15 fewer to 10 more)
Deep SSI	5,031 (12 RCTs)	Very low[a,b,c]	RR 0.77 (0.52 to 1.15)	37 per 1,000	8 fewer per 1,000 (18 fewer to 5 more)
Superficial SSI	2,976 (8 RCTs)	Very low[a,b]	RR 0.70 (0.35 to 1.41)	23 per 1,000	7 fewer per 1,000 (15 fewer to 9 more)
GPC SSI	4,093 (9 RCTs)	Low[a,c]	RR 0.51 (0.32 to 0.81)	27 per 1,000	13 fewer per 1,000 (19 fewer to 5 fewer)
GNR SSI	4,093 (9 RCTs)	Very low[a,b,c]	RR 1.29 (0.69 to 2.40)	9 per 1,000	3 more per 1,000 (3 fewer to 13 more)
MRSA SSI	1,568 (4 RCTs)	Very low[a,b,c]	RR 0.32 (0.01 to 7.88)	1 per 1,000	1 fewer per 1,000 (1 fewer to 9 more)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Patient or population: SSI.
Setting: Major orthopaedic procedures.
Intervention: VCM powder.
Comparison: Control.
GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimated effect.
CI, confidence interval; RR, risk ratio.
[a] Risk of bias is high, mostly in outcome evaluation.
[b] CI is wide.
[c] RIS was not met.

significant. The efficacy of VCM powder was also not significant in all subgroups, including the type of procedures and with or without implants. Moreover, there was only one RCT that showed effectiveness out of 13 RCTs evaluated. Although the number of RCTs increased rapidly after the previous ICM consensus, our TSA still revealed an inconclusive result. Thus, there still remains a possibility that the future cumulative data may turn efficacious. However, from the available data at this point, we believe that there is insufficient data to support the routine use of VCM powder as a measure to prevent SSI. This result aligns with a recent meta-analysis on spine surgery that focused on RCTs [115].

Several potential limitations exist. This meta-analysis included surgeries from various specialties, such as spine surgery, arthroplasty, and high-risk tibial fractures, with varying follow-up definitions and durations, potentially influencing results. Also, most trials were conducted in low- to middle-income countries, limiting generalizability to high-income settings. Additionally, over half of the studies focused on spine surgery, and no RCTs examined sports medicine procedures, such as ligament reconstruction, further restricting applicability. Furthermore, excluding observational studies may have led to an underestimation of adverse events.

Conclusion

Based on the available data, although topical VCM powder may have efficacy in reducing GPC SSI, we do not recommend routine usage of topical VCM powder as a measure to prevent SSI/PJI, as it failed to show a significant reduction in overall SSI/PJI in major orthopaedic procedures. Given the very low certainty of evidence and the insufficient study population, additional trials are still required to determine its efficacy.

Question 7: Are there any concerns for the use of topical antibiotics (e.g., vancomycin) in patients undergoing major orthopaedic surgery?[7]

Response/Recommendation

Topical antibiotics (TA) have been associated with rare complications, including aseptic wound complications, delayed wound healing, and systemic absorption risks potentially resulting in nephrotoxicity. There are also theoretical concerns for an increased risk of antibiotic resistance or tissue toxicity, leading to delayed bone healing/fusion.

Level of Evidence: Moderate

Delegate Vote: Agree 89.1%, disagree 4.4%, abstain 6.5% (super majority, strong consensus)

Rationale

Surgical site infections (SSIs) and periprosthetic joint infections (PJIs) remain major challenges in major orthopaedic surgeries. The incidence rates of SSI and PJI range from 0.4 to 2.4% in primary joint arthroplasties and can reach up to 10% in revision surgeries [116–119]. These infections impose a tremendous burden on patients through prolonged recovery times and reduced quality of life, while also placing considerable financial and logistical strain on health care systems [120–122]. The management of these infections is further complicated by the growing prevalence of antibiotic-resistant organisms, which limit the effectiveness of traditional systemic therapies [123].

Topical antibiotics (TA), including vancomycin powder, antibiotic-loaded polymethylmethacrylate (PMMA), intra-articular infusion, and advanced carriers such as calcium sulfate (CS), hydrogels, and collagen fleece, have emerged as strategies for preventing and treating infection. When treating PJI and complex bone infection, these modalities offer localized, high-dose antimicrobial delivery, targeting pathogens directly at the surgical site while minimizing systemic toxicity [123–127]. Additionally, they address the challenge of biofilm-associated infections in poorly vascularized tissues [128].

Despite their potential, the use of TA raises several concerns, including the risk of local wound complications, tissue toxicity, concerns of antibiotic resistance, and variable efficacy due to inconsistent application techniques [129,130]. Understanding these factors is crucial for optimizing their use in orthopaedic surgeries.

To address the question posed earlier, we performed a comprehensive systematic review to identify literature that directly addressed the safety of topical antibiotics, exploring diverse delivery methods, such as powders, liquids, ceramic beads, PMMA, and biodegradable materials, with a focus on safety and cost-effectiveness.

Hypersensitivity reactions

Reports of allergic reactions, including hypersensitivity, have been rare in the included studies, with a single case of an anaphylactic reaction attributable to topical rifampicin. Nevertheless, caution should be exercised, particularly in patients who have known sensitivities to antibiotics such as vancomycin [131,132]. Milder hypersensitivity reactions, such as localized pruritic or erythematous skin changes, can occur and may warrant close monitoring and consideration for allergy testing [133].

Wound complications

High concentrations of TA, particularly vancomycin powder and CS beads, are associated with aseptic wound complications. These complications, which may include delayed wound healing, seroma formation, and wound dehiscence, could potentially impact overall surgical outcomes and necessitate further intervention [134,135]. The presence of CS beads has been linked to increased wound drainage, possibly due to their rapid dissolution and osmotic effects, which may delay wound closure and healing [136,137]. Furthermore, factors such as patient comorbidities and the surgical technique where the TAs are applied may influence the incidence and severity of these complications.

Systemic absorption and toxicity

Although designed for localized delivery, systemic side effects of glycopeptides have been observed, occasionally leading to complications such as AKI [138,139]. There have been no concerns of clinically relevant raised serum levels or ototoxicity with topical glycopeptides [140]. Clinicians should remain vigilant in patients who have pre-existing renal impairment or those receiving concurrent nephrotoxic medications. Monitoring renal function postoperatively in high-risk individuals may be advisable [141]. Despite the low risk of systemic toxicity, consideration to evaluate the pharmacokinetics of TA in different patient populations can refine safety recommendations.

Tissue toxicity

There is no important clinical evidence in orthopaedics that attributes the use of TA to cytotoxic effects that contribute to pseudoarthrosis in spinal surgery or delayed/nonunion in trauma surgery [142–144]. *In vitro* studies have indicated that high concentrations of certain antibiotics may have transient inhibitory effects on osteoprogenitor proliferation, but these effects appear to be dose dependent and not clinically relevant in orthopaedic applications [145]. Additionally, the incorporation of antibiotics

[7] These authors contributed to Question 7: Thananjeyen Srirangarajan, Sebastian Braun, Gwo-Chin Lee, Bingyun Li, Daniel Ramírez, Justinas Stucinskas, Edward M Vasarhelyi

into biomaterials, such as PMMA or collagen fleece, has not been associated with compromised bone healing, supporting the overall biocompatibility of these delivery systems [122,146]. An improved understanding of long-term bone healing outcomes with different antibiotic carriers may further strengthen clinical recommendations.

Antibiotic resistance

The potential correlation between the use of topical antibiotics and the emergence of antimicrobial resistance has not been explored in orthopaedic surgery. This theoretical association has been the impetus behind the recommendations from various authorities, including the Centers for Disease Control, to avoid placing topical antibiotics in the wound. This issue needs to be studied further in the future. However, the unique pharmacokinetic profile of TA potentially allows for high initial peak concentrations that rapidly reduce bacterial loads, decreasing the selective pressure that promotes resistance [147]. When combined with systemic antibiotics, this dual approach enhances infection prevention by providing both immediate localized action and sustained systemic coverage [148]. Evidence in bone infection management suggests that using antibiotic combinations in local carriers may further mitigate resistance risks while improving bactericidal efficacy [149,150]. To maximize these benefits, appropriate dosing strategies and adherence to evidence-based protocols may improve standardization.

Economic considerations

Vancomycin powder is relatively inexpensive, but its routine use must be weighed against its potential to prevent costly reoperations due to infection. Multiple studies in spinal surgery have demonstrated cost savings of over $100,000 per 100 spinal fusion operations with the use of prophylactic TA [126,151]. Variability in application modalities and indications complicates cost-effectiveness analyses. Newer carriers, such as hydrogels and collagen fleece, may offer improved efficacy but often come at higher costs.

In conclusion, topical antibiotics, such as vancomycin, may have a role in the reduction of infections in major orthopaedic surgeries, particularly for high-risk patients. However, concerns about aseptic wound complications and systemic toxicity must be considered. The need for standardized protocols and high-quality evidence is paramount to ensure their safe and effective use. Future research should prioritize long-term safety evaluations to guide clinical decision-making.

Question 8: Should prophylactic antibiotics be repeated in patients who have excessive blood loss?[8]

Response/Recommendation

Readministering prophylactic antibiotics should be considered if blood loss exceeds 1,200 mL. Additionally, intraoperative redosing is recommended after two half-lives of the antibiotic have passed since initial preoperative administration or if there is a large volume of fluid replacement.

Level of Evidence: Limited

Delegate Vote: Agree 87.8%, disagree 7.3%, abstain 4.9% (super majority)

Rationale

Perioperative prophylactic antibiotics are administered to reduce the risk of surgical site infection (SSI). Prophylactic antibiotics are administered before making the skin incision. The question of whether prophylactic antibiotics should be redosed has been addressed by many guidelines, including the prior ICM in 2018 [152]. The World Health Organization, National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines Network, and Centers for Disease Control and Prevention guidelines on SSI prevention do not provide a recommendation on intraoperative redosing due to limited clinical evidence. In 2013, the American Society of Health-System Pharmacists, jointly with the Infectious Diseases Society of America, the Surgical Infection Society, and the Society for Healthcare Epidemiology of America, published guidelines recommending intraoperative redosing after two half-lives of the antibiotic have passed since initial administration. This recommendation was based on pharmacokinetic and pharmacodynamic principles, as there is widespread agreement that antibiotic levels should remain above the minimal inhibitory concentration (MIC) of the likely SSI pathogens throughout the surgical procedure, from incision to closure [153, 154]

The available data reveal that redosing of prophylactic antibiotics is somewhat dependent on the half-life of the administered antibiotic and renal clearance of the patient. Serum antibiotic concentrations may be reduced by blood loss and fluid replacement, especially in the first hour of surgery when drug levels are high [155–157]. The precise effects of blood loss and fluid replacement are difficult to predict and will depend upon the antibiotic used and the time and rate of blood loss and fluid replacement. In general, prophylactic antibiotics need to be redosed if the surgical procedure lasts more than 240 minutes (when using antibiotics with a short half-life, such as cefazolin), if there is a large blood loss (> 1,200 to 2,000 mL), and/or if there is large-volume fluid replacement.

We conducted a comprehensive systematic review to evaluate the state of current literature related to the redosing of prophylactic antibiotics. After screening by four experts, 25 articles were deemed to be appropriate for full review and data extraction.

A systematic review with meta-analysis, including two randomized controlled trials (RCTs) and eight cohort studies comprising 9,470 patients, was published in 2022. The primary outcome was adjusted odds ratio (OR) for SSI after receiving preoperative surgical antibiotic prophylaxis (SAP) with additional intraoperative redosing (intervention) compared to a single dose of preoperative SAP (control). There were two studies that only used cefazolin, one study used ampicillin and sulbactam, and the other studies reported several regimens, with some including cefazolin.

Pooled ORs for SSI in patients receiving intraoperative redosing compared to those without redosing were 0.47 (95% confidence intervals [CI]: 0.19 to 1.16, $I^2 = 36\%$) for RCTs and 0.55 (95% CI: 0.38 to 0.79, $I^2 = 56\%$) for observational cohorts. The authors concluded that intraoperative redosing in addition to preoperative SAP reduces the incidence of SSI when compared to a single dose of preoperative prophylaxis. A sufficiently powered placebo-controlled RCT examining intraoperative redosing may be unethical given the present findings, but the optimal redosing protocol remains unclear [158].

Articles on specific antibiotics used in orthopaedic procedures are reviewed below.

Cefazolin

There were two well-controlled studies of surgical prophylaxis with cefazolin that similarly demonstrated minimal effects of blood loss on drug concentrations during total hip arthroplasty (THA) and spine fusion procedures. Meter et al. examined the effect of intraoperative blood loss and volume resuscitation during

[8] These authors contributed to Question 8: Renjy Nelson, Ben Kendrick, Panayiotis J. Papagelopoulos, Nicolás Enviado, Natividad Benito, Javad Parvizi

THA on serum levels of cefazolin in 18 patients. At four hours after administration, the serum level of cefazolin was 45 mcg/mL, which corresponds to a conservative intraosseous concentration of 10 to 30% of serum concentration, which would exceed the MIC for *Staphylococcus aureus* (0.5 μg/mL), despite an average intraoperative blood loss of 1,137 ± 436 mL. This led the authors to conclude that with blood losses of up to two L, it is not necessary to redose cefazolin any earlier than four hours to maintain the cefazolin concentration above the MIC for the most common infecting organisms [159]. The authors repeated the study in 19 patients undergoing instrumented posterior spinal fusion and found that there was no significant difference between preoperative and intraoperative cefazolin clearance, and there was no correlation between blood loss and cefazolin in pharmacokinetic parameters (area under the curve (AUC), Vd of central compartment, Vd at steady state, mean resonance time, or half-life) and that less than 10% of cefazolin was lost. Cefazolin concentration at four hours post skin incision was 27 μg/mL, which equated to a bone concentration of at least 2.7 μg/mL, which is higher than the MIC of cefazolin to most organisms. The authors concluded that it was not necessary to shorten the dosing interval of cefazolin for less than four hours for blood losses up to 1,200 mL [160].

Lopez-Sosa et al. performed a prospective observational study on 12 children undergoing spinal fusion. The mean blood loss was 1,156 mL with average blood replacement of 628.5 mL and fluid replacement of 1,712.5 mL. Mean cefazolin concentration dropped 62.3 and 81% at two and three hours of surgery, respectively. They concluded first that cefazolin half-life was around 90 minutes, which is consistent with other studies, and second, cefazolin concentrations did not inversely correlate with blood loss volume or blood and fluid volume replaced. They postulated that serum levels were maintained at the expense of tissue levels because of the tissue's dynamic equilibrium [161].

Swoboda et al. attempted to determine the effect of intraoperative blood loss on prophylactic cefazolin and gentamicin serum and tissue concentration in a prospective study of elective spinal procedures with expected large blood loss. At 60 minutes after the incision, blood loss correlated with cefazolin tissue concentrations ($r = -0.66$, $P = 0.05$) and the clearance of gentamicin from the tissues ($r = 0.82$, $P = 0.01$). They concluded that additional doses of cefazolin should be administered when the operation exceeds three hours and blood loss is greater than 1,500 mL. A dose of gentamicin greater than 1.8 mg/kg should be administered more than 30 minutes before the surgical incision [162].

Gentamicin

Markantonis et al. investigated the effects of surgical blood loss and fluid volume replacement on gentamicin concentrations in serum and tissue in patients undergoing colorectal surgery. Gentamicin was administered at a standard dose of two mg/kg, and blood and tissue samples were obtained concurrently at specific times. The mean concentration at incision was 7.83 (0.82) μg/mL and decreased to 2.60 (0.28) μg/mL at skin closure, resulting in borderline effectiveness even for susceptible Gram-negative microorganisms (MIC-1.0). A strong negative correlation was found between the intravenously administered fluids and gentamicin concentrations in serum and tissues ($P \leq 0.04$) [163].

Vancomycin

Klekamp et al. prospectively studied patients undergoing orthopaedic procedures with either large or small blood loss who also received vancomycin prophylaxis to determine the effect of intraoperative volume shifts on serum vancomycin concentrations. There were six index patients in the large blood loss group (> two L) and seven in the control group (blood loss < two L). The mean intraoperative fluid resuscitation, excluding blood products, was 12.4 and 5.1 L, respectively. There was a modest inverse correlation between blood loss and the intraoperative serum half-life of vancomycin. Although controls maintained slightly higher intraoperative vancomycin concentrations at each time point, there was no statistically significant difference between the groups with regard to absolute concentrations or rate of decline. After eight hours, the serum concentration of vancomycin exceeded the MIC-90 for *S. aureus* by approximately eightfold in all but one case, who was morbidly obese and had massive blood loss. Thus, blood loss during orthopaedic procedures has a minimal effect on the intraoperative kinetics of vancomycin, and redosing vancomycin is rarely indicated [164].

Çaglar et al. prospectively studied the pharmacokinetic changes in vancomycin when used for surgical prophylaxis for revision hip arthroplasty. While the mean serum vancomycin levels were above the estimated vancomycin minimum effective level (MEL) of five mg/L at three hours, 62.1% of patients had vancomycin concentrations above the MEL at 12 hours after the infusion. There was a statistical difference in intraoperative blood loss between patients with low and high vancomycin concentrations (19.6 ± 7.2 versus 13.5 ± 4.0, respectively, $P = 0.016$). ROC curve analysis revealed that blood loss volume greater than 1,150 mL and blood loss/body weight ratio more than 18.5 were significant for estimating vancomycin levels below the MEL at 12 hours postoperatively (AUC = 0.793 ± 0.16, $P = 0.009$; AUC = 0.753 ± 0.12, $P = 0.025$, respectively). Other variables such as fluid replacement, drain volume, and length of surgery were not significant [165].

Cloxacillin

A small pharmacokinetic analysis of cloxacillin levels in children undergoing major facial and neck surgery demonstrated that the associated massive blood loss led to serum cloxacillin concentrations below therapeutic levels for a major proportion of the surgery [155].

Question 9: Is there a role for dual antibiotic prophylaxis for patients undergoing orthopaedic procedures?[9]

Response/Recommendation

No, we do not recommend routine systemic dual antibiotic preoperative prophylaxis for patients undergoing orthopaedic procedures without known methicillin-resistant *Staphylococcus aureus* (MRSA) colonization.

Strength of Recommendation: Limited

Delegate Vote: Agree 91.8%, disagree 7.2%, abstain 1.0% (total consensus, unanimity)

Rationale

Perioperative antibiotic prophylaxis for orthopaedic procedures is recommended in most cases, typically with first- or second-generation cephalosporins as a first-line agent due to their coverage and clinical efficacy [166–169]. Dual antibiotic prophylaxis with an additional agent, most commonly vancomycin or an aminoglycoside, has been proposed to provide additional coverage for methicillin-resistant *Staphylococcus aureus* (MRSA) or Gram-negative bacteria in high-risk patient populations [169]. However, there is limited guidance on the benefits of dual antibiotic prophylaxis in orthopaedic procedures, when they are indicated, and with which antibiotics.

[9] These authors contributed to Question 9: Zachary K. Christopher, Óliver Marín-Peña, Raul Garcia-Bógalo, David Figueroa, Samuel Parra Aguilera, Dace Vigante, Trisha N. Peel

We completed a comprehensive literature review to identify studies related to perioperative systemic dual antibiotic prophylaxis in patients undergoing orthopaedic procedures. Searches were performed using the MEDLINE, Embase, and Cochrane search engines through September 2024 for the populations of "orthop[a]edic procedures," "orthop[a]edic surgeries," "arthroplasties," and "orthop[a]edics," with "dual antibiotic prophylaxis," "dual-agent antibiotic prophylaxis," "antibiotic prophylaxis," and "surgical prophylaxis" in various combinations with various Boolean operators. Inclusion criteria consisted of English language studies that investigated systemic, perioperative dual antibiotic prophylaxis for patients undergoing an orthopaedic procedure. Studies were excluded that were non-English language, nonhuman studies, studies evaluating local or regional prophylaxis only, retracted papers, case reports, noncomparative studies, review articles, other systematic reviews, or studies that did not report clinical follow-up or patient data. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria were followed in the study. Our initial search yielded 1,327 studies to screen. After screening titles and abstracts and duplicate removal, 111 full texts were read, and 21 studies met the full criteria to be included in the analysis.

Overall, high-quality studies are quite limited on this subject. There has only been a single randomized controlled trial comparing single to dual antibiotic prophylaxis in the orthopaedic literature. In 2023, Peel et al. randomized 4,113 total hip (THA), total knee (TKA), and shoulder arthroplasty patients after modified intention-to-treat analyses to either cefazolin or cefazolin plus 1.5 grams (g) vancomycin prophylaxis [170]. Patients who had MRSA colonization were excluded. Overall, the addition of vancomycin was not superior to prophylaxis with cefazolin alone. In shoulder arthroplasty, infection occurred in zero of 15 patients in the vancomycin group and one of 15 patients in the placebo group. In patients undergoing knee arthroplasty, surgical-site infections occurred in 5.7% of the vancomycin group, and 3.7% of the placebo group (relative risk, 1.52). Among patients undergoing hip arthroplasty, surgical-site infections occurred in 28 of 920 patients (3.0%) in the vancomycin group and 29 of 930 patients (3.1%) in the placebo group (relative risk, 0.98). There was no increased risk of kidney injury in the vancomycin group.

We identified 20 additional observational studies that addressed the question of dual antibiotic prophylaxis and met the inclusion criteria. The remainder of these were retrospective cohort studies with heterogeneity in patient populations, study sizes, and antibiotic selection.

Most of the data comparing regimens of dual antibiotic prophylaxis comes from the arthroplasty literature, particularly with a cephalosporin and a glycopeptide. Several were institutional-level retrospective cohort studies comparing two groups of patients or groups before and after a practice change. Sewick et al. [169] retrospectively reviewed 1,828 primary total joint arthroplasties that received either cefazolin or cefazolin and vancomycin and found no difference in infection rate between the two groups (1.4 versus 1.1%, $P = 0.636$). Lamplot et al. [171] compared 1,224 patients undergoing primary TKA who received cefazolin prophylaxis to patients who routinely received cefazolin and one gram of vancomycin after a change in practice. There was a substantial reduction in SSI (2.24 versus 0.49%, $P = 0.001$). The patient cohort had a large percentage of patients with BMI > 30, immunosuppression, rheumatoid arthritis, and ASA > class 2. However, the historical control was from 2001 to 2004. Tornero et al. [172] performed a similar study in patients undergoing both THA and TKA, before and after a practice change. They compared a group receiving cefuroxime 1.5 grams at induction with an additional 1.5 grams after two hours to a group receiving cefuroxime and teicoplanin 800 mg at induction. They also found a large reduction in PJI (3.5 versus 1.3%, $P < 0.05$). Barbero-Allende et al. [173] retrospectively reviewed 1,514 primary hip and knee arthroplasties and compared a cohort of patients who received cefazolin to cefazolin and teicoplanin and found a significant reduction in PJI (2.7 versus 1.0%, $P = 0.04$). The three more recent retrospective comparative studies in the arthroplasty literature noted reductions in SSIs or PJI after adding a second antibiotic (either glycopeptide or aminoglycoside) to a cephalosporin for prophylaxis, often in high-risk patients [174–176].

In the revision arthroplasty literature, a 2014 study by Liu et al. [177] demonstrated that the targeted use of vancomycin and cefazolin in patients undergoing revision TKA significantly reduced the rate of infections (7.89 versus 3.13%, $P = 0.046$), notably in MRSA. It is important to note their high rate of MRSA and PJI at the institution at baseline.

There were four large database studies that have attempted to evaluate the utility of dual antibiotic prophylaxis as well. Ponce et al. [178] used the Veterans Affairs Database to identify 18,830 patients who underwent primary THA and TKA and compared those who received cefazolin, vancomycin, or both. They found no difference in SSIs at 30 days between groups. Branch-Elliman et al. performed a study including 33,848 patients undergoing orthopaedic procedures who received a beta-lactam with or without additional vancomycin and found no difference in 30-days SSIs. There were two additional large database studies by Zastrow et al. [179] and Dettmer [180] that found small differences in infection reduction when adding a second agent during hip, knee, and shoulder arthroplasty. These large database studies must be interpreted with caution, as it is difficult to control for all possible confounders.

There were four retrospective comparative studies in the spine literature that compared cefazolin surgical prophylaxis to a cephalosporin and vancomycin in higher-risk patients, and three of the four noted reductions in SSI by the Centers for Disease Control and Prevention criteria or deep wound infection [181–184]. A few additional studies provide contrasting views, with mixed results in retrospective series in hip fracture and sarcoma populations [185–188].

A practitioner must weigh the risks and benefits of potential side effects when administering dual antibiotic prophylaxis. Acute kidney injury is a common complication of dual therapy, particularly with gentamicin [189] and vancomycin [190]. Courtney et al. noted that dual prophylaxis with cefazolin and vancomycin was an independent risk factor for AKI after primary THA and TKA (odds ratio 1.82, confidence interval: 1.25 to 2.64, $P = 0.002$). This study administered vancomycin for 24 hours; however, perhaps single doses may confer less risk, as indicated by Burger et al. [175].

In conclusion, there is insufficient evidence to support the role of dual antibiotic prophylaxis in patients undergoing routine orthopaedic procedures. Only one randomized controlled trial has been performed, with the remainder of the evidence limited to retrospective comparative cohorts or comparisons before and after practice changes. These retrospective studies do not control for confounding variables, and selection bias is likely present. Based on low-quality evidence, there may be a role for the use of dual antibiotic prophylaxis in patients undergoing orthopaedic procedures, including patients with known MRSA colonization, immunosuppression, or revision surgery; however, further well-conducted, randomized controlled trials are required to examine the role of dual prophylaxis in these patient populations. Further

research is needed on the optimal antibiotic and dosing when dual prophylaxis is administered.

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The Journal of Arthroplasty 41 (2025) S53–S59

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The Journal of Arthroplasty

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General Topics

2025 ICM: Decolonization

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Question 1: Is there a role for preoperative dental screening in patients undergoing major orthopaedic procedures?[1]

Response/Recommendation

No. There is no concrete evidence that routine preoperative dental screening is needed in patients undergoing major orthopaedic procedures.

Level of Evidence: Strong

Delegate Vote: Agree 70.4%, disagree 25.4%, abstain 4.1% (strong majority, moderate consensus)

Rationale

Surgical site infection (SSI) is a serious complication following orthopaedic procedures, carrying major implications for patient morbidity, mortality, and health care costs. The possibility of oral infections contaminating the surgical site and causing SSI or periprosthetic joint infection (PJI) has prompted the widespread implementation of preoperative dental screening, yet its efficacy continues to be a matter of debate [1]. Proponents argue that it identifies and addresses potential sources of oral infection like periodontal disease or dental caries, thereby reducing bacterial load and minimizing hematogenous spread [2,3]. Conversely, critics point to the insufficient evidence supporting its effectiveness in reducing SSI/PJI rates, arguing that the costs, delays, and inconvenience may not be justified for every patient, particularly those who have good oral health or are undergoing low-risk procedures [4,5].

Although our research question focused on the major orthopaedic procedures, most studies identified through our literature search pertained specifically to arthroplasty, with only one examining the role of preoperative dental screening in elective spinal surgery [4]. There were three online databases (PubMed/Medline, Scopus, and Embase) that were searched from inception to September 2024 to identify all the studies investigating the association between preoperative dental screening and the rates of SSI/PJI in patients undergoing major orthopaedic procedures. The initial database search yielded 2,115 articles, from which 428 duplicates were removed, resulting in 1,686 records available for screening based on title and abstract. Among these, 1,658 were excluded, leaving 28 papers for full-text evaluation. Ultimately, five studies [1–3,6,7] met the eligibility criteria and underwent qualitative and quantitative synthesis in our meta-analysis, which directly compared the SSI rates between patients who have and who do not have preoperative dental screening to examine the risk ratio of SSIs between these patient groups. There were 12,586 patients in the dental screening group and 10,892 patients in the no-screening group. The pooled analysis showed no statistically significant difference in the risk of SSI/PJI between the two groups (risk ratio: 0.92, 95% confidence interval 0.52 to 1.63) (Figure 1). However, moderate heterogeneity was observed among the studies ($I^2 = 57\%$), suggesting some variability in the results. Importantly, age was recognized as a significant confounding factor ($P = 0.0128$), indicating that the relationship between dental screening and SSI/PJI is affected by patient age.

The included studies demonstrated low to moderate quality of evidence, with none being a randomized controlled trial. Although most studies involved primary total hip arthroplasty and TKAs, the populations may have different risks of infection. Merging diverse populations that exhibit variations in age, sex, medications, or comorbidities could lead to inaccurate conclusions. Kwan et al. and Lampley et al. found no significant difference in PJI rates between patients who underwent routine preoperative dental clearance

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to doi: 10.1016/j.arth.2025.10.096.

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https://doi.org/10.1016/j.arth.2025.10.096
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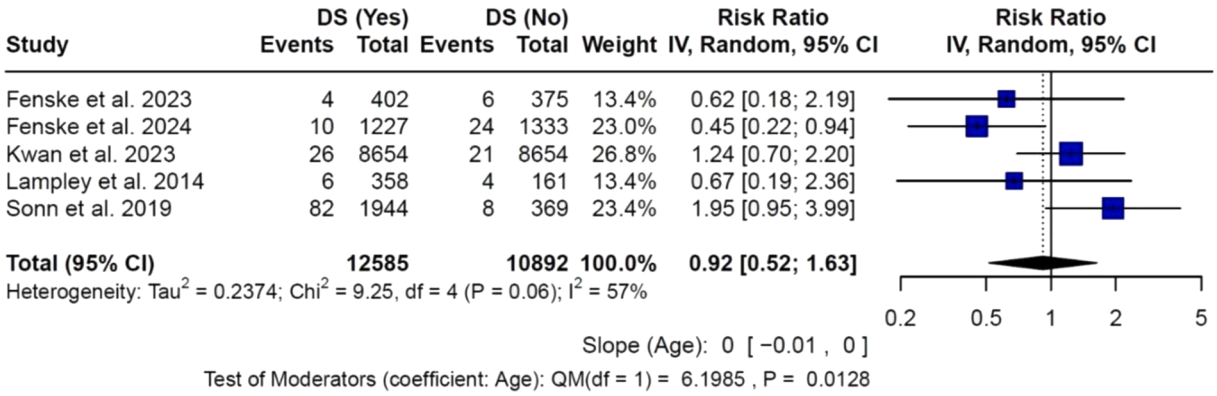

Figure 1. Forest plot illustrating the risk ratio of surgical site infection/periprosthetic joint infection (SSI/PJI) in patients who have preoperative dental screening compared to those who do not.

and those who did not [1,7]. Fenske et al. reported no overall association between early infection rates and preoperative oral screening; however, they found that the screening by either a dentist or an orthopaedic surgeon significantly impacted the prevalence of PJI [3]. Tokarski et al. found that 12% of patients failed dental clearance, with risk factors including tobacco use, poor flossing habits, a history of tooth extraction, age, narcotic use, and not having visited a dentist in the past 12 months [8]. Sonn et al. found no statistically significant association between complications (including PJI) and preoperative dental evaluations or extractions [2]. Tye et al. found that an orthopaedic surgeon's oral examination demonstrated a high positive predictive value in identifying high-risk patients needing an oral surgical intervention before total joint arthroplasty [5]. Mirzashahi et al. showed a significant association between SSI and caries, gingivitis/periodontitis, and a history of dental abscess in patients undergoing elective spinal surgery [4]. Vuorinen et al. concluded that the inspection and treatment of dental pathology in all patients are important interventions before elective arthroplasty due to the high need for dental care revealed by their unselected patient population [9].

In conclusion, our meta-analysis findings did not reveal a statistically significant difference in the risk of SSI/PJI between patients who underwent dental screening versus those who did not. Therefore, we do not recommend routine preoperative dental screening for patients undergoing major orthopaedic procedures. However, screening elderly patients may be recommended because the relationship between dental screening and SSI/PJI is affected by patient age, according to our meta-analysis. Ultimately, the decision should be individualized, considering patient risk factors and preferences, in consultation with their orthopaedic surgeon and dentist.

Question 2: Does preoperative skin decolonization reduce the incidence of surgical site infections (SSI) in patients undergoing major orthopaedic surgery?[2]

Response/Recommendation

Yes. The use of preoperative skin decolonization reduces the incidence of postoperative surgical site infections in patients undergoing major orthopaedic surgery.

Strength of Recommendation: Moderate

Delegate Vote: Agree 79%, disagree 11%, abstain 10% (strong majority, moderate consensus)

Rationale

Surgical site infection is a rare, but important complication following major orthopaedic surgery, with rates including 0.2% for primary total hip arthroplasty and 1.5% for total knee arthroplasty [10]. The SSIs are associated with substantial morbidity, prolonged hospital stays, and subsequent rehospitalization rates, resulting in over 3x health care costs [11]. An estimated 37% of SSIs are caused by *Staphylococcus aureus* [12]. Many SSIs are preventable when patients and hospital staff adhere to appropriate prevention practices, including prophylactic antibiotics, hand hygiene, minimizing traffic in the operating room, and decolonization of *S. aureus* carriers [13]. There is increasing evidence in the literature that patients colonized with *S. aureus* on skin flora are at increased risk of SSI and potentially periprosthetic joint infection [14].

A growing body of literature suggests that preoperative skin decolonization is associated with reduced rates of SSIs in elective orthopaedic surgery. A systematic review by Chen et al. of 19 studies on *S. aureus* screening and preoperative decolonization revealed that all studies demonstrated a reduction in SSIs or wound complications ranging from 13 to 100% in elective orthopaedic (total joints, spine, and sports) and trauma patients [15]. Another systematic review and meta-analysis of 32 papers by Ribau et al. demonstrated an increased risk of any infection after orthopaedic surgery (relative risk (RR) = 2.79 ± 0.45) or elective total joint arthroplasty (TJA) (RR = 1.70 + 0.17) without preoperative decolonization, demonstrating that all strategies were cost-effective, favoring universal decolonization without screening. A single-center prospective study of 7,338 patients undergoing elective orthopaedic surgery demonstrated that patients who tested positive for *S. aureus* (methicillin-resistant or methicillin-sensitive) and received a shower wash with 2% chlorhexidine once daily for five days and intranasal 2% mupirocin ointment demonstrated a significant reduction in infection rate relative to historical controls (0.19 versus 0.45%, $P = 0.0093$) [16]. Another prospective clinical study of 709 patients who did versus did not receive preoperative Methicillin-resistant *S. aureus* (MRSA) decontamination with chlorhexidine washcloths revealed a 50% or lower SSI in the intervention group relative to controls (1.1 versus 3.8%, $P = 0.02$) [17].

An increasing number of studies have examined the use of preoperative decolonization in the context of elective TJA. An individual prospective, observational single-center study of 1,966 patients undergoing elective TJA revealed zero SSIs in 636 patients completing the decolonization protocol who tested positive for *S. aureus* versus 12 SSIs in 1,330 control patients, translating to an estimated $231,741 in cost savings for the

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hospital [18]. This was followed up by a 2-years study of 2,284 patients undergoing elective TJA, demonstrating no staphylococcal SSIs in patients receiving chlorhexidine baths and intranasal mupirocin (0.321) and 19 of 321 in concurrent controls [19]. Rao et al. calculated that the overall SSI rate decreased to 1.2% in intervention patients who received preoperative decolonization from 2.7% in preintervention controls [19]. A retrospective study of 3,082 patients who underwent primary total hip arthroplasty between 2014 and 2020 revealed that patients treated with octenidine dihydrochloride preoperatively experienced decreased infection rates in patients who have diabetes (18.3% without treatment (15 of 82) versus 8.5% with treatment (13 of 153) [20]. A meta-analysis of 32 papers with a focus on TJA found increased risk of developing any infection (RR = 1.70 ± 0.17) and *S. aureus* infection (RR = 2.18 ± 0.41) without previous whole-body decolonization, concluding all strategies were cost-effective while universal decolonization without screening appeared more advantageous [21]. Use of preoperative skin decolonization may have potential benefits in upper extremity procedures as well. A randomized, prospective study of 100 consecutive patients undergoing shoulder surgery found that those who used 2% chlorhexidine gluconate cloths had decreased bacterial culture rates (66 versus 94%, $P = 0.0008$), including coagulase-negative *Staphylococcus* (30 versus 70%, $P = 0.0001$), a known cause of postoperative shoulder infections [22]. While it remains unclear what the preferred type of preoperative decolonization is, several meta-analyses have demonstrated the superiority of chlorhexidine in reducing normal bacterial flora relative to povidone-iodine [23,24].

Several other competing studies are less enthusiastic, while some demonstrate that no definite conclusion about the efficacy of preoperative decolonization can be made. A randomized, single-blinded trial of 1,894 patients undergoing general elective orthopaedic surgery revealed no significant difference in SSI rates at 90 days postoperatively (decolonized SSI risk 0.4% [one of 232], control SSI 0.4% [one of 233], risk difference 0%) [25]. Of note, this study was limited by low SSI numbers overall and could not draw a definite conclusion about the efficacy of routine preoperative decolonization. A prospective cohort study including 10,844 patients undergoing surgery by one of eight different surgical specialties (i.e., abdominal surgery, orthopaedics, urology, neurosurgery, cardiovascular surgery, thoracic surgery, plastic surgery, and solid organ transplantation) demonstrated no significant change in the rate of MRSA surgical site infection or nosocomial MRSA acquisition (1.11 per 1,000 patient-days relative to 0.91 per 1,000 patient-days, $P = 0.29$) [26]. Of note, the generalizability to orthopaedic procedures of this study is limited due to the involvement of other specialties and the fact that most patient screening/treatment, 88%, was performed at the time of hospital admission. In addition, a study by Scharf et al. found no statistically significant benefit in preoperative decolonization in patients [20]. Of note, this study was limited to 30-day infection risk and indeed found such findings when subdividing patients by American Society of Anesthesiologists status or presence of diabetes. Interestingly, the largest study of 4,266 consecutive spinal surgery patients investigating preoperative chlorhexidine gluconate shower use before spinal surgery was associated with significantly decreased odds of SSI (odds ratio = 0.15, 95% confidence interval [0.03 to 0.55], $P < 0.01$) relative to controls [27]. Overall, the few studies that did not demonstrate a benefit to preoperative skin colonization are often limited by follow-up period, use/timing of preoperative skin decolonization, sample size/power, and overall generalizability.

Conclusion

Preoperative skin decolonization appears to reduce the incidence of surgical site infections (SSIs) in major orthopaedic surgeries, with most studies suggesting it as a cost-effective approach. While some studies demonstrate significant reductions in SSIs through decolonization protocols using mupirocin and chlorhexidine, others are inconclusive, showing no statistically significant benefit. Of note, such studies are limited by sample size/power, follow-up, and methodology differences. However, due to the association of SSIs with severe morbidity, extended hospital stays, and higher health care costs, the preventive benefits of screening with decolonization remain a recommended strategy.

Question 3: Is there a role for universal screening and decolonization for Methicillin-resistant *Staphylococcus aureus* in patients undergoing major orthopaedic procedures?[3]

Response/Recommendation

Currently, there is no evidence to support universal screening for methicillin-resistant *S. aureus* (MRSA) to infer any benefit in patients undergoing orthopaedic procedures. Given the cost-effectiveness of modern decolonization protocols, we recommend universal nasal decolonization in all patients undergoing major orthopaedic procedures, preferably using a nonantibiotic antiseptic agent.

Level of Evidence: Moderate.

Delegate Vote: Agree 72.7%, disagree 18.2%, abstain 9.1% (strong majority, moderate consensus)

Rationale

Nasal colonization with *S. aureus* in patients undergoing surgery is increasingly prevalent and has been shown to increase the risk of surgical site infection (SSI) by 3- to 6-fold [28]. Current protocols for the eradication of nasal *S. aureus* carriage consist of the administration of topical or systemic antimicrobial agents [29,30] and subsequent screening for methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) using culture or gene sequencing-based techniques [31]. However, the efficacy of these interventions in mitigating the risk of SSI remains unclear and is inconsistent across the existing literature [32–34].

We conducted a systematic review to ascertain whether the screening and decolonization of the MRSA group decreased the risk of SSI compared with the control group (no screening and decolonization) in orthopaedic procedures.

A random effects model with a random intercept logistic regression was used [35]. Heterogeneity was evaluated using the I^2 statistic and the *Chi*-square test. The systematic review included 10 studies encompassing 55,816 patients to evaluate the impact of MRSA screening and decolonization on the development of SSI following orthopaedic surgery [36–45]. The majority of included studies were retrospective cohort studies (n = 6, 60%), with historically controlled trials (n = 2, 20%) and prospective cohorts (n = 2, 20%) comprising the remainder. Heterogeneity across studies was substantial, with between-study variance estimated at $\tau^2 = 0.856$ (95% confidence interval (CI): 0.304 to 4.392) and $\tau = 0.925$ (95% CI: 0.551 to 2.096). The I^2 statistic of 93.2% (95% CI: 89.5 to 95.6%) indicated that over 93% of the variability in effect estimates

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arose from actual differences among studies rather than chance, further supported by the Q test (Q = 132.32, degrees of freedom (df) = 9, $P < 0.0001$).

In total, 10 studies evaluated the SSI risk between patients who received both screening and decolonization when compared to those who did not receive screening or decolonization. The pooled prevalence of MRSA colonization across studies reporting this metric was 3.1% (0.47 to 5.0%). Although the risk of SSI in the MRSA decolonization group was lower than the control group (0.76 versus 1.05%), under the random-effects model, MRSA decolonization did not significantly reduce the risk of SSI (OR = 0.62, 95% CI: 0.32 to 1.22, $P = 0.17$). Among the 10 studies, four concluded no difference in SSI rates between decolonized and control groups, while five favored screening and decolonization. Notable outliers included the study by Malcolm et al. (2016), which reported a pronounced decrease in SSI risk (odds ratio (OR) = 0.03, 95% CI: 0.002 to 0.50), and the study by Baratz et al. (2015), which observed a paradoxically increased risk of SSI in screened and decolonized patients (OR = 4.26, 95% CI: 3.00 to 6.05).

Subgroup analysis of arthroplasty procedures (90,316 patients) yielded similar results (OR = 0.65, 95% CI: 0.31 to 1.38, $P = 0.26$), with heterogeneity remaining high ($I^2 = 93.3\%$, $\tau^2 = 0.970$). Larger cohorts more frequently supported decolonization, whereas smaller studies reported mixed outcomes. Moreover, five studies evaluated the cost-effectiveness of MRSA screening and decolonization, and all concluded that it can be a cost-effective approach [36,46–49]. While this analysis found no statistically significant reduction in SSI risk with MRSA decolonization (OR = 0.62, $P = 0.17$), the high heterogeneity ($I^2 > 93\%$) underscores critical variability in study designs, decolonization protocols, and patient populations. More extensive studies highlighted potential benefits, and cost-effectiveness was noted in select settings, emphasizing the need for tailored approaches.

Based on currently available literature, universal screening protocols for MSSA and MRSA in patients undergoing orthopaedic procedures appear to have limited utility. In light of recent evidence demonstrating the cost-effectiveness and efficacy of modern universal decolonization protocols [50], we recommend routine nasal decolonization of all patients undergoing major orthopaedic procedures, preferably using a nonantibiotic antiseptic agent.

Question 4: What is the optimal nasal decolonization agent for patients undergoing major orthopaedic surgery?[4]

Response/Recommendation

While mupirocin remains the guideline-recommended standard, concerns over cost, resistance, and efficacy persist. Povidone-iodine appears to be a cost-effective alternative with comparable outcomes in reducing colonization and infection rates in major orthopaedic surgeries.

Level of Evidence: Moderate

Delegate Vote: Agree 91.2%, disagree 8.8%, abstain 0% (total consensus, unanimity)

Rationale

S. aureus has been described in the literature as the main culprit for surgical site infections (SSIs) after major orthopaedic surgery procedures [51,52]. Therefore, multiple strategies have been implemented to curb the risk of staphylococcal infection during the postoperative period, such as antimicrobial body washes for the skin and nasal decolonization. The Centers for Disease Control and World Health Organization endorse the use of chlorhexidine gluconate (CHG) body wash and nasal decolonization with 2% mupirocin ointment [53,54]. However, the American Academy of Orthopaedic Surgeons refrains from recommending nasal decolonization in its guidelines for preventing prosthetic joint infections, citing the lack of robust level 1 evidence in the orthopaedic field [55].

Given that a positive nares culture for *S. aureus* has been described as an independent risk factor for SSI, many places provide selective mupirocin decolonization in *S. aureus* carriers [56,57]. However, universal decolonization with povidone-iodine (PI) has been proposed as a cost-effective alternative, reducing concerns over mupirocin resistance [58–60]. Consequently, it is important to determine which nasal decolonization agent is more effective in decreasing the risk of SSIs in orthopaedic procedures.

Historical Cohorts and Single-Intervention Studies

Most studies analyzing nasal decolonization exhibit a before-and-after protocol design. Moreover, compared to nonintervention, these studies examined the impact of decolonization and infection rate after implementing a single nasal agent. From 10 studies evaluating the use of nasal mupirocin and CHG skin decolonization [61–63], seven studies found a decrease in *S. aureus* SSI rates compared to the period before the intervention, ranging from 0.5 to 3.8% [64–70]. Most of the studies administer the mupirocin two to three times per day for at least five days before surgery. Baratz et al. found the use of mupirocin nasal ointment was an effective strategy for decolonization in 95 of 121 patients (78%) but had no impact on the rates of *S. aureus* SSIs (before intervention 0.38 versus after intervention 0.68%) [62]. Moreover, in the study by Stambough et al., mupirocin universal decolonization was compared to selective decolonization with the same agent. They found a decrease in overall SSIs (0.2 versus 0.8%; $P = 0.013$) and *S. aureus* SSIs (0.09 versus 0.5%; $P = 0.01$) after the implementation of universal decolonization [71]. The results of the latter study favor the use of universal mupirocin and could help explain the incongruent rates of decolonization and *S. aureus* infection rates seen in the study by Baratz et al. The efficacy of mupirocin versus no decolonization has been evaluated in two randomized controlled trials (RCTs). However, one of them was stopped after an interim analysis due to concerns regarding the feasibility of the study, secondary to the low number of infected patients in the postoperative period [72]. Kalmeijer et al. performed a double-blind, randomized, placebo-controlled study, finding that the patients in the intervention group had a lower postoperative nasal carriage rate (16.5 versus 78.2%, $P < 0.05$), with a nonsignificant effect on the incidence of postoperative MSSA infections (mupirocin group, 1.6 versus placebo group, 2.7%). Of note, this study used pulsed-field gel electrophoresis to evaluate endogenous infection rates (e.g., matching between preoperative and postoperative bacterial isolates), which showed endogenous *S. aureus* infections were five times lower than in the placebo group (0.3 and 1.7%, respectively; relative risk, 0.19; 95% CI, 0.02 to 1.62) [73]. The comparable infection rates in this study between cohorts could potentially be explained by the limited sample size.

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Alternatives to Mupirocin

Povidone-iodine has recently emerged as a promising agent for nasal decolonization in orthopaedic surgery procedures. Rezapoor et al. performed a placebo-controlled RCT comparing 10% off-the-shelf PI to 5% PI skin and nasal antiseptic (SNA) and to placebo for nasal decolonization in 429 patients undergoing major orthopaedic procedures. Postoperative nares cultures showed that PI-based SNA was significantly more effective at decolonizing *S. aureus* four hours after treatment (seven of 34, 21%) compared to 10% off-the-shelf PI (five of 29, 52%) and placebo (19 of 32, 59%; $P = 0.003$). However, there was no difference in the cultures at 24 hours, highlighting the short length of antimicrobial activity of the PI [74]. The PI compound has also been effective in decreasing the rates of *S. aureus* infections in the acute setting. Urias et al. described a historical cohort of patients undergoing operative treatment for lower-extremity fractures before and after the implementation of a decolonization protocol of nasal PI SNA preoperatively and a CHG bath the night before the surgery. In a multivariate regression model, decolonization was a protective factor for developing SSI (odds ratio (OR) 0.18, 95% CI, 0.039 to 0.822; $P = 0.027$) [75]. All these studies administer PI 1 to 2 hours before skin incision.

Alcohol-based substances and antiseptic solutions such as polyhexanide are other alternatives for nasal decolonization. One descriptive study, in which 70% alcohol was implemented for nasal decolonization, found a periprosthetic joint infection rate of 1.4 and 4.3% in primary and revision arthroplasty procedures, respectively. However, none of the infected cases were caused by Staphylococcal species [76]. Conversely, Bostian et al. found that patients who used an alcohol-based nasal decolonization regimen were at a lower risk of SSI compared to a historical control group (five of 779, 0.64% versus 10 of 647, 1.55%; $P = 0.048$.) [77]. Only one study by Wandhoff et al. has evaluated the incidence of SSI in patients undergoing nasal, oral, and skin decolonization with polyhexanide. They found that universal use of this protocol in patients undergoing primary total joint arthroplasty had a lower *S. aureus* SSI rate compared to a control group who did not receive decolonization (0.24 versus 0.14%, $P = 0.17$). However, it was not statistically significant [78].

Comparative Studies

Only two studies have compared postoperative SSI rates using different agents. Torres et al. compared the use of universal PI decolonization against selective mupirocin decolonization only in patients who had a positive culture for MRSA (41 of 849 patients). Both groups exhibited an infection rate of 0.8%, but the mupirocin cohort showed increased costs [60]. In the only comparative RCT, Phillips et al. randomized a cohort of 1,539 patients undergoing spinal surgery and hip or knee arthroplasty to receive nasal decolonization with mupirocin or PI SNA. Using an intention-to-treat analysis, *S. aureus* deep SSI developed in five of 855 and one of 842 patients (0.58 versus 0.12%; $P = 0.200$) in the mupirocin and PI cohorts, respectively. However, using a per-protocol analysis, there was a significantly higher rate of *S. aureus* deep SSIs in the mupirocin group (five of 763, 0.65 versus zero of 776, 0%; $P = 0.030$) [79].

Recent studies have explored alternative decolonization methods. For instance, antimicrobial photodynamic therapy has been investigated as a nonantibiotic approach to nasal decolonization [80,81], demonstrating a notable reduction of SSI in orthopaedic and spinal surgeries. This technique addresses concerns related to antibiotic resistance and has been implemented in multiple Canadian hospitals, with ongoing clinical trials in the United States.

Conclusion

Limited comparative data make it difficult to establish the superior nasal decolonization agent. While mupirocin remains the guideline-recommended standard, concerns over cost, resistance, and efficacy persist. Povidone-iodine skin and nasal antiseptic (PI-SNA) appears to be a cost-effective alternative with comparable outcomes in reducing colonization and SSI rates in major orthopaedic surgeries. Further research into new agents is necessary to ensure effective decolonization strategies for orthopaedic procedures.

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The Journal of Arthroplasty 41 (2025) S60–S73

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

General Topics

2025 ICM: Nutrition

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Question 1: Should patients undergoing major orthopaedic procedures be screened for malnutrition?[1]

Response/Recommendation

Yes, there appears to be a role for preoperative screening for malnutrition in patients undergoing major orthopaedic procedures.

Level of Evidence: Moderate (super majority, strong consensus)

Delegate Vote: Agree: [84.6%], Disagree: [10.3%], Abstain: [5.1%]

Rationale

Malnutrition can be broadly defined as any nutritional imbalance that encompasses both deficiencies and excesses in energy, protein, and nutrients [1,2]. Causes of malnutrition include poor nutritional intake, increased metabolic requirements, malabsorption, or improper processing of nutrients, which can originate from chronic disease, acute injury or illness, or starvation [3]. Furthermore, although malnutrition was traditionally associated with a low (< 18.5) body mass index (BMI), there is now a growing body of evidence to demonstrate that a high BMI (> 30) is also a significant risk factor for the development of malnutrition, with obesity being noted in 42.9% of malnourished patients [4–6]. Risk factors for malnutrition are multifactorial, as increased age, increased medical comorbidities, decreased activity level, and lower socioeconomic status all contribute to a patient's nutritional status [7–10]. The prevalence of malnutrition in the adult population ranges between 8.5 and 30% [5,11,12]. However, clinical signs of malnutrition become apparent only in extreme cases.

Based on data spanning several years, it is now well-established that malnutrition is an independent predictor of adverse outcomes in patients undergoing major surgical procedures [13–16]. The physiologic stress during the perioperative period requires increased metabolic demands to facilitate tissue healing. Additionally, reduced oral intake in the perioperative period contributes to a hypermetabolic-catabolic state that can deplete metabolic reserves [17–20]. Ultimately, malnutrition impairs wound healing by inhibiting collagen synthesis and impairs the immune system by decreasing lymphocyte count [21,22].

A systematic review of existing literature on the screening for malnutrition before major orthopaedic surgery was performed using the following databases: Embase, PubMed, and Cochrane. The primary outcome of this review was to determine any difference in perioperative outcomes for patients who were classified as malnourished preoperatively compared to those who had a normal nutritional status. Only levels I to III evidence studies with

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to 10.1016/j.arth.2025.10.077.

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https://doi.org/10.1016/j.arth.2025.10.077
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a comparative group were included. Overall, 773 manuscripts were identified, and 94 studies were considered eligible for full-text review. From these, 77 studies were eligible for final inclusion. There were 39 studies on total joint arthroplasty (TJA), seven on revision TJA, 29 on adult spinal surgery, and two that included patients undergoing adult spinal surgery and TJA [5,11,23–97].

After reviewing the available literature, we were able to conclude that malnutrition is a recognized and modifiable risk factor for surgical site infection (SSI) [98]. The impact nutrition has on surgical outcomes and the role of perioperative optimization have been demonstrated across all orthopedic subspecialties [99–107]. In particular, the TJA and spine literature have shown an association between malnutrition and increased rates of wound complications, SSI, periprosthetic joint infection (PJI), prolonged hospitalizations, renal complications, and mortalities [5,6,11,21,23–26,28,29,53,57,78,83,86,93,94,108].

Despite the known association between malnutrition and poor surgical outcomes, there are no guidelines on screening for malnutrition before major orthopedic procedures [109]. There is no gold standard test for malnutrition. Several surrogates exist, which include serological markers, anthropometric measurements (e.g., BMI or calf circumference), and standardized screening tools (e.g., Perioperative Nutrition Screen [PONS]) [110–114]. Currently, serological markers are most frequently used to assess nutritional risk in the orthopedic literature, with albumin < 3.5 g/dL, total lymphocyte count < 1,500 cells/mm^3, and/or transferrin level < 200 mg/dL commonly used as thresholds to define malnutrition. Although there is limited evidence to support vitamin D as a standard marker in assessing nutritional status, hypovitaminosis D (serum 25-hydroxyvitamin D level < 30 ng/mL) has been linked to increased perioperative complications after TJA and spine surgery, including higher rates of PJI, unplanned revision surgery, and venous thromboembolism [98,112,115–118]. Other serum markers, including prealbumin, zinc, and iron, are less useful for the nutritional assessment of this patient population [112]. Furthermore, while prealbumin has been less commonly studied than albumin, it has been shown to reflect short-term changes in nutritional status [119].

Although a large percentage of orthopedic surgeons reported restricting access to arthroplasty in the setting of malnutrition, prior literature has been unable to determine which patients should undergo preoperative nutritional evaluation or what parameter is best for assessing nutritional status [68,120–122]. This is largely due to the heterogeneity of diagnostic markers for malnutrition. In order to achieve universal adoption, preoperative screening protocols for malnutrition should enable routine identification of at-risk patients and initiation of interventions if needed. Developing such a protocol is of particular importance, given the high prevalence of sarcopenia and frailty among the geriatric population undergoing elective TJA, spine surgery, and other major orthopedic procedures [8,9,123].

There is research to suggest that universal screening for malnutrition in patients undergoing TJA is cost-effective and beneficial for surgical outcomes [124–126]. A single-institution retrospective review of 30,863 TJA patients found that of serum markers for malnutrition, albumin had the highest specificity (98.1%; 95% confidence interval [CI], 97.8 to 98.4%) and area under the curve (0.61; 95% CI, 0.55 to 0.67) for predicting the development of PJI [26]. In a meta-analysis of eight studies and 175,563 patients, the authors found that patients who had an albumin < 3.5 g/dL were more likely to develop a postoperative wound complication (odds ratio [OR]: 2.18, 95% CI: 1.92 to 2.47) when compared to patients who had a normal albumin level [108]. Another meta-analysis of seven studies and 72,811 patients demonstrated a nearly two-fold increase in all-cause complications when hypoalbuminemia (predominantly defined using a cutoff of < 3.5 g/dL) was present before TJA [127].

In spine surgery, a number of studies have demonstrated that hypoalbuminemia was an independent predictor of 30-day readmission, nonunion, sepsis, postoperative infection, and mortality [23,128]. In a meta-analysis that included 26 studies and 86,065 patients, an albumin level of < 3.5 mg/dL was found to significantly increase the odds of SSIs (OR: 2.08, 95% CI: 1.66 to 2.62), readmission (OR: 1.67, 95% CI: 1.24 to 2.27), and death (OR: 6.01, 95% CI: 4.51 to 8.01) [129]. The Congress of Neurological Surgeons released guidelines recommending preoperative nutritional assessment due to evidence that serum markers of malnutrition can predict adverse events after spine surgery [130].

Surgeons should be vigilant of the modifiable risk factors that can be addressed preoperatively to reduce postoperative complications. There is a clear consensus that TJA and spine patients who had normal nutritional parameters have fewer complications, especially related to wound healing and infection. Thus, nutritional assessment with serum albumin (cutoff level of 3.5 g/dL) at a minimum should be obtained in the preoperative setting to identify malnourished patients. There is less evidence to support routine screening with transferrin and total lymphocyte count, as guidelines to delay surgery on these two markers alone are limited. If a more selective screening protocol is to be utilized, an age cutoff of 55 years may be most appropriate. In one study, the authors demonstrated that 98.3% of patients under the age of 55 years had normal malnutrition screening laboratories [5]. Recently, the Geriatric Nutritional Risk Index (GNRI), which combines serum albumin and ideal weight percentage, has been shown to be an effective screening tool for malnutrition in TJA patients [38,75,131,132]. In addition to preoperative nutritional assessment, it is important to consider routine preoperative nutritional optimization, including safe weight loss in the obese population, consumption of a high-protein diet, amino acid supplementation, and good glycemic control [133–138].

Considering the low potential for complications with nutritional optimization, the available data suggest that evaluation and intervention for malnutrition may improve patient outcomes and should be considered before major orthopaedic procedures [139,140]. In the era of value-based health care, nutritional optimization of patients undergoing major orthopedic procedures is an integral part of comprehensive surgical care and can be accomplished in a cost-effective manner [140–143].

Conclusions

The current literature suggests that serological markers (albumin at a minimum with a cutoff level of 3.5 g/dL) should be obtained several weeks before elective major orthopedic surgery to help stratify patients based on nutritional risk and allow time for appropriate intervention.

Question 2: Is there a role for nutritional supplementation for the prevention of surgical site infection (SSI) in patients undergoing major orthopaedic surgery?[2]

Response/Recommendation

Protein-based nutritional supplementation reduces the occurrence of early surgical site infection (SSI) in major orthopaedic surgery, particularly in patients who are in poor nutritional status.

[2] These authors contributed to Question 2: Carlo L. Romano, Wael K. Barsoum, Muhammad A. Chinoy, Serban Dragosloveanu, Gérard C. Giordano, Takeshi Morii, Wayne E. Moschetti, Cristian Scheau, Takeaki Yamamoto.

Level of Evidence: Limited

Delegate Vote: Agree: 87%, Disagree: 8%, Abstain: 5% (Super Majority, Strong Consensus)

Rationale

Malnutrition or suboptimal nutrition, commonly found in orthopaedic and trauma patients, can impair immune response, delay wound healing, and increase susceptibility to infections, including SSIs after major orthopedic and trauma surgical procedures [144–148]. Moreover, hypoalbuminemia, a proxy of malnutrition, has been identified as a risk factor for failure of surgical treatment of PJI, including debridement and retention as well as one- or two-stage revision surgery [149–151].

Nutritional supplementation has been increasingly investigated in the last decade [152,153] and recently recognized by some authors as an important aspect of preventing SSIs in orthopedic patients [154].

In particular, protein supplementation with or without other nutritional supplements, including amino acids and vitamins, has been shown to reduce the incidence of early SSIs in patients undergoing major orthopaedic surgical procedures. Goncalves et al. [155] reported on a retrospective study on patients aged $\geq$ 60 years undergoing elective orthopaedic-cemented or uncemented total hip or knee arthroplasty and divided into two groups: control and immunonutrition (a mix of proteins, arginine, omega-3, and nucleotides). The immunonutrition group was instructed to start oral intake of the nutritional supplement five days before and to resume it five days after arthroplasty. Logistic regression analyses showed that patients in the immunonutrition group had a 55% reduction in infectious complications (odds ratio [OR], 0.45; 95% CI, 0.30 to 0.68; $P < 0.001$). Chen et al. [156] conducted a recent systematic review and meta-analysis on the role of high protein-based diet strategies containing (or not containing) carbohydrates, fat, vitamins, and minerals. Randomized trials in older patients who have a hip fracture (aged $\geq$ 50 years) were included. Overall, 18 studies involving 1,522 patients met the inclusion criteria, providing substantial data for analysis. High protein-based diet strategies were found to be associated with significantly elevated albumin levels as well as a significant risk reduction in infective complications (odds ratio 0.54, 95% CI 0.39 to 0.76), reduced incidence of pressure ulcers, and total complications. Length of hospital stay was also significantly reduced, with a tendency toward a lower mortality risk and readmission rate, although not statistically significant. The overall compliance with the high-protein diet ranged from 64.7 to 100%.

More recently, a retrospective study on patients undergoing spinal fusion surgery [157] disclosed that patients receiving the supplemental diet (n = 229) demonstrated fewer wound complications (7 versus 21%, $P = 0.004$) and reoperations (3 versus 11%, $P = 0.016$) compared to those who do not have supplementation (n = 56). Patients who had normal preoperative prealbumin levels experienced more wound complications without the supplemental diet (5 versus 18%, $P = 0.025$). A similar trend was seen in patients who had low preoperative prealbumin (12 versus 26%, $P = 0.12$). The postoperative nutritional program was designed by a registered dietitian to supplement, but not replace, regular meals and increase the nitrogen balance. Components of the diet consisted of a mix of proteins, collagen, specific amino acids, vitamins, zinc, and other components. This study confirmed the findings of a prior study by Saleh et al., whose prospective randomized controlled trial (RCT) of 103 patients undergoing elective primary spine surgery demonstrated significantly lower rates of perioperative wound healing complications (3.4 versus 17.9%, $P < 0.05$). The trial also showed that patients receiving supplementation had 10 times lower rates of in-hospital minor complications (2.1 versus 23.2%, $P < 0.01$), while subgroup analysis demonstrated that malnourished patients who received perioperative nutritional supplementation had lower rates of minor complications during admission (0 versus 34.4%, $P = 0.01$) and return to the operating room within 90 days (0 versus 12.4%, $P = 0.04$). The intervention group received nutritional supplementation (protein shake) twice daily from postoperative day zero to two weeks postdischarge.

Scientific evidence concerning other nutritional supplements and their impact on postsurgical infection is limited. Arginine and glutamine alone have been reported to enhance wound healing, even if not specifically in orthopedic surgery [158], and a four-oral probiotics regimen has been suggested to reduce the occurrence of postsurgical infection in a heterogeneous series of trauma patients [159].

Recent systematic reviews and meta-analyses do not support a statistically significant role in preventing postsurgical infection complications in orthopedic and trauma patients for vitamin C [160], vitamin D [161], or zinc [162] when used alone.

Concerning the methodological aspects of the available literature, it is worth noting that SSI and wound complications are often endpoints included among others, with only isolated studies specifically addressing septic complications. Furthermore, a univocal definition of these two endpoints is lacking across the studies, while the observational period is restricted to a maximum of 12 weeks after index surgery, with no information regarding the impact of nutritional supplementation on long-term implant-related infection rate, cost-effectiveness, and possible side effects.

Conclusions

There is limited evidence supporting the role of protein-based nutritional supplementation in reducing SSIs, particularly in malnourished patients or nutritionally at-risk patients undergoing major orthopaedic surgery. Nevertheless, the assessment and correction of patients' nutritional status must be considered in infection management algorithms in orthopaedics, particularly with regard to the prevention of SSIs, even if the effectiveness of supplementation may vary based on the individual patient factors, and further studies are needed to refine guidelines on nutrient dosages, timing, and the comparative efficacy of different supplements.

Question 3: Does the level of preoperative vitamin D have an influence on the incidence of SSI/PJI in patients undergoing major orthopaedic surgery?[3]

Response/Recommendation

There is consistent evidence demonstrating that vitamin D deficiency is associated with increased risk of subsequent SSIs and/or prosthetic joint infections in patients undergoing major orthopaedic surgery, particularly in lower extremity arthroplasty. There is no clear evidence as to whether perioperative vitamin D supplementation can mitigate this increased risk.

Strength of Recommendation: Moderate

Delegate Vote: Agree: 85.3%, Disagree: 8.8%, Abstain: 5.9% (Super Majority/Strong Consensus)

Rationale

Vitamin D is critical in modulating the human body's calcium axis, maintaining bone mineral density, and regulating the immune system [163]. Given its essential role in innate immunity, determining the influence of vitamin D deficiency (VDD) on the

[3] These authors contributed to Question 3: Armin Arshi, John K. Cordero, David Novikov, Atsuhiro Fujie, Aydin Gahramanov, L. Bogdan Solomon, Nicolas S. Piuzzi, Boopalan Ramasamy, James Kigera

rates of SSI and PJI is a focus of researchers and clinicians. This is critical given the high prevalence of VDD, cited as 41.6% in the general United States population and up to 75% of patients undergoing arthroplasty [164,165]. Most of the relevant literature on VDD in arthroplasty pertains to hip and knee TJA. Generally, it is accepted that serum 25-hydroxyvitamin D levels below 20 ng/mL are associated with a higher incidence of postoperative complications, including PJI, and may be a modifiable risk factor in TJA [166]. However, the majority of studies are observational rather than interventional and thus cannot infer causation [167].

An observational study by Maeir et al., published in 2014, highlighted the importance of this topic, identifying a VDD prevalence rate of 64% in those undergoing primary hip and knee TJA. Additionally, they found a 52% prevalence in those undergoing aseptic revision and 86% in those undergoing septic revision ($P < 0.001$) [168]. Due to this association, these authors and others recommended vitamin D supplementation as a potential intervention to reduce the risk of PJI. A similar study was published by Signori et al. in 2015, which included patients who had PJI and surgically treated osteoarticular infections. In their cohort, both aseptic and infection-related cases had serum vitamin D levels below reference values. Conversely, they observed that the average vitamin D values of patients who had aseptic failure were significantly lower than those with infection (18.5 ± 6.5 versus 13.6 ± 9.4 ng/mL, $P < 0.05$) [169].

Perhaps the most promising study was an *in vivo* mouse model by Hegde et al. Researchers implanted a stainless steel implant in vitamin D-deficient, sufficient, and "rescued" mice who received parenteral supplementation three days before surgery. They concluded that VDD results in increased bacterial burden and neutrophil infiltration, and that this effect can be reversed with preoperative repletion of vitamin D [170]. The same group followed up in 2018 with a retrospective study that included 6,593 patients, 868 of whom had VDD. They showed that the cohort with VDD had a higher risk of SSI necessitating irrigation and debridement (odds ratio (OR) 1.76, $P = 0.001$) as well as prosthesis removal (OR 2.97, $P < 0.001$) at the 1-year follow-up. Notably, no assessment of whether vitamin D repletion could mitigate the risk was performed in this study [166]. Traven et al. had similar results in their retrospective case-control study that included 126 TJA patients. They found that VDD, while controlling for nutritional parameters such as albumin and transferrin, was associated with an increased risk of 90-day complications, including PJI as a reason for revision surgery [171]. Furthermore, they showed that revised PJI patients were more likely to have VDD as compared to aseptically revised patients (72.7 versus 48.4%, $P = 0.016$). The researchers concluded that VDD should be considered a modifiable risk factor for complications following revision arthroplasty.

Recently, in a prospective database study published in 2024, Birinci et al. compared patients who received a single oral dose of 7.5 mg two weeks before index surgery (n = 488) with a group whose preoperative vitamin D levels were unknown and who did not receive vitamin D supplementation (n = 592). The total number of complications (8.6 versus 4.3%, respectively; $P = 0.005$), superficial wound infection (2.5 versus 0.2%, respectively; $P < 0.001$), and postoperative cellulitis (2.2 versus 0%, respectively; $P < 0.001$) were statistically higher in the patient group who did not receive vitamin D supplementation. They concluded that preoperative vitamin D supplementation in deficient TJA patients may reduce postoperative complications, including superficial wound infection and postoperative cellulitis. Furthermore, they specifically recommend a single preoperative oral dosage of 300,000 U to correct VDD and improve TJA outcomes [172].

Conclusion

There is consistent evidence that VDD in the early postoperative period following primary arthroplasty is a risk factor for complications, including PJI, SSI, and wound problems [173]. More specifically, several observational studies correlate serum vitamin D concentrations to a reduced incidence of orthopedic infection, consistent with studies in other specialties that demonstrate VDD as a risk factor for infection [174,175]. This suggests that supplementation may improve outcomes. However, most studies are inconsistent regarding when vitamin D levels were measured, with some studies evaluating levels at the point of infection diagnosis, while others report baseline levels [176]. Additionally, there is limited data on the optimal route of administration and dosing of vitamin D. In summary, further large-scale, prospective studies are needed to establish the clear causation of complications and infection from VDD and standardize recommendations for vitamin D optimization in orthopedic surgery patients.

Question 4: Is there an increased risk of surgical site infection (SSI)/periprosthetic joint infection (PJI) in patients undergoing major orthopaedic surgery who have had prior bariatric surgery?[4]

Response/Recommendation

The current evidence is insufficient and conflicting. It shows a trend toward both decreased and increased risk of SSI/PJI in patients who have prior bariatric surgery who undergo joint arthroplasty when compared to the general arthroplasty population or obese controls.

Level of Evidence: Moderate

Delegate Vote: Agree 92.1%, Disagree 2.6%, Abstain 5.3% (Total Consensus, Unanimity)

Rationale

Obesity, defined as a body mass index (BMI) of ≥ 30, has reached alarming proportions internationally [177]. Recent studies have suggested that the prevalence of morbid obesity (BMI ≥ 40) is projected to rise in the United States (US) and the United Kingdom (UK) [178,179]. Although lifestyle modification is advocated as the first-line treatment for obesity, this may be difficult to sustain in morbidly obese patients [180]. In obese patients undergoing TJA, there is a significantly increased risk of SSI and/or PJI [181,182]. Hence, bariatric surgery has been proposed as a weight-loss strategy to mitigate this risk [183]. Nevertheless, others have suggested that bariatric surgery may induce a catabolic state and may increase the risk of SSI/PJI [184].

There were 22 studies that reported on the results of TJA after bariatric surgery [185-206]. Among these, one was RCT [186] and one was retrospective case series [199]. The remaining 19 studies were observational. There were seven of these studies that provided total hip arthroplasty (THA) [185,190,192,194,195,204,206] data, while 14 provided total knee arthroplasty (TKA), allowing for subgroup analyses [186,187,189,192–194,196,198,200–203,205,206]. There were four studies that combined the data on both THA and TKA [187,188,191,199]. All but four studies were conducted in the US [186,187,192,200]. The overall prevalence of SSI/PJI was 1.81% [95% CI: 1.08 to 2.68] in patients receiving TJA after bariatric surgery [185–191,193–206]. When stratified by type of TJA, this was 2.34% [95% CI: 1.03 to 4.11] for those undergoing THA

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[185,190,194,195,204,206] and 1.88% [95% CI: 0.85 to 3.21] for those undergoing TKA [186,189,193,194,196,198,200–203,205,206].

As the comparative incidence of SSI/PJI is time-dependent, we quantified this using hazard ratios (HRs). When these are not reported, the HR is estimated using the technique described by Shor et al. [207]. We found no statistically significant difference in the risk of SSI/PJI [HR = 0.81, 95% CI: 0.62 to 1.05] between patients undergoing TJA following bariatric surgery and obese controls [185,186,188–190,193,194,196,198,201,202,204–206]. This did not vary based on the type of TJA, with an HR of 0.80 [95% CI: 0.58 to 1.11] for THA [185,190,194,204,206] and 0.78 [95% CI: 0.57 to 1.07] for TKA [186,189,193,194,196,198,201,202,205,206]. Similarly, when considering the general arthroplasty population as a control, we found no statistically significant difference in the risk of SSI/PJI [HR = 1.44, 95% CI: 1.00 to 2.08] [187,189,190,192,195,196]. Subgroup analysis indicated no statistically significant difference in the risk of SSI/PJI among THA patients [HR = 1.20, 95% CI: 0.77 to 1.87] [190,192,195] and TKA patients [HR = 1.61, 95% CI: 0.91 to 2.83] [187,189,192,196].

The risk of SSI/PJI was significantly higher in patients undergoing TJA following bariatric surgery when compared to nonobese controls [HR = 1.61, 95% CI: 1.13 to 2.29] [185,193,198,201,202,205]. Further analysis revealed that this risk was consistently elevated in postbariatric surgery patients in the TKA subgroup [HR = 1.67, 95% CI: 1.04 to 2.70] [193,198,201,202,205]. Only one THA study provided this comparator, reporting an HR of 1.54 [95% CI: 1.22 to 1.95] [9]. Several of these studies compared the complication profile based on the type of bariatric surgery [185,196,201,202]. Bains et al. found that gastric bypass was linked to a lower SSI/PJI risk than sleeve gastrectomy [185]. Similarly, Meller et al. found that gastric bypass and sleeve gastrectomy were associated with a lower SSI/PJI risk than laparoscopic banding [196]. In contrast, Sax et al. reported no difference in SSI/PJI risk between gastric bypass and sleeve gastrectomy [202]. Additionally, Ryan et al. reported no difference in overall reoperation rate, although gastric bypass patients experienced a higher number of SSI/PJI. The statistical significance of this was not discussed [201].

Also, the impact of the timing of bariatric surgery on the risk of complications was examined in five studies [185,188,195,201,205]. Bains et al. found no difference in SSI/PJI among those performed within six months, from six to 12 months, and after one year [185]. Similarly, Inacio et al. found no difference in SSI/PJI risk between those who underwent TJA within two years and those who had it performed after two years of bariatric surgery [188]. There were three additional studies that reported no effect of bariatric surgery timing on the risk of revisions or complications, although these did not specifically address SSI/PJI. [195,201,205]. Future research is needed to evaluate whether specific types of bariatric surgery and the timing of such surgery influence the outcomes of subsequent TJA.

Overall, there is only low to moderate evidence supporting the above findings. Almost all studies in this area are retrospective and, therefore, have inherent bias [208]. The only RCT had a median follow-up of two years for the bariatric surgery group and 2.3 years for the obese control group. Furthermore, of the 41 patients randomized to the bariatric surgery group, more than a quarter subsequently declined further arthroplasty. This raises doubts about the external validity of their findings [186]. Also, the CI for comparing SSI/PJI risk between patients undergoing TJA following bariatric surgery and obese controls was wide and very close to attaining statistical significance, therefore indicating a small fragility index [209]. A small fragility index warrants further robust studies comparing outcomes in patients who have prior bariatric surgery to obese controls.

Conclusion

The reviewed studies demonstrate conflicting evidence in terms of either increased or decreased rates of SSI/PJI after bariatric surgery in morbidly obese patients who undergo TJA. There is a need for further studies to determine the effect of bariatric surgery on the rate of SSI/PJI in these patients.

Question 5: Does gut microbiome have a role in the development of surgical site infection (SSI) and/or periprosthetic joint infection (PJI) in patients undergoing major orthopaedic surgery?[5]

Response/Recommendation

The gut microbiome contributes to the development of SSIs and PJIs, particularly in patients who have known gut dysbiosis (e.g., inflammatory bowel disease or prior Clostridium difficile infection).

Level of Evidence: Limited

Delegate Vote: Agree: 82%, Disagree: 12%, Abstain: 6% (Super Majority, Strong Consensus)

Rationale

Both SSI and PJI are multifactorial complications influenced by various perioperative factors [210–212]. Despite advancements in prevention strategies, infection rates have not declined much, if at all, underscoring the need to reexamine our current understanding of the causes of SSI. In recent years, a large body of evidence has emerged implicating patients' own endogenous sources of microbes (nose, oral cavity, skin, and the gut) in the majority of SSIs [213–220]. The role that gut microbiota may play in causing SSI and PJI has been investigated in particular [221–225]. The gut microbiome is a diverse microbial community unique to each individual, which begins colonization at birth and varies based on ethnicity, diet, and environment. It plays a critical role in maintaining normal physiological functions and immune defense mechanisms against external pathogens through immune mediators, regulatory hormones, and short-chain fatty acids [226–238]. Recent studies indicate that the largest immune organs are the lymph nodes, bone marrow, and spleen. However, the gastrointestinal tract contains around 70% of the plasma antibody-producing cells in our body, which play a major role in the humoral immune system [239–244].

Dysbiosis, defined as a disruption in microbial balance, reduces diversity and depletes protective commensal species. This state has been associated with compromised gut barrier function, increased gut permeability, and an increased risk of infections caused by pathogens such as *Staphylococcus aureus*, Enterococcus, and Proteus [245]. Dysbiosis has been associated with diseases such as inflammatory bowel disease and *Clostridium difficile* infections [224,246,247] and may arise from prolonged antibiotic use or unhealthy dietary habits, both of which disrupt normal gut physiology [243–248].

Apart from well-known causes, such as local contamination, hematogenous spread, and adjacent infections [249], emerging evidence suggests that gut dysbiosis could also contribute to SSI and PJI. Preclinical studies support the hypothesis that gut dysbiosis may enable bacterial translocation from the gastrointestinal tract to distant surgical sites either through hematogenous spread independent of immune cells or via transport by immune cells

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such as neutrophils and macrophages [224,250–252]. A proposed mechanism for immune-mediated microbial transport is the "Trojan Horse" hypothesis, where microbial components cross the cell membrane of immune cells, survive intracellularly in cytosol, and are transported to sites of inflammation, such as the surgical site, where they may be released and contribute to infection [251–261]. While this hypothesis remains under investigation, it underscores the potential role of the gut microbiome in influencing postsurgical infections [254,256,257].

To investigate the potential association between gut microbiome and orthopedic infections, a systematic review was conducted. Using the appropriate Medical Subject Headings terms developed by librarians, we conducted a search in Medline, Embase, Cochrane Library, and Scopus and identified 237 reference lists of relevant studies from inception to December 2024. After screening and removing 66 duplicates, 14 studies met our criteria for full review and data extraction.

Levast et al. identified a significant reduction in gut microbiome diversity, increased mucosal inflammation, and higher gut permeability markers in patients receiving prolonged antibiotic treatments for bone and joint infections [258]. Chisari et al. conducted a matched-pairs cohort study of 608 patients, showing that inflammatory bowel disease patients were more likely to experience PJI or aseptic loosening postarthroplasty. Their prospective cohort study further revealed elevated levels of zonulin and soluble CD14 in PJI patients, indicating compromised gut barrier integrity [223,259]. *C. difficile* infection is known to be associated with poor patient outcomes and increased risk of 90-day readmission and complications after THA [260]. Deckey et al. demonstrated an increased risk of PJI in patients who have *C. difficile* infections within two years before THA, reinforcing the connection between prior gut dysbiosis and complications [262]. These findings collectively suggest that dysbiosis compromises immune function and gut permeability, increasing susceptibility to surgical infections, though definitive clinical studies remain limited.

Currently, several ongoing RCTs aim to explore the relationship between gut microbiome and SSI/PJI. The International Joint Center at Acibadem Hospital University is conducting studies (NCT06791993) to evaluate the impact of prebiotics/probiotics on gut microbiome following exposure to routine prophylactic antibiotics for surgery. Sharma et al. are investigating the effect of prebiotics on the gut microbiome in PJI patients who are planned for a two-stage revision surgery [262]. Additionally, the Gut Microbiome in Orthopedics (GUMBO) study in Canada (NCT06371950) aims to examine the relationship between gut microbiome, patients' outcomes, implant migration, and bone density. Moreover, the artificial intelligence-based approach in TKA study out of Italy (NCT06634654) aims to build predictive models for post-TKA outcomes based on structural, genetic, biomechanical, clinical, psychological, biological, stress-related, inflammatory, gut microbiome, and demographic data. Meanwhile, Abdeen et al. from Boston Medical Center (NCT06636669) are conducting an RCT to assess the impact of administering a probiotic for six weeks after revision surgery for PJI, focusing on infection rates.

Defining gut dysbiosis and monitoring gut barrier integrity in clinical studies remains challenging due to the complexity of contributing factors and the lack of standardized indicators. Current research often relies on measures such as the Firmicutes/Bacteroidetes (F/B) ratio, Microbial Health Index (MHI), or plasma biomarkers like zonulin, soluble CD14, and lipopolysaccharides to assess gut permeability and overall microbiome health. Although no prospective clinical studies have directly established a causal link between gut microbiome alterations and SSI/PJI, existing evidence supports the hypothesis that gut dysbiosis impairs immune function and elevates infection risk [263].

Future research should prioritize developing reliable biomarkers for defining gut dysbiosis and establishing standardized methods to investigate the effect of prebiotics or probiotics in maintaining microbial diversity [264]. A deeper understanding of the gut-immune-joint axis has the potential to provide groundbreaking insights into infection prevention strategies for major orthopedic surgery [265–272].

Question 6: Does the use of probiotic agents have any role in preventing surgical site infection (SSI)/periprosthetic joint infection (PJI) after major orthopaedic surgery?[6]

Response/Recommendation

Probiotic agents may play a supportive role in preventing SSIs and PJIs after major orthopaedic surgery by modulating the gut microbiota, enhancing immune responses, and mitigating microbial dysbiosis.

Level of Evidence: Weak

Delegate Vote: Agree: 65.9%, Disagree: 26.8%, Abstain: 7.3%

Rationale

The gut microbiome's role in systemic immunity has garnered major attention due to its influence on systemic inflammation, infection susceptibility, and postoperative recovery. Dysbiosis, or an imbalance in gut microbiota, has been specifically linked to systemic immune dysfunction, which may exacerbate susceptibility to PJIs in these patient populations. Additionally, emerging evidence from studies measuring markers of gut permeability, such as zonulin and soluble cluster of differentiation 14 (sCD14), indicates that compromised gut barrier integrity may be a critical mediator in PJI development [273].

Disruption of the gut microbiota, or dysbiosis, has been identified as a critical risk factor for infections, including PJIs. A preclinical mouse model demonstrated that animals with altered gut microbiota experienced a 73% higher infection rate compared to controls, which had a 50% infection rate. This underscores the essential role of the microbiota in immune modulation and infection resistance. Dysbiosis resulted in weakened systemic immune responses and marked by diminished macrophage activity and impaired production of inflammatory mediators crucial for pathogen clearance. In contrast, mice with intact gut microbiota exhibited robust immune responses, including effective macrophage recruitment and cytokine production, which reduced infection rates by over 20% compared to dysbiotic mice [274].

Dysbiosis has also been linked to increased gut permeability, facilitating the translocation of microbial products such as lipopolysaccharides into systemic circulation. Elevated lipopolysaccharide levels can induce chronic low-grade inflammation, characterized by heightened interleukin-6 and tumor necrosis factor alpha levels, which impair perioperative immune function. A recent prospective cohort study revealed that zonulin, a marker of gut permeability, was significantly elevated in patients who have PJI compared to those undergoing aseptic revision (7.6 ± 6.1 versus 4.6 ± 3.8 ng/mL; $P < 0.001$). This finding highlights an association between gut barrier dysfunction and increased PJI risk, emphasizing the need for targeted strategies to maintain gut integrity in susceptible patient populations [275].

Surgical interventions can disrupt gut microbiota, leading to dysbiosis. A meta-analysis of gastrointestinal surgeries

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demonstrated a postoperative reduction in beneficial bacteria (Lactobacilli and Bifidobacteria) alongside an increase in potentially pathogenic species (*Pseudomonas*, Enterobacteriaceae, *Staphylococcus*, and *Enterococcus*). Notably, patients receiving synbiotic or probiotic therapy had lower rates of postoperative infections and a faster restoration of gut microbiota balance. These findings align with emerging orthopaedic research suggesting that preserving gut microbiota integrity may help mitigate systemic inflammation and infection risk, reinforcing the potential role of probiotics as adjunctive therapy in PJI prevention [276].

The gut microbiota is integral to maintaining systemic immune homeostasis. Dysbiosis, or the disruption of this balance, can lead to bacterial translocation, systemic inflammation, and impaired immune responses, thereby increasing the susceptibility to PJI. A major contributor to dysbiosis is prolonged antibiotic use, which has been shown to reduce microbial diversity by up to 50%, particularly affecting key commensal bacteria such as *Lactobacillus* and *Bifidobacterium*. This loss of beneficial microbes disrupts protective mechanisms, including the competitive inhibition of pathogens and the modulation of inflammatory responses, leaving the host more vulnerable to infections [273,277–280]. The "Trojan Horse" hypothesis further elucidates this process, proposing that gut-resident bacteria, such as *Staphylococcus aureus*, can translocate to distant sites via immune cells like neutrophils. These bacteria utilize immune cells as vectors, facilitating their migration to prosthetic joint areas and contributing to the development of PJI. Additionally, increased gut permeability exacerbates this issue by allowing microbial products, such as lipopolysaccharides, to enter systemic circulation. This triggers a pro-inflammatory state that weakens immune defenses at surgical sites, highlighting the need for strategies aimed at preserving gut microbial integrity in at-risk populations [273].

Preclinical studies have demonstrated that specific probiotic strains, such as *Lactobacillus rhamnosus* and *Bifidobacterium breve*, can reduce systemic inflammation and enhance local immune responses, both of which are crucial in mitigating the risk of PJI [281–283]. Murine models revealed that animals receiving probiotics experienced a 40% reduction in bacterial colonization on implant surfaces [284,285]. Furthermore, probiotic-treated mice exhibited increased levels of anti-inflammatory cytokines such as interleukin-10, which not only improved infection outcomes but also enhanced resistance to biofilm formation [286]. These findings suggest the potential for probiotics to serve as adjunctive therapies in reducing PJI risk by modulating both systemic and local immune responses.

Although clinical data specific to PJI remain limited, studies in broader surgical contexts provide compelling evidence of the potential benefits of probiotics. An RCT demonstrated that the use of *Lactobacillus plantarum* resulted in no difference in postoperative infectious morbidity events among elective abdominal surgery patients (13 versus 15%; $P = 0.74$). Furthermore, no difference in bacterial translocation ($P = 0.82$), gastric colonization with enteric organisms ($P = 0.42$), or serial serum C-reactive protein levels ($P = 0.49$ on postoperative day one; $P = 0.15$ on postoperative day seven) was seen between the control and intervention group (administered preoperative *Lactobacillus plantarum* 299 version) [287].

A meta-analysis of RCTs in patients undergoing major gastrointestinal surgery (e.g., colectomy, liver transplantation, hepatectomy, and pancreaticoduodenectomy) reported a significant reduction in nosocomial infections, with a 25% decrease in overall infection rates and a 30% reduction in hospital stays in groups treated with probiotics. These findings suggest a promising translational potential for probiotics in orthopedic applications, particularly in reducing postoperative complications and enhancing patient recovery. However, these findings should be interpreted with caution due to the reported risk of bias in the included studies [288].

While further orthopaedic-specific studies are required, these results support the integration of probiotics as adjunctive therapies to standard infection prevention protocols in surgical and orthopedic practices.

Probiotics play a crucial role in enhancing both innate and adaptive immune responses, which are vital in preventing infections associated with orthopedic implants. They stimulate macrophage activation, improve regulatory T-cell function, and promote the production of antimicrobial peptides such as defensins and cathelicidins. These actions collectively enhance pathogen clearance and reduce infection risk [286,289–292].The interplay between the gut microbiota and systemic immune regulation has profound implications for PJI prevention. Elevated markers of gut permeability, such as zonulin and sCD14, highlight the role of gut dysbiosis in systemic inflammation and immune dysregulation [275]. These disruptions can exacerbate susceptibility to PJIs by weakening host immune defenses and creating a pro-inflammatory environment. Targeting gut microbiota integrity through probiotics may mitigate these risks and enhance postoperative outcomes.

These mechanisms demonstrate the multifaceted potential of probiotics in reducing the incidence and severity of PJIs, providing a promising avenue for integrating gut microbiota management into orthopedic infection prevention protocols.

Despite promising findings, important challenges remain in incorporating probiotics into orthopedic care:

- **Heterogeneity of Probiotic Strains**: The efficacy of probiotics is highly strain-specific, making it difficult to generalize findings across different contexts. For instance, while *Lactobacillus reuteri* demonstrated efficacy in reducing systemic inflammation in one trial, other strains like *Lactobacillus casei* have produced inconsistent results [293–295]. Differences in dosing regimens and delivery methods further complicate standardization for orthopaedic applications.
- **Limited PJI-Specific Trials**: The majority of clinical evidence for probiotics focuses on reducing general SSIs, with limited data specific to PJI. There is a clear need for RCTs directly targeting TJA patients to establish strain-specific benefits and safety profiles.
- **Risk of Probiotic Use in Vulnerable Populations**: Immunocompromised patients, including those who are of advanced age or have comorbidities common in orthopaedic populations, may face rare, but serious risks associated with probiotic use, such as bacteremia or endocarditis. Case reports have documented instances where even well-characterized strains translocated to systemic circulation, emphasizing the need for careful patient selection and monitoring. These risks highlight the importance of balancing the potential benefits of probiotics with the safety concerns unique to vulnerable populations [296,297].

Addressing these challenges through rigorous, targeted research and improved standardization will be essential for translating the benefits of probiotics into routine orthopaedic practice.

Conclusions

Emerging evidence suggests that probiotics could play a role in preventing PJIs by enhancing immune function, reducing biofilm formation, and restoring microbial homeostasis. Preclinical and

limited clinical data highlight their potential, but robust, large-scale studies focused on orthopaedic populations are needed. The role of gut permeability, as evidenced by elevated zonulin and sCD14 levels, further underscores the gut-immune-joint axis as a critical area for future research. However, clinical data in orthopedic patients remain limited. Well-designed RCTs are required to further delineate the utility of probiotics for SSI and PJI prevention following major orthopaedic surgery.

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The Journal of Arthroplasty 41 (2025) S74–S78

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

General Topics

2025 ICM: Length of Stay and Discharging

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Question 1: Does hospital length of stay have any influence on the rate of surgical site infection (SSI)/periprosthetic joint infection (PJI) in patients undergoing major orthopaedic procedures?[1]

Response/Recommendation

Yes. Longer hospital lengths of stay (LOS) are associated with an increased risk of SSI/PJI. However, using the available data, the real cause behind this association could not be explained.

***Level of Evidence*:** Strong

Delegate Vote: Agree: 81.3%, Disagree: 9.3%, Abstain: 9.3% **(Super Majority, Strong Consensus)**

Rationale

Surgical site infections (SSIs) and periprosthetic joint infections (PJIs) are major concerns after major orthopaedic surgeries, impacting patient outcomes and health care costs. There are modifiable and nonmodifiable risk factors for SSI/PJI, including patient- and surgeon-related factors. Although several perioperative measures, such as preoperative patient optimization, Methicillin-resistant *Staphylococcus aureus* (MRSA) decolonization, or use of prophylactic antibiotics, have been described before, the influence of hospital LOS on the rates of SSI/PJI and the antibiotic resistance of the corresponding pathogens is less reported. Several studies have investigated the relation between prolonged LOS and the risk of SSI/PJI. While some studies have identified a correlation between prolonged LOS and increased SSI risk [1–3], others have found no significant association [4,5]. This discrepancy may be attributed to the complex interplay of factors influencing SSI development, such as patient demographics, comorbidities, type of surgical procedure, and postoperative care.

Triantafyllopoulos et al., in their retrospective study of 36,494 primary total hip arthroplasties (THAs), observed an association between longer LOS and PJI, but this association was not independent of other factors such as obesity and coronary artery disease [6]. Similarly, Smucny et al., using the Nationwide Inpatient Sample database to review 241,193 patients undergoing total shoulder arthroplasty, reported an association between increased LOS and SSI, but the causal relationship remained unclear due to potential unmeasured confounders [7]. These findings underscore the challenges in isolating the independent effect of LOS on SSI rates.

Several studies explore the influence of longer LOS on the risk of infection. Ridgeway et al. reported that the length of hospitalization before surgery was significantly associated with an increased risk of SSI after THA and hemiarthroplasty [1]. In addition, patients undergoing a hemiarthroplasty stayed in the hospital for longer than patients undergoing a THA due to optimization before surgery. Another study by Omeis et al. also identified increasing LOS as a significant risk factor for SSI in patients undergoing spinal tumor surgery [2]. To find a cutoff value, Song et al. reported that a preoperative hospital stay of more than three days was a risk factor for SSI after THA and total knee arthroplasty [3].

Contrary to most studies reporting the relation between longer LOS and increased risk of SSI/PJI, enhanced recovery programs or day surgeries have not shown this relation. Yuan et al., in their retrospective analysis of a prospectively established database of patients undergoing posterior thoracolumbar fusion for degenerative spinal deformity, found that an enhanced recovery program successfully reduced postoperative LOS without increasing SSI rates [8]. Similarly, Mundi et al., DISusing the American College of Surgeons National Surgical Quality Improvement Program database to evaluate 330,000 patients, reported that same-day discharge and accelerated discharge (1-d LOS) after total joint arthroplasty did not increase the risk of SSI [9]. Therefore, rapid recovery is not considered a

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to 10.1016/j.arth.2025.08.036.

Declarations: The study protocol was registered in International Prospective Register of Systematic Reviews (CRD42025645959).

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https://doi.org/10.1016/j.arth.2025.08.036

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concern for infection, and the surgeons who routinely do rapid recovery or outpatient joint arthroplasty surgery favor early discharge to reduce the risk of SSI/PJI.

The relationship between prolonged LOS and SSI rates has been reported in various studies focusing on specific patient populations and surgical procedures [10]. Although most of the studies investigate this relation in joint arthroplasty and spine surgeries, the risk of SSI was shown to be higher in trauma and pediatric orthopedic surgeries when the LOS was prolonged as well [11–14].

We conducted a systematic review and meta-analysis of the available literature to answer this question. PubMed/Medline, Scopus, and Embase databases were searched from inception to September 2024 to identify all the studies investigating the association between LOS and SSI/PJI in patients undergoing major orthopedic procedures. This meta-analysis included eighteen studies, comprising a variety of designs: six prospective cohort studies, one prospective two-subcohort study, one retrospective two-subcohort study, seven retrospective case-control studies, and three retrospective database cohort studies utilizing databases, all examining the association between LOS and the rate of SSI/PJI in patients undergoing major orthopedic procedures. [7,12,15–29]. Studies with participants who had prolonged LOS because of infection were excluded. Figure 1 compares the mean values of different parameters in patients who have and do not have an SSI/PJI. Heterogeneity was found to be moderate-high in subgroups and overall (I^2 = 97% trauma, 98% arthroplasty, 58% spine, 100% general orthopedics, and 100% total). The combined mean difference of the studies was calculated as 7.78 days (95% confidence interval: 3.75 to 11.80). These results showed statistically significantly longer LOS in SSI groups. In the specific subgroup of general orthopedics, there was no statistically significant difference in the mean LOS between the groups with and without SSI. It was also not affected by age, body mass index, or sex (P = 0.5725). Using the available data, neither determining a cutoff value for the LOS nor identifying rates of SSI/PJI for different LOS intervals was possible. More importantly, the included studies did not explain why longer LOS was associated with an increase in infection risks.

Prolonged hospital stay before orthopedic surgery is a potential risk for the acquisition of antibiotic-resistant microorganisms. In implant-related orthopedic surgery, including for arthroplasty, there are fewer articles. In terms of antibiotic resistance of future SSI pathogens, Davat et al. retrospectively investigated if the methicillin resistance of SSI due to staphylococci (the hallmark of orthopedic SSI) was in association with the LOS immediately before the index surgery and found no more resistance [30] and necessity to broaden the spectrum of perioperative antibiotic prophylaxis during surgery after a long hospitalization period.

In conclusion, the present systematic review and meta-analysis demonstrated a statistically significant relationship between LOS and the risk of subsequent SSI/PPJI, indicating that prolonged LOS is associated with an increased risk of SSI/PJI after major orthopaedic surgeries, whereas the association with more resistant SSI pathogens remains less clear. This finding underscores the importance of optimizing LOS in orthopaedic surgery to minimize SSI/PJI risk and improve patient outcomes. However, with the available data, we cannot completely explain why an increased LOS would influence the rate of infection. Probably, the reason is multifactorial and may be associated with other risk factors in longer LOS, such as patients' immune suppression, revision surgery, or the American Society of Anesthesiologists score.

Question 2: Does the discharge disposition (home versus a facility) of a patient influence the risk of surgical site infection (SSI) and/or periprosthetic joint infection (PJI) in patients undergoing major orthopaedic procedures?[2]

Response/Recommendation: Available evidence suggests that nonhome discharge is associated with a higher risk of SSI and/or periprosthetic joint infection (PJI).

Level of Evidence: Moderate

Delegate Vote: Agree: 67.7%, Disagree: 6.5%, Abstain: 25.8% (Strong Majority, Moderate Consensus)

Rationale

With the increasing demand for total joint arthroplasty (TJA) worldwide and the increasing importance of cost-effective patient care, optimizing postoperative care and discharge planning has become a critical aspect of patient management toward maximizing clinical outcomes in a cost-conscious manner. Patient discharge disposition following major orthopedic surgery, which is likely multifactorial and includes home or subacute or acute nursing/rehabilitation postacute care (PAC) facilities, may play a key role in influencing both clinical outcomes and health care costs [31]. While inpatient rehabilitation facilities (IRFs) and skilled nursing facilities (SNFs) aim to provide structured alternative postoperative recovery settings to address the postoperative needs of patients following major orthopedic surgery, albeit at higher costs, home discharge has gained increasing preference due to potential benefits, including lower complication rates, improved functional recovery, and reduced health care expenditures [32–35]. However, the impact of different discharge dispositions on postoperative complications, particularly SSI and periprosthetic joint infections (PJI) following major orthopedic surgery, remains controversial.

Discharge disposition is likely predicated, at least partially, on multiple patient-related factors. In a multivariate analyses of predictors for discharge to an inpatient facility, Fu et al. identified age > 75 years as the strongest predictor (odds ratio [OR]: 2.76; 95% confidence interval [CI], 2.61 to 2.91), followed by predischarge complications (OR: 2.42; 95% CI, 2.02 to 2.91), nonindependent functional status (OR: 2.09; 95% CI, 1.85 to 2.35), and a modified Charlson Comorbidity Index > 5 (OR: 2.02; 95% CI, 1.90 to 2.15) [32].

Despite the relatively high utilization of PAC services and associated costs, evidence remains limited regarding the associated clinical impact on postdischarge outcomes [31]. Recent literature suggests that patients undergoing major orthopedic surgery who are discharged to nonhome facilities experience both inferior functional outcomes and an increased risk of 30-day complications and readmission [33–37]. Despite concerns for selection bias in this scenario, given that lower-functioning, higher-risk patients who have limited social support would be more likely to be discharged to nonhome facilities, evidence utilizing propensity matching and multivariate regression analyses in other studies has demonstrated a significant increase in ORs for complications among those who have nonhome discharge postoperatively [32,38].

A more detailed examination of complication rates, specifically SSI and deep infection, reveals varying results across different studies. In the arthroplasty literature, Fu et al. analyzed a cohort of 54,837 patients, of whom 26% were discharged to inpatient facilities (SNF and IRF). Their propensity-matched regression analysis

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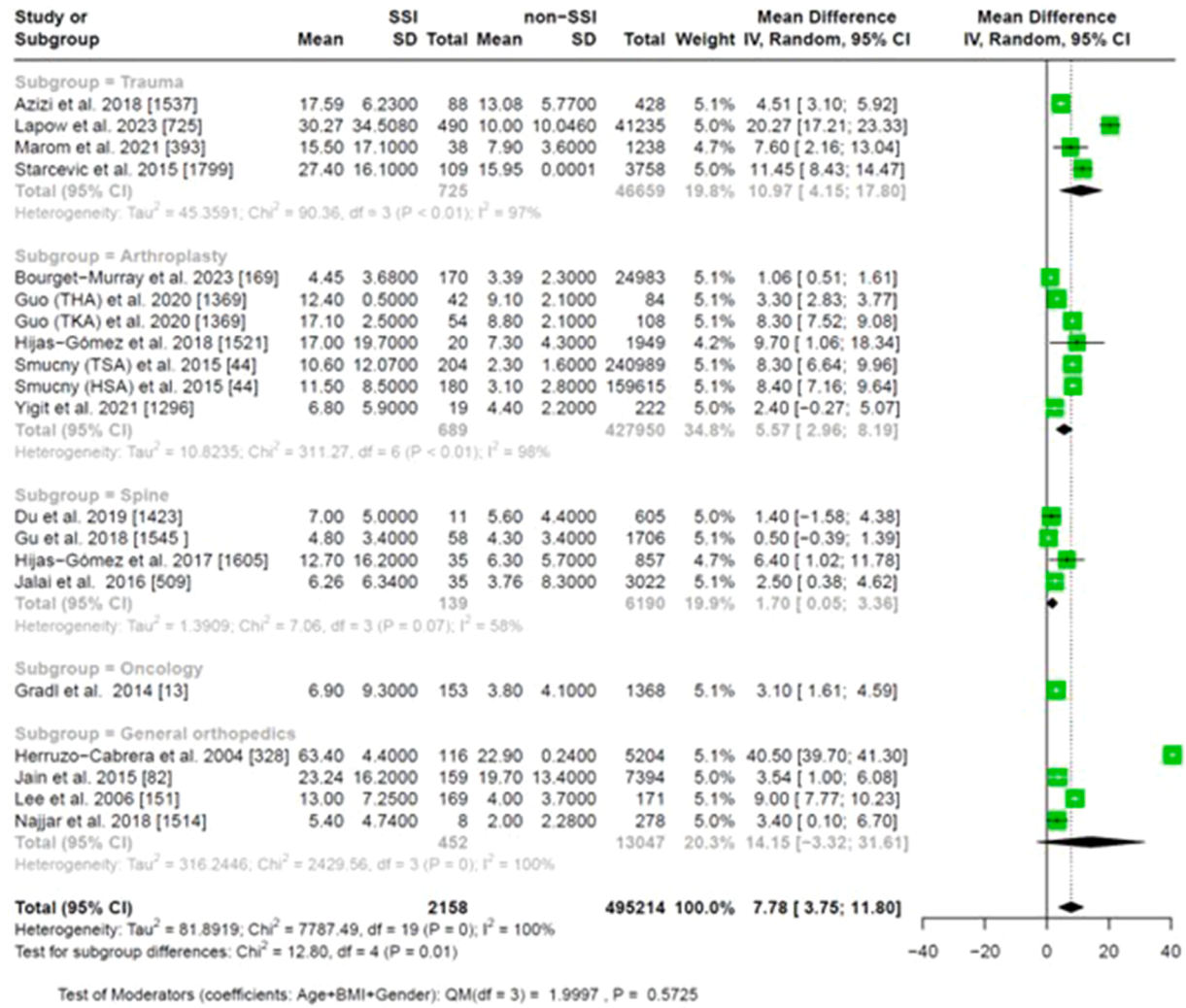

Figure 1. Forest plot illustrating the mean difference in LOS between patients with and without SSI/PJI, with results presented for orthopedic subgroups. LOS, lengths of stay; SSI, surgical site infection; PJI, periprosthetic joint infection.

demonstrated that discharge to an inpatient facility rather than home was significantly associated with an increased risk of wound complications, including SSI, organ/space infection, and wound dehiscence (OR: 1.31; 95% CI, 1.09 to 1.57; $P = 0.004$) [32].

Similarly, a 2018 study by Stone et al. found that among 7,466 TJA patients, those discharged to SNFs had a significantly higher risk of SSI/PJI within the first 90 days (19.6 versus 10.3%, $P = 0.02$) [39]. Another study by Malik et al. reported that patients undergoing hip hemiarthroplasty, total hip arthroplasty (THA), or open reduction and internal fixation for hip fractures had an increased risk of wound complications (both superficial and deep SSI) when discharged to an inpatient facility (OR: 1.79; 95% CI, 1.10 to 2.91; $P = 0.01$) [33].

Treu et al. further demonstrated that among patients undergoing hemiarthroplasty or THA for femoral neck fractures, those discharged to SNFs had significantly higher 90-day and 1-year PJI risks compared to those discharged home (OR: 4.55, $P = 0.001$ and OR: 3.08, $P = 0.03$, respectively). In addition, the time to PJI development was significantly shorter in SNF patients (38 versus 231 days, $P = 0.01$). When comparing SNF to IRF, SNF patients had significantly higher 90-day and 1-year PJI risks (OR: 3.45, $P = 0.04$ and OR: 3.76, $P = 0.03$, respectively). However, no significant difference was observed between the IRF and home discharge groups [37]. Another study analyzing 35,973 patients undergoing posterior lumbar fusion surgery compared those discharged home with those discharged to IRF/SNF. The results showed significantly lower rates of SSI (0.91 versus 1.68%, $P < 0.0001$), deep wound infection (0.61 versus 1.14%, $P < 0.0001$), organ/space infection (0.19 versus 0.53%, $P < 0.0001$), and wound dehiscence (0.19 versus 0.53%, $P < 0.0001$) in patients discharged home. In addition, SSI rates were significantly higher in patients who were discharged to SNF compared to those discharged to IRF (2.2 versus 1.04%, $P < 0.0002$), while no significant differences were found between these groups in terms of deep wound infection, organ/space infection, or wound dehiscence [40]. Similarly, Park et al. [36] analyzed 13,050 lumbar surgery patients and found that home discharge was protective against SSI compared to IRF/SNF within 30 days postoperatively (OR: 0.47).

Contrary to these findings, there are also studies reporting no significant difference in terms of SSI/PJI between different patient discharge dispositions. Mayer et al. [34] analyzed 78,821 THA patients (home discharge: 75.4%) and 137,675 total knee

arthroplasty (TKA) patients (home discharge: 71.0%) and found no significant difference in SSI rates between the home and nonhome discharge (SNF, IRF) groups after propensity matching. However, all other complications, including cardiac, respiratory, readmission, and reoperation rates, were significantly higher in the nonhome discharge disposition group. Similarly, McLawhorn et al. [38] examined 101,256 patients undergoing primary TKA (home discharge: 69.7%) and found no significant difference in wound complications (superficial and deep SSI, organ/space infection) between the two groups in a propensity-adjusted multivariable regression analysis. Owens et al. [41] also investigated 34,610 patients undergoing primary THA or TKA (home discharge: 54.8%) and found no significant difference in SSI rates between the home and nonhome groups. However, they reported that discharge to an SNF was an independent risk factor for 30-day complications and readmission (OR: 1.9; 95% CI, 1.7 to 2.0).

Keswani et al. [42] analyzed 106,360 patients undergoing primary THA and TKA, where 70% were discharged home, 19% to an SNF, and 11% to an IRF. No significant difference was observed in superficial or deep SSI rates between home-discharge and SNF/IRF groups. However, their study found that organ/space infections and wound dehiscence were significantly higher in the nonhome discharge group, with no difference between SNF and IRF. Patients discharged to SNF and IRF had a higher risk of total adverse events (OR: 1.46 and 1.59, respectively). Padgett et al. [43] examined 8,145 patients undergoing primary TKA and performed propensity score matching, yielding 1,213 matched patients in the home versus IRF group and 492 matched patients in the SNF versus IRF group. The SSI rates were insignificant for both groups [home versus IRF group: 2.1 versus 1.8%, $P = 0.64$, and SNF versus IRF group: 3.4 versus 2.3%, $P = 0.37$]. A study investigating the impact of discharge disposition following shoulder arthroplasty analyzed 9,058 patients, with 88.2% discharged home and 11.8% to a nonhome facility (IRF, SNF). There was no significant difference found in SSI rates between the two groups (0.06 versus 0%) [44].

Beyond these comparisons, Fleischman et al. [45] investigated differences among patients discharged home based on whether they lived alone or with a caregiver. While significant differences were observed in in-hospital length of stay and the need for in-home physiotherapy, no significant differences were found in wound infection or PJI risk between the groups. Reoperation due to infection was required in 0.7% of patients living alone, compared to 0.79% in the control group ($P = 1.0$).

Another important consideration is that discharge disposition is a major determinant of the total cost in an episode of care following TJA. Home discharge with outpatient rehabilitation is approximately $6,000 less expensive than discharge to an SNF and $16,000 less expensive than discharge to an IRF [46]. In lower extremity arthroplasty, PAC constitutes more than one-third of total costs, primarily due to the utilization of IRFs and SNFs [47].

In addition, although regression models have attempted to account for various variables, the potential for confounding due to unmeasured factors cannot be entirely eliminated in observational studies [48]. For instance, a patient's socioeconomic status has been associated with both nonhome discharge and adverse events following TKA [49,50]. However, many studies have been unable to adequately define and compare this variable, making it a potential confounding factor.

Conclusion

The literature review demonstrated that nonhome discharge has been shown to be associated with the risk of overall complications and readmission following major orthopedic surgery; however, its impact on SSI and PJI remains unclear based on conflicting evidence.

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General Topics

2025 ICM: Skin Preparation

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Question 1: What is the most optimal intraoperative skin preparation agent for patients undergoing major orthopaedic procedures?[1]

Response/Recommendation

Question A: There does not appear to be a superior intraoperative skin preparation agent for patients undergoing major orthopaedic procedures.

Question B: Isopropyl alcohol must be part of the preoperative surgical site skin preparation.

Level of Evidence: Moderate

Delegate Vote: Question A: Agree: 73.5%, Disagree: 17.7%, Abstain: 8.8% (Strong Majority, Moderate Consensus)

Question B: Agree: 87.5%, Disagree: 8.3%, Abstain: 4.2% (Super Majority, Strong Consensus)

Rationale

Surgical Site Infection (SSI) prevention has been extensively investigated, and several steps are recommended for perioperative skin preparation, including preoperative washing, appropriate hair removal from the incision site, and reducing skin recolonization [1]. Cleansing the surgical site using a chlorhexidine gluconate (CHG) or povidone–iodine (PI) solution before incision is considered routine and reduces bacterial load at the surgical site [2–5]. Bacterial cell membranes are disrupted by CHG, whereas PI acts through bacterial protein denaturation [6]. In the most recent Cochrane meta-analysis regarding preoperative skin antisepsis, the authors concluded that the current literature lacked evidence to support the use of a particular solution [7]. However, the consensus was that the sterile skin preparation agent should contain alcohol based on recommendations from the Centers for Disease Control, the International Consensus Group Meeting, and prior studies [5,7–13].

Since this meta-analysis, Charehbili et al. published their cluster-randomized crossover trial consisting of 3,665 patients who underwent breast, vascular, colorectal, gallbladder, or orthopaedic surgery. Patients received either 0.5% CHG or 1% PI in an alcohol-based solution. The authors noted no statistically significant difference in the overall incidence of SSI between groups [14]. The Prep-it Investigators published two randomized controlled trials evaluating the optimal preoperative antiseptic solution for patients who suffered fractures. One study evaluated 1,638 patients who received either 4% CHG or 1% PI and underwent fixation for open fractures. The authors found no statistically significant difference in rates of SSI between groups [15]. The authors' subsequent multicenter randomized controlled trial consisted of 6,785 patients who had closed fractures who received either 2% CHG or 0.7% PI for skin preparation. The authors noted that skin antisepsis with PI in alcohol resulted in a lower proportion of SSIs than those who received CHG in alcohol [16]. In contrast, Ritter et al. published a prospective randomized trial of 279 consecutive patients who were randomized to receive 2% CHG with alcohol or 1% PI with alcohol for skin preparation intraoperatively. The authors found that skin antisepsis with CHG for surgery for closed trauma of the lower leg and foot led to statistically significantly fewer complications of wound healing compared to PI [17]. While a randomized controlled trial by Shadid et al. demonstrated no statistically significant differences in postoperative wound complications or SSIs in 49 patients undergoing clean foot surgery who received skin preparation with either 0.5% CHG or 1% PI, both with alcohol [18].

Regarding spine surgery, Patrick et al. published their randomized controlled trial of 407 patients who received 2% CHG in alcohol or 1% PI in alcohol for intraoperative skin preparation before spine surgery. The authors found that the sequential application of PI and CHG more effectively reduced contamination of surgical wounds than PI alone based on intraoperative skin cultures [10].

Regarding hip and knee arthroplasty, three randomized controlled trials have been published since the prior Cochrane

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to 10.1016/j.arth.2025.10.105.

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https://doi.org/10.1016/j.arth.2025.10.105
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meta-analysis. Cho et al. performed a randomized controlled trial of 150 patients undergoing primary total knee arthroplasty who received intraoperative skin antisepsis with either 10% PI, 2% CHG after 1% PI, or 1% PI after 2% CHG, all with alcohol. Based on rates of bacterial cultures after skin preparation, the authors noted that CHG after PI or PI after CHG was superior to PI alone [19]. Peel et al. published their cluster randomized controlled trial of 780 patients undergoing primary total knee or hip arthroplasty who received either 0.5% CHG in alcohol or 1% PI in alcohol for intraoperative preparation. The authors noted no differences in superficial wound complications between the two groups, but on secondary analysis, the PI group had greater efficacy for preventing SSI [20]. Droll et al. published their randomized controlled trial of 105 patients undergoing primary total hip arthroplasty who received either 2% CHG or 0.7% PI for intraoperative skin preparation. Using intraoperative cultures, the authors noted that PI was more effective than CHG at eliminating skin flora at the hip on initial application, but the two solutions were equally effective by time of closure [21].

Regarding the shoulder, Blonna et al. published their randomized controlled trial of 40 patients who had proximal humerus fractures who underwent intraoperative skin preparation with either 1% PI or 4% CHG, followed by PI. The authors noted that although both approaches reduced *Staphylococcus aureus* and *Propionibacterium acnes* skin burden, the double skin preparation was more effective against coagulase-negative *S. aureus* [22]. In addition, Dorfel et al. found that 3.2% PI in alcohol showed benefits over 2% CHG in alcohol in aerobic and anaerobic flora culture positivity of the shoulder based on their randomized crossover study [23]. A randomized controlled trial of 22 patients by Hancock et al. found no statistically significant reduction in the growth of *P. acnes* over 14 days with CHG and benzoyl peroxide compared with CHG alone [24].

Given the heterogeneity of data based on surgical site, there does not appear to be an optimal intraoperative sterile skin preparation agent for all patients undergoing major orthopaedic procedures. In accordance with the review by Dockery et al. on preoperative skin preparation agents and surgical sites, the decision to use a particular sterile skin preparation agent should be based on the most likely pathogens of a surgical site and be combined with isopropyl alcohol [25].

Question 2: Is there a role for the use of antiseptic incise drapes in patients undergoing major orthopaedic surgery?[2]

Response/Recommendation

Possibly. The use of an antiseptic incise drape may result in a reduction in postoperative infections in patients undergoing major orthopaedic surgery.

Level of Evidence: Limited

Delegate Vote: Agree: 78%, Disagree: 14.8%, Abstain: 7.3% (Super Majority, Strong Consensus)

Rationale

Surgical site infection (SSI) and periprosthetic joint infection (PJI) represent a devastating complication. Prevention is the key to reducing their incidence and avoiding severe consequences that markedly affect both patients and the health care system.

Plastic adhesive skin drapes were introduced approximately three decades ago to serve as a lining for skin incisions. The aim was to reduce wound infection rates by preventing bacteria from the surrounding skin from contaminating the exposed tissues during surgery [26].

The use of incise draping has become popular among orthopaedic surgeons. For example, in one study, the members of the Belgian Society for Orthopaedics were asked to complete an online questionnaire consisting of 28 questions regarding the use of surgical antimicrobial prophylaxis measures. A total of 228 practicing orthopaedic surgeons participated, with 67.5% using impregnated drapes, 12.3% using unimpregnated drapes, and 20.3% reporting never using drapes [27].

Surgical prevention involves proper asepsis and antisepsis and meticulous attention to surgical principles that minimize the potential for entry of microbes into the surgical site, including those from the patient's own skin flora. The use of plastic adhesive drapes, sterile stockings, and personal protective equipment has not clearly demonstrated a reduction in the risk of infection [28].

The use of adhesive plastic drapes does not always result in a reduction of periprosthetic infection. For example, a study included a total of 2,266 patients, with 1,129 (49.8%) assigned to the adhesive drape groups and 1,137 (50.2%) to the control groups. A significant reduction in positive skin blade culture results was observed with the use of antimicrobial drapes compared to no adhesive drapes (3.81 versus 12.19%; $P = 0.031$). However, there was a more than twofold increase in skin contamination beneath the peeled-off drape before wound closure compared to the levels observed before the application of the adhesive drape (10 versus 4%; $P < 0.01$). Importantly, no significant difference in the risk of PJI was identified between antimicrobial adhesive drapes and nonantimicrobial adhesive drapes (1.0 versus 1.2%; $P = 0.46$) [29]. In another study, 12.0% of incisions with adhesive drapes and 27.4% without adhesive drapes were positive for bacterial colonization. It appears that the iodophor-impregnated adhesive draping significantly reduces bacterial colonization of the incision [30]. A study on 62,087 primary total knee arthroplasty (TKA) patients demonstrated an association between the use of antimicrobial adhesive drapes and a reduction in the risk of revision due to PJI [31].

The duration and the type of surgery also influence the rate of surgical site contamination and the role that incise draping may play in reducing such an event. In one study, when incise draping was not utilized, the rate of contamination was lower in patients undergoing total hip arthroplasty with a lower surgical time than TKA with a higher contamination rate (odds ratio 16.562, $P < 0.01$). The proper application of iodine-impregnated drapes effectively reduced contamination risk ($P < 0.001$). Moreover, prolonged operative duration was identified as a contributing factor to bacterial contamination in TKA ($P < 0.01$) [32].

In order to address the question posed above, we conducted a comprehensive systematic review of the literature. All potentially eligible studies were identified. After screening, studies that directly addressed the question of incise draping in orthopaedic surgery were included. A total of 5,241 patients who received antimicrobial-impregnated drapes and 4,533 patients in whom no antiseptic drape was utilized were compared. The incidence of PJI was 1.14% for patients who had antimicrobial drapes and 1.26% for those who had nonimpregnated drapes, indicating that the use of antimicrobial drapes does not reduce the incidence of PJI [33]. Preparing the surgical field is crucial and should be directly supervised by the surgeon to ensure a sufficiently large surface area for the incision drape, as well as proper placement of the liquid collection bag and its subsequent emptying [34]. The results suggest that the use of iodine-impregnated adhesive incision drapes can lower the bacterial contamination rate of scalpel blades used for skin incision. A significant difference was determined between positive skin blade culture results and incision drape usage ($P =$

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0.031) [35]. However, after 79 minutes, the use of plastic or nonplastic drapes shows no significant difference, casting doubt on their effectiveness in preventing SSIs [36]. We recommend it is important to clean the skin again with antiseptics if the incise drape is removed by the surgeon [37].

An issue related to the use of incise draping relates to the lift-off of the drape from the skin. Studies have shown that lift-off of the drape, particularly with a separation of greater than 10 mm, results in a considerably higher contamination rate (odds ratio 3.54 [95% confidence interval 1.64 to 11.05]; $P = 0.0013$) [38]. There are various strategies that have been explored in reducing the lift-off of the drape. The use of preoperative degreasing agents such as 70% isopropyl alcohol has been shown to reduce drape lifting in moist conditions [39]. Reapplication of antiseptic solutions before the final adhesive drape also significantly reduced the rate of superficial SSI in elective total joint arthroplasty patients [40]. We believe that implementing all of these mitigation strategies concurrently will lead to a synergistic effect for infection control following lower extremity total joint arthroplasty [41–44].

Conclusions

There is a recognized role for the use of antiseptic incision drapes in preventing contamination of the surgical field. However, their effectiveness in reducing SSIs has not been definitively confirmed. After an exhaustive review of the information, we conclude that the proper use of adhesive drapes under the previously mentioned conditions helps reduce surgical wound contamination. However, it has not been proven to decrease the risk of periprosthetic infection. Moreover, improper use of these adhesives could, in some cases, further increase the risk of surgical infection.

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The Journal of Arthroplasty 41 (2025) S83–S88

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The Journal of Arthroplasty

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General Topics

2025 ICM: Surgical Site Irrigation

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Question 1: What is the optimal irrigation solution for the patients undergoing major orthopaedic procedures?[1]

Response/Recommendation

In total joint arthroplasty (TJA) and spine surgery, the literature supports the use of dilute povidone-iodine (PVP-I) as an irrigation solution to reduce infection rates.

Level of Evidence: Moderate

Delegate Vote: Agree: 74.5%, Disagree: 13.9%, Abstain: 11.6% (Strong Majority, Moderate Consensus)

Rationale

A total of 1,285 studies were identified from PubMed and Embase databases using relevant MeSH terms and keywords and were screened in duplicate through the title and abstract stages. A total of 24 comparative studies with a total sample size of 114,076 patients were included [1–24]. The studies included five randomized controlled trials (RCTs), one pilot RCT, one prospective cohort, and 17 retrospective cohort studies. A majority of studies focused on primary (12 studies) or revision (two studies) TJA, with nine further studies on spine surgery and one study on open fractures.

Povidone-iodine

Povidone-iodine (PVP-I), either in isolation or as part of broader protocols (e.g., in addition to topical vancomycin or hydrogen peroxide), was the intervention evaluated in the vast majority of studies (20 of 24 studies). Of these, 14 studies across spine and TJA found significant reductions in infection rates with the use of PVP-I. There was a wide range of administration and dilution protocols. Although the most commonly cited protocol included 0.3% dilute PVP-I left in the wound for three minutes, this was not universal across studies. There were six of these studies that demonstrated significant reductions in infection rates with the use of dilute PVP-I compared to the standard of care (saline) [1,5,13,17,22,25]. There was one study that did not find a significant difference in the initial analysis, but did detect a significant reduction in infection rates for hip resurfacing cases and for total hip arthroplasty and total knee arthroplasty (TKA) cases after propensity matching [18]. Only one study, which evaluated revision TJA only, did not find a significant difference when comparing PVP-I to saline [4].

There were four studies that combined PVP-I with intrawound vancomycin (dubbed the “VIP” protocol by some studies) that also found significant reductions in infection rate [7,9,14,21], while one study using the VIP protocol did not find a significant difference [24].

There was one study that combined PVP-I with dilute hydrogen peroxide and found a significant reduction in infection rates in spine surgery [11]. There was one study of TJA patients that found a significant reduction in infection rates with the use of PVP-I lavage as part of a protocol that also included intravenous vancomycin and nasal mupirocin (termed “triple prophylaxis” by the authors) [16]. Also, a study of “triple wash,” or sequential irrigation with dilute PVP-I, followed by dilute peroxide and normal saline, was found to significantly reduce the superficial and deep infection rates in TKA patients.

Chlorhexidine

There were two retrospective cohort studies that evaluated the use of chlorhexidine lavage in TJA patients. There was one study

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.072.

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https://doi.org/10.1016/j.arth.2025.10.072
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that found a significant reduction in infection rates (1.1 versus 2.2%) with the use of chlorhexidine-cetrimide lavage [23]. In contrast, one study found no significant difference between chlorhexidine and saline in TJA infection rates [19].

Hydrogen peroxide

There was one retrospective cohort study that reported a significant reduction in infection rates with the use of dilute hydrogen peroxide compared to saline in spine surgery patients [8].

Soap

The multinational RCT Fluid Lavage in Open Fracture Wounds (FLOW) Trial evaluated saline and soap in open fracture patients and demonstrated a significantly higher risk of infection with the use of soap compared to saline [2].

Adverse events

There was one study that demonstrated that intra-wound use of dilute PVP-I led to sustained increases in systemic iodine levels as measured through urine output. However, this did not have an impact on thyroid function [12]. Chlorhexidine is known to have cytotoxic potential, and concerns have been raised about its prolonged use as a direct intrawound irrigation agent [26].

With regard to PVP-I specifically, concerns about the sterility of the fluid itself and its packaging have been raised. In the 20 included studies on PVP-I, eight specified whether or not the PVP-I used was sterile (sterile in seven, nonsterile in one), but 12 did not specify. There have been older (> 10 years ago) published reports raising concern about nonsterile and contaminated PVP-I [27–29]. There are no studies directly comparing sterile versus nonsterile PVP-I, and sterile PVP-I is not readily available in all settings, but if and when available, it should be the preferred choice over nonsterile PVP-I.

Conclusion

Although the majority of studies seem to support some form of PVP-I as a beneficial irrigation solution to reduce infection rates. Numerous national guidelines, including the Centers for Disease Control [30], the International Consensus Meeting (2018), and a recent update from SHEA/IDSA/APIC [31], all recommend the use of sterile dilute PVP-I. We are aware of two large RCTs that will attempt to definitively establish the optimal irrigation solution and local antibiotic powder protocol in TJA.

Question 2: Is there an optimal volume of irrigation solution in patients undergoing major orthopaedic surgery?[2]

Response/Recommendation

No. Based on available evidence, the precise optimal volume of irrigation solution is not known.

Level of Evidence: Limited

Delegate Vote: Agree: 82%, Disagree: 14%, Abstain: 4% (Super Majority, Strong consensus)

Rationale

Determining an optimal irrigation volume in patients undergoing major orthopaedic surgery remains challenging due to the heterogeneity of surgical procedures, wound types, and patient factors. Although it is well established that irrigation is critical for reducing bacterial load and removing debris in open fractures, arthroplasty, and other orthopaedic interventions, current evidence does not provide a definitive volume threshold. Instead, a general principle has emerged: increasing irrigation volume can improve wound cleansing up to a certain point, but the ideal amount remains unknown.

Studies on open fracture management have investigated various irrigation volumes and pressures without identifying a definitive combination that consistently reduces complications. For example, the FLOW international survey, which included responses from 984 surgeons, standardized the minimum irrigation volumes based on the severity of open fractures using the Gustilo-Anderson classification: three liters for type I fractures and six liters for types II and III [32]. Building on this standardization, the FLOW trial—a prospective, multicenter, and randomized controlled study—evaluated the effects of irrigation solutions (soap versus saline) and pressures (very low, low, and high) on reoperation rates in 2,447 adult patients who had open fractures. The trial found reoperation rates of 14.8% (182 of 1,229) in the soap group versus 11.6% (141 of 1,218) in the saline group (hazard ratio, 1.32; $P = 0.01$). Regarding irrigation pressures, reoperation rates were similar across groups: 13.2% for high pressure, 12.7% for low pressure, and 13.7% for very low pressure ($P = 0.53$, $P = 0.89$, and $P = 0.62$, respectively). These findings suggest that very low–pressure irrigation is a cost-effective, acceptable alternative, with saline outperforming soap in reducing reoperation rates [33]. Using the same dataset, Sprague et al. [34] assessed the impact of irrigation solutions and pressures on health-related quality of life after open fractures. They concluded that neither solution type (soap versus saline) nor pressure significantly influenced quality of life, indirectly suggesting that irrigation volume alone might not determine outcomes. Likewise, investigations into septic arthritis of the shoulder have shown that larger volumes can aid in more complete decontamination and potentially lower reoperation rates, though no single optimal volume was defined [35]. Studies on arthroscopic lavage in rheumatoid knees and postoperative pain/swelling in knee procedures suggest that using ample fluid may confer symptomatic benefits, but do not quantify a precise optimal volume [36,37]. In spine surgery, increasing irrigation volume has been shown to reduce postoperative drainage; however, no significant improvements in short-term clinical outcomes have been documented [38].

In arthroplasty, increasing irrigation volumes has been shown to enhance the removal of bone and cement debris, though the exact optimal volume remains uncertain. Niki et al. [39] investigated this by collecting cement particles after different irrigation volumes in eight patients undergoing primary cemented TKA. Their findings suggest that four liters of pulse lavage irrigation is sufficient to effectively remove cement and bone debris after cementing TKA components. This volume may also aid in clearing bacterial particles, highlighting its potential role in infection prevention.

Reviews and early research emphasize that while adequate irrigation is critical, more is not always better. Excessive pressure or excessively high volumes can risk tissue damage or promote deeper bacterial penetration [40,41]. Although pulse lavage has demonstrated improved bacterial clearance in certain scenarios, it may also cause tissue injury if both pressure and volume are not carefully managed [41]. Comparisons of irrigation techniques in spinal surgery indicate that some lavage methods can reduce infection rates;

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however, these benefits appear to be influenced more by technique than by a specific optimal volume [42].

Conclusion

Available evidence underscores the importance of irrigation in orthopaedic surgery, but does not define an exact optimal volume. Clinicians must strike a balance between ensuring adequate irrigation for effective cleansing and avoiding mechanical or soft-tissue damage. Further high-quality, procedure-specific randomized controlled trials are essential to establish clearer guidance on optimal irrigation volumes for various orthopaedic conditions.

Question 3: Is there a role for the addition of topical antibiotics to saline irrigation solution bags for the prevention of surgical site infection/periprosthetic joint infection in patients undergoing major orthopaedic procedures?[3]

Response/Recommendation

No. The addition of topical antibiotics to the saline solutions to prevent periprosthetic joint infection (PJI) and surgical site infection (SSI) in major orthopaedic surgeries is not recommended, as it has not been shown to reduce the rate of SSI/PJI.

Strength of Recommendation: Moderate

Delegate Vote: Agree: 92.1%, Disagree: 1.9%, Abstain: 6.0%

Rationale

Intraoperative surgical irrigation is a common practice in orthopaedic procedures. The purpose of using an irrigation solution is to reduce the removal of tissue exudate, hematoma, foreign debris, nonviable tissue, and metabolic waste from the surgical field in an effort to reduce the potential for subsequent infection [43–45]. Many studies have been completed related to the identification of optimal irrigation solution [43].

We conducted a comprehensive systematic review to evaluate the potential role of topical antibiotics in reducing orthopaedic infections when added to the irrigation solution. Appropriate MeSH terms were developed by the librarians to conduct a literature search in two databases. Medline and Embase publications were identified, which were then screened by two experts to identify 23 final publications for inclusion in this systematic review.

After a detailed review of the current (limited) evidence, it appears that the addition of topical antibiotics like bacitracin and polymyxin to normal saline irrigation solution has no role in the prevention of orthopaedic infections.

There was one study by Goswami et al. [46] that investigated the *in vitro* efficacy of polymyxin and bacitracin against *Staphylococcus aureus* and *Escherichia coli* and did not detect a beneficial effect for the topical antibiotics used. Other studies have corroborated the latter and found that the addition of topical antibiotics (bacitracin, neomycin) did not enhance the removal of *S. aureus* biofilm from stainless screws, bone, and titanium compared to normal saline [47,48]. Schmidt et al. [49] demonstrated that the triple antibiotic (bacitracin 50,000 U/L, gentamicin 80 mg/L, and polymyxin 500,000 U/L) solution was not able to eradicate *Staphylococcus epidermidis* from the biofilm *in vitro*. An *in vitro* study suggests that the addition of polymyxin-bacitracin to saline irrigation solution is a futile exercise [46]. Taken within the context of its associated expense, risk of hypersensitivity, and impact upon antimicrobial resistance, our findings bring its widespread clinical usage into question [50].

There are few *in vivo* investigations comparing antibiotic irrigation with other solutions, and even fewer of these are specific to orthopaedics [51].

Owing to different pharmacokinetic properties and their efficacy, not all antibiotics can be instilled while irrigating wounds [43].

Few studies have shown that they are effective in preventing SSIs and prosthetic joint infections in major orthopaedic surgeries, including TJA [52–54].The most widely used antibiotics are polymyxin, bacitracin, and neomycin. More recently, the Food and Drug Administration has warned against the use of bacitracin in irrigation solutions and withdrawn bacitracin injections due to serious adverse effects of bacitracin, including nephrotoxicity and anaphylaxis [55]. In recent years, at least in the United States, many pharmacies do not provide bacitracin for use in irrigation solutions [55].

Most studies do not recommend adding an antibiotic to saline solution [56] because of the same effectiveness as saline solutions, associated costs [51], and its side effects, like allergic reactions [57,58], antibiotic resistance, and wound problems [59]. The two clinical practice guidelines issued by the World Health Organization [60] and the National Institute for Health and Care Excellence [61] advise that antibiotic incisional wound irrigation before closure should not be used for the purposes of preventing SSIs. Overall, the evidence supporting the use of antibiotics in wound irrigation in orthopaedics is not convincing. Although toxicity and adverse reactions to antibiotics are rare, they do occur [62].

When various antibiotic mechanisms of action, which take time and require the opportunity to bind to a specific target site, are considered, the level of effect when they are transiently washed over a wound is likely diminished or even improbable [63]. Theoretical concerns of the promotion of antibiotic resistance, coupled with major costs of antibiotic irrigation, are also important [51].

It should be understood that any routine prophylactic use of antibiotics may result in resistant organisms, and the wise stewardship of the use of antibiotics is an important part of surgical practice [54]. In the comparison of different solutions, antibiotic solutions are not superior to others [59,64]. Based on the International Consensus Meeting 2018 demonstrating benefit, the risks of antibiotic resistance, the known reactions, and the associated costs, antibiotics should not be utilized as an additive for irrigation in orthopaedic surgery [65].

Conclusion

Most studies have not supported adding antibiotics to the saline irrigation solutions for the prevention of PJI and SSI. Although limited studies have shown the possible effect, it is not possible to simply overcome the complications of adding antibiotics, which include problems caused by wound healing, allergic reactions, associated costs, and antibiotic resistance.

Question 4: Does the use of pulsatile lavage influence the rate of SSI/PJI after major orthopaedic procedures?[4]

Response/Recommendation

There is no concrete evidence that the use of pulsatile lavage influences the rate of SSI and/or PJI.

[3] These authors contributed to Question 3: Yazdi Hamidreza, Khorrami Amir Mohsen, Kocaoglu Hakan, Ricioli Walter, Rosso Federica, Filipenko Volodymyr, Zeng Yirong, Hamad Alenezi, Roger Torga Spak

[4] These authors contributed to Question 4: Pietro Simone Randelli, Sébastien Lustig, Bishnu Pokharel, Julian Guerra-Perez, Qiaojie Wang, Federico Jose Burgo, Tobias Siegfried Kramer, Ali Albelooshi, Alessandra Menon

Level of Evidence: Limited

Delegate Vote: Agree: 76.5%, Disagree: 8.9%, Abstain: 14.7% (Strong Majority, Moderate Consensus)

Rationale

Periprosthetic joint infection is the most common reason for hospital readmission following TJA, with an estimated incidence of approximately 1 to 2% [66,67]. The risk of developing an SSI is influenced by the degree of wound contamination at the time of surgery, as well as by the contaminating pathogens and their virulence [68].

Nearly all surgeons use wound irrigation at the end of surgery, following the traditional orthopaedic maxim that "the solution to pollution is dilution."

Pulsatile lavage is one method for the delivery of irrigation solutions to the surgical site. Pulsatile lavage was originally introduced by oral surgeons during the Vietnam War as a rapid method for irrigating heavily contaminated wounds [69]. Its mechanism of action relies on mechanical forces to remove debris, necrotic tissue, and microorganisms from the surgical site [70]. Pulsatile lavage has been shown to be effective in reducing bacterial contamination on different surfaces and plays an important role in treating patients who have PJI [71,72]. High-pressure saline pulsatile lavage (0.34 N/mm^2) has been demonstrated to significantly reduce bacterial contamination in various types of wounds [7374].

However, potential negative aspects of using pulsatile lavage must be considered. An *in vitro* study on contaminated human tibial fractures found that high-pressure pulsatile lavage caused major bone damage and intramedullary bacterial seedings [75]. Additionally, recent studies show that high-pressure pulsatile lavage may propagate bacteria into soft tissue [76].

In order to answer the question posed above, we performed a comprehensive systematic review. Using the MeSH terms developed by librarians, PubMed and Embase databases were searched to identify relevant publications. Initially, 543 articles were identified that were then screened by two independent reviewers to identify 35 studies that were then reviewed in full. Of the 35 assessed studies for eligibility, only one appeared to fit the inclusion criteria. Among the remaining 34 articles, 14 were not related to our search, five lacked a clear definition of SSI/PJI, and three had no available full text. Additionally, three studies focused exclusively on adults who have suspected PJI versus aseptic failure; two were not confined to the hip or knee, two were not human studies, two had aggregated data that were impossible to extract, and one was an expert opinion article. The only article that met the eligibility criteria [77] was a prospective randomized controlled trial, which was assessed as having "some concern" regarding overall risk of bias according to the RoB2 tool and a moderate-to-low Grading of Recommendations, Assessment, Development and Evaluations of evidence quality.

A total of 356 hip surgeries were included in this study: 192 cases in the control group and 164 in the pulsatile lavage group. In the control group (192 cases), 30 cases of infection were reported, including 10 deep infections. In the pulsatile lavage group (164 cases), nine infections occurred, with three classified as deep. Consequently, the overall infection rate was 15.6% in the control group compared with 5.6% in the pulsatile lavage group, while the deep infection rates were 5.6 and 1.8%, respectively.

The distribution of infection status was significantly different between the two groups. Specifically, deep infections were 10 (5.2%) in the control group compared to 3 (1.8%) in the pulsatile lavage group ($P < 0.009$). Thus, we reject the null hypothesis that infection rates are the same in both treatment groups and conclude that there is strong evidence indicating a higher infection rate in the control group than the pulsatile lavage group.

In conclusion, the literature appears to be deficient in high-level studies that evaluate the role of pulsatile lavage in the prevention of surgical infections in patients undergoing orthopaedic procedures. Although pulsatile lavage has been shown to be effective in reducing bacterial load in *in vitro* models, there is no concrete evidence (besides one level 1 study with a limited number of subjects) that the use of pulsatile lavage is effective in reducing infection. Considering the potential concerns of using pulsatile lavage, namely the transfer of superficial organisms from skin into deeper tissues, the economic and environmental cost associated with its use, and other concerns, we feel that a high-level study with a sufficient sample size is needed to explore this issue further.

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The Journal of Arthroplasty 41 (2025) S89–S99

Contents lists available at ScienceDirect

The Journal of Arthroplasty

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General Topics

2025 ICM: Corticosteroids or Disease-Modifying Antirheumatic Drugs

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ARTICLE INFO

Article history:
Available online 28 October 2025

Keywords:
rheumatoid arthritis
disease-modifying antirheumatic drugs
perioperative management
arthroplasty
surgical site infection
orthopaedic

Question 1: Should disease-modifying antirheumatic drugs (DMARDs) be stopped before major orthopaedic procedures?[1]

Response/Recommendation: Yes, biological and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs and tsDMARDs) should be stopped before major orthopaedic procedures. The exact time to withhold the drugs depends on the half-life of these drugs.

Level of Evidence: Strong

Delegate Vote: Agree: 85.2%, Disagree: 7.4%, Abstain: 7.4% (Super Majority, Strong Consensus)

Rationale

Disease-modifying antirheumatic drugs (DMARDs) are classified in this paper as proposed at the European League Against Rheumatism in 2013 [1]. This classification categorizes DMARDs based on their method of production into synthetic DMARDs and bDMARDs. Synthetic DMARDs are subdivided into conventional synthetic DMARDs (csDMARDs) and tsDMARDs [2]. These immunosuppressive and immunomodulatory therapies are used across a broad spectrum of rheumatic and musculoskeletal diseases [3]. These conditions include spondyloarthritis, juvenile idiopathic arthritis, autoimmune or connective tissue disorders such as systemic lupus erythematosus (SLE), and inflammatory bowel disease, as well as rheumatoid arthritis (RA) [4,5]. It is common to encounter patients undergoing major orthopedic procedures, such as total joint arthroplasty, who are taking DMARDs [6,7]. Patients who have inflammatory arthritis, such as RA, are known to have an increased risk of infections, and the use of DMARDs may further elevate this risk [3,8–15]. However, as active RA is also a risk factor for infection, balancing infection risk in the perioperative period is challenging [8,16]. Other complications, such as hip dislocation, venous thromboembolism, acute kidney damage, and cardiac complications, are also higher in patients who have inflammatory arthritis compared to those who have osteoarthritis [9,17].

The current question explores the potential risk of DMARDs and the subsequent risk of Surgical Site Infection after major orthopedic procedures. We conducted a systematic review, using

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to 10.1016/j.arth.2025.08.042.

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https://doi.org/10.1016/j.arth.2025.08.042
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specific Medical Subject Headings terms developed by librarians, to identify all relevant publications in the Medline and Embase databases, covering studies published up to November 2024. Search results yielded 426 publications in the English language. There were two authors who went through the title and abstract screening, and discrepant results were adjudicated by a third person. Then, 142 full articles were reviewed. Finally, 70 articles were included in this systematic review, and 38 articles were referenced in this manuscript. Particular attention was given to the new evidence and updated recommendations that have emerged since the previous international consensus meeting in 2018. There was one author who prepared the initial draft, and all contributors reviewed, provided feedback, and approved the final version.

The DMARDs play a crucial role in controlling disease activity and improving daily function in patients who have inflammatory conditions, but careful monitoring is essential to mitigate potential adverse effects, especially Surgical Site Infection during major orthopaedic procedures [3,9,10,14]. While the use of DMARDs may increase the risk of infections, discontinuation of DMARDs carries the potential to trigger disease flare-ups, since RA patients who have high disease activity are reported to experience frequent postoperative flare-ups, predicted to flare by six weeks [9,18–20].

In 2017, Goodman et al., in collaboration with the American College of Rheumatology (ACR) and the American Association of Hip and Knee Surgeons (AAHKS), developed evidence-based recommendations for continuing or withholding both conventional and bDMARDs perioperatively for total hip arthroplasty and total knee arthroplasty [18]. This content has been directly adopted in the international consensus meeting 2018. In addition, the British Society for Rheumatology also published safety guidelines related to DMARDs in 2019. Russell et al. also published a consensus statement for perioperative management of medication for rheumatologic and HIV disease in 2022 as a practical guideline from the Society for Perioperative Assessment and Quality Improvement [21]. In their document, it was recommended to take most immunosuppressant medications perioperatively, including on the day of surgery, except for cyclophosphamide, which was to be held for four weeks. For bDMARDs, most biologic agents were recommended to be held for an entire dosing cycle, except belimumab for severe SLE and the anti-interferon agent of anifrolumab, which were recommended for continuing. The Janus kinase (JAK) inhibitors were recommended to be held for three days preoperatively [21]. There is some evidence suggesting that JAK inhibitors may increase the risk of thrombotic events, raising concerns about whether patients receiving JAK inhibitor therapy should be considered high-risk for deep vein thrombosis/pulmonary embolism and managed with appropriate prophylaxis [22]. Further investigation on this matter is warranted.

The first ACR/AAHKS recommendation was updated in 2022 by convening a panel of rheumatologists, orthopedic surgeons, and infectious disease specialists. This updated guideline includes recently introduced immunosuppressive medications [23]. In the 2022 ACR/AAHKS recommendations, the use of csDMARDs remained unchanged, with the addition of apremilast as a medication. The guideline continues to conditionally recommend their perioperative continuation. Alternatively, regarding bDMARDs, various new drugs have become available since the 2017 guidelines, and several revisions have been made concerning their perioperative use. The summary of the 2022 ACR/AAHKS recommendations is presented in Table 1.

In 2023, Albrecht et al., in collaboration with the German Society for Rheumatology, published an updated recommendation regarding perioperative DMARDs use [24]. They recommended reducing the glucocorticoid dose to as low as possible two to three months before elective surgery (in any case $<$ 10 mg/d) but keeping the dose stable one to two weeks before and on the day of surgery. They recommended continuing csDMARDs, exceptions being a reduction of high methotrexate doses to $\leq$ 15 mg/wk and washout of leflunomide in patients at high risk of infection. They recommended that azathioprine, mycophenolate, and ciclosporin should be paused one to two days before surgery; JAK inhibitors should be paused three to four days before surgery; and, in patients undergoing bDMARDs treatment, surgery should be scheduled for the end of each treatment interval.

In 2024, James et al. published a perioperative management of systemic immunomodulatory agents in patients who have psoriasis and psoriatic arthritis [25]. In this review, tumor necrosis factor (TNF)-α inhibitors, abatacept, methotrexate, and cyclosporine were recommended to be continued through low-risk surgery. Alternatively, in patients undergoing total knee arthroplasty or total hip arthroplasty, the recommendations align with the 2022 ACR/AAHKS guideline to hold TNF-α inhibitors for one full dosing interval. Some studies have reported that the continuation of bDMARDs is not associated with an increased risk of infection [26,27]; however, a 2024 meta-analysis reported that the continued use of bDMARDs increases the risk of postoperative infection in orthopaedic surgeries [12]. Ongoing clinical studies are being conducted to ensure the safer use of DMARDs, and further evidence is anticipated to be established [28].

The reviewed studies and guidelines also focus on major orthopaedic procedures that include upper-extremity surgery, foot and ankle surgery, and spine surgery, but the evidence remains limited [29–32]. Saunders et al. conducted a critical analysis review in 2021 on the use of DMARDs in RA and SLE patients undergoing foot and ankle surgery. Their recommendations align closely with the 2017 ACR/AAHKS guidelines. They recommended the continuation of csDMARDs, withholding bDMARDs and JAK inhibitors before surgery, and resuming bDMARDs and JAK inhibitors only after the surgical wound shows signs of healing. In addition, they highlighted differences in the duration of drug discontinuation between severe and nonsevere SLE. For glucocorticoids, they recommended tapering to $\leq$ 20 mg/d whenever possible [33]. Hresko et al. conducted a review in 2022 on the use of DMARDs in hand and upper-extremity procedures for RA patients. Their recommendations are also adapted from the 2017 ACR/AAHKS guidelines, suggesting the continuation of low-dose corticosteroids ($\leq$ five mg/day) and csDMARDs, withholding bDMARDs for one dosing interval, and discontinuing JAK inhibitors for seven days before surgery. For high daily corticosteroid doses ($>$ 20 mg/day), individualized evaluation is recommended [34].

Despite the existence of various guidelines for major orthopedic procedures, evidence and expert consensus about recommendations for perioperative management of DMARDs in spine surgery have been limited. Several original and review articles have aimed to determine the association between DMARD use and clinical outcomes in patients undergoing spine surgery [35,36]. In 2021, Gaudiani et al. conducted a retrospective review to evaluate the association between preoperative DMARD use within 90 days before surgery and reoperation rates in patients undergoing spinal fusion [37]. The study included 90 patients in the TNF-α inhibitor group, 90 in the other DMARD group, and 123 in the control group. The odds of reoperation within one year were 3.1 (95% confidence interval: 1.4 to 7.0) and 2.2 (95% confidence interval: 0.96 to 5.3) times higher in the TNF-α inhibitor and other DMARD groups, respectively, compared to the control group. This study highlights the potential risk of DMARD use for reoperation in patients who have rheumatic and musculoskeletal diseases undergoing spinal fusion. Streufert et al. conducted a systematic review and meta-analysis in 2022. This meta-analysis included 703 patients who had RA and 2,569 patients who did not have RA from nine studies,

Table 1
The Summary of the 2022 ACR/AAHKS Recommendations for the Perioperative Management of DMARDs in Patients With Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty.

	Dosing Interval	Recommended Timing of Surgery Since Last Medication Dose
I. Medications to continue through surgery		
csDMARDs: continue through surgery (all patients)		
Methotrexate	Weekly	Anytime
Sulfasalazine	Once or twice daily	Anytime
Hydroxychloroquine	Once or twice daily	Anytime
Leflunomide (Arava)	Daily	Anytime
Doxycycline	Daily	Anytime
Apremilast (Otezla)[a]	Twice daily	Anytime
Glucocorticoids (all patients)[a,c]	Daily	Anytime
Severe SLE-specific medications: continue these medications in the perioperative period in consultation with the treating rheumatologist		
Mycophenolate motetil	Twice daily	Anytime
Azathioprine	Daily or twice daily	Anytime
Cyclosporine	Twice daily	Anytime
Tacrolimus	Twice daily (IV and PO)	Anytime
Rituximab (Rituxan)[a]	IV every 4 to 6 months	Month 4 to 6
Belimumab SC (Benlysta)[a]	Weekly	Anytime
Belimumab IV (Benlysta)[a]	Monthly	Week 4
Anifrolumab (Saphnelo)[a]	IV every 4 week	Week 4
Voclosporin (Lupkynis)[a]	Twice daily	Anytime
II. Medications to withhold prior to surgery[d]		
bDMARDs (all patients): Withhold these medications through surgery		
Infliximab (Remicade)	Every 4, 6, or 8 week	Week 5, 7, or 9
Adalimumab (Humira)	Every 2 week	Week 3
Etanercept (Enbrel)	Every week	Week 2
Golimumab (Simponi)	Every 4 week (SQ) or every 8 week (IV)	Week 5 or week 9
Abatacept (Orencia)	Monthly (IV) or weekly (SC)	Week 5 or week 2
Certolizumab (Cimzia)[a]	Every 2 or 4 week	Week 3 or 5
Rituximab (Rituxan)	2 doses 2 week apart every 4 to 6 month	Month 7
Tocilizumab (Actemra)	Every week (SC) or every 4 week (IV)	Week 2 or week 5
Anakinra (Kineret)	Daily	Day 2
IL-17 secukinumab (Cosentyx)[a]	Every 4 week	Week 5
Ustekinumab (Stelara)	Every 12 week	Week 13
Ixekizumab (Taltz)[a]	Every 4 week	Week 5
IL-23 guselkumab (Tremfya)[a]	Every 8 week	Week 9
JAK inhibitors (all patients): Withhold these medications 3 day prior to surgery		
Tofacitinib (Xeljanz)	Daily or twice daily	Day 4[b]
Baricitinib (Olumiant)	Daily	Day 4[b]
Upadacitinib (Rinvoq)	Daily	Day 4[b]
Not severe SLE: Withhold these medications 1 week prior to surgery		
Mycophenolate motetil	Twice daily	1 week after last dose[b]
Azathioprine	Daily or twice daily	1 week after last dose[b]
Cyclosporine	Twice daily	1 week after last dose[b]
Tacrolimus	Twice daily (IV and PO)	1 week after last dose[b]
Rituximab (Rituxan)[a]	Every 4 to 6 month	Month 7
Belimumab IV (Benlysta)[a]	Monthly	Week 5
Belimumab SC (Benlysta)[a]	Weekly	Week 2

[a] Medications added from ICM 2018.
[b] Recommendations that has changed since ICM 2018.
[c] Continuing their current daily dose rather than administering supraphysiologic doses of glucocorticoids on the day of surgery.
[d] Resuming medications withheld before surgery is conditionally recommended once the wound shows evidence of healing, typically about 14 day after surgery. Evidence of healing includes the absence of sutures or staples out, swelling, erythema, or drainage, and signs of surgical site infection.

Table 2
The Current Recommendations of the International Consensus Meeting (2025).

Patients with RA, AS, PsA, or JIA undergoing THA or TKA, continuation of csDMARDs, withholding biological DMARDs for one dose cycle, and with holding Janus Kinase inhibitors at least 3 days before surgery is conditionally recommended.
Patients with SLE undergoing THA or TKA, continuation of csDMARDs is conditionally recommended but depending on the severity of SLE, recommendations for continuing or withholding immunosuppressive or biological medications differ and final decisions should be made in consultation with the treating rheumatologist.
Patients with RA, AS, PsA, or SLE undergoing THA or TKA and receiving glucocorticoids for their rheumatic condition, continuation of the current daily dose of glucocorticoids rather than administering supraphysiologic doses of glucocorticoids on the day of surgery is conditionally recommended.
For other major orthopaedic procedures (e.g., upper limb or foot and ankle surgeries, and spinal surgeries), where evidence is limited, decisions should be made in consultation with the treating rheumatologist, referencing the optimization strategies used for THA and TKA until evidence specific to that procedure becomes available.
Resuming medications withheld before surgery is conditionally recommended once the wound shows evidence of healing, typically around 14 days postsurgery.

comprising seven retrospective cohort studies, one prospective cohort study, and one case-control study [38]. The analysis revealed that the relative risk of infection was 2.29 times higher in patients who have RA compared to those who do not have RA. In addition, the management of antirheumatic medication in the perioperative period for spine surgery was reviewed in seven articles, encompassing a total of 226 patients undergoing spine surgery. The findings indicated major variability in the timing, cessation, or continuation, and types of medications used, making it challenging to derive conclusive recommendations. However, it was emphasized that all RA patients should be perioperatively comanaged by a rheumatologist. The study also noted that, as in other areas of surgical practice, spine surgery requires further investigation to develop specific, patient-centered guidance for perioperative medication management to optimize patient outcomes and minimize risks.

In conclusion, many current guidelines recommend the continuation of csDMARDs, while suggesting a temporary discontinuation period for bDMARDs and tsDMARDs. There are conflicting results regarding the discontinuation of bDMARDs, and future studies with higher levels of evidence may lead to changes in optimal usage. However, based on our understanding of all the available evidence, we present our recommendations as outlined in Table 2.

Question 2: Does the use of anabolic corticosteroids increase the risk of superficial site infection and periprosthetic joint infection in patients undergoing major orthopaedic surgery?[2]

Response/Recommendation: Testosterone replacement (TRT) therapy is associated with a higher rate of all-cause revision and infection following major orthopaedic procedures. However, current data do not support routine perioperative discontinuation of TRT.

Strength of the Recommendation: Limited (Level IV)

Delegate Vote: Agree: 80.9%, Disagree: 8.5%, Abstain: 10.6% (Super Majority, Strong Consensus)

Rationale

Anabolic corticosteroids refer to synthetic derivatives of testosterone, and differentiating between their usage for performance enhancement versus TRT is essential. Use of anabolic corticosteroids for performance-enhancing purposes involves supraphysiological doses and is a public health risk linked to hypogonadism, cardiac impairment, neurodegeneration, coronary artery disease, and sudden cardiac death [39]. Ethical concerns and unreliable survey data in target populations limit knowledge of the long-term effects of anabolic corticosteroid abuse. In contrast, TRT aims to restore physiological levels in cases of hypogonadism and age-related testosterone decline. The hypogonadism in men study reported a 38.7% prevalence of hypogonadism (total testosterone < 300 ng/dL) in men aged 45 years and older, with higher rates in those with conditions such as hypertension, diabetes, and obesity [40]. Testosterone levels decrease by about 1% annually after age 40 years [41], and TRT has demonstrated benefits for bone density, muscle mass, body composition, sexual function, mood, erythropoiesis, and quality of life [42]. Most TRT prescriptions are written by primary care physicians, predominantly for older men who have age-related testosterone decline [43]. In this review, all studies address anabolic corticosteroids in the context of TRT.

This systematic review identified only one study directly examining the association between anabolic corticosteroid use and Surgical Site Infection/periprosthetic joint infection (PJI) risk in orthopaedic patients [44]. This retrospective study, involving 367 cases of joint-related complications in patients with TRT undergoing total hip arthroplasty (THA) and 1,151 in those with TRT undergoing total knee arthroplasty (TKA), revealed significantly higher rates of revision surgeries and PJI. This may be explained by the potential immunosuppressive effects of anabolic corticosteroids and increased skin flora burden. In addition, pre-existing bone health deterioration from prolonged low testosterone levels before initiation of hormone replacement therapy may not be fully mitigated by TRT, leading to increased postoperative complications.

A recent meta-analysis on sex-related differences in PJI treatment with debridement, antibiotics, and implant retention found higher infection eradication rates in women, suggesting a potential immunosuppressive effect of testosterone [45]. In addition, a correlation between serum testosterone levels and infection risk has been observed following total shoulder arthroplasty (TSA); men were identified as a risk factor for deep periprosthetic infections [46]. This increased risk may be partly due to the skin burden of *Cutibacterium acnes* (*C. acnes)*, which causes about 19% of infections post-TSA and has been identified as a predictor of deep *C. acnes* infection in revision cases [47,48]. Elevated testosterone levels in patients on TRT may promote *C. acnes* colonization [47]. Longwolf et al. similarly identified a significantly higher risk of vascular graft infections in hypogonadal men on TRT, particularly in lower extremities and procedures near the groin, where skin flora pose increased risks [49]. Despite these findings, current data do not support the routine discontinuation of TRT in the perioperative period.

The TRT may be correlated with increased risk of musculotendinous injury and subsequent repair failure [44]. Recent studies indicate that TRT is associated with a threefold increase in rotator cuff tears and a twofold increase in distal biceps ruptures, with TRT patients being more likely to require repeat rotator cuff repairs; meanwhile, androgen deficiency has also been linked to

[2] These authors contributed to Question 2: Felipe Moreira Borim, Cindy Zeng, Ernesto Guerra-Farfan, Serban Dragosloveanu, Prieto Hernan, Seok Ha Hong, Seung-Beom Han, Timothy Lording

higher rates of rotator cuff tears. Thus, further prospective studies are needed to better understand TRT's effects on musculotendinous injuries and healing [50–52].

Using the PearlDiver claims database, Collins et al. compared patients receiving perioperative TRT with controls undergoing THA and TKA. Within 2 years post-THA, the TRT cohort exhibited higher rates of all-cause revision (3.57 versus 2.34%; odds ratio (OR) 1.46; 95% confidence interval (CI), 1.21 to 1.75) and PJI (2.16 versus 1.43%; OR 1.67; 95% CI, 1.31 to 2.09). For TKA, the TRT group also had significantly elevated rates of septic revision (1.40 versus 0.95%; OR 1.44; 95% CI, 1.19 to 1.76), aseptic revision (3.05 versus 2.48%; OR 1.20; 95% CI, 1.05 to 1.37), all-cause revision (3.62 versus 2.78%; OR 1.27; 95% CI, 1.13 to 1.44), periprosthetic fracture (0.27 versus 0.21%; OR 1.53; 95% CI, 1.00 to 2.29), and aseptic loosening (0.97 versus 0.73%; OR 1.34; 95% CI, 1.06 to 1.69). Notably, the TRT cohort had fewer instances of manipulation under anesthesia/lysis of adhesions (4.30 versus 4.63%; OR 0.90; 95% CI, 0.81 to 1.00). However, the authors caution that while TRT is associated with poorer outcomes postarthroplasty, this does not imply causation [44]. The increased complication risk may reflect the long-term effects of untreated low testosterone levels, such as reduced bone mineral density, before the initiation of TRT and joint arthroplasty.

The limited scope of available studies presents major challenges to the reliability of these findings. Therefore, more comprehensive research on TRT in orthopaedic contexts is necessary to elucidate its safety, efficacy, and potential impacts on clinical outcomes.

Conclusions

The TRT–THA has been associated with higher rates of all-cause joint revisions and PJI [44]. Similarly, TRT–TKA has been linked to significantly increased rates of septic revision, all-cause revision, periprosthetic fractures, and aseptic loosening [44]. In TSA, a correlation has been observed between serum testosterone levels and infection risk [46]. Despite these risks, TRT may offer orthopedic benefits, including accelerated rehabilitation, improved recovery, enhanced bone-implant integration, and increased overall bone mineral density [53]. Clinicians must carefully weigh the potential immunomodulatory risks of anabolic corticosteroids against the adverse effects of chronic low testosterone levels on bone health, particularly in high-risk patients. Further research is essential to better understand the safety, efficacy, and clinical implications of TRT in orthopedic settings.

Question 3: Does chronic use of preoperative oral corticosteroids increase the risk of surgical site infection (SSI)/periprosthetic joint infection (PJI) in patients undergoing major orthopaedic surgery?[3]

Response/Recommendation

Yes. Chronic use of preoperative oral corticosteroids is associated with increased odds of developing SSI/PJI in patients undergoing major orthopaedic surgery.

Level of Evidence: Low

Strength of Recommendation: Limited

Delegate Vote: Agree: 92.7%, Disagree: 4.9%, Abstain: 2.4% (Unanimous, Strongest Consensus)

Rationale

Chronic preoperative use of oral corticosteroids has long been proposed to increase the risk of SSI and PJI in patients undergoing major orthopaedic surgery, with major costs to the patient and health care system [54,55]. However, prior studies have reported conflicting findings regarding the extent of this risk [56–59]. The challenge is further compounded in immunocompromised patients, who often require potent immunosuppressive medications that make it difficult to establish the relationship between corticosteroid use and infection risk [60–62]. Addressing this multifaceted issue requires a detailed exploration of several variables, including the type of surgery (e.g., spine, arthroplasty, arthroscopy, hand), the specific corticosteroid used, the duration and dosage of preoperative corticosteroid use, the timing of infection onset, patient comorbidities (such as autoimmune disorders), smoking status, and whether the studies provide recommendations on withholding corticosteroids preoperatively.

After screening 774 articles, full-text review of 64, and extraction of 38 articles, with removal of three duplicates and exclusion of four articles due to wrong study outcome, 31 studies reporting SSI and/or PJI met our inclusion criteria (Table 3). Studies included hip and knee arthroplasty, shoulder and knee arthroscopy, and hand surgery, with the two most numerous studies reporting on hip and knee arthroplasty and spine surgery. Patients within the studies were mostly all-inclusive, with six studies strictly looking at immunocompromised patients, including those who have rheumatoid arthritis and inflammatory bowel disease. We were able to compile and extract studies reporting on infection-related outcomes on 1,317,506 patients from 2008 to 2024, with 98,668 patients on chronic oral corticosteroids. There were 21 database studies and 10 practice registries from several countries, including Brazil, Spain, France, Denmark, China, and Japan, with the majority of the studies coming from the USA and from the National Surgical Quality Improvement Program (NSQIP). Since most studies were from NSQIP, the majority had only one month of follow-up but ranged up to 84 months. The studies reported a patient age range of 32 to 70 years, a women composition of 37 to 88%, and, among the 14 studies reporting race/ethnicity, eight were majority White, reflecting the demographics of their respective countries. Other variables such as American Society of Anesthesiologists, body mass index, corticosteroid type, and corticosteroid dosage were not reported in large enough numbers. The definition of chronic corticosteroid use also varied, with some defining it as 90 days of use before index surgery [63] or 30 days [64]; however, the majority of studies used NSQIP, which has a definition of 10 days of use in the last 30 days before surgery.

From the mentioned variables, we were able to stratify and isolate groups with confounding risk factors for infection, particularly immunocompromised patients and the type of surgery. Additional risk factors, such as dosage, duration, and corticosteroid type, along with other patient comorbidities, were considered, though studies lacked sufficient reporting on these factors.

Data from the studies were presented as dichotomous variables and odds ratios (ORs) with 95% confidence intervals (CIs). Dichotomous data were converted into 2 × 2 contingency tables, and ORs, 95% CIs, effect sizes, and standard errors were calculated for consistency. A meta-analysis was performed using Jamovi software (version 2.6.19.0, Sydney, Australia). A random-effects model was applied for the meta-analysis to account for variability among studies due to differences in populations, surgical procedures, and definitions of chronic corticosteroid use. This approach was deemed appropriate given the potential heterogeneity in the included studies. The heterogeneity was quantitatively assessed, with an I^2 value of 0.43% and τ^2 of 1e-04, indicating very low heterogeneity across the dataset. In addition, the Q-statistic was not significant ($P = 0.864$), further supporting the homogeneity of the study results. Forest plots were used to visualize effect sizes with 95% CI, and subgroup analyses were conducted to

[3] These authors contributed to Question 3: Zachary C. Lum, Joao M. Barretto, Udo E. Anyaehie, Amir Khoshbin, Gwo Chin Lee, Zongke Zhou, Wenwei Qian, Felipe M. Borim

Table 3
Table of Studies Included in the Analysis. Odds Ratio of Steroid Cohort Compared to Nonsteroid Cohort in Development of SSI/PJI.

Study Name	Year	Country	Database or Practice Registry	Level of Evidence	Total Sample Size	Type of Surgery	Immunosuppressed Patients? (Y/N)	Odds Ratio	95% CI Lower	95% CI Upper	Absolute SSI/PJI Risk %
Bains	2024	USA	Database, Pearldiver	3	42,340	TKA	Y	1.62	1.16	2.28	
Boddapati	2018	USA	Database, NSQIP	3	7,246	THA	N	1.92	0.95	3.86	0.63
Castano-Betancourt	2018	Brazil	Practice registry	3	598	THA, TKA	Y	3.16	1.39	7.22	
Cloney	2018	USA	Database, NSQIP	3	8,492	Posterior lumbar fusion	N	1.66			3.7
Cordero-Ampuero	2010	Spain	Practice registry	4	247	THA, hip hemiarthroplasty	N				
Cordtz	2018	Denmark	Database, Danish registry	4	1,946	THA, TKA	Y	2.12	0.9	4.98	
Everhart	2017	USA	Practice registry	4	707	TSA, shoulder hemiarthroplasty	N	8.16	2.14	31	
Fassler	2023	USA	NSQIP	3	39,876	Arthroscopic rotator cuff repair	N	0.3498	0.0215	5.6085	0
George	2019	USA	Database, Truven Marketscan + Medicare		10,923	Hip or knee arthroplasty	Y	1.4456	1.1154	1.8735	2.7
Gupta	2023	USA	Database, NSQIP	4	6,169	Hip hemiarthroplasty	N	2.304	1.128	4.704	
Haft	2024	USA	Database, Pearldiver	3	15,217	TKA	N	1.3	1.01	1.69	
Inoue	2022	Japan	Practice registry	3	1,128	THA, TKA	N	1.2923			1.7
Kebaish	2021	USA	Database, NSQIP	3	140,519	Posterior lumbar spine surgery	N	2.0113			3.0
Kittle	2020	USA	Database, NSQIP	3	403,546	THA, TKA, revision THA, revision TKA	N	1.5768			1.1
Koyama	2016	Japan	Practice registry	4	47	Spinal surgery	Y	1.263			
Latourte	2017	France	Database, Orencia RA registry	4	244	All orthopedic surgery	Y	3.012	0.1113	81.528	2.2
Lee	2020	USA	Database, NSQIP	3	1,188	ACDF	N	0.6165	0.1161	3.2733	0.51
Li	2023	China	Practice registry	3	650	TKA	N	4.023	1.276	12.683	4.5
Newton	2024	USA	Database, NSQIP	3	1,298	Wrist fusion, PRC, 4 corner fusion	N	3.2885	0.6882	15.71	2.2
Salt	2017	USA	Database, commercial insurance	4	2,212	TKA, THA	N	1.59	1.28	1.97	
Sciubba	2008	USA/ Canada	Practice registry	3	46	Sacral tumor resection	N				
Singla	2019	USA	Database, Pearldiver	3	360,005	Lumbar fusion surgery	N	1.88	1.41	2.01	2.8
Smolev	2024	USA	NSQIP	3	6,273	ORIF proximal humerus fracture	N	1.105	0.251	4.8667	0.94
Sugita	2016	Japan	Practice registry	3	279	Posterior spine surg and radiation for mets	N	2.9806	1.5141	5.8678	25.3
Thomas	2023	USA	Database, NSQIP	3	199,733	Lumbar spine surgery	N	2.0915	1.861	2.3505	3.2
Tihista	2020	USA	Database, NSQIP	3	26,734	Spine surgery, lumbar decompression	N	2.2493	1.3168	3.8422	2.4
Vasavada	2024	USA	Practice registry	3	1,315	Arthroscopy of knee, hip, shoulder, ankle, elbow	Y	3.65	0.4206	31.677	1.4
Xiao	2023	China	Practice registry	3	335	Endoscopic lumbar discectomy	N	7.65			
Westerman	2017	USA	Database, NSQIP	4	6,398	ACL surgery	N	3.02			
Gregory	2019	USA	Database, MarketScan	3	1,259	TKA, THA, TSA	Y	4.6			
Kawata	2018	Japan	Database, Japanese	3	30,536	ACL reconstruction	N	8.8074			

DMARD, disease-modifying antirheumatic drug; csDMARD, conventional synthetic DMARD; SLE, systemic lupus erythematosus; THA, total hip arthroplasty; TKA, total knee arthroplasty; JIA, juvenile idiopathic arthritis.Data were reproduced based on 2017, 2022 ACR/AAHKS guideline, and 2018 International consensus meeting (ICM) [4].
IV, intravenous; SC, subcutaneous; PO, oral; DMARD, disease-modifying antirheumatic drug; ACR, American College of Rheumatology; AAHKS, American Association of Hip and Knee Surgeons; csDMARD, conventional synthetic DMARD; bDMARD, biological DMARD; SLE, systemic lupus erythematosus; JAK, Janus kinase.NSQIP, National Surgical Quality Improvement Program; TKA, total knee arthroplasty; THA, total hip arthroplasty; TSA, total shoulder arthroplasty; ACDF, anterior cervical disc fusion; PRC, proximal row carpectomy; ORIF, open reduction internal fixation; ACL, anterior cruciate ligament; RA, rheumatoid arthritis; CI, confidence interval; SSI, Surgical Site Infection; PJI, periprosthetic joint infection.

stratify results based on patient characteristics (e.g., immunocompromised versus nonimmunocompromised) and types of surgery (e.g., spine surgery, hip and knee arthroplasty, and other orthopedic procedures). The findings were validated by analyzing back-transformed log ORs across the included studies.

When analyzing all orthopaedic surgeries combined, patients on preoperative oral corticosteroids had increased odds of sustaining SSI/PJI 2.34 OR [95% CI 1.27 to 4.22] in practice registries and OR 1.85 [95% CI 1.63 to 2.06] in database studies (Figures 1 and 2). Studies focusing on immunocompromised individuals (e.g., those who have rheumatoid arthritis or inflammatory bowel disease) reported an OR 1.71 [1.21 to 2.43] for SSI/PJI when comparing corticosteroid users to nonusers. In addition, studies on non-immunocompromised patients found an OR 1.88 [1.66 to 2.10] between corticosteroid and noncorticosteroid users. Across all different procedure types, the risk of developing SSI/PJI was higher

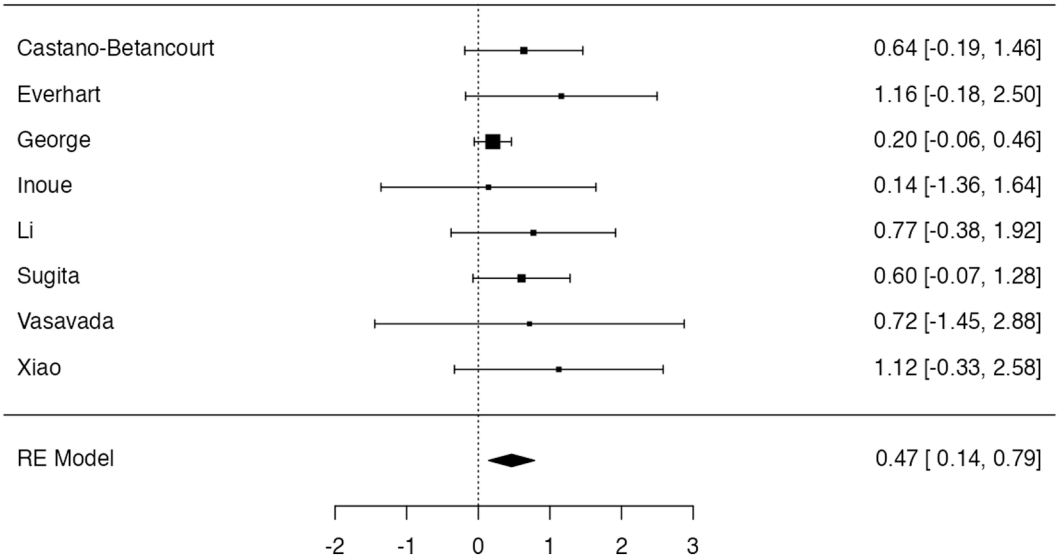

Figure 1. Forest plot of the effect size of only practice registries. Backlog odds transformation shows increased odds of SSI/PJI with chronic preoperative corticosteroid use of 2.34 odds ratio [95% CI 1.3 to 4.2]. SSI, Surgical Site Infection; PJI, periprosthetic joint infection; OR, odds ratio; CI, confidence interval; RE, random effect.

in corticosteroid users: spine surgery OR 2.02 [1.75 to 2.34], hip and knee arthroplasty OR 1.60 [1.33 to 1.88], and other orthopaedic surgeries, which showed the highest risk OR 4.75 [1.81 to 12.44] (Figures 3 through 5).

Chronic preoperative oral corticosteroids appear to have a major impact on the incidence of SSI/PJI. There were twenty of the included studies that concluded that SSI/PJI was increased in this patient population. Several others [65] had trended toward an increased odds of infection or were likely underpowered to detect a difference in infection rate [56,66].

Interestingly, immunocompromised patients had higher, yet smaller, odds of developing SSI/PJI, likely due to their comparator group, which had a combination of disease-modifying antirheumatic drugs and biologic medications, which have been reported to have higher SSI/PJI compared to conventional oral corticosteroids [67]. In addition, spine surgery had slightly elevated odds of SSI, as expected, but not as elevated as we would have imagined. This may be because the effects were expressed in OR and not absolute values, and groups within the corticosteroid spine cohort were compared to noncorticosteroid spine cohorts as well. Similarly, hip and knee arthroplasty studies had slightly lower odds of SSI/PJI, which may be expected compared to other types of orthopedic surgeries.

The remainder of orthopaedic surgeries (arthroscopy, wrist fusion, shoulder arthroplasty, and ACL reconstruction) had the highest odds of SSI/PJI, with two studies [68,69] contributing the most to this elevated risk. There were nine studies that investigated various types of orthopaedic surgeries, with these two studies accounting for over half of the weight in the analysis, both reporting significant associations between preoperative oral

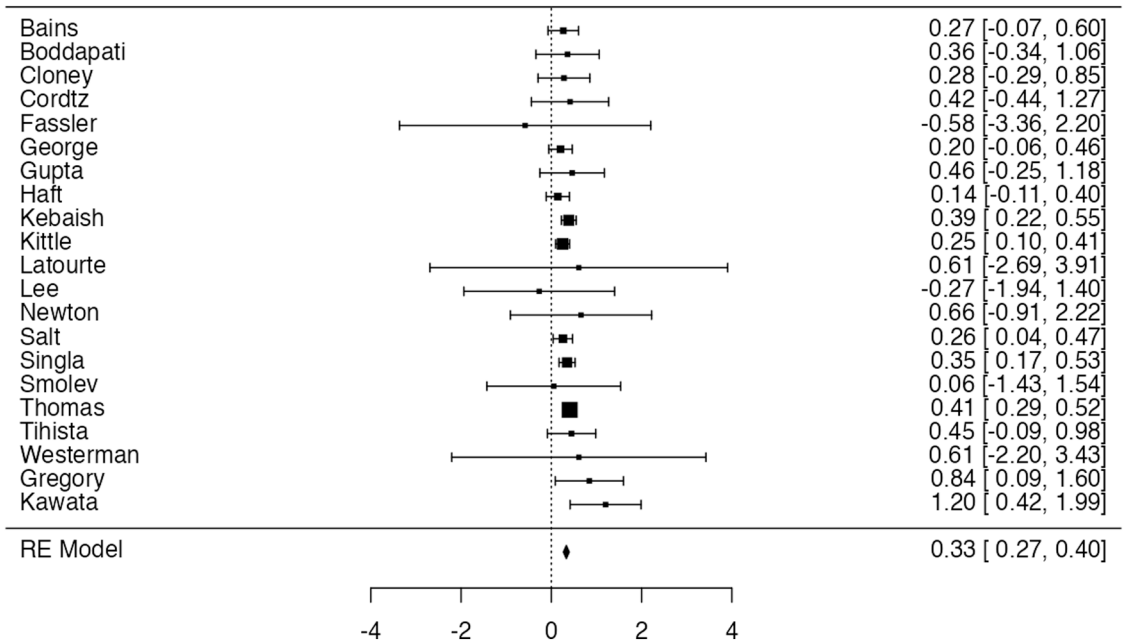

Figure 2. Forest plot of database studies only. Backlog odds transformation shows increased odds of SSI/PJI with chronic preoperative corticosteroid use of OR 1.85 [95% CI 1.6 to 2.1]. SSI, Surgical Site Infection; PJI, periprosthetic joint infection; OR, odds ratio; CI, confidence interval; RE, random effect.

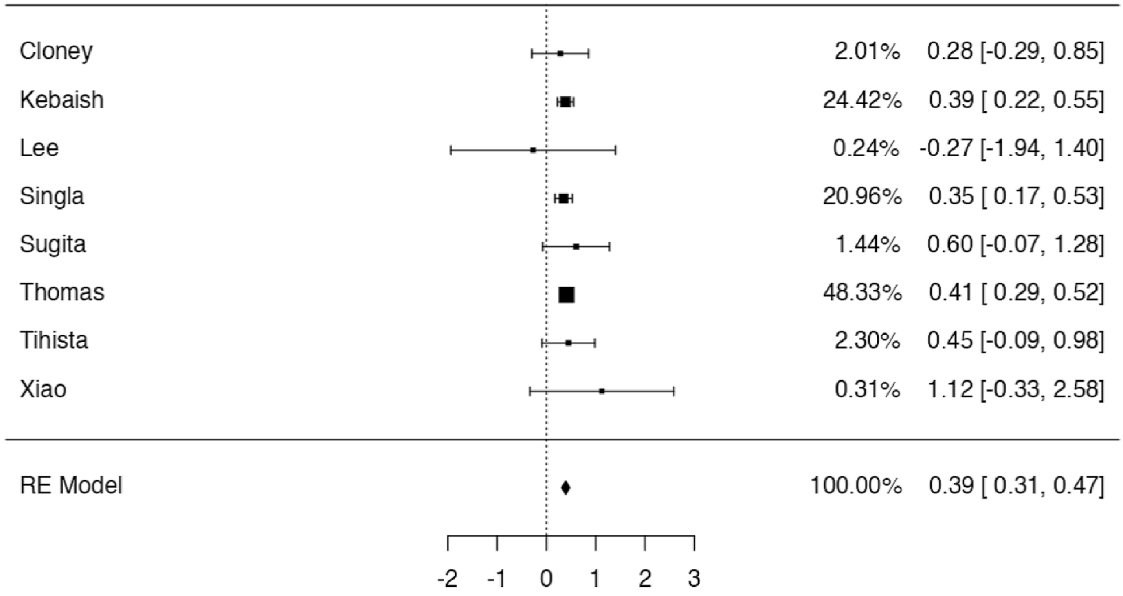

Figure 3. Forest plot of spine studies by effect size. RE, random effect.

corticosteroids and increased SSI/PJI risk. Only one arthroscopy study [68] out of four [61,70,71] suggested that chronic oral corticosteroid use heightened the risk of SSI/PJI. This discrepancy may be attributed to the low absolute values of SSI/PJI in these studies, where even small increases in absolute values translate into substantial OR changes. For example, Kawata et al. reported an absolute SSI/PJI rate of 1.2% in the noncorticosteroid group versus 9.7% in the corticosteroid cohort, while other arthroscopy studies reported noncorticosteroid rates of 0.1, 0.4, and 0.6%, and corticosteroid rates of 0, 1.4, and 0%, respectively [61,70,71]. Everhart et al. highlighted the risk of infection in shoulder arthroplasty with an OR of 8.16 and wide 95% CI (2.1 to 31.0), indicating a potentially strong association but with substantial uncertainty. This variability underscores the need for caution in interpreting such findings, particularly when CI are broad, reflecting imprecision in the estimates due to smaller sample sizes or low event rates. The study further emphasizes the importance of contextualizing these results within specific surgical procedures and patient populations to better understand the underlying risks and to develop tailored strategies for mitigating infection in corticosteroid-using patients.

There were several potential limitations of this analysis. Since we had a relatively large, inclusive group of studies, a combined analysis of all orthopedic surgeries can confer too much heterogeneity in the analysis. However, our I^2 by restricted maximum-likelihood random effects model reported a Tau^2 of 1e-04, I^2 of 0.43%, and H of 1.004, indicating low heterogeneity of the data. We also evaluated practice registries and database registries separately, acknowledging their inherent differences. In addition, our analysis included immunocompromised patient populations that had competing risks of SSI/PJI with immunomodulatory drugs and

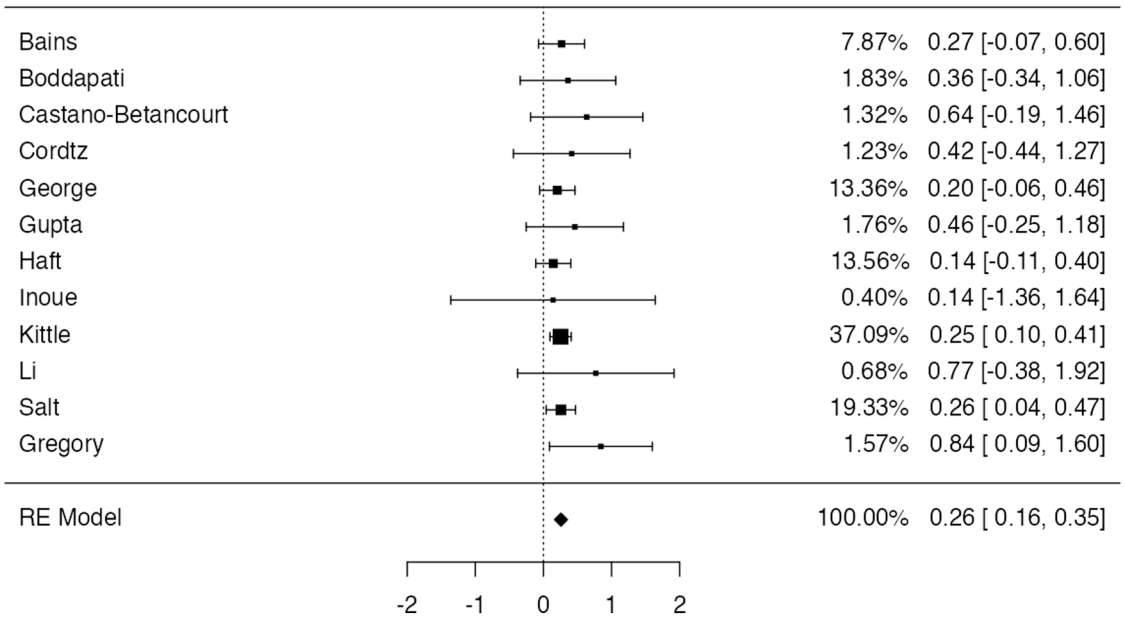

Figure 4. Forest plot of arthroplasty studies by effect size. RE, random effect.

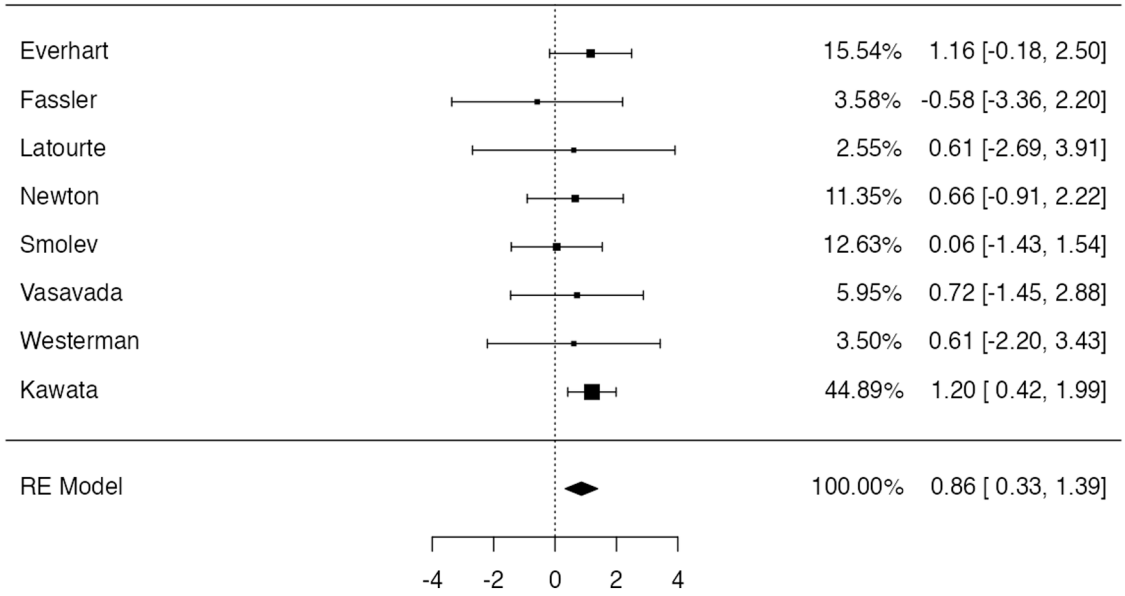

Figure 5. Forest plot of other orthopedic studies by effect size. RE, random effect.

varying types of orthopaedic surgery, which have the largest different absolute value risks for infection, ranging from 0.6 to 25% [59,72]. Each study included a corticosteroid arm and a control arm; therefore, the absolute value infection rates were compared to each specific surgery, and the data were expressed in OR with 95% CI. The between-group comparisons were adjusted to ensure accurate representation of the odds associated with preoperative corticosteroid use. Also, three of the smallest sample size studies had missing data that excluded them from the meta-analysis calculation [66,73,74]. Their exclusion would likely have minimal effect on the conclusion, as the majority suggested oral corticosteroid had an increased association with SSI/PJI.

The use of chronic preoperative oral corticosteroids is associated with a significant increase in the risk of SSI/PJI across various types of orthopedic surgeries and a wide range of patient populations, including immunocompromised patients. These results suggest that careful counseling is recommended when caring for surgical candidates on preoperative oral corticosteroids, and further research is warranted to better define the risks associated with specific corticosteroid dosage and duration, and whether an oral holiday of corticosteroids would have a beneficial effect on SSI/PJI. By synthesizing data from over 1.3 million patients, we provide evidence that preoperative oral corticosteroids contribute to higher odds of SSI/PJI. Clinicians should weigh these risks against the therapeutic benefits of corticosteroids and optimize patient management strategies to mitigate infection risks wherever possible.

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The Journal of Arthroplasty 41 (2025) S100–S103

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General Topics

2025 ICM: Gloves

Elido Perez, Leanne Ludwick, Daniel Diego Ball, Felipe Moreira Borim, David Figueroa, Amjad Hossain, Geert Meermans, Debabrata Padhy, Roberto Rossi, Rosa Silva, Ruben Limas Telles, Charles Vogely, Saheed Yakub, Luigi Zagra

Question 1: How many pairs of gloves should the surgical team wear during major orthopaedic procedures?[1]

Response/Recommendation

With a high percentage of outer glove perforation during major orthopaedic procedures, there is a clear need for an additional barrier, which is provided by the second pair of gloves.

Level of Evidence: Strong

Delegate Vote: 89.7% agree, 6.9% disagree, 3.5% abstain (super majority, strong consensus)

Rationale

Surgical gloves serve as a barrier to protect both the patient and the surgical team from contamination with pathogens that can result in infection. Minimizing contamination is critical during major orthopaedic surgeries, as infection is a devastating complication [1]. Among surgeons, there are varying practices regarding the number of pairs of gloves worn during procedures. Although numerous studies have investigated the effectiveness of double gloving, the conclusions remain varied. Factors such as the complexity of the surgery, the potential for glove perforation, and the risk of contamination [2] contribute to the need for a deeper analysis and more consistent guidelines in practice.

In order to address the posed question, we conducted a comprehensive systematic review. Using the appropriate MeSH terms developed by librarians and a search of two databases, which included PubMed and Embase, a total of 421 publications were identified. After merging 83 duplicates, 338 records remained for screening based on titles and abstracts. Following the assessment of titles and abstracts for eligibility, 97 studies advanced to the full-text screening phase. However, the full-text review revealed substantial heterogeneity among the studies, rendering them ineligible for a pooled analysis. Furthermore, very few clinical studies specifically addressing this topic were identified. As a result, the assignment necessitated a narrative approach.

Most surgical gloves are made of latex, vinyl, nitrile, or neoprene. They can be either unpowdered or powdered. Latex surgical gloves are the most commonly used; however, their main disadvantage is that they often cause allergies. Some surgical gloves are made of woven materials, mostly cotton. Not all the articles we consulted compare the same types of surgical gloves.

Orthopaedics is one of the surgical specialties where surgeons choose to wear two pairs of gloves most frequently [3], and most surgeons prefer to wear two pairs of gloves in hopes of reducing infection [4], but also for self-protection. Very few surgeons wear a single pair of gloves during a major orthopaedic surgery; these could be either conventional or the so-called orthopaedic gloves. The obvious problem is that if the glove needs to be changed, becomes contaminated, or suffers a puncture, the surgeon's hands will be immediately exposed since there is no other barrier [4,5].

We found only one paper that studied punctures in a single glove system during major orthopaedic surgery. The study found a 12% puncture rate during hip arthroplasties, a major risk; therefore, the same study suggests using a double-glove system to reduce the likelihood of perforation and contamination [6]. The case could be made that orthopaedic gloves offer a thicker barrier and a higher resistance to abrasion when compared to conventional gloves. There are those who choose these gloves due to the enhanced protection that they offer, but they come with a cost because of their reduced tactile sensitivity and hand fatigue. In contrast, the performance of double conventional gloves has been found to be similar to that of a single orthopaedic glove [7].

It is crucial to prevent infection, even before the incision is made. This is why many surgeons often double-glove to reduce the possibility of contamination during patient draping for joint arthroplasty surgery; at this stage, 15% of gloves become contaminated. This occurs more frequently in hip surgeries than in knee surgeries and tends to affect the dominant hand. This contamination could be recognized; it may be visible in the form of a tear or may go unnoticed [8].

In major orthopaedic surgeries, such as joint arthroplasty, it is common to encounter sharp bone edges and instruments that can easily puncture the gloves. In fact, between 18.4 and 59% of all outer gloves can be punctured, and 8.4 to 25% of all inner gloves [9–11]. Often, a damaged glove is recognized immediately;

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.110.

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https://doi.org/10.1016/j.arth.2025.10.110
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Table 1
Recommendations for How Often Gloves Should Be Changed.

Category	Recommendation	Reference
Time-based protocols	Change gloves every 40 to 90 minutes to reduce contamination during prolonged surgeries.	[24][26]
	Change gloves at 20-minute intervals during total hip arthroplasty.	[25]
Stage-based protocols	After draping.	[18][23][25]
	After cementing in arthroplasty to address contamination and solvent exposure.	[18][19]
	After trial component reduction and before wound closure in total knee arthroplasty.	[19]
	During fracture reduction and plating in open reduction and internal fixation procedures, especially at the first fixed steel plate stage.	[20]
	Immediately after arthrotomy in revision cases for prosthetic joint infection.	[22]
General recommendations	Replace gloves immediately if perforation is suspected, such as when caught in rotary devices, regardless of visible integrity.	[27]
	Indicator gloves may help identify perforations and contamination.	[28][29]
	Explore extra augmentation of gloves in areas with high risk of perforations, particularly the index finger and thumb on both hands.	[28]

however, as shown by Demircay et al. [10]. Only 14.4% of the outer glove perforations and 6.97% of the inner glove perforations were recognized during joint arthroplasty surgery. Most of the time, the surgery proceeds without the realization of any glove perforations.

It has consistently been demonstrated that the member of the surgical team who needs to pay special attention to their gloves is the main surgeon, as they are statistically the person most prone to glove perforation [12–14]. This may be because the main surgeon is the one performing active manual tasks, using instruments, and operating drills and saws, while the assistants tend to have a less dynamic role [15].

Special attention needs to be paid to the gloves when performing a revision joint arthroplasty, as up to 57% of the cases in revision hip arthroplasty, as reported by Boyarov et al. [14], are puncture-related, which is 15% more than in primary hip arthroplasties. Similar trends have been reported by Enz et al. [16] and Carter et al. However, these last two studies failed to break down the data and do not provide specifics on whether the revision surgeries were for the hip or knee.

Very few studies have been able to establish an association between glove puncture and an increased risk of surgical site infection (SSI). Jid et al. [2] found that after a puncture of both the inner and outer gloves during a primary total knee arthroplasty, the rate of SSI was 9.1%. In contrast, the rate of SSI was 0.5% in cases where no gloves were punctured.

Conclusion

Surgical gloves provide a barrier that helps reduce infections in patients and also prevents the surgical team from coming into contact with infectious biological products, materials, or secretions. A single pair of gloves poses a high risk for contamination if the gloves fail. The likelihood of a glove puncture increases with the complexity of the case, meaning that in revision arthroplasties, punctures are more common than in primary joint arthroplasty. Furthermore, the number of outer glove punctures differs markedly from the punctures in the inner gloves. Based on the current evidence, two pairs of gloves should be worn when performing a major orthopaedic procedure.

Question 2: How often should gloves be changed during major orthopaedic procedures?[2]

Response/Recommendation

To minimize the risk of infection due to glove contamination and perforation, gloves should be changed at the following critical stages during surgery: after draping, after fracture reduction and plating, after bone preparation and trial component reduction, immediately after arthrotomy in revision cases for periprosthetic joint infection (PJI), before implantation of total joint arthroplasty, after cementation, and before wound closure. Additionally, gloves should be replaced at least once every 40 to 60 minutes during prolonged procedures or when they become entangled in surgical equipment.

Strength of the Recommendation: Weak

Delegate Vote: 79.4% Agree, 8.6% Disagree, 12.1% Abstain (Super Majority, Strong Consensus)

Rationale

Prolonged surgical procedures increase the risk of introducing pathogens into the surgical site, potentially leading to surgical site infections and periprosthetic joint infections (PJI) [17,18]. Sterile surgical gloves are essential for minimizing these risks by preventing the transfer of cutaneous bacteria [19]. While double gloving is now standard practice, no standardized guidelines exist for the timing of glove changes during surgery. This review aims to present evidence on the optimum frequency of glove replacement to reduce the risks of contamination and perforation, ultimately preventing surgical site infection/PJI. (Table 1)

Several studies have evaluated glove contamination and perforation at specific stages of orthopaedic procedures. In total hip arthroplasty, Beldame et al. analyzed glove contamination and perforation rates across four stages: draping, incision and bone preparation, cup and stem implantation, and reduction [18]. They reported contamination rates of 3.06, 2.2, 2.63, and 6.09% at each stage and perforation rates of 1.8, 5.02, 5.55, and 0.59%. They found that replacing the contaminated gloves with new sterile gloves rendered subsequent samples negative in 80% (16 of 20) cases. Based on these findings, they recommended renewing the entire team's outer gloves after draping, at the end of the bone preparation phase (due to high perforation risk), after joint reduction (highest contamination), and after cementing (to address contamination and solvent exposure). Similarly, Karakus and Sari studied 300 total knee arthroplasty cases and observed perforation rates of 8.1% after the femoral cut, 14.8% after the tibial cut, 52.6% during trial component reduction, 7.4% after prosthesis placement, and 17% during wound closure [19]. They recommended changing gloves after trial component reduction and before wound closure. In open reduction and internal fixation procedures, Li et al. analyzed 408 gloves collected during 30 cases and reported an overall contamination rate of 30.15%, with the highest rates (58.54%) occurring during fracture reduction with the first fixed steel plate stage [20]. They emphasized the need for more frequent glove changes during stages with high contamination risks, such as fracture reduction with the first fixed steel plate stage. Lee et al. similarly recommended

[2] These authors contributed to Question 2: Leanne Ludwick, Geert Meermans, Daniel Diego, Felipe Borim Moreira, Saheed Yakub, Luigi Zagra, Amjad Hossain

nonspecific frequent glove changes after seeing contamination rates increase for the primary surgeon at the end of the case (0 versus 11.4%) and for the scrub nurse after opening packaging and delivering artificial inserts (0 versus 14.3%) [21].

In revision cases for periprosthetic joint infection (PJI), Ludwick et al. collected gloves every 20 minutes and found that contamination rates were higher after arthrotomy (70%) compared to samples collected before this stage (40%) [22]. They recommended changing gloves immediately following arthrotomy to limit bacterial spread.

Draping has also been identified as a surgical step with potential for contamination. Makki et al. studied 125 pairs of gloves during 46 total joint arthroplasty cases and found that gloves used during draping frequently became contaminated [23]. They randomized cases into three protocols: Group A replaced the top layer of double gloves after draping, Group B used triple gloves and removed the outer layer after draping, and Group C removed the top layer of double gloves and started the procedure with a single pair. Groups A and B had 0% contamination rates, leading to the recommendation that top gloves should be replaced immediately after draping rather than only removing the top glove and wearing a single glove.

Time-based protocols have also been investigated to address contamination and perforation during longer surgeries. Al-Habdan et al. randomly collected 842 gloves (526 double gloves and 316 single gloves) from 150 pediatric orthopaedic cases [24]. They found that perforation rates increased with operative time: 10.7% for single gloves and 0% for double gloves in surgeries lasting less than one hour, compared to 53.6% for single gloves and 25.6% for double gloves in surgeries lasting one to two hours. They recommend double gloving, but also discuss the potential to change gloves every 40 to 60 minutes. Al-Maiyah et al. conducted a randomized trial comparing glove perforation and contamination rates in total hip arthroplasty cases [25]. The study group changed gloves after draping, at 20-minute intervals, and before cementation, while the control group only changed gloves after draping and before cementation. The study group had significantly lower perforation (4.2%) and contamination rates (44%) compared to the control group (11.7 and 76%). Kaya et al. proposed a more conservative protocol, suggesting glove changes approximately every 90 minutes or whenever gloves are excessively contaminated with surgical fluids [26]. This was recommended after they found the mean time to glove perforations to be 92.7 ± 50.2 minutes. These findings highlight the utility of regular glove changes during longer procedures to minimize contamination risk.

In addition to time- and step-based protocols, it has also been suggested that gloves should be changed immediately if they become compromised or contaminated. Goldman et al. found that gloves caught in rotary devices during surgery were perforated in 52% of cases, highlighting the need for immediate glove replacement in such situations, regardless of visible glove integrity [27]. Demircay et al. also found perforations in 181 of 983 (18.4%) outer gloves and 43 of 511 (8.4%) inner gloves despite changing gloves hourly [28]. They suggested exploring extra augmentation of gloves in areas with a high risk of perforations, particularly the index finger and thumb on both hands. Tao et al. also proposed frequent glove changes with potential use of indicator gloves as well [29].

Conclusions

Overall, the literature highlights how frequent glove changes during major orthopaedic surgeries may help to reduce infection risks, particularly after draping, at high-risk stages, or during prolonged procedures, such as those longer than one hour. Gloves should also be replaced immediately if they become visibly compromised or entangled in surgical equipment. While no standard protocol exists, the recommendations of these studies provide a framework to guide glove-changing practices in major orthopaedic surgeries.

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The Journal of Arthroplasty 41 (2025) S104–S108

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The Journal of Arthroplasty

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General Topics

2025 ICM: Surgical Procedure Time

Pietro Simone Randelli, Khalid Merghani, Bülent Atilla, Dmitry Efimov, Lyes Ait El hadj, Darío E. Garín Z, Sébastien Lustig, Ramneek Mahajan, Felipe Caroca Marazzi, Alessandra Menon, Nikolai Nikolaev, Bishnu Pokharel, Emilio Romanini, Neil P. Sheth, Eleftherios Tsiridis, Mark Wu, Matthias D. Wimmer

Question 1: Does operative time influence the incidence of surgical site infection (SSI)/periprosthetic joint infection (PJI) after major orthopaedic surgery?[1]

Response/Recommendation

Yes. There is a direct correlation between operative time and the subsequent risk of SSI/PJI.

Level of Evidence: Moderate

Delegate Vote: Agree 85%, Disagree 8.3%, Abstain 6.7% (Super Majority, Strong Consensus)

Abstract: N/A

Rationale

Surgical site infection (SSI) and periprosthetic joint infection (PJI) are among the most concerning complications of orthopaedic surgery, particularly hip and knee arthroplasties [1]. The overall incidence of PJI in total knee and hip arthroplasties is around 1% [2]. Risk factors for SSI are broadly classified into patient-related and surgery-related factors. Numerous risk factors for SSI and PJI have been posited. Other questions in this meeting will address all the risk factors related to SSI/PJI. Operative time is frequently cited as an independent and potentially modifiable risk factor for SSI [3].

This comprehensive systematic review was conducted to examine the potential relationship between operative time and the risk for subsequent SSI/PJI. Using MeSH terms developed by librarians, we conducted a search of two databases, PubMed and Embase, to identify all eligible studies. Out of 320 articles assessed for eligibility, 19 were included in the study. There were 97 studies that were excluded because they focused on comparisons between adults who have suspected PJI and those who have aseptic failure. Additionally, 68 articles were not confined to the hip or knee, 36 did not clearly define the criteria for SSI or PJI, and 27 contained no extractable data. Furthermore, 18 articles did not report operative time, 18 were unavailable in full text, and 10 were unrelated to our study. There were five articles that were not published in English, and five focused on hip or knee surgical procedures other than total hip and total knee arthroplasties (including two on hip hemiarthroplasty, one on proximal femoral fracture, one on unicondylar knee arthroplasty, and one on high tibial osteotomy). An additional 15 articles were excluded for other reasons, including duplicates [4], editorials [2], revision arthroplasty [2], treatment of PJI [2], alternative surgical approaches to the hip [1], postoperative readmission [1], resident training [1], and nonhuman studies [1], as shown in the attached flowchart.

There were six out of 19 included studies that were multicenter studies. There were 11 studies that focused on knee arthroplasty, two on hip arthroplasty, and six that included both. There were eight studies that followed the Centers for Disease Control and Prevention (CDC) criteria for defining SSI-PJI, while the others used definitions from the World Health Organization (WHO), the International Consensus Meeting (ICM), the Musculoskeletal Infection Society (MSIS), or clinical outcome guidelines.

There were 16 studies that were retrospective cohort studies, one was a prospective cohort study, and two were retrospective case-control studies. Out of 17 cohort studies, 12 were classified as good quality, one as fair, and four as poor quality based on the Newcastle-Ottawa Scale (NOS) for cohort studies. The case-control studies were rated as having good quality according to the Newcastle-Ottawa Scale for case-control studies. Only four of the studies received funding.

There were 19 studies with 535,031 major orthopedic surgeries (total knee and hip arthroplasties) (4,559 patients in the SSI/PJI group and 530,472 patients in the no SSI/PJI group) that were finally included for qualitative and quantitative analyses.

The following forest plot (Figure 1) summarizes a meta-analysis comparing the mean operative time between the SSI/PJI and no SSI/PJI groups.

The overall mean difference (MD) of 15.2 minutes (95% confidence interval (CI) 9.8 to 20.6; $P < 0.00001$) indicates strong evidence that operative time is significantly longer in major orthopaedic surgeries complicated by infections (Figure 1).

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.081.

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https://doi.org/10.1016/j.arth.2025.10.081
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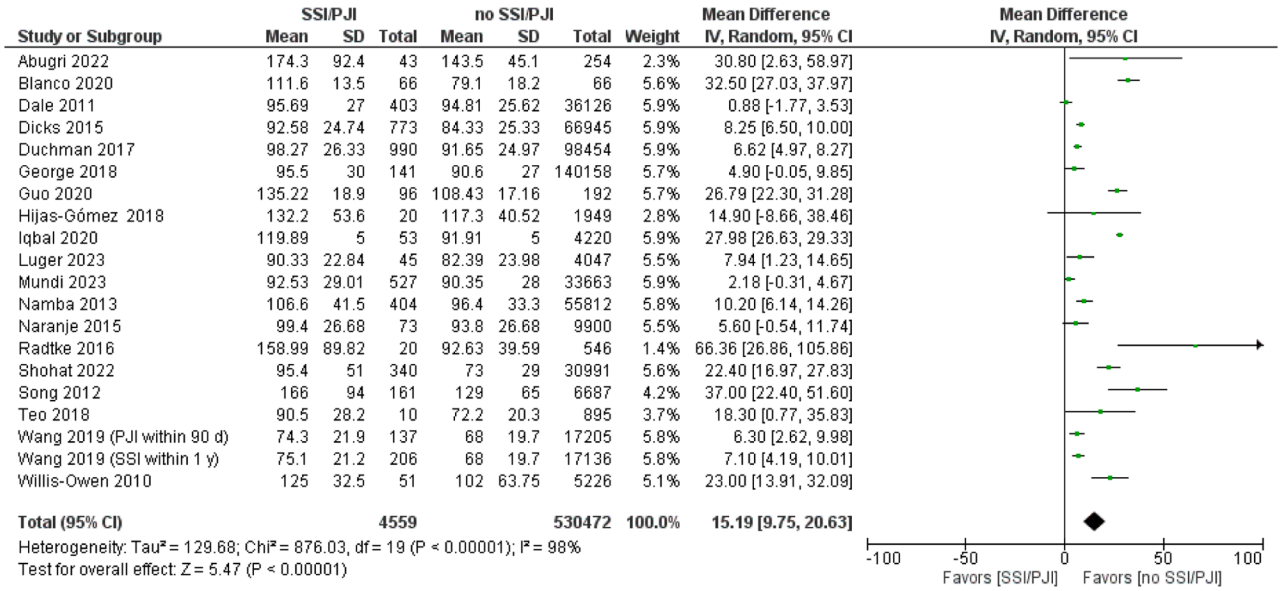

Figure 1. Forest plot of comparison: SSI/PJI versus no SSI/PJI, outcome: Operative time (minutes). CI, confidence interval; d, days; PJI, periprosthetic joint infection; SD, standard deviation; SSI, surgical site infection; y, years.

Very high heterogeneity was detected ($I^2 = 98\%$, $P < 0.00001$; Figure 1), suggesting substantial variability among studies, likely due to clinical or methodological differences, so interpretation should account for confounding factors (e.g., type of surgery, standardized duration, and surgical techniques).

Most studies, like the ones performed by Guo et al. [5] and Ikbal et al. [4], show a positive effect, meaning a longer operative time in major orthopaedic surgeries complicated by infections. Some studies have confidence intervals crossing zero, indicating that in those cases, the difference is not statistically significant [6,7].

The results of the sensitivity analysis remained stable and consistent with those of the main analysis after the exclusion of studies [8–12] of fair and poor quality according to the Agency for Healthcare Research and Quality (AHRQ) standards (Figure 2). Heterogeneity among studies remains very high, suggesting that there are still important methodological or clinical differences among the included studies.

A funnel plot analysis for the primary outcome visually shows a relatively symmetrical distribution of studies around the central line representing the mean effect size, which suggests no significant evidence of publication bias. However, a few studies with higher SEs deviate from the central trend, possibly reflecting variability in study results or small sample sizes (Figure 3).

There are numerous reasons why longer operative times could potentially increase the risk of subsequent SSI/PJI. With prolonged

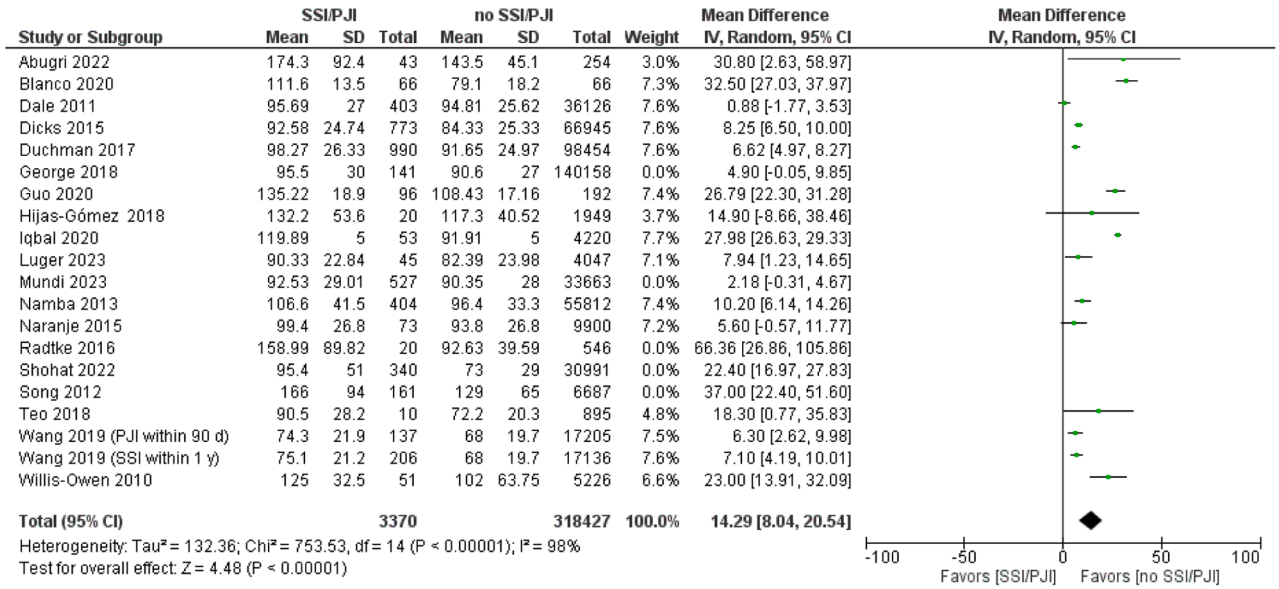

Figure 2. Forest plot of comparison: SSI/PJI versus no SSI/PJI, outcome: Operative time (minutes), illustrating the sensitivity analysis restricting data only to studies of good quality according to the AHRQ standards. AHRQ, Agency for Health Care Research and Quality); CI, confidence interval; d, days; PJI, periprosthetic joint infection; SD, standard deviation; SSI, surgical site infection; y, years.

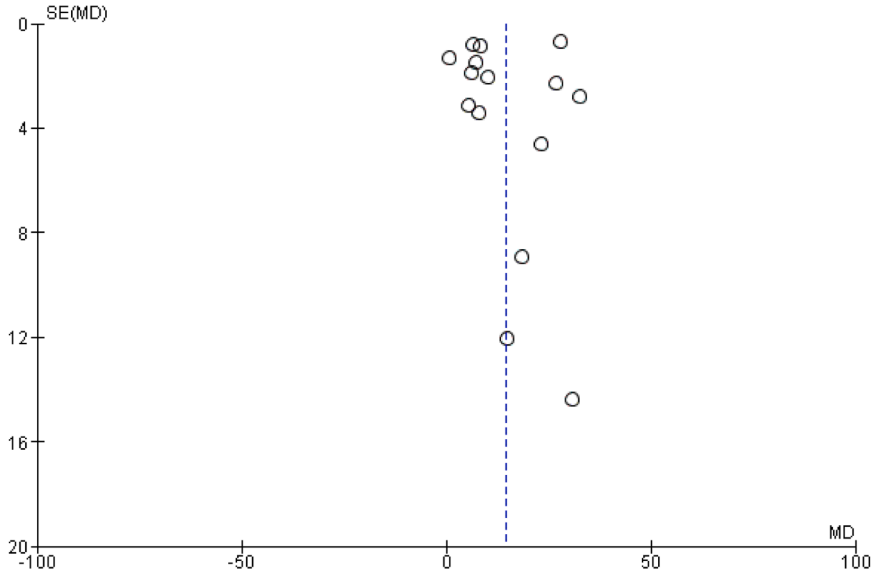

Figure 3. Funnel plot of comparison: SSI/PJI group compared to no SSI/PJI group; outcome, operative time.

operative time, the risk of surgical incision contamination increases [13,14]. Moreover, a longer operative time predisposes patients to a higher risk of tissue desiccation, which may further increase the probability of contamination and microbial proliferation. Prolonged operative time is also associated with a longer tourniquet time, which can cause persistent wound hypoxia and increase susceptibility to infection [15]. Additionally, there is a direct link between operative time and blood loss [16]. With increasing operative time, the circulating volume and oxygen-carrying capacity are reduced, and tissue concentrations of antibiotics decrease [17].

In addition, several factors can affect the operative time, including case complexity, surgeon experience and fatigue, operating room staff expertise, and use of cement, among others. Anis et al. demonstrated that younger age, being a man, higher body mass index (BMI), low surgical volume, and use of antibiotic-loaded cement were significantly associated with longer operative times [18].

In conclusion, the results of our systematic review and meta-analysis show that operative time is significantly longer in patients who develop infections (SSI/PJI), supporting the hypothesis that longer operative times may be a risk factor for postoperative infections, but it should be interpreted in the context of other confounding factors.

Question 2: Does the size and extent of soft-tissue dissection influence the incidence of surgical site infection (SSI)/ periprosthetic joint infection (PJI) after major orthopaedic surgery?[2]

Response/Recommendation

Yes. The extent and size of soft-tissue dissection during major orthopaedic surgery significantly influence the risk of developing surgical site infections (SSIs) and periprosthetic joint infections (PJIs). There are several factors contributing to increased surgical dissection that have been identified in the literature, but no universally accepted definition exists. Nevertheless, current understanding indicates a strong correlation between the degree of soft-tissue dissection and the risk of SSI and PJI. Several plausible mechanisms may underlie this association, and some contributing factors are potentially modifiable to reduce infection risk.

Strength of Recommendation: Low level of evidence

Delegate Vote: 87.5% Agree, 5.4% Disagree, 7.1% Abstain (Super Majority Consensus)

Rationale

Soft-tissue dissection impacts postoperative outcomes, particularly infection risk. Factors such as incision length, wound perfusion, depth, and tissue condition influence SSIs and PJIs. Key considerations include surgical approach, tissue handling, operative duration, and dead space management [19–23].

This systematic review was conducted to investigate the relationship between the extent and size of soft-tissue dissection and the subsequent risk of surgical site infection (SSI) or periprosthetic joint infection (PJI). The search strategy was designed to identify human-based studies published between 1990 and the present. The search was limited to English-language publications, with the exception of randomized controlled trials (RCTs), for which no date restriction was applied. PubMed identified 238 potentially eligible publications. After screening by two independent reviewers, 206 publications were excluded, leaving 32 studies for comprehensive review and data extraction.

Surgical factors

There are several studies evaluating the depth of the soft-tissue envelope (which intuitively would require a longer skin incision for surgical exposure) adjacent to the surgical site and its effect on developing an SSI or PJI. In the region of the hip, a lateral soft-tissue thickness of greater than five cm was associated with a higher rate of SSI, PJI, and the need for revision [24]. The same group reported that lateral approaches encountered more adipose tissue than anterior-based approaches and were more likely to be associated with women and correlated with BMI [25]. Bell et al. reported the contrary that radiographic measurement of subcutaneous fat thickness was not a valid tool to predict return to the operating room for wound complications [26].

[2] These authors contributed to Question 2: Khalid Merghani, Matthias D Wimmer, Darío E. Garín Z, Ramneek Mahajan, Felipe Caroca Marazzi, Neil P Sheth

The subcutaneous location of the knee has resulted in more studies looking specifically at the soft-tissue envelope surrounding the knee and its relationship with SSI and PJI. Several authors have demonstrated that patients who have a deeper subcutaneous adipose layer anterior to the knee are associated with a significantly increased risk of early reoperation, wound complications, and PJI [27–29]. The role of BMI alone is unclear, as studies have shown that BMI alone is not associated with the same risk [27,29], but others have demonstrated that BMI is a better predictor of PJI than anterior soft-tissue thickness [30].

Other procedures, such as posterior cervico-thoracic fusion and open reduction and internal fixation of acetabular fractures, have not demonstrated a clear relationship between soft-tissue envelope thickness and PJI [31–33]. Several studies clearly demonstrate that longer operative times are associated with higher rates of patient morbidity, readmission rates, blood loss, need for blood transfusion, SSI, and longer hospital length of stay [34–36]. The longer the wound is open to room air, the higher the rate of SSI and PJI. In the setting of extensile surgical approaches and prolonged surgical time, a repeat dose of prophylactic antibiotics may be warranted.

Unaddressed voids can result in seromas or hematomas, which may facilitate infection. The correlation between soft tissue defects and PJI is paramount in orthopedic surgery, especially after total knee arthroplasty (TKA). Complications related to wound healing, such as infections, have a major impact on patient outcomes, with infection rates post-TKA ranging from 0.33 to 10.5% [37]. Effective management of these complications requires prompt assessment and intervention, including debridement and appropriate soft tissue coverage [37]. Various reconstructive techniques, including perforator and free microvascular flaps, are critical for addressing soft-tissue defects while also considering infection control [38]. Furthermore, the timing of surgical interventions is essential in preventing additional complications [22]. The collaboration between orthopaedic and plastic surgical specialists is crucial for optimizing outcomes in patients who have soft-tissue defects associated with PJI, underscoring the necessity for a multidisciplinary approach in treatment planning [22,38].

Patient-specific factors

Preoperative soft-tissue conditions, including scarring and prior surgical interventions, significantly influence PJI rates, particularly in extended surgical approaches [39]. Factors such as obesity, diabetes, and prior surgeries are linked to increased infection risk, with compromised tissue integrity heightening wound complications [28,39]. Optimizing modifiable risk factors and meticulous surgical techniques are essential, especially for managing complex defects in irradiated areas.

Tissue perfusion plays a crucial role in SSI risk, particularly in TKA. Wyles et al. demonstrated that laser-assisted indocyanine green angiography enhances surgical decision-making by visualizing real-time perfusion, reducing complications such as wound necrosis [23]. Similarly, adequate preoperative soft-tissue coverage, including prophylactic perforator flaps, has been associated with improved outcomes and lower implant infection rates [40].

Managing comorbidities is vital in reducing PJI risk, especially in extensive procedures. Diabetes, obesity, and malnutrition have been identified as key contributors to SSI [39,41]. A retrospective review found that preoperative prognostic nutritional index (PNI) and subcutaneous fat thickness were independent risk factors for deep SSI after posterior lumbar interbody fusion [42]. Moreover, optimizing soft-tissue coverage timing did not significantly reduce complications, reinforcing the importance of comprehensive preoperative assessments [22,39]. Addressing modifiable factors such as smoking and anemia further improves wound healing and surgical outcomes [39].

Nutritional status also plays a critical role in SSI risk. Lower preoperative prognostic nutritional index, increased fat thickness, and poor serum albumin levels are independent predictors of deep SSIs following posterior lumbar interbody fusion[42]. Obesity and malnutrition consistently correlate with higher SSI rates across orthopedic procedures [42]. Targeted nutritional interventions could enhance outcomes and reduce health care costs associated with postoperative complications.

Wound factors

The presence of concurrent wounds complicates PJI management by increasing infection risk and necessitating complex surgical interventions [38]. Wound closure techniques, including muscle and perforator flaps, improve soft-tissue coverage and reduce infection rates [38]. Early reconstructive intervention enhances prosthesis retention, while bacterial contamination from other wounds underscores the need for thorough debridement and meticulous soft-tissue management [41]. Collaboration between plastic and orthopedic surgeons has proven beneficial in addressing these challenges, ensuring comprehensive care for compromised knee arthroplasties [38]. Tailored, timely management strategies are essential for optimizing outcomes in PJI cases with concurrent wounds [41].

Perioperative factors

Preoperative nutritional status significantly influences SSI risk, potentially leading to prosthetic joint infections (PJI) [41]. Lower prognostic nutritional index values and increased fat thickness are associated with higher SSI rates following posterior lumbar interbody fusion [42]. Obesity, diabetes, malnutrition, surgical invasiveness, and procedure duration further contribute to SSI risk. Addressing modifiable risk factors during surgical planning is essential for reducing PJI incidence, improving patient outcomes, and minimizing health care costs.

Procedural innovations and adjuncts

Innovations in surgical techniques have improved PJI prevention, particularly in TKA [43]. Prophylactic soft-tissue augmentation with perforator flaps enhances coverage and reduces infection risk [40]. Technologies like laser-assisted indocyanine green angiography aid in evaluating tissue perfusion, minimizing wound necrosis [23]. A multistep extremity salvage protocol, emphasizing collaboration between orthopaedic and plastic surgeons, further optimizes soft-tissue management [38]. Additionally, antibiotic-laden cement or spacers provide infection control in high-risk cases.

In conclusion, and based on our understanding of the current literature, there appears to be a direct correlation between the extent of soft-tissue dissection and the subsequent risk of SSI/PJI. There are numerous reasons that could potentially explain this correlation that was discussed above.

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The Journal of Arthroplasty 41 (2025) S109–S113

Contents lists available at ScienceDirect

The Journal of Arthroplasty

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General Topics

2025 ICM: Anesthesia

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Question 1: Does the type of administered anesthesia (general versus regional) influence the rate of surgical site infection /periprosthetic joint infection (SSI/PJI) in major orthopaedic surgery?[1]

Response/Recommendation

Based on current evidence and the delegate vote, regional anesthesia (RA) appears to reduce the risk of SSI and PJI in major orthopaedic surgery compared with general anesthesia (GA). While most available data are observational, the consensus strongly favors the use of RA whenever feasible, and further prospective studies are warranted to confirm these findings.

Strength of Recommendation: Weak

Delegate Vote: Agree: 68.4%, Disagree: 21.1%, Abstain: 10.5% (Majority Support)

Rationale

We conducted a comprehensive systematic review to evaluate the effect of administered anesthesia (general versus regional) on the rate of SSI/PJI in major orthopaedic surgery. Appropriate medical subject headings) terms were developed by the librarians to conduct a literature search in two databases, Medline and Embase publications, then screened by two experts to identify 13 final publications for inclusion in the systematic review.

Many orthopaedic surgical procedures can be performed with either RA or GA. The RA seems to reduce postoperative complications by minimizing sympathetic activation, inflammation, venous stasis, and the need for endotracheal intubation and positive pressure ventilation [1–3]. Postoperative complications, particularly SSIs, are a major concern in major orthopaedic surgery. The SSIs after knee and hip arthroplasty can significantly worsen surgical outcomes, increasing both morbidity and mortality [4].

In 10 studies, the superiority of RA in reducing the risk of SSI and PJI in arthroplasty and trauma surgeries was highlighted [5–14]. However, two studies did not observe significant differences between the two anesthesia methods [15,16].

A comprehensive registry study that included 779,491 patients who underwent total hip arthroplasty (THA) and total knee arthroplasty (TKA) found that RA was linked to a reduced risk of SSI, with odds ratios (ORs) of 0.87 for THA and 0.84 for TKA [8]. A systematic review comprising 15 studies demonstrated that patients receiving spinal anesthesia were 23% less likely to develop postoperative SSIs compared to those who received GA (OR: 0.77) [6].

An observational study involving 3,909 arthroplasties conducted by Scholten et al. showed an OR for PJI of 2.0 (95% confidence interval 1.0 to 3.7) for patients who had GA compared to those who received spinal anesthesia matched by propensity scores [5]. Another meta-analysis indicated that GA significantly raised the incidence of postoperative SSI compared to spinal anesthesia, with both unadjusted (OR: 0.77) and adjusted (OR: 0.84) analyses supporting this finding [12].

A population-based study of 3,081 patients undergoing THAs or TKAs reported that the odds of SSI for patients receiving GA were 2.21 times higher than those who underwent the procedures with spinal or epidural anesthesia. This finding was consistent even after adjusting for age, sex, comorbidities, surgeon experience, and hospital teaching status [11].

Not only is GA associated with an increased risk of SSI, but the duration of anesthesia itself is also considered an independent risk factor contributing to this increase [13]. Deep SSIs were notably less frequent in the RA group, with an OR of 0.38 compared to the GA group [14].

Also, it was observed that RA not only lowers the risk of superficial infections but also significantly reduces the risk of systemic infections, including sepsis [7]. In two separate studies focused on revision TKA, the risk of SSI was also found to be 1.43 and 1.32 times higher for patients under GA [9,10].

In the International Consensus Meeting 2018, the evidence either favored neuraxial anesthesia over GA or showed no difference in reducing the SSI risks after THA/TKA. No evidence supports

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to doi: 10.1016/j.arth.2025.10.108.

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https://doi.org/10.1016/j.arth.2025.10.108

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GA, and neuraxial anesthesia is strongly recommended when feasible [17].

While two studies favored RA or reported no significant differences, the predominantly retrospective nature of the existing research highlights the need for high-quality prospective studies to validate these findings. Nevertheless, in the absence of evidence supporting GA and with a consistent trend favoring RA, RA should be prioritized as the anesthetic method of choice for major orthopaedic procedures, whenever clinically feasible.

Conclusions

This analysis demonstrates that RA offers major advantages over GA in major orthopaedic surgeries, particularly in reducing the incidence of SSI and PJI. The physiological benefits of RA, such as reduced sympathetic activation, minimized inflammation, and lower systemic infection risks, make it a compelling choice.

Question 2: Does intraoperative normothermia influence the rate of subsequent surgical site infection (SSI)/ periprosthetic joint infection (PJI) in major orthopaedic surgery?[2]

Response/Recommendation

Unknown. There is inconclusive evidence regarding the role of maintaining intraoperative normothermia for the prevention of SSI/PJI. However, we recommend that intraoperative normothermia be maintained to reduce complications.

Level of Evidence: Limited

Delegate Vote: Agree: 85%, Disagree: 9%, Abstain: 6% (Super Majority, Strong Consensus)

Rationale

Hypothermia is a difficult factor to assess in terms of periprosthetic infections in orthopaedics. Authors have described the negative effects of hypothermia after other major surgeries, like abdominal surgery. They have found that even mild perioperative hypothermia can increase the incidence of postoperative complications (e.g., increased mortality, increased bleeding, sepsis, stroke, SSI) [18–22]. In orthopaedics, one would not knowingly make a person hypothermic because of the potential other ill effects on our patients. In fact, one recent study showed increased 30-day mortality in major orthopedic surgeries, so the question of whether hypothermia leads to increased infection rates might be less relevant [23].

To compile this review of the topic, we conducted a systematic review to clarify the efficacy of normothermia over hypothermia in reducing SSI in major orthopaedic surgery, including spine surgery, fracture surgery, and joint arthroplasty. Following International Consensus Meeting guidance, we searched MEDLINE (via PubMed), CENTRAL, and Embase for all randomized controlled trials and observational studies, including longitudinal/cohort studies, case-control studies, controlled before-and-after studies, and cross-sectional studies published through November 2024 that reported the outcome of the surgical patients. We included all adult patients with primarily closed surgical incisions after spine surgery, trauma/fracture surgery, and joint arthroplasty of any joint, both with and without implants. We also included fracture fixation for open fractures if the wound was primarily closed, as well as outpatient, emergent, elective, and revision surgery. Of the 1,353 articles that were subjected to title and abstract screening, we shortlisted 49 articles for full-text screening. We excluded 38 articles and added three articles through a hand search. This left 14 observational studies that were included in our final analysis [23–36].

We found that four musculoskeletal surgery–related studies had patients who became hypothermic during surgery and were compared to normothermic patients and found to have an increased infection rate [24–27]. However, this was inconclusive because another seven studies have not shown that hypothermia led to an increased infection rate [28–32,35], and one study found that normothermia had a higher infection rate than the hypothermic group [33]. Other studies have found an increased incidence of other adverse events in hypothermic patients, including increased mortality [23,24,34,36].

For multiple reasons, tabulating this topic across studies and doing a true meta-analysis with a statistical analysis is not appropriate. This is because there were different operations (with different times of procedure, i.e., some over two hours, some shorter) and different hypothermia definitions or threshold temperatures (36.0 versus 35.5°C), as well as the retrospective nature and often incomplete data collected.

The fact that many studies routinely used cointerventions to prevent hypothermia, such as passive or active warming systems based on other physiological mechanisms (e.g., irrigation fluid or gas warming), as well as stricter temperature control in the study context compared with standard practice, may also explain the difficulty in observing a clinically relevant beneficial effect with normothermia. For instance, many studies do not control for the fact that obese patients, who are more prone to having an infection, are also more likely to retain normothermia. The total advantage of sustaining normothermia may have been underestimated as a result of these positive effects on the control group members. In addition, as stated earlier, the hypothermic threshold was re-established as 35.5°C by the Prevention of Operative Thermal Emissions and Complications by Thermoregulation Study [37], which was not used in prior studies (often 36°C).

As stated above, hypothermia has been linked to increased SSI and PJI rates in four studies, as follows: Frisch et al. reviewed 1,525 hip fracture cases and found a 17% rate of intraoperative hypothermia (< 36° C), which was significantly associated with deep SSIs (odds ratio 3.30, $P = 0.022$) [24]. Charles-Lozoya et al. reported a 25% mortality rate in hypothermic patients (< 35° C) with hip fracture cases (n = 300), with significantly higher SSI and transfusion rates [25]. Hu et al. (n = 2,692) identified intraoperative temperatures < 36.4° C as an independent infection risk in open fractures [26]. Dyck et al. analyzed 12,636 hip/knee arthroplasties and found that maintaining immediate postoperative temperatures between 36 and 38° C was linked to fewer SSIs [27].

Conversely, seven studies found no overall link between hypothermia and infection: Williams and El-Houdiri found that there was no increase in infection risk with hypothermia in primary arthroplasty patients [28]. Vicentini et al. [29] (n = 18,791) showed that normothermia, as part of a perioperative care bundle, did not reduce SSI risk. Frisch et al. [30] (n = 2,397) found no increase in complications despite greater blood loss with hypothermia. Liedl et al. [31] (n = 236) found no SSI increase from hypothermia alone, though risks were higher with elevated hemoglobin A1c patients. Yamada et al. [23] (n = 8,841) found no difference in SSI risk in hypothermic patients. Abugri et al. (n = 297) and Reina et al. (n = 941) found that hypothermia was not significantly associated with SSIs [32,35]. There was one study, Jildeh et al. [33] (n = 657), that found a higher risk of SSIs with normothermia in shoulder arthroplasty.

Other studies noted broader benefits of normothermia: Yamada et al. linked hypothermia with increased 30-day mortality in major orthopedic surgeries (as did Charles-Lozoya et al. [25]) (pooled odds ratio 4.55 (95% confidence interval 2.26 to 9.18). Pan et al. (n = 616) found that hypothermia increased blood loss and transfusion rates in total hip arthroplasty/total knee arthroplasty

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[34]. Charles-Lozoya et al. and Goel et al. also found that hypothermia increased transfusion rates [25,36].

There are several potential limitations to this review. All of the studies evaluated were observational studies with various definitions for SSI and normothermia with various follow-up periods. As stated, there are vast heterogeneities, and the nature of observational studies may affect the interpretation. In addition, although several studies linked increased risk of 30-day mortality with hypothermia, the number of observational studies evaluating mortality was very limited (n = two). Moreover, as we did not include a pediatric population, reproducibility and generalization of this population may be limited. Also, there are three important phases (pre-, intra-, and postoperative) for maintaining normothermia, but the association between these phases was not evaluated. Furthermore, there are several active body surface warming systems considered useful for preventing inadvertent hypothermia, but the effect of these different systems has not been evaluated.

Conclusions

Based on our results, we suggest maintaining normothermia as a measure to reduce the risk of 30-day mortality in adult patients undergoing major orthopedic surgeries. Maintaining normothermia reduced SSIs in the three fracture studies, but it was inconclusive for this outcome in the other orthopedic populations.

Question 3: Does administration of intravenous (IV) corticosteroids (dexamethasone) during major orthopaedic procedures increase the risk of subsequent surgical site infection (SSI)/periprosthetic joint infection (PJI)?[3]

Response/Recommendations

No. There is no concrete evidence linking intraoperative administration of low-dose IV corticosteroids to an increased risk of subsequent SSI/PJI.

Level of Evidence: Limited

Delegate Votes: Agree: (90.9%), Disagree: (2.2%), Abstain: (6.9%) (Total consensus, Unanimity)

Rationale

In recent years, there has been an interest in IV administration of corticosteroids during surgery to reduce the incidence of nausea and pain [38]. During the recent World Expert Meeting, administration of IV corticosteroids during surgery was discussed and strongly endorsed [39]. The use of IV corticosteroids has been shown to reduce the need for postoperative narcotics and pain medications after distal radius fixation, elbow fracture surgery, and total joint arthroplasty. Patients treated with taper doses of IV corticosteroids after these surgeries have been shown to have less postoperative pain and improved range of motion [40–42]. Recent studies have demonstrated the effectiveness of perioperative high-dose corticosteroid administration after total hip and knee arthroplasty in reducing postoperative inflammatory response, pain, nausea, and vomiting, and also accelerating postoperative rehabilitation [43–45]. However, there are insufficient data on the optimal dose of IV corticosteroids, considering side effects and the relation to SSI or PJI. Furthermore, contraindications for the administration of IV corticosteroids during surgery are not known [45]. A potential adverse effect of IV corticosteroids relates to the potential increase in subsequent SSI and/or PJI.

To evaluate the question posed here, we performed a comprehensive systematic review. All relevant literature was identified using medical subject headings terms and a search of PubMed and Scopus databases. A total of 5,980 articles were identified on initial screening. After excluding duplicates, 5,128 publications remained. After further review, 83 studies were found to meet the inclusion criteria and were selected for full review and data extraction. We subgrouped the studies into four groups: (1) single low-dose (up to 10mg dexamethasone) corticosteroids, (2) single high-dose (more than 10 mg dexamethasone) corticosteroids, (3) multiple low-dose corticosteroids, and (4) multiple high-dose corticosteroids.

Single Low-Dose Intravenous Corticosteroids

The review of 15 publications in this category that reported on the rate of SSI showed that the incidence was comparable between the corticosteroid group (one event in 740 patients) and the placebo group (one event in 737 patients), yielding a relative risk (RR) of 0.98 (95% confidence interval [CI]: 0.14 to 6.76) [46–60]. In addition, six studies focusing on PJI outcomes showed no events in either the corticosteroids group (zero of 272) or the placebo group (zero of 267) [51–53,56–58].

Single High-Dose Intravenous Corticosteroids

There were fourteen studies that reported SSI outcomes, with more events in the corticosteroids group (eight events in 607 patients) compared to the placebo group (three events in 611 patients) (RR: 1.99, CI: 0.71 to 5.60) [53,61–73]. Furthermore, nine studies on PJI reported an increased incidence in the corticosteroids group (nine of 384) compared to the placebo group (four of 358) (RR: 2.2, CI: 0.72 to 6.76) [53,65,67–73].

Multiple Low-Dose Intravenous Corticosteroids

There were 13 studies on SSI outcomes that observed a slightly higher number of events in the corticosteroids group (five of 640) versus the placebo group (three of 638), with an RR of 1.45 (CI: 0.45 to 4.66) [38, 48, 58, 72–81]. For PJI, three studies showed no events in the corticosteroids group (zero of 84) and two events in the placebo group (two of 92) (RR: 0.23; CI: 0.01 to 4.59) [37,72–81].

Multiple High-Dose Intravenous Corticosteroids

There were three studies on SSI outcomes that reported on one event in the corticosteroids group (one of 158) compared to none in the placebo group (zero of 160) (RR: 3.12, CI: 0.13 to 74.85) [82–84].

For the SSI and PJI outcome, we have downgraded the evidence one level due to indirectness and two levels due to imprecision, "insufficient number of events and short follow-up period," so the evidence was downgraded from high to very low. Data from nonrandomized controlled trial and retrospective studies supported the results of our meta-analysis. Vournin et al. [85] studied 18,872 total joint arthroplasties and found no statistically significant difference in PJI rate at about 5-year follow-up between patients who received IV five to 10 mg dexamethasone and the nondexamethasone group (odds ratio 1.05, 95% CI 0.71 to 1.54, $P = 0.77$). Also, Klement et al. and Richardson et al. found no statistically significant difference in PJI risk after administration of eight to 10 mg dexamethasone with total joint arthroplasty [86,87]. Godshow et al. 2019 showed that, in their retrospective cohort, administration of IV dexamethasone did not increase the risk of PJI or affect the serum glucose level [88]. Jorgensen et al. [89], in a prospective cohort study including 1,442 patients who received a preoperative high-dose corticosteroid (125 mg methylprednisone), found no statistically significant increase in infections at 3-month follow-up.

Conclusions

Based on available data, administration of low-dose IV corticosteroids during major orthopaedic surgeries does not seem to result in an increase in the rate of postoperative SSI/PJI. There is low evidence that administration of a single or multiple high-dose IV corticosteroids during major orthopaedic procedures may

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increase the risk of SSI/PJI. However, all studies available have a relatively small sample size, are victims of type II statistical error, and carry immense heterogeneity. Thus, there is a need for large-sized randomized controlled trials investigating the risk of SSI/PJI as a primary outcome in patients receiving perioperative IV corticosteroids.

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General Topics

2025 ICM: Surgical Environment

David Milligan, Moritz Wagner, Natividad Benito, Sulaiman Alazzawi, Ali Albelooshi, Sina Babazadeh, Francisco Baixauli, Timothy S. Brown, P. Maxwell Courtney, Henry Fu, George Grammatopoulos, Carl Haasper, Gary Hooper, Atul F. Kamath, Nanne Kort, Yona Kosashvili, David Liu, Stavros G. Memtsoudis, Ruben A. Morales-Maldonado, Benjamin F. Ricciardi, N Amir Sandiford, Alfredas Smailys, Mark J. Spangehl, Qiaojie Wang, Tina S. Wik, Piers Yates, Simon W. Young

Question 1: Does the use of laminar airflow reduce risk for surgical site infection/periprosthetic joint infection in patients undergoing major orthopaedic procedures?[1]

Response/Recommendation

There is no evidence to demonstrate that the use of traditional laminar airflow (LAF) systems is effective in reducing surgical site infection (SSI) or periprosthetic joint infection (PJI) in orthopaedic surgery.

Strength of Recommendation: Strong

Delegate Vote: Agree 95.8% Disagree 4.2% Abstain 0% (Super Majority, Strong Consensus)

Rationale

The effectiveness of laminar airflow (LAF) systems in reducing SSIs and PJIs during orthopaedic surgeries have been a subject of debate. In their landmark paper, Lidwell et al. (1982) [1] reported reduced infection rates when using LAF in a multicenter randomized controlled trial (0.6% in LAF compared to 1.5% in conventional settings), but they failed to control for confounders, including antibiotic prophylaxis. Furthermore, conventional turbulent ventilation systems have evolved, and current designs with high-efficiency particulate air filters cannot be compared to historical systems. The International Consensus meeting (ICM) 2018 [2] declared that LAF was not necessary in orthopaedic procedures. The World Health Organization recommends against the use of the LAF system [3].

Using a review of PubMed and Embase (Ovid) databases, we evaluated the current evidence to support the use of LAF in reducing SSI and PJI. There were 33 studies included, of which 10 were [4–13] in the most recent systematic review and meta-analysis [14], including studies from 2000 to 2022. They concluded that the overall pooled odds ratio (OR) against the use of LAF of all included studies was 1.70 (95% confidence interval (CI) 1.10 to 2.64), and the overall pooled risk ratio was 1.27 (95% CI 1.02 to 1.59) with $P < 0.05$. Other earlier systematic reviews [15,16] found no significant advantage of LAF in reducing PJIs following total knee arthroplasty, with some studies even reporting higher infection rates for total hip arthroplasty [6,9].

Observational studies provide conflicting evidence. Brandt et al. [6] reported an increased likelihood of SSIs in LAF-equipped operating rooms for total hip arthroplasty, with an OR of 1.63. Conversely, Kakwani et al. [5] found no infections in LAF settings compared to a 4% infection rate in non-LAF rooms for Austin-Moore hemiarthroplasties. A recent study by Wang et al. [12] compared two high-volume arthroplasty hospitals with the same surgical staff and protocols that differed only in the ventilation system used. They found LAF was not associated with a reduction of the risk of PJI (adjusted OR, 0.94; 95% CI, 0.40 to 2.19; $P = 0.89$).

Level 1 evidence provided by two recent randomized clinical trials [17,18] has been limited to assessing air quality by quantifying particulate load and colony-forming units (CFUs), but they had low patient numbers, and although they both demonstrated better air quality using LAF, they were unable to show any improvement in SSI or PJI. LAF, as commonly used, fails to address the environment outside of the immediate laminar flow zone, which is about a 3 m^2 area, leaving implant and instrument trays exposed to any unclean air that may inadvertently blow off the floor or personnel outside the laminar flow zone.

Perhaps the strongest evidence comes from registry-based studies using large databases. Hooper et al. [9], using data from the New Zealand Joint Registry, found higher infection rates in LAF-equipped operating rooms (OR = 1.6). Meanwhile, Pinder et al. [11] identified no discernible advantage of using LAF for orthopedic trauma.

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.08.063.

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https://doi.org/10.1016/j.arth.2025.08.063
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Conclusions

This review does not support the routine use of LAF in major orthopaedic procedures. LAF is not only expensive but it is also resource-intensive and requires major investment in installation, high energy consumption, and considerable maintenance. Consequently, in settings with limited resources, funds may be better allocated to interventions with demonstrable efficacy, such as preoperative skin preparation and standardized infection prevention protocols. However, maintaining clean air exchange rates and controlling contamination in critical zones should remain a priority, regardless of LAF use.

Question 2: Does the frequency of operating room door openings influence the rate of SSI/PJI in major orthopaedic surgery?[2]

Response/Recommendation

An increased number of operating room (OR) door openings (DOs) is associated with elevated levels of airborne particles, potentially contributing to a higher risk of SSI/PJI.

Level of Evidence: Moderate

Delegate Vote: 88.2% agreed, 7.9% disagreed, 3.9% abstained

Rationale

An increased number of particles in the OR air is thought to be directly linked to the rate of subsequent SSI [19]. Thus, minimizing airborne contamination in the OR is considered an important factor to reduce infections after major orthopaedic procedures [20–23]. There is no agreement on the optimal method for monitoring air quality within the OR [24–28], and there is no consensus on the maximum concentration of airborne particles that is "acceptable" in the OR (i.e., not associated with increased SSI risk) [29]. Particle counting is technically less demanding and more easily implemented in practice compared to microbiological sampling, which requires microbiological cultures, and is thus the preferred method of quantifying air quality. Particle counting provides indirect insights into air quality [30], as it does not consider whether particles carry viable microbes, termed CFUs, potentially causing infection, or just dead matter. However, studies have highlighted the correlation between particulate matter and airborne viable bacterial counts [24]. Therefore, the quality of air in the OR significantly affects microbial contamination levels [31,32]. Microbial load in the OR is influenced by factors such as air filtration systems, LAF [33], and frequency of DO [34]. However, the most important source of contamination is human [29]; the ultraclean air standard can only be found in an empty OR [35].

Laminar airflow systems, while designed to reduce particulate contamination, are susceptible to disturbance from DOs and human traffic, which can undermine their efficacy [36,37]. Door openings are thought to elevate contamination through two principal mechanisms. The number of DOs correlates with the number of staff present in the OR [38]. Also, DOs disrupt the LAF in the OR, increasing turbulence and facilitating the spread of airborne particles and bacteria into the surgical field [33,34,37,39,40]. Andersson et al. [37] highlighted a positive correlation between traffic flow, number of persons present, and duration of surgery, causing a 68% increase in CFU/m^3. Experimental and observational research, along with simulation studies, has investigated the impact of OR traffic [41,42]. Mears et al. [42] demonstrated that 77 of 191 total joint arthroplasties (TJAs) experienced a loss of positive OR pressure due to DOs, allowing airflow to reverse from the hallway into the OR. This disruption, though considered temporary, led to a total time of 9 minutes of doors being open per case, raising concerns about the time required to restore pressurization. Conversely, Weiser et al. [34] found that a single DO did not compromise positive pressure but noted that simultaneous openings of two doors allowed outside air to enter. They suggested that OR contamination was more directly attributable to personnel activity rather than DOs alone. The presence of personnel and OR traffic measured by the frequency of DOs has been consistently identified as a significant contributor to the increased concentration of airborne particles in the OR [24,41,43,44]. Observational studies have shown a clear association between the number of individuals present and the frequency of DOs, with a corresponding rise in aerosolized particles, 41% of those being CFUs [24].

Several investigations have examined the rate and causes of DOs during elective TJA procedures [25,33,34,45]. Reported DO rates ranged from 0.19 to 0.65 per minute for primary TJAs and up to 0.84 per minute for revision TJAs; however, there is wide variability in the literature. The total number of DOs per case averaged between 13.4 [46] and 66 [22] for primary arthroplasties and 135 DOs for revision arthroplasties [22]. The pre- and post-incision time periods (of a surgical case) saw the highest DO frequencies [25,30]. Operating room traffic flow during surgeries was categorized in a study, totalling 529 DOs during 30 operations (mean 18 DOs per case) [37], with 33.5% (177) categorized as necessary, 34.8% (184) as semi-necessary, and 31.7% (168) as unnecessary. Necessary DOs were most often due to retrieving instruments or materials (25.9% of total openings, n = 137) and expert consultations (7.6%, n = 40). Semi-necessary openings primarily involved surgical team transitions (14.4%, n = 76) and breaks for lunch or coffee (20.4%, n = 108). Unnecessary openings were often attributed to social visits (8.5%, n = 45) or no detectable reasons (17.6%, n = 93) [37]. Another study found that of 9,657 cases reported, necessary DOs made up 8.4%, breaks were minimal at 1.5%, supplies contributed to 23.3%, social visits/information to 12.5%, and no reason was documented for a striking 47% [40]. Overall, unjustified traffic was noted to be substantially high (12.5 to 25%) across multiple studies [25,37].

Even though it seems highly plausible that high numbers of CFU/m^3 increase the risk of SSI, this has never been scientifically proven to date. Nevertheless, most studies assessing OR traffic, OR particle load, and OR particle counting assume that SSI risk is linked to CFU concentration. Pulido et al. [39] emphasized the likely causal relationship between overall SSI rates and OR traffic, which could frequently be avoided, emphasizing the importance of timing and procedural practices during surgery to avoid traffic. Similarly, microbial and particulate contamination risk increases with procedural interruptions, highlighting the need for adherence to strict environmental controls [30].

Monitoring OR traffic and enforcing access restrictions during critical phases of surgery have been suggested as measures to mitigate these risks [47]. Babkin et al. [23] identified SSI rates following knee arthroplasty, linking these to perioperative practices. Standardized infection control measures, including effective cleaning protocols and minimized OR interruptions, were highlighted as critical.

Conclusion

Although the direct correlation between DO during surgery and increased infection rates is not definitive, it is clear that any disruption to the sterile environment can increase the potential for contamination. A large body of literature exists demonstrating the direct relationship between increased airborne particles, OR traffic, DOs, and the total number of personnel present in the OR. The OR door should be opened as infrequently as possible, and

[2] These authors contributed to Question 2: Moritz Wagner, Sina Babazadeh, Carl Haasper, George Grammatopoulos

when it must be opened, precautions should be taken to minimize the risk of introducing pathogens into the sterile field. There are no sufficiently large-scale studies to scientifically demonstrate a critical threshold in the number of airborne particles, and there are no clinical studies proving a direct relationship between airborne CFU and infection risk. Practical measures, such as limiting DOs through continuous education of OR personnel, warning signs outside doors [48], monitoring traffic [26], and optimizing ventilation systems, are essential for minimizing airborne contamination [27]. Studies investigating OR traffic and DOs recommend limiting DOs. Strategies to limit OR traffic include avoidance of unjustified traffic through organizational and procedural optimization, staff information [49], and information/warning signs [50,51]. Future studies should investigate the direct relation between MCP/m^3 and PJI rates to establish potential thresholds.

Question 3: Is there a role for the use of personal protection systems (surgical helmets/spacesuits) in the prevention of SSI/PJI after major orthopaedic procedures?[3]

Response/Recommendation

There is no high-level evidence that personal protection systems (PPS) reduce the incidence of SSI/PJI. In contrast, inappropriate use of PPS may increase contamination of the surgical wound.

Level of Evidence: Strong

Delegate Vote: Agree 92.5% Disagree 5.6% Abstain 1.9% (Super Majority, Strong Consensus)

Rationale

Personal protection systems, comprising surgical helmet systems and protective attire, are widely used in TJA for their potential to reduce infection by creating barriers between surgical personnel and the sterile field. Initially introduced by Sir John Charnley [52] as a fully enclosed body exhaust suit, creating airflow from within the suit to outside the operating room, it resulted in an over 90% reduction in PJI. The exhaust tubing was found to be impractical and cumbersome, leading to its replacement with non-exhaust systems in recent decades. However, evidence regarding their effectiveness is mixed, with some studies suggesting potential contamination risks associated with improper use of PPS [52–55]. The other reason to use a PPS is to help protect the surgical team from airborne contamination from the patient.

In order to answer the above question, we searched PubMed and Embase (Ovid) databases from 1969 to 2024. The delegates were informed of a current systematic review and meta-analysis [56], which has been accepted for publication in *Clinical Orthopaedics and Related Research*, 2025. All delegates critically reviewed this and agreed that it was a comprehensive analysis of the research question and, as such, should form the basis of our recommendation. A further seven studies were added after assessment of the database search.

In the comprehensive review by Kamath et al., surgical helmets were reported to have widespread contamination, particularly when improper donning techniques were employed. Activating the fan of the surgical helmet before complete gowning caused major contamination, including microbial spread up to five feet around the surgeon [57]. Similarly, Tarabichi et al. [58] observed reusable helmets often cultured positive for pathogens, highlighting the inconsistent sterilization practices in many institutions and emphasizing the need for standardized cleaning protocols to mitigate these risks. Lynch et al. again observed a marked reduction in bacterial contamination when helmet fans were run for at least three minutes before entering the operating room, suggesting an easy-to-implement contamination control measure. However, Hubble et al. [59] found that certain types of gowns worn with surgical helmets, particularly balloon-cotton clothing, exacerbated contamination risk.

The positive pressure airflow generated by helmet fans presents a potential contamination pathway. Studies reviewed by Kamath et al. and others highlighted increased airborne particle and microbial contamination. Fraser and Young et al. [60] demonstrated much egress of contaminated air from the glove-gown interface and recommended sealing this region with tape. Tateiwa et al. found that while surgical helmets effectively minimized microbial spread during critical surgical steps, particle contamination increased during personnel movements. Optimizing the helmet design may mitigate these risks. For example, using a toga setup instead of a two-piece gown significantly reduced contamination near critical areas [56]. Similarly, dual-fan systems demonstrated better air exhaust control than single-fan models, directing airflow away from the sterile field.

Direct evidence linking surgical helmets to reduced infection rates remains limited. Retrospective analyses of registry data have yielded mixed results. Hooper et al. [55] observed increased revision rates due to deep infections in helmet-equipped surgeries, but more recent multivariate analyses found no significant differences when confounding factors were adjusted. Lynch et al. [57] suggested that contamination risks could be mitigated without increasing infection rates if proper protocols were followed.

Conclusions

There is no high-level evidence that PPS reduces the incidence of SSI/PJI. Inappropriate use may increase wound contamination. If surgical helmets are used, activating the fans only after complete gowning, use of dual-fan systems or toga setups, and a standardized donning procedure, which includes sealing the gown-glove interface with adhesive tape, may further mitigate contamination risks. Improved cleaning and bioburden reduction protocols are essential for reducing bacterial reservoirs in reusable helmets. Educating surgical teams on the proper use of surgical helmet systems is imperative.

Question 4: Does the number of personnel in the operating room influence the incidence of SSI/PJI in major orthopaedic surgery?[4]

Response/Recommendation

Evidence does not confirm the influence of the number of personnel in the operating room on SSI/PJI. However, indirect evidence supports minimizing personnel to reduce air contamination. It is recommended that this measure be included in a bundle of strategies to minimize bacterial burden in the operating room environment.

Level of Evidence: Moderate

Delegate Vote: Agree 86.4%, Disagree 9.1%, Abstain 4.6% (Super Majority, Strong Consensus)

Rationale

Surgical site infection acquisition depends on several factors, mainly the exposure to bacteria and the host's capacity to control

[3] These authors contributed to Question 3: David Milligan, Gary Hooper, Benjamin F. Ricciardi, Atul F. Kamath, Mark J. Spangehl, P. Maxwell Courtney, Tina S. Wik, Simon W. Young

[4] These authors contributed to Question 4: Natividad Benito, Ruben A. Morales-Maldonado, Francisco Baixauli, Alfredas Smailys, Sulaiman Alazzawi, Timothy S. Brown, Stavros G. Memtsoudis, Henry Fu

the unavoidable bacterial contamination of the surgical wound [61]. Surgical site infections are typically caused by bacteria inoculated into the surgical site at the time of surgery, mostly from the patient's endogenous flora (70 to 90% of cases could arise from the patient microbiome) [62,63]. Less frequently, SSI pathogens may originate from exogenous sources, including surgical personnel, the OR environment (including air), and all tools, instruments, and materials used during the procedure [64,65].

The operating room (OR) air may contain microbial-laden dust, lint, skin squames, or respiratory droplets [64]. According to some experimental research, such as that by Ritter et al. in 1975, it is believed that personnel present in the OR are the main source of particles in the air and that the microbial air level in the OR is directly proportional to the number of people moving about the room [65]. Each person sheds millions of particles per day, and skin debris may carry bacteria; both *Staphylococcus aureus* and *Staphylococcus epidermidis* (the principal causative organisms of PJIs) are shed into the environment on skin scales. [66,67] Thus, bacterial shedding by OR staff is a potential source of intraoperative contamination [64]. As a result, several guidelines (1999 Centers for Disease Control and Prevention, 2010 Association for Professionals in Infection Control and Epidemiology) have recommended for many years to limit the number of people and OR DOs to a minimum [64,68]. The ICM on Musculoskeletal Infection 2018 also endorsed keeping OR traffic to a minimum. However, due to a lack of strong evidence supporting these measures, other recent guidelines on the prevention of SSIs do not specifically address this issue and do not propose associated recommendations [69–71].

We conducted a literature review including articles published in English after 1990 that met the following inclusion criteria: original research articles that examined orthopaedic surgeries in humans or simulated scenarios and provided an explicit analysis of "the number of personnel in the OR" as a potential-independent variable of SSI (or a surrogate variable of SSI like air contamination), even if it was not the principal independent variable. Studies were excluded if they only analyzed "traffic flow" or "OR DOs" without explicitly considering the number of people in the OR. While these factors are closely related, there is another specific question in the present ICM regarding the potential connection between OR DOs and SSIs.

In seven studies, the outcome was the OR air contamination, measured by the bacterial counts expressed in CFUs and/or the number of particles [72–78]. The outcome was the contamination of the implant in one study [79] and the incidence of SSIs in another study [80].

The methodology in the seven studies evaluating air contamination varied markedly, complicating the analysis and comparison of results [72–78]. Among these studies, there were four single-center ones [72–75]. and three multicenter investigations [75,77,78]. All but one study, a simulated investigation in an OR, were performed during surgical procedures, with the number of operations averaging between 20 and 60, except for one study that included over 1,200 operations [75]. Microbiological air counts were assessed using active sampling in two studies conducted at the same hospital in Sweden [73,74], while both passive and active sampling methods were utilized in four studies [72,75,77,78], (with air particles in the OR additionally measured in two of them). In the "simulated study," only air particles were analyzed [76]. The samplers and ventilation systems in the ORs varied across the studies. Among the seven studies analyzed, three found a positive correlation between the number of persons in the OR and the count of CFU or particles [74–76]. However, in two of these studies, the analysis was not adjusted for other variables [75,76], and in one of them (the simulated study), the correlation was only observed when the LAF ventilation system was turned off [76]. The third study demonstrated the effect of the number of personnel on CFU counts in a conventional ventilation system compared to an LAF system [74]. Conversely, four studies found no correlation between the number of personnel and air contamination [72,73,77,78]. Nevertheless, two of these studies demonstrated a relationship with traffic flow and the frequency of DOs in a multivariate analysis [72,73]. The remaining two studies found no statistically significant impact from any of these factors [77,78]. However, both studies reported a low level of air contamination in the OR, and in one of them, the number of personnel and DOs were minimal and differed slightly between operations, [78], which may have contributed to the negative findings.

Bible et al. analyzed 105 consecutive cases of surgical spine that required instrumentation and evaluated implant contamination [79]. Cases were randomized to have all implant trays either remain uncovered ($n = 54$) or covered ($n = 51$) with sterile surgical towels on opening until implants were required for the case. Although coverage of implants was found to significantly reduce the implant contamination rate, other factors, such as the number of scrubbed personnel, were not significantly associated with implant contamination. More than 2,700 clean surgeries performed in a large single center in the United States, including 734 orthopaedic procedures, were examined in a retrospective study.[80] In the univariate analysis, as the number of people increased, there was a steady rise in the infection rate. In the multivariate analyses, the American Society of Anesthesiogists score and the duration of surgery were statistically significant risk factors for SSI. All other factors, including age, sex, urgency, preoperative length of stay, and the number of people in the OR, were not predictive of SSI. Although the number of personnel did not reach statistical significance with logistic regression, further evaluation of the data revealed that longer surgical procedures were associated with a steady increase in the number of people in the OR.

The number of personnel and traffic during operations, intuitively and based on initial investigations, appear to influence OR air contamination and the rate of SSIs. But, while the evidence shows that the duration of surgery contributes to SSI incidence, studies on the effects of personnel and traffic exhibit contradictory results. Most research has relied on surrogate endpoints, such as CFU counts in the air, to assess SSI risk. Yet, air sampling as a scientific data collection method poses challenges. Notably, there is no international standard for air sampling during surgery, making it difficult to assess and compare results from different samplers. Additionally, a specific correlation between airborne bacteria levels and subsequent SSI has not been established [81]. Although proper ventilation systems in the OR are essential for diluting and removing microorganisms shed from skin scales and preventing wound contamination, numerous parameters can influence their performance. Many other factors can affect air contamination, making it challenging to measure all of them accurately and simultaneously. Nevertheless, while airborne contamination is common, it currently seems unlikely that this results in a bacterial inoculum that overwhelms local immunity and the effect of surgical antimicrobial prophylaxis [81].

Despite the challenges in demonstrating the potential influence of the number of personnel in the OR on SSIs, this factor is one of many that collectively enhance the discipline and behavior of OR staff. They can contribute to creating a safer environment and ultimately help to prevent SSIs.

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The Journal of Arthroplasty 41 (2025) S120–S128

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

General Topics

2025 ICM: Sutures and Dressings

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Question 1: Does the type of wound closure (sutures versus staples versus glue) influence the rate of infections in major orthopaedic surgery?[1]

Recommendation

There is no single wound closure method that consistently outperforms others.

Level of Evidence: Low

Delegate Vote: Agree: 95.0%, Disagree: 5.1%, Abstain: 0% (Super Majority, Strong consensus)

Rationale

The relationship between wound closure methods and the risk of surgical site infections (SSIs) or periprosthetic joint infections (PJIs) in major orthopaedic surgery has been widely studied in the literature, but with mixed conclusions. Various factors, including the surgical site, patient comorbidities, and the specific wound closure technique, complicate effective statistical comparisons.

Current wound closure methods range from metallic staples to tissue adhesives, absorbable sutures, braided sutures, or antibiotic-coated sutures. Each method has unique advantages and potential drawbacks depending on the type of wound and surgical site. Low-tension wounds over the hip or spine are generally well-suited to sutures and tissue adhesives. In contrast, high-tension wounds, such as those around the knee or ankle, may benefit more from staples or barbed sutures [1].

Conventionally interrupted knotted sutures have been a mainstay of orthopaedic wound closure. However, they have been criticized for increasing focal tissue ischemia, stitch abscess formation, and prolonged closure times [2]. Barbed sutures have emerged as an alternative, offering reduced closure times and eliminating knot-related complications [3]. However, the advantage of a barbed suture over a conventional braided suture remains questionable. Although closure in THA cases was reported to have higher wound infection rates with braided sutures, in total knee arthroplasty (TKA) closures, a higher infection rate was observed after barbed sutures [4,5].

Metallic staples show varying infection rates depending on the procedure. In THA, staples are associated with a higher risk of SSI. In a large randomized controlled trial (RCT) of 535 THA patients, Mallee et al. [6]found a threefold increase in SSI risk with staples as compared to sutures, odds ratio (OR) = 2.8, $P = 0.057$. Similar comparisons have been noted by Van de Kuit, Krishnan, Rui, and Smith, arguing that the infection could be attributed to soft-tissue reaction to stainless steel or titanium staples or improper surgical technique, leaving overlapping or inverted wound edges, causing persistent oozing and open skin entry points [1,7–9]. Even traumatic proximal femoral surgeries closed with staples reported higher wound infection rates than sutures [10].

Conversely, studies reporting on TKA cohorts have shown significantly lower infection rates with staples. Campbell et al. [11] noted a 19.6% infection rate with sutures versus 7.2% with staples. Similarly, Newman and Mudd [12,13]also reported lower infection rates with staples, 0 versus 4%. Explaining that the greater space between staples may provide an advantage in terms of oxygenation and, therefore, proper wound healing and lower infection risk [3].

Some studies have also noted comparable infection rates between sutures and staples, reporting no significant differences in either THA or TKA [14,15]. Multiple prospective RCTs have reported no significant differences in infection when comparing tissue adhesives, stapling, and suturing [16,17]. Glennie et al. and Khan et al. [18,19] noted that an increased wound discharge was associated

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.086.

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https://doi.org/10.1016/j.arth.2025.10.086
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with staple closure, but the risk of infection was comparable across techniques.

Tissue adhesives, such as cyanoacrylate, offer bactericidal properties and can form a mechanical barrier against microorganisms. However, while adhesives have been associated with improved cosmetic outcomes and patient satisfaction, their impact on infection rates has been inconsistent [20]. Studies have reported significantly lower infection rates with tissue adhesives in spinal procedures compared to sutures or staplers [21,22]. However, in knee, hip, or trauma surgeries, adhesives may pose a higher infection risk, with Miller et al. reporting a 3.2% infection rate with adhesive closure versus 2.4% with staples, and similar findings observed by Raja et al. and Lee et al. [20,23,24].

The importance of a layered closure in ensuring prevention of infection has been comprehensively described by Snyder et al. [25], in a systematic review of wound closure techniques, reporting significantly lower infection rates with multilayer antimicrobial sutures, with the risk of deep SSI ranging from 0 to 1.1% and superficial SSI ranging from 0 to 1.3%. Comparatively, traditional closure methods, either plain sutures, staples, or adhesives, had a 14.8% rate of superficial SSI and a 3.9% rate of deep SSI. In a separate large observational study of 2,000 arthroplasty patients who had set integrated care protocols, Snyder et al. [26]reported a 0% infection rate after using watertight multilayer closure with barbed sutures and tissue adhesives.

The noninvasive closure systems, such as zipper-like devices, are gaining attention for their ease of use and minimal wound complications [27]. These systems offer comparable infection rates to staples and reduce operative time, providing an alternative for patients requiring a quicker recovery and self-removal capability [28].

Conclusion

The influence of wound closure techniques on SSI and PJI rates in orthopaedic surgery depends on the surgical site, wound tension, and patient-specific factors. Although no single method consistently outperforms others, evidence supports tailored approaches. Sutures and tissue adhesives are effective for low-tension wounds. Staples may be preferable for high-tension sites like the knee, but they carry higher infection risks in THA. Barbed sutures reduce closure time but have a higher risk of infection. Tissue adhesives have mixed outcomes, with promising results in spine and small-joint surgeries. Multilayer antimicrobial sutures provide the most reliable reduction in SSI rates.

Question 2: Does the use of triclosan-impregnated sutures reduce the risk of subsequent SSI in patients undergoing major orthopaedic procedures?[2]

Response/Recommendation

Yes. Triclosan-impregnated sutures, compared to sutures without any antibacterial coating, may result in a reduction of the risk of SSI after major orthopaedic procedures.

Strength of Recommendation: Limited

Delegate Vote: Agree: 84%, Disagree: 11%, Abstain: 5% (Super Majority, Strong Consensus)

Rationale

Sutures are made of a foreign material that is routinely inserted into a surgical site at the end of procedures. As our surgical sites are more likely to be contaminated at the end of the procedure [29], it is easy to understand that the use of a material with a broad-spectrum antibacterial agent that actively inhibits the colonization of the most common organisms associated with SSI may play an important role. Although the use of triclosan-coated sutures to prevent SSIs has been recommended internationally by various guidelines [30–32], there are limited data in the field of orthopaedics.

To answer the posed question above, we conducted a comprehensive systematic review and meta-analysis to clarify the efficacy of triclosan-impregnated sutures over nonantimicrobial sutures in reducing SSI in clean surgeries, along with the evidence among major orthopaedic surgeries, including spine surgery, trauma/fracture surgery, and joint arthroplasty.

As there was a well-organized systematic review [33], which was a part of the recent National Institute for Health and Care Excellence (NICE) guideline [31], we adopted the same search strategy and added the literature that was published after their review [33], following International Consensus Meeting guidance. We did not include other antibacterial sutures (e.g., chlorhexidine-coated sutures) as they are not available universally.

We identified 383 articles that were subjected to title and abstract screening. We shortlisted seven articles for full-text screening, added 13 articles from the previous SR [33], and another article from our hand search. There were five studies that were excluded, and the remaining 16 RCTs were included in our final analysis for clean surgeries [34–49]. We used Grading of Recommendations Assessment, Development and Evaluation to evaluate the certainty of the evidence and created a summary of findings table to describe the results [50].

Evidence was available from various countries, including the USA, Korea, Pakistan, Turkey, Taiwan, Brazil, Norway, the United Kingdom, Sweden, Finland, and China, on various surgical procedures, including spine, open reduction internal fixation, THA, and TKA, arthroscopy, breast, cardiac, cerebrospinal fluid shunt, and lower limb arterial surgeries. All studies were published between 2011 and 2024 and reported outcomes of a month or longer. The methods and types of triclosan-impregnated sutures varied among studies, with four studies using Stratafix symmetric PDS plus [34,35,44,49]. The definition used for SSI/PJI/fracture-related infection (FRI) varied among studies, with five studies using the Centers for Disease Control and Prevention criteria [37,42,45–47].

From our analysis focusing on all 16 RCTs (N = 5,780), triclosan-impregnated sutures were significantly more effective for preventing overall SSI/PJI/FRI in patients undergoing clean wound surgeries with primarily closed surgical incisions compared to sutures without any antibacterial coating (relative risk [RR] 0.76; 95% confidence interval [CI] 0.62 to 0.94, moderate certainty of the evidence, Figure1). In this analysis, the *Z*-curves crossed the trial sequential monitoring in our trial sequential analysis (TSA), suggesting a conclusive result. Moreover, publication bias was not likely, as the comparison-adjusted funnel plot did not seem to show asymmetry (Egger's test: $P = 0.26$). This finding was consistent with our sensitivity analyses, including studies with $\geq$ 12 weeks of follow-up (RR 0.34; 95% CI 0.13 to 0.85), and when excluding studies with high risk of bias (RR 0.76; 95% CI 0.59 to 0.97). Similar preventive effects were also seen in our subgroups of the adult population (RR 0.78; 95% CI 0.64 to 0.96), high-income countries (RR 0.78; 95% CI 0.62 to 0.98), and industry-funded studies (RR 0.65; 95% CI 0.46 to 0.91). The preventive effect was not significant in middle-income countries.

Very low to low quality evidence showed that the triclosan-impregnated sutures had neither benefit nor harm compared to nonantimicrobial sutures for the purpose of preventing superficial SSI, deep SSI, reoperation, adverse events, wound dehiscence, hematoma, and death.

[2] These authors contributed to Question 2: Koji Yamada, Natsumi Saka, Shunsuke Katsumi, Takeshi Morii, Azlina Amir Abbas, Willy Paul Stangl, Wierd Zijlstra, Derek T Ward, Roger Rojas Sayol

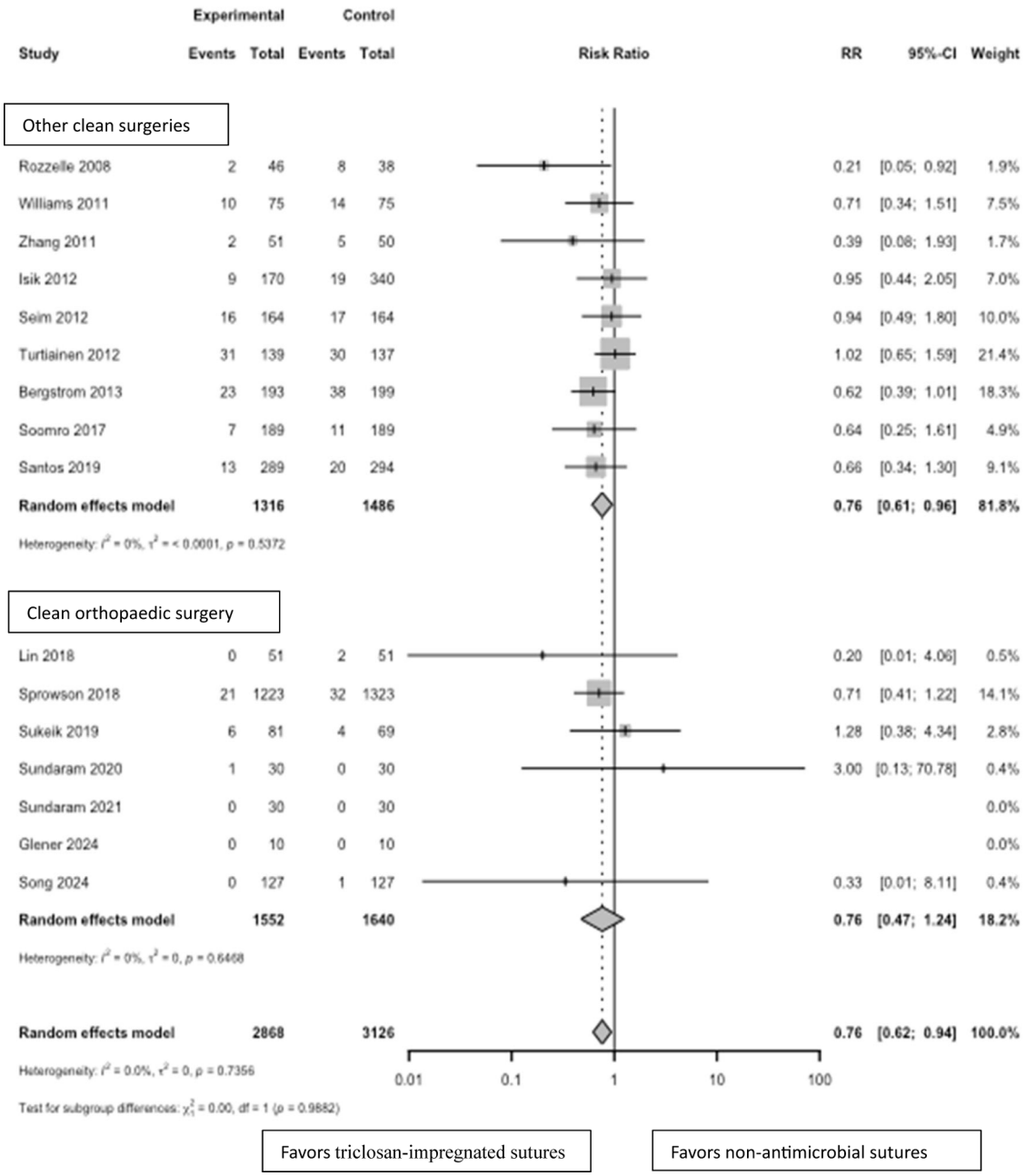

Figure 1. Meta-analysis results—all SSI/PJI/FRI. PJI, periprosthetic joint infection; FRI, fracture-related infection; SSI, surgical site infection.

When focusing on major orthopaedic procedures (seven RCTs, n = 3,192), although there was a trend toward efficacy, triclosan-impregnated sutures failed to show their effect on preventing overall SSI/PJI/FRI (RR 0.76; 95% CI 0.47 to 1.24, Figure 1). However, the result was highly influenced by a single large-sized RCT (13), and the cumulative number of patients did not exceed the required information size, and the *Z*-curves did not cross the trial sequential monitoring or futility boundary, suggesting an inconclusive meta-analysis result.

Although inconclusive evidence, the trend toward the use of triclosan-impregnated sutures in major orthopaedic procedures was aligned with what we found in all clean procedures, without any evidence against its use. From the inconclusive TSA results, it is difficult to establish any conclusive decisions regarding major orthopaedic procedures. However, our results were more likely to be just underpowered. As all clean procedures share very similar SSI pathogens and infecting mechanisms, we believe this material may be recommended in our field, along with the other clean procedures, due to the promising results among various clean surgeries.

There are several potential limitations. Triclosan-impregnated sutures are generally costly compared to nonantimicrobial sutures. But a cost analysis was not performed for this document. The recent NICE guideline suggested that triclosan-impregnated sutures were cost-saving compared with non-triclosan absorbable sutures by an average of £13.62 per patient from their cost analysis [31,33]. But there remains the issue of generalizability in other countries due to the different payer systems, including low- and middle-income countries. Also, we have excluded all other types of antimicrobial sutures. Reproducibility and generalization of our

results are not warranted for these sutures. In addition, although the number of studies funded by the industry was limited, they were all from the same company (Ethicon Inc., Johnson & Johnson, Cincinnati, Ohio, USA). Furthermore, the magnitude of adverse events may be underestimated, as we did not include observational studies. Moreover, the methods/types of triclosan-impregnated sutures and the SSI definition varied among studies. These heterogeneities may have affected our results.

Conclusion

From the promising results in all clean procedures, with a similar trend in major orthopaedic procedures, we believe triclosan-impregnated sutures may be effective in minimizing the risk of SSI in our field, which is aligned with global recommendations [29–31]. But from its inconclusive evidence, more robust trials with standardized surgical protocols, especially in low- to middle-income countries, are still needed to further validate its effectiveness in major orthopaedic procedures.

Question 3: Is there a role for the use of resorbable agents that can deliver antibiotics locally for the prevention of infection in patients undergoing major orthopaedic surgery?[3]

Response/Recommendation

Yes. There appears to be a role for the use of resorbable agents for the delivery of local antimicrobials. Although a whole host of resorbable agents exist, the most studied are calcium sulfate and hydrogel agents.

Level of Evidence: Limited

Delegate Vote: Agree: 59.2%, Disagree: 27.3%, Abstain: 13.5% (Simple majority, Low/no consensus)

Rationale

A total of nine studies were identified [51–59], including three RCTs [53,58,59], one case-control study [51], three retrospective cohort studies [54,56,57], and two case series [52,55]. There were eight of nine studies that included patients undergoing primary or aseptic revision arthroplasty (including megaprostheses for oncologic reconstruction) [51,53–59]s, while one study included spine surgery patients [52]. A total of 1,205 patients were included (57.9% women).

There were five studies that evaluated the use of calcium sulfate beads (Stimulan), with or without vancomycin added [52,54,55,57,58]. There were two studies that evaluated an antibiotic-loaded hydrogel coating (DAC) [51,53]. There was one study that evaluated a hydroxyapatite-collagen scaffold loaded with vancomycin [59]. Also, one study evaluated calcium carbonate beads loaded with gentamicin (HERAFILL).

Of the five studies evaluating the use of calcium sulfate beads, four comparative studies were pooled for analysis. There were three of the four studies found significantly reduced infection rates with the use of calcium sulfate beads, while the noncomparative study found a 0% infection rate with the use of calcium sulfate beads.

There was one RCT that evaluated a vancomycin-loaded hydroxyapatite-collagen scaffold in TKA patients and found a significant reduction in rates of prosthetic joint infection (0 versus 4.1%, $P = 0.014$) [59]. Also, one study evaluating calcium carbonate beads loaded with gentamicin found a significant reduction in reinfection rate in second-stage TKA for previous prosthetic joint infection (0 versus 17.9%, $P = 0.025$) (56).

There was one study that reported an adverse event potentially related to the resorbable agent; Lum et al. [55], in their noncomparative study, reported one case of prolonged serous drainage (1.9%), which required irrigation, debridement, and liner exchange; however, it was negative for infection workup. A previous systematic review has also raised concerns about possible hypercalcemia with the use of calcium sulfate beads, with a rate of 4.2%, and a rate of 0.28% of patients requiring active management of the hypercalcemia [60].

Overall, nearly all studies evaluating resorbable antibiotic delivery agents have found low or reduced infection rates compared to the standard of care, including in one study compared to nonantibiotic-loaded calcium sulfate beads plus antibiotic powder. Thus, there is likely a role for these agents in high-risk patients. However, the effect sizes in the pooled data should be interpreted with caution, given the overall small number of relatively low-quality studies available. As well, it is unclear whether the resorbable delivery agent itself matters; however, the slow elution and resorption over time does seem to be important, given that one study using plain beads plus antibiotic powder in the control group still found a significant effect favoring antibiotic-loaded beads.

Question 4: Which surgical dressing is optimal for reducing surgical site infection after major orthopaedic surgery?[4]

Response/Recommendation

Active dressings, and particularly hydrofiber dressings, are superior to passive dressings in reducing SSI after major orthopaedic surgery.

Level of Evidence: Level 2

Delegate Vote: Agree: 57.0%, Disagree: 25.1%, Abstain: 17.9%

Rationale

Proper wound management after major orthopaedic surgery, including elective total joint arthroplasty (TJA), is crucial to prevent superficial and deep SSIs [61]. This includes the use of the proper wound dressing postoperatively. There are numerous options available for wound coverage after surgical procedures. Dressings can be basic/passive (e.g., gauze or cotton absorbent) versus advanced/active (e.g., hydrogels, hydrocolloids, films), occlusive versus nonocclusive, hydrophilic versus hydrophobic, include antimicrobial agents, or be composed of a “glue-glue-as-a-dressing” (usually made of cyanoacrylate) [62]. The ideal dressing is likely one that absorbs exudate while maintaining a moist environment, can provide a barrier from contamination from surrounding skin and the external environment, and ideally includes an antimicrobial agent that is broad-spectrum and does not lead to increased bacterial resistance [63,64]. Effective antimicrobial agents used in wound dressings include silver, polyhexamethylene biguanide, and manuka honey. These agents have broad antimicrobial properties and have been shown to work against fungi and bacteria, even resistant organisms such as methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus* [65–70]. Dressings used in orthopaedic surgery should additionally be highly conforming and flexible to accommodate movement, especially at joints, like the knee, and should be cost-effective.

In a quest for the best postoperative dressing, Dumville et al. conducted a Cochrane database study encompassing 29 RCTs, mostly involving nonorthopaedic procedures [71]. This extensive

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[4] These authors contributed to Question 4: Shahid Noor, Muhammad Shoaib bin Shakeel, Andrea Baldini, Giuseppe Calafiore, Giandomenico Logroscino, Antonio Solano, Joseph Albert Karam

review found no clear superiority of one specific type of dressing in reducing SSI and concluded that available studies in the literature are of very low quality. In a systematic review and network meta-analysis more focused on TJA, Kuo et al. [72]evaluated 21 studies utilizing 12 different types of dressing after 7,293 TJA procedures. They found antimicrobial dressings to have the most efficacy for preventing PJI. Negative-pressure wound therapy dressings had the highest rate of blister formation. Hydrofiber dressings were not found to offer a significantly reduced rate of infection compared to standard dressings. Yuan et al. [73]conducted a meta-analysis comparing active dressings versus passive dressings after hip or knee arthroplasty. They included 16 prospective and retrospective studies involving 2,765 subjects. They found active dressings to have significantly lower wound complications and fewer dressing changes.

Indeed, many orthopaedic centers have recently transitioned from basic dressings to advanced or active dressings after TJA. Hydrofiber dressings have particularly gained interest and have become the standard of care in many centers. These dressings are made of sodium carboxymethylcellulose, which forms a gel on contact with exudate and can hold up to 30 times its weight [62]. In order to better understand the role of hydrofiber dressings in reducing infection after major orthopaedic surgery, we conducted a comprehensive review of the literature. Using the Medical Subject Headings terms created by the librarians, we searched the Scopus and Medline databases to identify 4,718 potentially eligible studies. After initial screening by two independent reviewers, 15 studies were left for full review and data extraction, including four meta-analyses [74–88]. We found two retrospective studies that identified a lower rate of PJI with the use of hydrofiber after TJA. Cai et al. [76]demonstrated a significantly reduced rate of PJI with the use of hydrofiber dressings in a retrospective study of 1,778 patients undergoing TJA, with an OR of 0.165 (95% CI: 0.051 to 0.533) after multivariate analyses. Similar findings were identified by Grosso et al. [79]in another retrospective study of 1,173 patients undergoing TJA. They also performed a multivariate analysis for risk of PJI and found that the use of hydrofiber dressing conferred a protective effect with an independent OR of 0.092 (95% CI 0.017 to 0.490). Although several prospective studies have attempted to further evaluate the effect of hydrofiber dressings on outcomes after TJA, they were grossly unable to identify a significant difference in infection rates, mostly related to low numbers of study subjects, coupled with the low incidence of infection [74,75,78,80,82,84–86,88,89]. Systematic reviews and meta-analyses thus attempted to compile the data and address this question. Chen et al. [17]conducted a meta-analysis comparing hydrofiber dressing to standard dressing or absorbent dressings after TJA. They included five studies with a total of 3,721 participants. They found lower infection rates with hydrofiber and absorbent dressings and lower blistering rates in hydrofiber dressings than the other two dressings. Sharma et al. [87], in a broader meta-analysis including 12 RCTs, found decreased wound complications after film dressings or hydrofiber dressings than passive dressings, without, however, demonstrating a significant effect on the rate of actual PJI.

Also, a recent meta-analysis by Mundi et al. [83]included five RCTs comparing hydrofiber dressings to standard dressings. They were not able to show any effect on PJI; however, the studies had a smaller number of patients, limited follow-up, and overall poor methodology. All three of these meta-analyses showed a significantly reduced number of dressing changes with the hydrofiber dressing. This is not a trivial benefit, as it minimizes skin trauma, avoids painful events, and reduces the risk of wound contamination. Despite these advantages, the higher cost of hydrofiber dressings may pose challenges for widespread adoption, particularly in resource-limited settings. Nevertheless, potential savings from reduced hospital stays and fewer secondary interventions may offset initial expenses, particularly for high-risk patients [62,75,86].

Conclusion

In conclusion, advanced active dressings, particularly hydrofiber wound dressings, should be considered a preferred option for postoperative wound care in orthopaedic surgeries. Their role in reducing infection, improving patient comfort, and enhancing healing makes them a valuable addition to surgical practice. Although further high-quality studies are recommended to explore their true efficacy in preventing deep infections, these advanced dressings align with evidence-based practices aimed at optimizing surgical outcomes and improving patient care standards.

Question 5: Is there a role for the use of incisional negative pressure wound therapy in patients undergoing major orthopaedic surgery?[5]

Response/Recommendation

Yes. Consider using incisional negative pressure wound therapy (iNPWT) as a measure to prevent SSI, PJI, and FRIs in patients undergoing major orthopaedic surgery.

Strength of Recommendation: Moderate

Delegate Vote: Agree: 77%, Disagree: 16%, Abstain: 7% (Strong Majority, Moderate Consensus)

Rationale

Despite existing evidence on the effectiveness of iNPWT for the prevention of SSI, iNPWT is still not standard practice in the field of orthopaedics [90]. Therefore, we conducted an up-to-date systematic review and meta-analysis to clarify the efficacy of iNPWT over standard-of-care dressing in reducing SSI/PJI/FRI in major orthopaedic surgery, including spine surgery, fracture surgery, and joint arthroplasty, following the provided International Consensus Meeting guidance. We identified all RCTs of any design (e.g., RCTs and quasi-RCTs) published until November 2024 that assessed the effect of iNPWT on adult patients undergoing clean surgeries, including major orthopaedic surgery, in reducing SSI. We also included fracture fixation for open fractures if the wound was primarily closed.

We identified 2,875 articles that were subjected to title and abstract screening. We shortlisted 71 articles for full-text screening and added two articles following a hand search. There were 59 studies excluded, and the remaining 14 RCTs (N = 4,100) were included in our final analysis [91–104]. We used Grading of Recommendations Assessment, Development and Evaluation to evaluate the certainty of the evidence and created a summary of findings table to describe the results [105].

Evidence was available from various countries, including the United States, the United Kingdom, Italy, Australia, North America, Germany, and China, on various surgical procedures, including primary and revision THA/TKA and fracture surgeries. There was no study focusing on spinal and upper extremity procedures. All studies were published between 2012 and 2023, with most of the studies reporting outcomes with 1-month or longer follow-up. There were four studies that used Centers for Disease Control and Prevention criteria for the definition of SSI/PJI [91,92,96,99],

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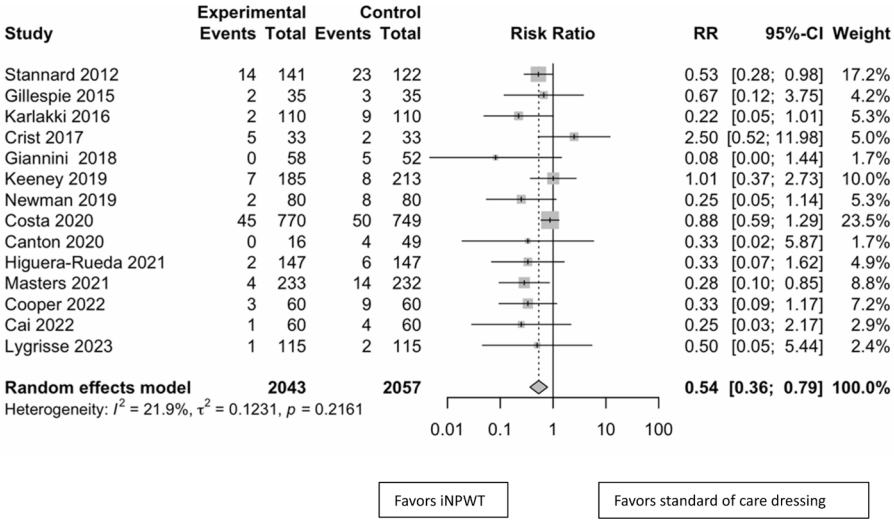

Figure 2. Meta-analysis results—all SSI/PJI/FRI. PJI, periprosthetic joint infection; FRI, fracture-related infection; SSI, surgical site infection.

whereas seven studies did not describe their definition of infection [95,97,98,101–104].

From our analysis focusing on all SSI/PJI/FRI, with moderate certainty of the evidence, iNPWT was significantly effective for preventing all SSI/PJI/FRI in patients undergoing clean wound surgeries with primarily closed surgical incisions compared to standard of care dressings (RR: 0.54; 95% CI 0.36 to 0.79, Figure 2). Publication bias was likely, as the comparison-adjusted funnel plot seemed to show asymmetry (Egger's test: $P = 0.039$). In the TSA, the cumulative number of patients did not exceed the required information size, and the *Z*-curves did not cross the trial sequential monitoring or futility boundary, suggesting an inconclusive meta-analysis result. This finding was consistent with our sensitivity analyses, including studies with $\geq$ 30 days of follow-up (RR 0.55; 95% CI 0.35 to 0.87), and when excluding studies with high risk of bias (RR 0.46; 95% CI 0.21 to 1.00). Similar preventive effects were found among our subgroups focusing on clean surgery (RR 0.44; 95% CI 0.27 to 0.73), high-income country (RR 0.55; 95% CI 0.37 to 0.81), elective surgery (RR 0.43; 95% CI 0.23 to 0.81), PICO (RR 0.55; 95% CI 0.30 to 0.98), and PREVENA (RR 0.51; 95% CI 0.32 to 0.81). There was no significant preventive effect in middle-income countries and fracture surgeries.

For the secondary outcomes, low-certainty evidence showed that iNPWT may reduce the risk of superficial SSI and wound dehiscence. If we add two RCTs evaluating the risk of seroma, low-certainty evidence showed that iNPWT may reduce the risk of seroma [106,107]. But, very low–to-low-certainty evidence showed that the iNPWT has neither benefit nor harm compared to the standard of care for the purpose of preventing deep SSI, skin necrosis, hematoma, skin blistering, reoperation, adverse events, and death.

From our results, iNPWT was significantly effective compared with standard of care dressing for preventing all SSI in adult patients with primarily closed surgical incisions after lower extremity/acetabular fracture surgery and hip/knee joint arthroplasty. Moreover, consistent results were found in the sensitivity analyses, and similar preventive effects were found in various subgroups. But, the majority of the trials were industry-sponsored (eight RCTs), and there seems to be a chance of publication bias, with an inconclusive TSA result. To note, there is another concern regarding its cost. As these devices are generally costly, there remain some issues regarding cost-effectiveness. Unfortunately, the evidence regarding this issue is still limited; therefore, further studies are required in this area.

There are several potential limitations. We did not perform cost analyses. Further well-designed studies are required to address the cost-effectiveness, especially in low- and middle-income countries, as its efficacy was not clear in this population. Also, although there were 4,100 subjects included in our primary outcome, we have downgraded the evidence level due to the imprecision based on our inconclusive TSA result. In addition, although there was no major difference in adverse events, this may be underestimated, as we did not include observational studies. Furthermore, we failed to show effectiveness in fracture surgery. The possible explanation for this finding is the additional skin and soft-tissue damage after the injury, which may not be controlled even with the application of iNPWT. Although the cumulative data showed a trend toward effectiveness, the benefit of iNPWT may be more apparent to those without soft-tissue injuries. Moreover, there was no RCT focusing on spinal and upper extremity procedures. Considering the difference among other orthopaedic procedures, reproducibility and generalization may not be warranted in these surgeries. Also, the number of studies with low risk of bias was very limited, and the definition and follow-up period used to assess SSI/PJI varied among studies. These heterogeneities may have affected our results and, therefore, need to be interpreted with caution.

Conclusion

Based on our results, we recommend the use of iNPWT to minimize the risk of SSI in adult patients with primarily closed surgical incisions after lower extremity/acetabular fracture surgery and joint arthroplasty of the hip and knee. This is aligned with the global recommendations, including the NICE [108], the World Health Organization [109], and the American College of Surgeons and Surgical Infection Society guidelines [110], all of which recommend the use of iNPWT for the purpose of reducing the risk of SSI.

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The Journal of Arthroplasty 41 (2025) S129–S138

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

General Topics

2025 ICM: Coated Implants

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Question 1: Does the use of silver-coated implants reduce the incidence of surgical site infection/periprosthetic joint infection in patients undergoing major orthopaedic surgery?[1]

Response/Recommendation

Yes. The use of silver-coated implants has been shown to reduce the incidence of surgical site infections (SSIs) and periprosthetic joint infections (PJIs) when megaprostheses are required for reconstruction in oncologic or septic orthopaedic surgery

Level of Evidence: Moderate

Delegate Vote: Agree: 76.2%, Disagree: 17.4%, Abstain: 6.5% (moderate consensus)

Rationale

The increasing use of megaprostheses in orthopaedic oncology and complex revision or trauma surgery has led to a dramatic rise in infection rates associated with these implants [1]. This risk is much higher than that observed in standard reconstructive surgeries [2]. Given the complexity of treatment, the associated morbidity and mortality, and the substantial economic burden, infections involving megaprostheses require special consideration. Various strategies have been developed to mitigate infection risks and prevent bacterial adhesion and subsequent biofilm formation on the extensive metallic surface of these implants [3]. These include surface modifications, antiseptic coatings, and antibiotic-loaded hydrogels (ALHs), with varying degrees of success. Among these, silver ion coatings have gained major clinical attention due to their ability to prevent bacterial and fungal colonization and to hinder biofilm growth [4,5].

Different companies employ various techniques to coat implants with silver ions [5]. These range from a thin silver layer (10 to 15 microns) followed by a 0.2-micron gold coating to regulate silver ion release (MUTARS©, Implantcast) [6] to a dual-layer structure comprising a deep one cm silver layer combined with TiAg20 N (PorAg©, LINK) [7]. Another approach includes anodization of the titanium surface to attach silver ions, creating 5-micron circular features containing amorphous titania with stored silver (AGluna©, Stanmore) [8,9]. Although some authors have suggested differences in the effectiveness of these coatings [10], no current evidence supports these claims.

The first clinical series evaluating silver-coated megaprostheses was published by Hardes et al. [6], reporting on 125 patients undergoing humeral, femoral, and tibial reconstruction following tumor resection. Among them, 51 received silver-coated implants, resulting in a lower PJI rate (5.9%) than noncoated implants (17.6%). Similarly, Donati et al. [11] reported a reduced infection rate in 38 out of 68 oncologic patients who had silver-coated implants (2.6 versus 10% in noncoated implants). Wafa et al. [12] further confirmed these findings in a high-risk cohort, reporting an infection rate of 11.8% in silver-coated megaprostheses versus 22.4% in standard implants.

However, other studies have not consistently demonstrated this protective effect. Pala et al. [13] analyzed 187 megaprostheses for oncologic reconstructions and found no significant difference in infection rates (6.7% in the silver-coated group versus 7.2% in the noncoated group). Notably, silver-coated implants were predominantly used in high-risk patients. Similarly, Vicente et al. [14], in the largest series of two-stage septic revisions (distal femoral replacement, proximal femoral replacement, total femoral replacement, hemipelvis reconstructions), reported comparable infection rates (20 versus 17%). The largest published cohort by Parry et al. [9], reporting on 89 silver-coated megaprostheses versus 305 noncoated implants, found no significant infection rate difference (12.4 versus 7.5%). However, they concluded that silver-

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to doi: 10.1016/j.arth.2025.10.088.

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https://doi.org/10.1016/j.arth.2025.10.088
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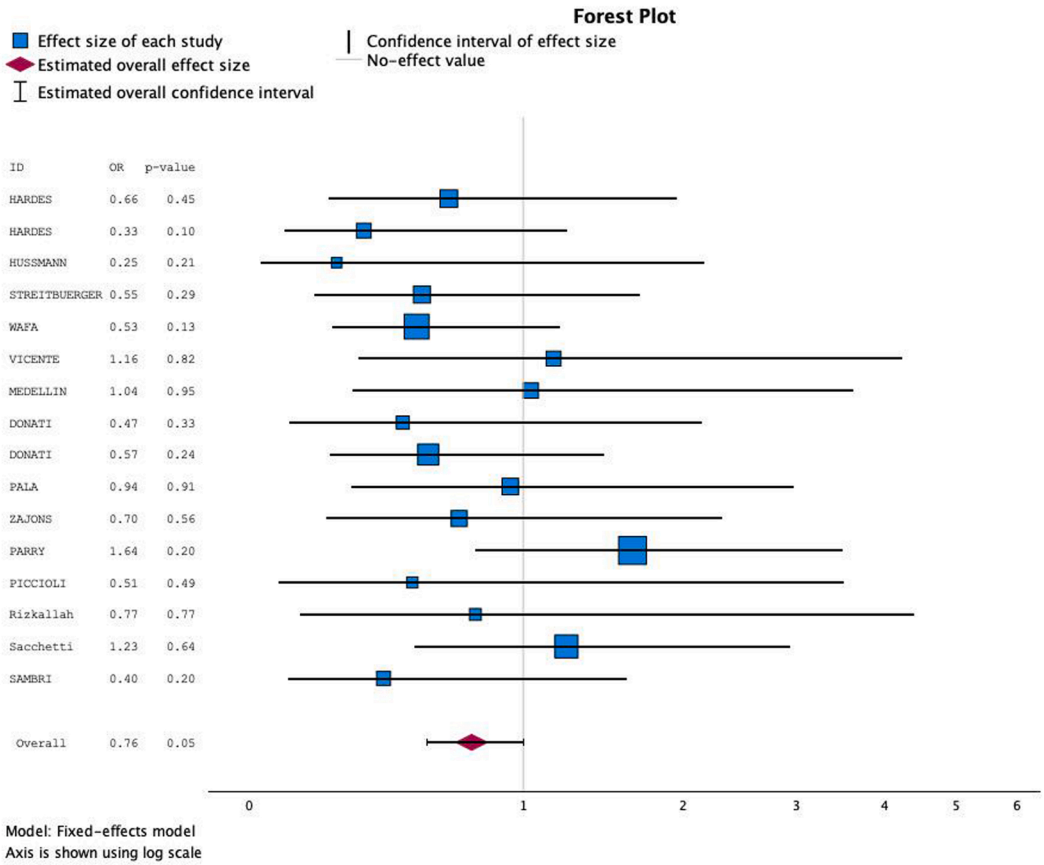

Figure 1. Forest plot evaluating the role of silver-coated implants in the prevention of infection.

coated megaprostheses might be beneficial in reducing infection risk in high-risk patients requiring megaprosthetic reconstruction. A pooled analysis of 718 silver-coated megaprostheses versus 965 noncoated implants demonstrated a significantly lower PJI risk in the silver-coated group (11.5 versus 15.5%, $P < 0.05$) ([6,9,11–24]). (Figure 1)

Beyond infection prevention, silver-coated implants may also improve implant survival in cases of PJI. Wafa et al. [12] reported that debridement, antibiotics, and implant retention (DAIR) procedures were successful in seven of 10 silver-coated implants versus six of 16 noncoated implants. Vicente et al. [14] did not observe significant differences (DAIR success rate of two of three versus three of five). Additionally, silver-coated implants appear to reduce the need for salvage amputations. Pala et al. [13] reported that only one out of eight reinfected patients required amputation with silver-coated implants, compared to three out of five in the noncoated group. Parry et al. [9] similarly observed fewer amputations (four of eleven failures in silver-coated implants versus nine of 23 in noncoated implants). Sambri et al. [23] also found a significant difference in amputation rates (one of three failures in silver-coated implants versus eight of ten in noncoated implants).

Given these promising findings, some authors have explored extending silver coating to other orthopaedic implants. Kawano et al. [25] demonstrated that silver oxide coating on hydroxyapatite in uncemented acetabular implants did not impair osseointegration. The same group [26] published a series of 50 primary hip arthroplasties with silver coatings, reporting no failures due to infection or aseptic loosening over a minimum 5-year follow-up, suggesting its potential role in preventing PJI. Additionally, silver-coated arthrodesis nails have been used for failed two-stage PJI treatment in knee arthroplasty, achieving infection resolution in seven of eight and eight of eight patients in studies by Savvidou et al. [8, 24] and Wilding et al. [27], respectively. However, further research is needed to determine whether silver-coated implants are beneficial in procedures with inherently low infection risks.

A reported complication associated with silver-coated implants is argyria, a condition characterized by the accumulation of silver particles in tissues, leading to localized or systemic skin discoloration. Hardes et al. [28] analyzed local silver concentrations around megaprostheses and found levels well below toxic thresholds. Although systemic complications related to silver exposure remain unproven, Glehr et al. [29] reported no direct correlation between local discoloration and systemic silver concentration, a finding further supported by Smolle et al. [30]. Localized argyria has been reported in 8 to 23% of patients treated with the MUTARS© system [29,30]. Therefore, patients should be informed of this potential complication before implantation.

In summary, most published series suggest that silver-coated megaprostheses are safe and reduce the risk of PJI in oncologic and septic revision surgery. Additionally, they appear to offer a protective effect on implant survival in the event of infection, improving DAIR success rates and decreasing the need for salvage procedures such as amputations. However, the latter findings require validation in larger studies.

Question 2: Does the use of povidone iodine–coated orthopaedic implants reduce the incidence of PJI and SSI?[2]

Response/Recommendation

Current evidence suggests that iodine-coated orthopaedic implants are associated with a low and reduced risk of superficial and deep infection in cases of bone tumors and infected revision arthroplasty. Future studies may benefit from longer follow-up and larger cohort sizes to more definitively establish the relationship between iodine-coated implants and risk of infection.

Level of Evidence: Limited

Delegate Vote: Agree: 60%, Disagree: 24.4%, Abstain: 15.6% (Simple Majority; Low/No Consensus)

Rationale

Periprosthetic joint infection is a devastating complication following primary or revision joint arthroplasty, which carries a substantial risk of morbidity and mortality. A PJI most commonly occurs via the development of a biofilm and bacterial adherence to implant surfaces. A biofilm is the formation of pathogens and microbial cells that form strong interactions with an extracellular matrix, replete with polysaccharides, biopolymers, proteins, teichoic acids, lipids, and extracellular DNA, to survive and propagate. In order to attach to arthroplasty components, biofilm undergoes a four-stage process: cellular adhesion, cellular aggregation, biofilm maturation, and cellular detachment.

In the first stage of biofilm formation, bacteria attach to the biomaterial surface in a reversible manner [31–33]. It is reversible due to the characteristics of the external environment, including pH, composition, and temperature, among others [34,35]. If successful, these adhesions can propagate to form microcolonies [36,37]. Once microcolonies have been established, the bacterial colony unit attracts more nutrients and spreads toward the periphery of the biomaterial device [38–41]. As the colony gains more nutrients and spreads further, the infection naturally worsens until it experiences environmental stresses that prevent further growth and propagation.

Several decades ago, Anthony Gristina developed the “race for the surface” hypothesis, which describes how the colonization of the surface of a prosthetic device or implant within the human body is a “race” between microbes and host cells [42]. Whichever group of cells inhabits the implant surface first is likely to remain there in perpetuity. This theory helps us understand not only which environments and characteristics are likely to allow for biofilm formation but also helps us to understand ways in which to thwart the colonization of pathogens on the surface of prosthetic components.

The type of implant surface can substantially impact the rate and severity with which a PJI can occur. The type of implant surface is divided into two broad categories: antibacterial coatings and modification of the surface itself. Within antibacterial coatings, there are both active and passive coatings. Active coatings release antibacterial agents to actively destroy bacteria, whereas passive coatings prevent bacteria from attaching or propagating on the biomaterial surface. Modification of the surface itself is rarely used, as it can impact the ability of the prosthesis to integrate within host tissues.

Active coatings on arthroplasty components are geared toward killing bacteria and other microorganisms that can form biofilms [42]. Active coatings can further be subdivided into contact-based and release-based mechanisms [43]. Contact-based active coatings create adhesions to surfaces of specific antibacterial agents, which aid in the killing of those microorganisms. These materials are often synthetic, such as quaternary ammonium compounds, which exert their bactericidal capabilities via a charge imbalance [45]. Specifically, this means that the positively charged calcium and magnesium compounds preferentially bind to the negatively charged phospholipid membrane of the bacteria on the outer surface of the biofilm. This covalent bond disrupts the cellular membrane of the microorganism and leads to bacterial cell death. Natural quaternary ammonium compounds are also available, such as antimicrobial peptides (AMPs) and AME bactericidal agents [41–50]. The AMPs and AMEs are groups of peptides that can initiate a series of chemical reactions leading to bacterial cell death. Onaizi et al. [51] evaluated the use of AMPs for antibacterial coatings of medical implants and demonstrated that the use of AMPs has a broad range of antimicrobial killing potential.

Release-based mechanisms are described as systems with carriers for bactericidal agents that can be eluted over time in a controlled manner. These coatings can be created with hydrogels, ceramics, or polyelectrolyte multilayers. A new technology has incorporated silver cations and anions with highly oxidized iodine [52]. Another new technology incorporates low molecular weight therapeutic agents composed of a polymeric matrix that can store multiple antimicrobial drugs [53]. Furthermore, antimicrobial agents, such as antibiotics, can be “wrapped” in release-based mechanisms for scheduled elution and delivery to a biofilm. For example, an antibacterial device, TYRX, is an absorbable antibacterial wrap that can deliver antibiotics to a site of biofilm formation. In a study of 500 high-risk cardiac patients, this wrap was able to deliver minocycline and rifampin and reduce infection by up to 90% compared to a control group [54].

Passive coatings do not release bactericidal agents to the biofilm, but rather prevent bacterial adhesion to prosthetic devices and components. An example of passive coating can be found in ultraviolet irradiation of titanium dioxide, which decreases bacterial adhesion without having any effect on osseointegration [55]. Polymer coatings can also be applied as a coating to orthopaedic implants to inhibit bacterial adhesion. For example, hydrophilic polymethacrylic acid, polyethylene oxide, and protein-resistant polyethylene glycol have all shown the ability to reduce bacterial adhesion in biofilm formation [56,57]. Other organic compounds, such as albumin [58], hydrogels [59–61], and silicone-nitride ceramics [62,63], have shown efficacy in the literature in reducing rates of postoperative infection in orthopaedic procedures.

Iodine-coated implants have recently gained popularity as a way to reduce the rates of PJI and reoperation following arthroplasty procedures. Iodine is abundant in the thyroid and is one of the heaviest elements. It is also commonly paired with povidone to form povidone iodine, which is a widely used antiseptic in operating rooms worldwide. Iodine generally does not incur any antibacterial resistance to it, which makes it an appealing antiseptic and coating option for implants. Iodine-coated prostheses generally consist of a povidone iodine electrolyte as the coating combined with an anodic oxide film.

Iodine is generally treated with Ti-6Al-4-V titanium implants with success in reducing rates of infection. For example, Inoue et al. [64] demonstrated in an in vivo analysis that the mean viable bacterial activity was significantly lower on iodine-coated titanium surfaces versus control surfaces. Another study

[2] These authors contributed to Question 2: Sean B. Sequeira, Humaid Al-Farii, Vijay Kumar, Michael A. Mont

validated the use of iodine-coated external fixation pins in rabbit models, which found that pins coated with iodine were more effective at reducing signs of infection and inflammation of the pins [65]. Additionally, this study found that the osteoconductivity of the pins was enhanced in the presence of an iodine coat. Miwa et al. [66] also evaluated the incidence of infection following the use of iodine-coated knee arthroplasty implants for malignant bone tumor resection. Among 302 patients, they found that 33 (10.9%) patients developed an SSI. They also concluded that the use of an iodine-coated implant was associated with a reduced risk of PJI compared to noncoated implants (odds ratio: 0.29; $P = 0.039$).

There are several prospective cohort studies that have analyzed the rate of infection following the use of iodine-coated prostheses compared to noncoated implants. A prospective clinical study on the use of iodine-coated implants in the prevention and treatment of SSIs found that the infection rate for these implants was low, even for immunocompromised hosts, which made the postoperative infection less severe and more manageable [67]Another study analyzed the impact iodine-coated megaprostheses may have in the prevention and treatment of deep periprosthetic infection [67]. Between July 2008 and May 2013, 47 patients with malignant bone tumors or septic arthritis with osteomyelitis were treated with iodine-coated megaprostheses. The authors found that, after 30.1 months of follow-up on average, only one patient out of 47 had a SSI, which was treated with antibiotics alone. Moreover, thyroid tests concluded that there were no abnormalities associated with thyroid function in any patient. Also, Kabata et al. [68] performed a clinical trial assessing how the use of iodine-supported implants impacts the infection rates following complex primary, revision, or infected arthroplasties. After 33 months, none of the 30 joints among the 28 patients were found to have clinical evidence of an infection, and thyroid function remained stable. Moreover, no evidence of loosening or hardware complications was detected within the follow-up period. These data may suggest that iodine-coated implants are a reasonable option to prevent and treat cases of infected arthroplasty.

As previously mentioned, cytotoxicity is generally a concern with the use of these coated prosthetic components—if they are harmful to the adhesion and propagation of bacteria and biofilm, they may also be harmful to host cells and osseointegration. Studies like Ueoka et al. [69,70], in which they evaluated the antibacterial activity of iodine-coated titanium implants in a rat model and demonstrated the reduction in bacterial cell viability and survival, still leave unanswered questions regarding the toxicity and osseointegration of such implants. Copper and zinc coatings have substantial potential in the reduction of bacterial adhesion and biofilm formation, but are not devoid of cytotoxicity to host cells and osseointegration [70–73].

In conclusion, there are several options for prosthetic coating during orthopaedic and arthroplasty procedures to reduce the risk of biofilm formation and PJI. Especially with the advent and popularization of silver nanoparticles and iodine-coated agents, the appropriate concentration can have excellent results in the reduction of postoperative infection. Nevertheless, these antibacterial coatings do not come without their limitations. The risk of cytotoxicity and poor osseointegration, not to mention antibacterial resistance, looms large as recognizable limitations from their widespread use. As we continue to search for ways to mitigate and prevent PJI and postoperative infection following arthroplasty, biomaterials and antibacterial coatings on prosthetic devices should continue to be studied and optimized for regular clinical use.

Question 3: Are there modified implant surfaces proven to reduce the incidence of clinical infection following major orthopaedic procedures?[3]

Response/Recommendations

Systematic reviews of numerous *in vitro* and *in vivo* animal basic science studies have shown the combined positive antibacterial and osteogenic effect of novel surface modifications and nanostructured orthopaedic implants. However, the preclinical positive effects have not yet been translated into meaningful positive clinical outcomes.

Level of Evidence: Strong.

Delegate Vote: Agree: 79.6%, Disagree: 12.2%, Abstain: 8.2% (Super Majority, Strong Consensus).

Rationale

A PJI represents one of the most devastating complications in joint arthroplasty, with a prevalence of 1 to 2% after primary joint arthroplasty and 4% after revision [74,75]. It is also the most common reason for early revision [76]. A PJI has a severe impact on morbidity and mortality rates, and quality of life is markedly affected in these patients [74].

Various strategies have been developed to eliminate the effect of infection risk factors, such as patient optimization, ultra-clean surgical operation rooms, preoperative preventive antibiotics, improved surgical techniques, and implants with modified surfaces [77,78].

The aim of this systematic review was to evaluate the efficacy and safety of nanotechnology-modified implants (other than silver, povidone iodine, and hydrogel surface-modified surfaces) in reducing the incidence of clinical infection in major orthopaedic procedures.

Research Strategy

A systematic computer-based literature review search with predefined criteria was performed according to the Preferred Reporting Items for Systematic Review and Meta-analyses guidelines in the Scopus and PubMed databases. The research methodology used a combination of MeSH terms developed by librarians and was intended to capture any relevant publications. All electronic literature searches were conducted by four authors (TK, AK, SC, and PC) and an experienced librarian. The above authors independently screened the titles and the abstracts to identify relevant studies. In cases of disagreement, a final decision was made by the liaison author. Only full-text articles were eligible for our study. There were no publication date limitations set. Additional inclusion criteria included the following: (1) studies written in the English language; (2) studies on nanotechnology-modified implant surfaces; (3) experimental in vitro or in vivo studies; (4) clinical studies using nanotechnology-modified implants; (5) relevant review papers; and (6) relevant systematic review and meta-analysis studies. Exclusion criteria included the following: (1) silver-coated implants; (2) povidone iodine–coated implants; and (3) hydrogel-coated implants.

From the initial search, 3,999 studies (2,946 from PubMed, 1,053 from Scopus) were identified and imported for screening. Covidence identified and removed 122 duplicates. The titles and abstracts of 3,877 studies were screened by the authors, and 3,450

[3] These authors contributed to Question 3: Theofilos Karachalios, Simon Coffey, Pawel Chodor, Alexandros Koskiniotis

studies were considered irrelevant (applying additional inclusion and exclusion criteria). Subsequently, the full text of 425 studies was accessed by the authors, and a further 87 studies were excluded (not meeting the inclusion and exclusion criteria). In the end, 338 studies were included in this systematic review. Of these 338 relevant studies, 198 were *in vitro* experimental studies, while 14 were *in vivo* animal studies relevant to nanotechnology-modified implant surfaces. There were 117 papers that were basic science reviews relevant to antimicrobial coatings and nanotechnology-modified implant surfaces. There were nine systematic reviews and meta-analyses relevant to modified implant surfaces that were also found. It has to be stressed that no human clinical study relevant to the reduction of the incidence of clinical infection in major orthopaedic procedures was found.

The application of nanotechnology, novel surfaces, and coatings was reported in 198 studies using a variety of experimental settings. Antimicrobial efficacy was studied using different bacterial strains (mainly *Staphylococcus aureus*). Osseointegration and biocompatibility were studied in eukaryotic cells. A variable antimicrobial spectrum of reduced bacterial growth and inhibition of biofilm formation, and an unaffected or enhanced interface bone ingrowth was reported.

The application of novel nanotechnology surfaces and coatings was also evaluated in animals and reported in 14 studies. Antimicrobial efficacy was studied using different bacterial strains (mainly *S. aureus*). Osseointegration and biocompatibility were studied in various animal models (mainly rats). A variable antimicrobial spectrum of reduced bacterial growth and inhibition of biofilm formation, and an unaffected or enhanced implant osseointegration were also reported.

In recent years, several attempts have been made by scientists and engineers to develop antibacterial strategies related to materials and surfaces with antibacterial properties [79,80]. These strategies include antiadhesion polymer coatings, superhydrophilic, superhydrophobic, and liquid-infused surface coatings, and bacteria-killing coatings [79,80]. Nanomodification of implants is a good option and has the potential to induce different types and degrees of antibacterial effects in a clinical setting. At the same time, implant nanostructures should not adversely affect osteogenic activity and osseointegration. Mechanical, chemical, and physical methods are used for the nanomodification of titanium alloy surfaces [81,82]. Nanomodification of titanium implant materials differs widely by means of nanostructure formation procedures, formation of nanomaterial coatings, and nanomorphology. Nanomaterials are classified by structure form: clusters (made of solid nanoparticles), nanorods (made of nanowires), coatings (made of films), and nanotubes (made of pillars). Nanomaterials are also classified by the existence of antibacterial active ingredients: metal ion antibacterial active ingredients and oxide photocatalytic antimicrobial materials. All of these nanostructures can inhibit or kill bacterial microorganisms [81,82].

Systematic reviews have already shown the combined positive antibacterial and osteogenic effect of novel surface modifications and nanostructured orthopaedic implants in in vitro and in vivo studies [77,78,83,84]. However, despite the enormous effort that basic scientists, engineers, and orthopaedic surgeons have put into the development and evaluation of antibacterial nanostructured orthopaedic implants, the preclinical positive effects have not yet been translated into meaningful positive clinical outcomes related to major orthopaedic procedures [84–92].

Moreover, the possible toxic effects of these nanomodified implant surfaces on other cellular lineages surrounding orthopaedic implants have already been addressed in *in vitro* studies and should be further investigated [93].

Question 4: Does the use of hydrogel-coated implants reduce the incidence of SSI/PJI in patients undergoing major orthopaedic surgery?[4]

Response/Recommendation

Hydrogel-coated implants may reduce the incidence of infection following major orthopaedic surgery.

Level of Evidence: Limited.

Delegate Vote: Agree: 66.7%, Disagree: 15.1%, Abstain: 18.2% (strong majority, moderate consensus).

Rationale

Implant-related infections, particularly PJIs, remain a major cause of failure—especially in total hip and knee arthroplasties [94,95]. Bacterial biofilm formation is widely recognized as a critical factor in the development and persistence of PJIs and other implant-related infections [96,97]. Key properties of implant surfaces, such as roughness, hydrophobicity, and electrostatic charge, facilitate bacterial adhesion and subsequent colonization [98]. To mitigate these challenges, intraoperative strategies have been developed to enhance the antibacterial properties of implants, including the application of antiseptic or antibiotic coatings. Romano et al. have outlined the ideal characteristics for such coatings: they should demonstrate broad-spectrum antibacterial efficacy *in vivo*, be easy to handle and cost-effective, and, importantly, avoid local or systemic toxicity while supporting proper bone healing and implant integration [99].

Hydrogel coatings have emerged as a promising approach that may fulfill these criteria. Various hydrogel systems are currently under preclinical investigation [100,101], and hyaluronic acid–based hydrogels already available on the market have demonstrated safety in both *in vitro* and *in vivo* settings [102,103]. However, the efficacy of hydrogel coatings in reducing surgical site and PJIs remains unclear due to the limited available literature.

To answer the question posed above, we conducted a comprehensive systematic review to evaluate the clinical outcomes of hydrogel use in orthopaedic surgery compared to control cases. A comprehensive search of the Scopus and PubMed databases identified 545 studies for screening. After removing 61 duplicates, 484 studies were assessed for eligibility; 469 were excluded, leaving 15 full-text articles for review. Ultimately, 13 studies met the inclusion criteria and were included in the final analysis. Among these, two studies were classified as level II evidence [104,105], four as level III [106–110], and the remainder were case series [111–116]. Data were extracted to compare infection rates between patients receiving hydrogel-coated implants and control groups, when available. The studies were subdivided into two groups: the first group (seven studies) involved the use of hydrogel in elective orthopaedic surgery—such as joint arthroplasty, spinal surgery, and fracture fixation (Table 1)—while the second group (six studies) examined hydrogel coatings used in patients who have established infections undergoing one- or two-stage joint revision (one-stage exchange [OSE] and two-stage exchange [TSE]) (Table 2). The main antibiotics used were gentamicin and vancomycin.

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Table 1
Summary of Studies in Which a Hydrogel Coating was Used for the Prevention of Infection.

Author (year)	LoE	Study Design	Primary Country	Multi-Center	Total N	Mean Age	Sex, F %	Mean F-U (Months)	Population ALH/ Control (If Any)	N ALH/ Control	Infection Rates ALH/ Control	Other Complications ALH/Control (Types)
Corona (2024)	IV	Retrospective, case series	Spain	No	11	53	36.3%	24	Instrumented AKA	11	0%	1 stump necrosis of the anterior flap, 1 soft-tissue infection, 1 dual cone breakage
De Meo (2020)	III	Retrospective, matched case-control study	Italy	No	34	75	64.7%	12.4	THR with/without ALH	17/17	0%/35.3%	2 prolonged wound discharge, 1 systemic/ 1 dislocation, 1 prolonged wound discharge, 1 nerve deficit, 2 systemic
De Meo (2023)	IV	Retrospective, case series	Italy	No	37	63	45.9%	36	ORIF	37	2.7%	1 delay consolidation, 1 aseptic loosening
Malizos (2017)	II	RCT	Italy	Yes	256	62/59	55.9%	18.1	ORIF with/without ALH	126/127	0%/4.7%	5 delayed wound healing, 2 delayed union/ 7 delayed wound healing, 5 delayed union
Parbonetti (2021)	IV	Retrospective case series	Italy	No	73	62	49.3%	12	Primary or revision LVF	73	0%	
Romano (2016)	II	RCT	Italy	Yes	373	69/71	58.4%	14.5	TJA with/without ALH	189/184	0.53%/5.9%	2 delayed wound healing, 1 TH dislocation, 1 knee stiffness, 2 DVT/7 delayed wound healing; 1 THA dislocation, 2 knee stiffness; 2 DVT
Zoccali (2021)	III	Retrospective, matched case-control study	Italy	Yes	86	46	44.2%	24	MegaTJA with/ without ALH	43/43	0%/13.9%	1 intraoperative fracture, 1 femoral diaphysis fissure, 1 hematoma, 2 aseptic loosening, 5 oncological disease progression/1 implant dislocation, 2 intraoperative femoral fissure, 1 transient femoral nerve palsy, 2 aseptic loosening, 6 oncological disease progression.

LoE, level of evidence; N, numbers; F-U, follow-up; AKA, above knee amputation; THR, total hip revision; ALH, antibiotic loaded hydrogel, ORIF, open reduction internal fixation; LVF, lumber vertebral fusion; TJA, total joint arthroplasty; n.r.: not reported; TH, total hip; DVT, deep vein thrombosis.

Table 2
Summary of Studies in Which Hydrogel Coating was Used for Already Established Infection.

Author (year)	LoE	Study Design	Primary Country	Multicenter	Total N	Mean Age	Sex, F %	Mean F-U (Months)	Infection Site and Type	Treatment with ALH	N ALH/ Control (If Any)	% Infection Relapse ALH/ Control (If Any)	Other Complication ALH/ Control (If Any)
Capuano (2018)	III	Prospective, matched case-control	Italy	Yes	44	71	59%	29.3	Hip/knee PJI	OSE	22/22 TSE	9.1%/13.6%	0
Corona (2021)	IV	Retrospective, case series	Spain	No	10	52	20%	27	Segmental distal femur FRI	TSE	10	0%	2 aseptic loosening (CPS fixation failure)
De Meo (2023)	IV	Retrospective, case-control	Italy	No	16	67	50%	26.1	Hip/knee PJI	DACRI	7/9 DAPRI	11.1%/0	0
Franceschini (2020)	IV	Retrospective, case series	Italy	No	28	n.r.	n.r.	24	Hip PJI	TSE	28	7.1%	0
Pellegrini (2021)	IV	Retrospective case series	Italy	No	10	69	50%	37.2	Hip PJI	OSE	10	0%	0
Zagra (2018)	III	Retrospective, matched case-control study	Italy	No	54	64	54%	30	Hip PJI	TSE	27/27 TSE	0%/14.8%	1 dislocation (open reduction)/1 dislocation (closed reduction)

LoE, level of evidence; N, numbers; F-U, follow-up; ALH, antibiotic loaded hydrogel; PJI, periprosthetic joint infection; OSE, one-stage exchange; TSE, two-stage exchange; DACRI, debridement, antibiotic coating and retention of implants; DAPRI, debridement, antibiotic pearls and retention of implants; n.r., not reported; FRI, fracture-related infection.

There were four studies that compared hydrogel-coated implants with uncoated implants (joint arthroplasty or internal fixation hardware) in a total of 375 patients who received hydrogel-coated implants, among whom only one case of infection was reported, compared with 29 infections among 371 control patients [104,105,108,109]. Follow-up periods ranged from 12.4 to 24 months. Notably, all these studies reported a significantly lower incidence of infection with the use of ALH: one randomized controlled trial investigated its use in trauma patients ($P = 0.03$) [105], while the other three studies (one randomized controlled trial and two retrospective matched case-control studies, with $P = 0.003$, $P = 0.0001$, and $P = 0.02$, respectively) focused on primary, revision, and mega implants in total joint arthroplasty [106,110,111]. There were two additional case series in the first group that evaluated high-risk fracture fixation (37 patients) and primary or revision instrumented lumbar vertebral fusion (73 patients), reporting infection rates of 2.7 and 0%, respectively, with a minimum follow-up of 12 months [113,115]. Also, one case series described the use of hydrogel as a coating for single-stage transcutaneous osseointegrated prostheses in above-knee amputations, with no infections reported after a median follow-up of 27 months [111].

In the second group, six studies evaluated the use of hydrogel in established infections. In one study, its application during DAIR procedures for acute PJI was compared with the application of antibiotic-loaded calcium sulfate beads, with no significant differences observed ($P = 0.36$) [19]. There were two studies assessing OSE with ALH that yielded promising results [106,115]; in one, Capuano et al. [106] compared a hydrogel-coated OSE with an uncoated TSE, finding no statistically significant difference in infection eradication between the groups. There were three additional studies that reported on cementless TSE procedures applying ALH: one case series documented failure in two out of 28 cases of cementless hip TSE [21], another case series on post-traumatic septic TSE of the distal femur reported no infections [110], and a retrospective matched case-control study by Zagra et al. [107] observed no infections in the treatment group compared to four infections in the control group ($P = 0.11$).

The available evidence highlights the potential benefits of hydrogel coating of orthopaedic implants. Our findings suggest that ALH may be particularly beneficial in high-risk settings—such as open fractures or complex reoperations and revisions, where it could protect the new implant, especially in cementless prostheses and in cases of one-stage or reimplantation after two-stage procedures of infected total joint arthroplasty, when tailored antibiotics can be used. However, the limited number of studies, their heterogeneity, and small sample sizes underscore the need for further high-quality research to establish definitive recommendations for its use.

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The Journal of Arthroplasty 41 (2025) S139–S150

Contents lists available at ScienceDirect

The Journal of Arthroplasty

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General Topics

2025 ICM: Wound Drainage

Seyed Mohammad Javad Mortazavi, Alfredas Smailys, Pawel Bartosz, Jay Shah, Jakrapun Pupaibool, AbdulRahman Babaqi, Colin Baker, Hatem Bakr, Andrea Baldini, Marti Bernaus, Jerzy K. Bialecki, H. John Cooper, Padhy Debabrata, Volodymyr Filipenko, Victor M. Ilizaliturri Jr., Al-Amin Kassam, Fatih Kucuckdurmaz, Julio César Palacio, Nilo Paner, Mohammad Poursalehian, James Purtill, Alex J. Ramsden, Julie Reznicek, Augustinas Rimkunas, David Rodriguez-Quintana, Mahdi Sahebi, German Salazar, Rubén Arriaga Sánchez, Toshiyuki Tateiwa, Carlos Bracho Velasco, Saheed Yakub, Mehmet Kursat Yilmaz, Valérie Zeller, Zongke Zhou

Question 1: What is the optimal management of patients who have persistent wound drainage who have undergone a recent major orthopaedic procedure?[1]

Response/Recommendation

Persistent wound drainage (PWD) after major orthopaedic surgery requires a systematic approach. Initially, one should rule out infection by checking for local and systemic signs such as erythema, purulence, and fever. If infection is not suspected, apply nonoperative measures such as local wound care, risk factors, minimizing motion at the surgical site, and adjusting venous thromboembolic event prophylaxis. If drainage continues beyond seven days despite nonoperative management, investigate thoroughly for infection and consider surgical intervention, including irrigation and debridement.

Level of Evidence: Moderate

Delegate Vote: 84.9% Agree, 10.1% Disagree, 4.9% Abstain (super majority: strong consensus)

Rationale

Definition of persistent wound drainage (PWD)

Persistent wound drainage (PWD) refers to continued fluid leakage (i.e., serous, serosanguinous, or purulent) from the surgical wound beyond the expected early postoperative period [1–8]. Most wound healing disturbances leading to short drainage duration are noninfectious [4,9]. Surgical disruption of the superficial capillaries may cause minor, temporary serous, or serosanguinous postoperative wound drainage. If drainage persists, an infectious workup is indicated [9]. Delayed wound healing may allow pathogens to penetrate deeper skin layers, resulting in retrograde infection [5,10]. Studies suggest that the risk of infection increases substantially when drainage lasts more than five days [4,11]. There is no comprehensive definition for the duration and amount of PWD. However, studies have reported PWD as lasting from two to nine days postoperatively [4,12–14]. In 2013 and 2018, the International Consensus Meeting on periprosthetic joint infection (PJI) defined PWD as more than two × two cm of drainage on the wound dressing beyond 72 hours following the initial surgery [15, 16]. However, it is essential to recognize that different types of dressings influence both the volume and duration of drainage, which adds complexity to this matter [17].

Differentiating Infectious versus Noninfectious Wound Drainage

A PWD can be categorized into noninfectious and infectious types. Noninfectious drainage commonly appears early in the postoperative period, though in cases involving certain sealed antibacterial dressings, clinicians may only recognize it after dressing removal. This fluid is often serous or serosanguinous in nature, with no appreciable odor or signs of local tissue destruction. It typically resolves with conservative management once anticoagulation and other modifiable risk factors are addressed [18]. Moreover, mild elevations in inflammatory markers are common and may reflect normal postoperative physiology rather than infection [19].

Infectious wound drainage necessitates prompt intervention [6]. Systemic and local signs of infection may be present. Systemic signs of infection include fever, chills, and tachycardia. Local signs include erythema, induration, and warmth of the surgical site, as well as purulent drainage or the presence of a sinus tract [6,20]. Fever is considered physiological in the first three to five days after the initial surgery [21–23]. Nevertheless, temperatures exceeding 39 °C, especially if persistent for multiple days or occurring more

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https://doi.org/10.1016/j.arth.2025.10.090
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than three to five days postsurgery, warrant further investigation [4,24,25]. An infectious complication of PWD should be suspected if C-reactive protein (CRP) levels rise after 72 hours post-TJA or remain elevated for more than seven days after TJA [5,26]. The erythrocyte sedimentation rate and white blood cell levels are less appropriate for diagnosing infections in cases of PWD [5,26,27]. Currently, there are no universally established criteria to differentiate infectious PWD from noninfectious PWD.

Nonoperative Management of Persistent Wound Drainage

When no clinical or laboratory indicators suggest infection, conservative strategies should be considered.

Activity Modification and Immobilization

Excessive motion can aggravate drainage, especially early in the postoperative course [28,29]. Restricting joint movement through bracing, discontinuing continuous passive motion, or temporarily pausing physical therapy can be beneficial. These measures are typically short-term interventions aimed at promoting stable wound healing [30,31].

Wound Care and Dressings

Wound care plays a central role in managing PWD. Absorbent dressings and pressure bandages are often the first line of management [32,33]. If drainage continues, negative pressure wound therapy (NPWT) can be considered. The NPWT has been shown to reduce seromas, hematomas, dehiscence, and infection. The NPWT often achieves a dry wound within 24 hours [34] and has been shown to lead to cessation of PWD in the majority of patients [35]. Although prophylactic NPWT shows benefit in preventing seroma and hematoma formation, widespread routine use is generally not cost-effective [36]. However, it may be considered prophylactically in patients at higher risk for PWD [37].

Anticoagulation Management

Anticoagulation can exacerbate or prolong drainage by contributing to persistent oozing from the surgical site. A short-term cessation of venous thromboembolic event prophylaxis may be justified based on the patient's overall risk and the specific anticoagulant in use [38]. Alternatively, switching to an agent with a lower risk of PWD, such as aspirin, can be an effective strategy if clinically appropriate [4,38–41]. These adjustments should be individualized and closely monitored to balance the benefits of preventing thrombotic events with the risk of complications from prolonged wound drainage.

No Prophylactic Antibiotics

The routine use of prophylactic antibiotics has neither been shown to reduce the incidence or severity of PWD nor does it lower the rate of wound infections in this specific scenario [42,43]. As a result, current recommendations are against the use of prophylactic antibiotics in the absence of clear signs of infection.

Risk Factor Optimization

Focusing on modifiable risk factors can significantly influence wound outcomes. Good glycemic control in diabetic patients, smoking cessation, and adequate nutritional support—especially in malnourished patients—are critical for promoting wound healing [5,6,8,44–48]. Surgeons should also inspect the incision site, particularly at both ends, to ensure that the closure is adequate; if not, reclosure can prevent continued drainage [49].

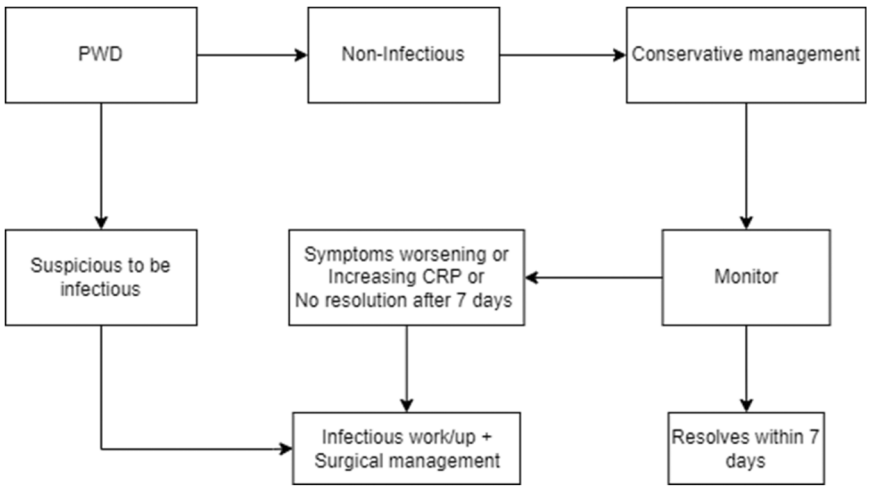
Monitoring

Also, ongoing evaluation of wound drainage is essential. Daily monitoring will help determine if drainage is diminishing, and tracking CRP levels may help detect any developing infection or persistent inflammatory process (19). If these measures do not result in a reduction of drainage within a reasonable time frame, infection must be considered.

Operative Management for Infectious Wound Drainage

If PWD does not improve after several days of conservative management, or if the drainage volume increases, local or systemic signs of infection develop, CRP levels rise, or drainage persists beyond seven days without an identifiable cause; operative management must be strongly considered [12].

Surgical management generally begins with the aspiration of any hematoma; in cases involving TJA, joint aspiration should be performed as well (33). The wound is then explored, with multiple intraoperative samples taken for culture. Thorough debridement of any necrotic or probably infected tissue is essential. Extensive irrigation is recommended to help clear the surgical site of probable infectious material. In cases of TJA, if the infection involves the joint itself, a Debridement, Antibiotics and Implant Retention (DAIR) procedure along with modular component exchange is recommended [8,33,50,51]. After surgery, patients should be



Clinical management algorithm for persistent wound drainage (PWD) following total joint arthroplasty.

started on empiric antibiotic therapy, which is subsequently adjusted once culture results are available [33,50,51]. In many cases, an extended course of antibiotics is advised to ensure complete resolution of the infection [52].

Potential Limitations

The literature on PWD is limited and mainly focuses on total joint arthroplasty (TJA), with varying findings. PWD is multifactorial and patient-specific, making a universal management protocol challenging. The duration for noninfected PWD to consider infected or at risk of infection varies in the literature, and there is no universally accepted definition of infected PWD. High-quality research is needed to develop clear criteria for identifying patients who would benefit most from surgical intervention.

Question 2: What are the predictors for developing wound-related problems after major orthopaedic procedures?[2]

Response/Recommendation

Important predictors for wound-related complications are uncontrolled diabetes (Hb1Ac levels > 7.7 mg/dL), obesity, presence of multiple comorbidities (American Society of Anesthesiologists class > 3), malnutrition, delay in surgery (trauma cases), prolonged operative time, age over 70 years, smoking, alcohol abuse, and colonization with methicillin-resistant *Staphylococcus aureus* (MRSA).

Level of Evidence: Strong

Delegate Vote: 87.9% Agree, 7.4% Disagree, 4.7% Abstain. (super majority, strong consensus)

Rationale

The identification of risk factors for wound-related complications, such as persistent wound drainage (PWD), wound dehiscence, delayed healing, and surgical site infections (SSIs), is critical in the context of major orthopedic surgeries. These complications increase mortality and morbidity, prolong hospital stays, and elevate health care costs following procedures such as total hip arthroplasty (THA) and total knee arthroplasty (TKA), as well as femoral and tibial fracture fixation.

To identify these factors, a comprehensive literature review and screening were conducted using Scopus and PubMed databases. The initial screening identified 1,948 studies, of which 83 were included after a detailed review. The review focused on major orthopedic procedures, including hip and knee arthroplasties, as well as femoral and tibial fracture osteosynthesis in the adult population. A qualitative analysis identified 111 risk factors. Only the most prevalent risk factors with the highest evidence are discussed. Where odds ratios are provided, they represent the weighted mean of the mean of odds ratios (wOR) reported across the studies.

The overall wound-related complication rate was 3.61% in major orthopaedic procedures, with 23,466 complications reported in the selected articles out of 649,911 patients.

Diabetes, particularly when uncontrolled, emerged as the most frequently studied risk factor, with an average weighted odds ratio (wOR) of 1.47. Studies generally encompassed diabetes mellitus as both types 1 and 2 [53–56]. Moderate evidence supported diabetes as a significant risk factor after multivariate adjustments [53,56,57]. However, some studies reported controversial findings, as significance disappeared after analyzing for confounding variables [54,57]. Strong evidence identified glycated hemoglobin (HbA1c) levels > 7.7 mg/dL as a significant risk factor for wound complications (wOR 2.39) [58–60]. Meanwhile, fructosamine was reported to better reflect glycemic control and predict adverse events compared with HbA1c [61]. A fructosamine level of 293 μmol/L was identified as the optimal cutoff associated with complications [61,62]. Patients with elevated levels were reported to be 6.7 to 11.2 times more likely to develop PJI) [61,62]. Preoperative blood glucose levels were associated with 1.5 times greater odds of PJI and were reported as 277 mg/dL for patients who have diabetes and 193 mg/dL for those who do not have diabetes [63].

Obesity was also found to be strongly associated with wound complications [54,64,65]. The weighted odds ratio across studies was 1.70 for patients with a body mass index (BMI) of 30 or higher, rising to 2.26 for those with a body mass index of 40 or above.

Strong evidence linked the American Society of Anesthesiologists Physical Status Classification class > 3 to wound complications, with most studies reporting significant associations (wOR 1.99) [55,66]. A subset of studies employing multivariate analysis has reported that individual conditions, such as cardiovascular disease or chronic renal and hepatic dysfunction, are not significant independent predictors of wound complications [67,68]. In contrast, other studies examining end-stage renal disease (ESRD) have identified an increased risk of infection following THA, with a hazard ratio of up to 2.91 for early infections [69,70]. Similarly, individual studies have reported elevated risk of surgical site infections in patients who have liver disease and chronic venous insufficiency [71,72]. These conflicting findings highlight the importance of comprehensive tools, such as the American Society of Anesthesiologists classification, in assessing cumulative risk. However, individual comorbidities may require separate, thorough analyses of specific complications to form strong recommendations.

Malnutrition was well established as a risk factor for wound complications, with strong evidence identifying it as significant (wOR 1.85) across included studies [73,74]. In the literature, it was defined through methods, including serological markers, anthropometric measurements, and nutrition scoring tools, with serum albumin levels < 3.5 g/dL and serum total lymphocyte counts (TLC) < 1,500 cells/mm^3 being the most used criteria [75]. Lower total lymphocyte count values were reported to be significantly associated with delayed wound healing (wOR 1.51) [76]. Similarly, serum albumin levels below 3.5 g/dL were strongly supported as a significant risk factor (wOR 1.96) [78,79]. Additionally, moderate evidence highlighted the albumin-fibrinogen ratio as a potential risk factor (wOR 4.06) [77]. Nutritional indices have demonstrated effectiveness in assessing nutritional status and predicting postoperative complications, such as Onodera's prognostic nutritional index (OPNI), which is composed of serum albumin and total lymphocyte count within the equation [80]. These findings emphasize the critical role of nutritional status in wound healing, underscoring the importance of incorporating nutritional assessment into preoperative risk evaluations.

Factors related to the procedure can be directly influenced by the medical team, offering opportunities to mitigate risks. Strong evidence identified prolonged time to operation as a significant risk factor (wOR 2.87) [57,81]. Wound infection in an elderly population was reported in 2.3% of cases, with surgical delays exceeding 24 hours identified as a significant risk factor (odds ratio (OR) 3.48; 95% confidence interval (CI) 1.1 to 10.8; $P = 0.023$) [81]. Moderate evidence associated the prolonged duration of surgery with wound complications (wOR 1.62) [66,82]. Prolonged duration of surgery was defined variously across studies, necessitating consideration of methodological differences. The mean operative duration for TKA complicated by SSI was reported to be significantly longer at 90.5 ± 28.2 minutes compared to 72.2 ±

[2] These authors contributed to Question 2: Alfredas Smailys, Carlos Bracho Velasco, David Rodriguez-Quintana, Andrea Baldini, German Salazar, Hatem Bakr, Augustinas Rimkunas

20.3 minutes for TKA without SSI [83]. Operative times exceeding 135 minutes were reported to be associated with an increased risk of both wound and systemic complications [57]. While the exact cutoff for surgical duration is yet to be determined for specific procedures and regions, it is well established that shorter operative times are preferable.

The use of an external fixator was supported by moderate evidence as a risk factor (wOR 3.09) [56,83]. However, external fixator use reflects the severity of the injury and was developed to allow soft-tissue recovery before definitive fixation, addressing the unacceptably high infection rates associated with early attempts at plate fixation [83]. Therefore, labeling external fixation as a risk factor is misleading, while its use should be reserved for complex cases to balance the benefits against potential risks.

Postoperative observations can offer valuable insights into potential infections. Moderate evidence identified persistent postoperative wound drainage as an independent risk factor for surgical site infection [84,85]. Drainage persisting into the second week was reported as the strongest risk factor for joint infection, with an OR of 50.83 (95% CI 11.41 to 226.51) [33]. Evidence for postoperative hematoma as a risk factor remained limited [86]. While moderate evidence identified revision surgery as a risk factor (wOR 5.02), [87] strong evidence supported increased age as a demographic risk factor for wound complications (wOR 1.83) [54,88].

Age over 70 years was identified as an independent risk factor for surgical site infections, with an adjusted OR of 2.85 (95% CI 1.26 to 6.43; $P = 0.0118$) [36]. Sex was also associated with postoperative wound complications, with moderate evidence supporting being a man as an independent risk factor (wOR 1.52) [55,89]. Smoking and alcohol abuse were supported by moderate evidence as independent risk factors, with weighted average odds ratios of 3.31 and 1.59, respectively [55,87].

Strong evidence associated surgical site infections with MRSA (wOR 9.03) [56,89,90]. A history of MRSA infection or colonization was identified as the most significant predictor of infection (OR 7.20; 95% CI 2.61 to 19.85; $P < 0.001$) [4]. A positive nasal swab for MRSA has also been reported as a predictor of infection [89,90].

Conclusions

This comprehensive review identified some important risk factors that are associated with wound-related complications after major orthopaedic procedures. Identifying and addressing the associated risk is pivotal for optimizing preoperative patient management and improving outcomes. By recognizing potential risks, health care providers can implement targeted interventions to minimize postoperative wound complications and better inform patients and their families about anticipated outcomes.

Question 3: Do surgical drains increase the risk of subsequent surgical site infection in patients undergoing major orthopaedic procedures?[3]

No. Surgical drains do not increase the risk of surgical site infection and periprosthetic joint infection.

Level of Evidence: High

Voting: Agree 74.4%, Disagree 12.8%, Abstain 12.8% (moderate consensus)

Rationale

The use of surgical drains after major orthopedic surgeries remains controversial. Current recommendations suggest that

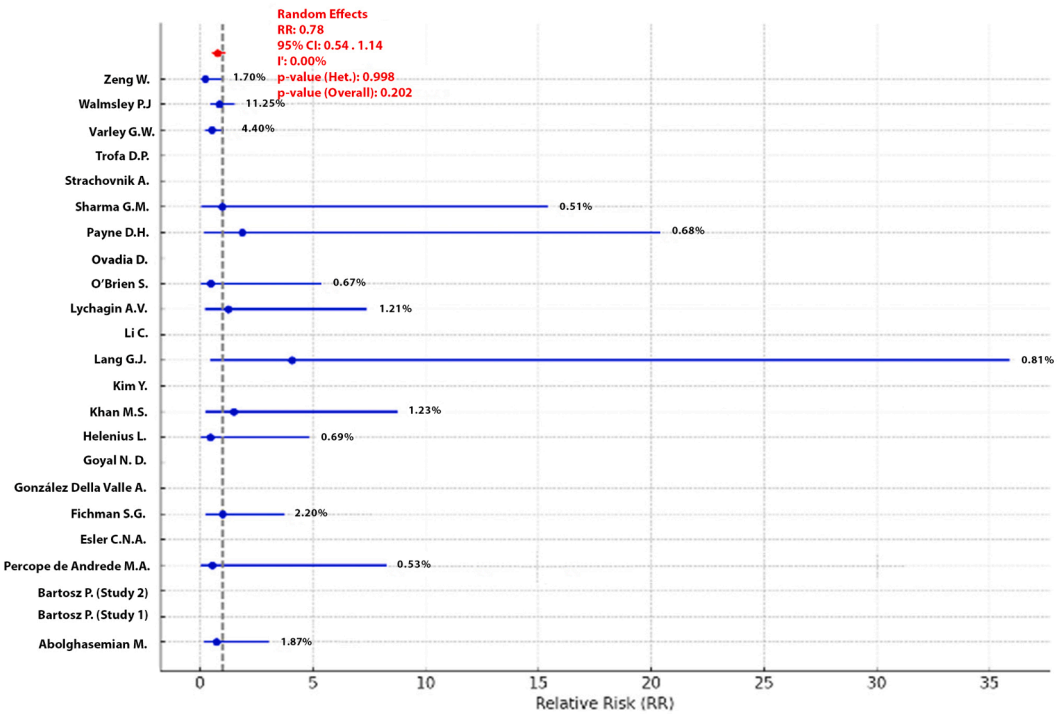


Figure 1. Forest plot for the infection risk. RR, relative risk; CI, confidence interval; I^2, heterogeneity.

[3] These authors contributed to Question 3: Pawel Bartosz, Jerzy K. Bialecki, Padhy Debabrata, Volodymyr Filipenko, Alex J. Ramsden, Toshiyuki Tateiwa, Saheed Yakub, Zongke Zhou

Table 1
Systematic Reviews and Data of Infection, Blood Loss, Blood Transfusion, and Wound Problems.

Study	Year	Type of Surgery	Study Number	Infection (SS Difference) 0-No, 1-YES	Blood Loss (SS Difference) 0-No, 1-YES	Blood Transfusion (SS Difference) 0-No, 1-YES	Wound Problem (SS Difference)
Chen Z. Is wound drainage necessary in hip arthroplasty? A meta-analysis of randomized controlled trials	2014	THA	15	0	NA	0	1 (favors drains)
Clifton R. Closed suction surgical wound drainage after hip fracture surgery: a systematic review and meta-analysis of randomized controlled trials	2008	trauma	6	0	NA	0	0
Hong K. Autologous blood transfusion drainage compared with no drainage in total knee arthroplasty: A meta-analysis and systematic review	2017	TKA	7	0	NA	0	NA
Kelly E.G Systematic review and meta-analysis of closed suction drainage versus nondrainage in primary hip arthroplasty	2014	THA	16	0	1 (favors no-drain)	1 (favors drains)	NA
Li N. Comparison between autologous blood transfusion drainage and no drainage/closed suction drainage in primary total hip arthroplasty: a meta-analysis	2014	THA	12	0	0	0	0
Li N. Comparison of complications in one-stage bilateral total knee arthroplasty with and without drainage	2015	TKA	3	0	NA	NA	NA
Migliorini F. Closed suction drainages in lower limb joint arthroplasty: A level I evidence-based meta-analysis	2022	THA, TKA	25	0	NA	1 (favors no-drains)	NA
Nanni M. Wound drainages in total hip arthroplasty: to use or not to use? Review of the literature on current practice	2013	THA	10	0	1 (favors no-drains)	1 (favors no-drains)	NA
Parker M.J. Closed suction surgical wound drainage after orthopedic surgery	2007	THA, TKA, trauma, shoulder	36	0	NA	1 (favors no-drains)	1 (favors drains)
Parker M.J. Closed suction drainage for hip and knee arthroplasty: A meta-analysis	2004	THA, TKA	18	0	1 (favors no-drains)	1 (favors no-drains)	1 (favors drains)
Si H.B. No clear benefit or drawback to the use of closed drainage after primary total knee arthroplasty: A systematic review and meta-analysis	2016	TKA	12	0	0	1 (favors no-drains)	1 (favors drains)
Yang H. Effect of wound drainage on the wound infection and healing in patients undergoing spinal surgery: A meta-analysis	2024	spine	11	0	NA	NA	1 (favors drains)
Zan P. Closed suction drainage versus no drainage in total hip arthroplasty, a meta-analysis of randomized controlled trials	2016	THA	12	0	0	1 (favors no-drains)	1 (favors drains)
Zhang Q. Comparison between closed suction drainage and nondrainage in total knee arthroplasty: A meta-analysis	2011	TKA	15	0	NA	1 (favors no-drains)	1 (favors drains)
Zhang Q. Are closed suction drains necessary for primary total knee arthroplasty? A systematic review and meta-analysis	2018	TKA	NA	0	0	1 (favors no-drains)	0
Zhao C. Influence of posterior spinal surgery drainage on hematoma and infections at surgical sites: A systematic review and meta-analysis	2024	spine	7	0	NA	NA	NA
Zhou X. Do we really need closed suction drainage in total hip arthroplasty? A meta-analysis	2013	THA	20	0	0	1 (favors no-drains)	NA

SS, statistical significant; THA, total hip arthroplasty; TKA, total knee arthroplasty.

routine use of drains after primary total hip or knee arthroplasty is not advised [90]. However, there is no consensus regarding the use of surgical drains after trauma, spine, or shoulder surgeries. An increasing number of surgeons today avoid using drains, even for complex procedures such as hip or knee revision arthroplasties [91–93].

We performed a literature review using PubMed and Scopus databases, incorporating MeSH terms. This search yielded 3,660 papers, of which 572 were duplicates. After reviewing titles and abstracts, we excluded 2,960 studies and an additional 83 following full-text review, leaving 43 papers for final analysis. These included 25 randomized controlled trials (RCTs), 17 systematic reviews, and one national registry study. We extracted data on infection rates, blood loss, blood transfusions, and wound complications.

Infection

Most studies did not show statistically significant differences in infection rates between drain and no-drain groups (meta-analysis of RCTs shown in Figure 1; relative risk (RR) 0.78; 95% confidence interval (CI) 0.54 to 1.14; $P = 0.202$). Only two papers show statistical differences between groups. Keemu et al. reported higher infection rates in patients who had drains following primary TKA based on the Finnish national registry [95]. Conversely, Zeng et al.

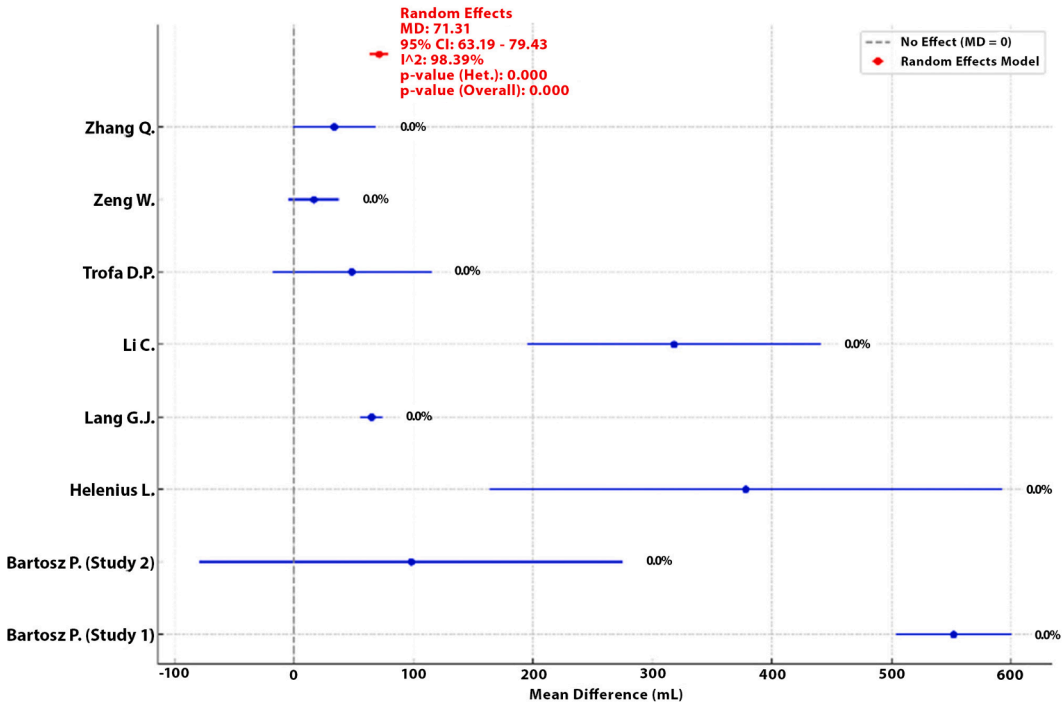


Figure 2. Forest plot for blood loss. MD, mean difference; CI, confidence interval; I^2, heterogeneity.

demonstrated significantly higher infection rates in patients who did not have drains after primary total hip arthroplasty in their RCT based on the Chinese population [96]. Systematic reviews similarly found no significant differences in infection rates between the two groups (Table 1).

Blood Loss and Blood Transfusion

Blood loss and blood transfusion are independent risk factors for periprosthetic infections. Despite the use of tranexamic acid to reduce blood loss during orthopedic surgeries, blood transfusions remain necessary [97]. Among 12 studies reporting data on blood

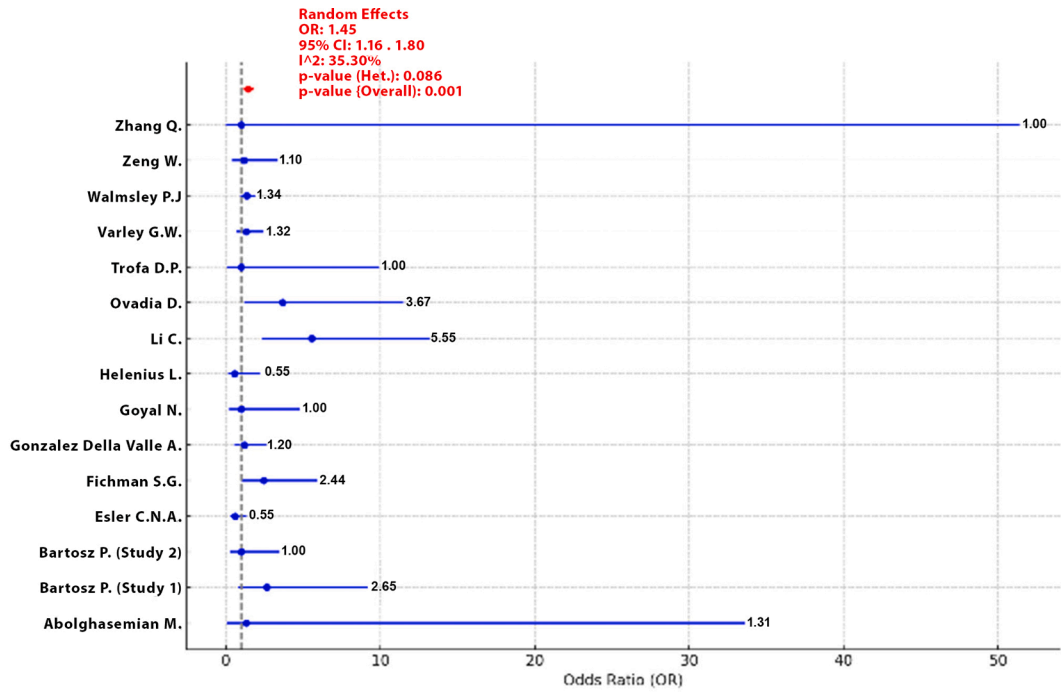


Figure 3. Forest plot for blood transfusion. OR, odds ratio; CI, confidence interval; I^2, heterogeneity.

loss, six RCTs observed greater blood loss in patients who had drains [92,93,96,98–100]. Meta-analysis of eight studies confirmed these findings, with 95% CI: 63.19 to 79.43; $P > 0.05$ (Figure 2). Systematic reviews and registry data further supported these results, with drained patients experiencing higher blood loss [95,107–109].

There are 15 RCTs that examined blood transfusion rates, and all five studies showing differences found lower transfusion rates in patients who did not have drains [92–94,96, 98,99,102,105,106,109–114]. Meta-analysis confirmed statistically significant lower transfusion rates in the no-drain group (OR: 1.45; 95% CI: 1.16 to 1.8; $P = 0.001$, Figure 3). This trend was also supported by 10 systematic reviews, although four reviews did not observe statistically significant differences (Table 1) [107–109,115–125].

Wound Problems

Wound complications, including prolonged oozing and ecchymosis, were more common in patients who did not have drains. Among 16 RCTs reporting on wound complications, three studies favored the use of drains [2–4,6,8,11–13,15,20–23,36–38]. Similarly, among 10 systematic reviews, only one study reported fewer wound problems in nondrained patients, and six studies favor drains [109,114,115,119–123,125,129].

We also analyzed the types of surgeries that compared the use of drains with no drains. In 16 papers, patients underwent total hip arthroplasty, while 19 papers focused on total knee arthroplasty, and three papers included patients undergoing both procedures. There were five studies that compared patients after spine surgery, four studies focused on trauma patients, and two studies involved shoulder surgery patients [92,98–115,116–135].

Conclusions

After analyzing all the papers, we found no significant difference in infection risk between patients who did or did not have drainage following major orthopedic surgeries. The average group size in RCTs was 210, and in systematic reviews, it was 1,992. Given that the infection risk after total hip arthroplasty is approximately 0.4% in recent publications, these sample sizes are insufficient to achieve statistically significant differences in this parameter [136]. Larger, well-designed, multicenter, and possibly multinational prospective randomized studies are necessary to answer these fundamental questions.

Question 4: Are skin swabs useful for isolation of the infective organism causing surgical site infection after major orthopaedic procedures?[4]

Response/Recommendation

No. Skin swabs are not useful for isolation of infective microorganisms causing surgical site infection after major orthopaedic surgery. Skin swabs after any major orthopedic surgery run the risk of identifying the wrong microorganisms or missing the true infective microorganism. Antimicrobial strategies based on these skin swabs can misguide treatment and must not be considered.

Level of Evidence: Moderate

Delegate Vote: Agree 90%, Disagree 6%, Abstain 4% (total consensus, unanimity)

Rationale

Infection after any orthopaedic surgery is a disastrous complication. Redness, tenderness, warmth, or discharge from or around the wound may, in some cases, be localized to the suture line but, in most cases, portend deep-seated infection. Diagnosing a deep infection remains a challenge despite tremendous strides being made in serology, microbiology, and radiology [137].

Identifying the microorganism by culture is the preferred method, and as the adage goes, "well begun is half done—collecting the correct sample is indeed well begun." Deep tissue from around the implant/bone or within the joint is considered to be a must for accurately identifying the infective organism.

Though PJI-focused definitions [138,139] do not include skin swabs, they are commonly used worldwide after many other major orthopaedic surgeries, as they are easy to collect and avoid an invasive procedure for collecting deep samples [140]. Swabbing the sinus tract was discussed during the last International Consensus Meeting in 2018, and a recommendation with a strong consensus (96%) was made against the use of skin swabs to isolate infective organisms [138].

To address the above question, this comprehensive systematic review was conducted. Using the MeSH terms developed by librarians, three databases (PubMed, Scopus, and Embase) were searched to identify 453 potentially relevant studies. After screening by two independent reviewers, 14 studies were deemed to be relevant and meet the inclusion criteria. A full review of these studies was conducted, and data were extracted.

In the prospective study by Tetreault et al. [141] on 55 infected THA/TKA, concordance between superficial swabs versus deep tissue/synovial fluid aspiration culture was evaluated. The criteria for concordance were strict, ensuring that the culture and susceptibility patterns were correlated. Only 47.3% of skin/wound swabs matched deep cultures. The false positive rate was 43.4%, while the false negative rate for the swabs was 19%.

In another study by Cune et al. [140], in their retrospective cohort of 56 acute PJIs, they kept a broad definition where even one microorganism matched was considered concordant. This makes it difficult to evaluate polymicrobial samples to determine the true infective organism. Excluding the polymicrobial samples, there was only 60% concordance between superficial and deep samples. They concluded that though superficial swabs are easy to obtain, deep-tissue cultures provided more meaningful information and should be utilized for proper isolation of the infective organisms. In the latter study, a high predictive value (PPV) was noted when *S. aureus* or Gram-negative bacilli were isolated on superficial swabs (100 and 85%, respectively). A similar analysis by Tetreault et al. (5) showed only 52% concordance with *S. aureus*, while only 40% for Gram-negative organisms. The results for other Gram-positive bacilli were poor in both studies. More importantly, Tetreault et al. [141] suggested that almost 42% of cases would have different antimicrobials if based solely on superficial skin swabs, which could have negative implications on outcomes, as suggested by studies on osteomyelitis as well [142]. There was no difference based on whether the joint was a hip or a knee in either study.

In a similar retrospective study for calcaneal fracture surgery complicated by infection, Backes et al. [143] had 33 cases where both deep and superficial cultures were taken. In 40% of the cases, the organism isolated in deep culture was different from the skin swab. Out of the overall cohort of 55 deep infections, 31% were mistaken for superficial and treated accordingly. The authors recommended an aggressive approach to management to obtain deep cultures and not rely only on superficial swabs for diagnosis of infection or identification of microorganisms. Desai et al. [144] showed that only two discharging pin sites, after K-wires for distal end radius fractures, were culture positive out of 14 discharging pin sites. Both were treated with antibiotics and achieved

[4] These authors contributed to Question 4: Jay Shah, Julie Reznicek, Nilo Paner, Colin Baker, Fatih Kucuckdurmaz, Hatem Bakr

complete healing. The other 12 were culture negative and went on to heal with appropriate wound care.

The literature on spine surgeries also highlights similar findings. Dobran et al. [145] showed that only 75% of wound swabs were culture positive, of which only 62% healed with antimicrobial therapy directed against the microorganism. There were 38% that required further surgery and deep cultures. Gaines et al. [146], in their retrospective review of posterior instrumentation cases, had four patients who had a sinus, with two cases having scanty *S. aureus* growth. The concordance rate was 50%, with one deep culture being negative and one showing *Streptococcus* species (as opposed to *S. aureus* on the skin swab).

Interestingly, Cacopardo et al. [147] and Kristopaitis et al. [148], in their case reports, reported *Clostridium* species growth on skin/sinus swabs. *Clostridium macginleyi* was cultured from a pediatric spine instrumentation patient who had developed a recurrent sinus by Cacopardo et al. [147]. This responded to antibiotics, but required two courses for complete eradication. Kristopaitis et al. [148] had a patient after an L4 to L5 laminectomy who developed meningitis due to *C. perfringens.* This patient, unfortunately, succumbed, and the autopsy showed cranial and spinal meningitis with choroid plexitis due to *C. perfringens*.

A study by Alam et al. [149] from the world's largest Transcutaneous Osseointegration Following Amputation (TOFA) registry showed that periportal swabs did not correlate with the diagnosis of infection in multivariate regression analyses. Of the 57 patients who had positive deep cultures, only 42 had positive periportal swabs. There were 45% of bacterial strains on deep culture that were missed on the periportal skin swab. Similar to the results from Tetreault et al. [150], in 58% the antibiotics based on superficial swabs would be incorrect, potentially leading to treatment failure.

A study done with a mixture of orthopaedic surgical procedures by Ochs et al. [149] strongly recommended deep samples over superficial after having a concordance rate of only 40% in their study. The sensitivity of the swabs is only 44% in identifying the microorganism with reduced colony count.

Conclusions

Though skin swabs are easy to obtain and can identify microorganisms, they should not be considered representative of deep infection, as many times the isolated organisms may be the microbiome of the skin and not the true pathogen causing the infection. Basing treatment strategies on skin swab cultures is erroneous, especially for deciding the antimicrobial regimen, and can lead to treatment failures. The studies show an unsatisfactory concordance rate with deep sample culture, and we hence do not consider using skin swabs useful for identifying the infective microorganism after major orthopedic surgery.

Question 5: Is there a role for swab culture of draining fluid from a sinus tract in patients who have an orthopaedic infection?[5]

Response/Recommendation

No. Swab cultures of draining fluid from a sinus tract are not reliable, as they are prone to contamination from external sources, which can compromise their diagnostic value and may lead to a false diagnosis. Obtaining deep tissue and bone cultures remains the mainstay of isolating infecting organisms in orthopedic infections.

Level of Evidence: Moderate.

Delegate vote: Agree 88.7%, Disagree 6.7%, Abstain 4.6% (super majority, strong consensus).

Rationale

A sinus tract, which forms a direct connection between infected bone/joint and the skin, is commonly associated with chronic infections like chronic osteomyelitis and serves as one of the major criteria for the diagnosis of PJI [151–154]. The communication between the sinus tract and the skin surface can introduce contamination by external microorganisms, which may not be the actual causative agents of the infection. Although superficial swab cultures taken from the wound or sinus tract can help identify microorganisms, they may not accurately represent deeper tissue infection. This highlights the need for additional diagnostic methods to ensure precise identification and appropriate treatment. It is important to note that while the data discussed here also include information from studies on chronic osteomyelitis, these recommendations are specifically intended for PJI.

Superficial swab/sinus tract culture (STC) was initially considered adequate in identifying causative microorganisms in chronic osteomyelitis, but its reliability has been questioned in multiple studies. Perry et al. [155] found that superficial swab cultures correlated approximately 70% with intraoperative cultures, with a higher correlation of about 90% for *Staphylococcus aureus* (*S. aureus*) and monomicrobial infection. In their study, STC was more accurate than needle biopsy. In a prospective study of 141 patients who had chronic osteomyelitis and a sinus tract, Bernard et al. [156] found that two concordant deep sinus tract cultures with bone contact predicted causative microorganisms in 96% of cases. The accuracy was higher for monomicrobial infections compared to polymicrobial infections (94 versus 79%). Conversely, Patzakis et al. [157] demonstrated that STC failed to match the microorganisms found in bone cultures in nearly half of the cases. Similarly, Ulug et al. [158] observed that only 38% of STCs were concordant with bone cultures, suggesting that reliance on STCs could lead to a false diagnosis and incorrect treatment. Mackowiak et al. [159] found that only 44% of STC-matched microorganisms were identified in intraoperative bone specimens. While *S. aureus* isolated from sinus tracts often correlated with bone cultures, other pathogens did not exhibit the same correlation. Akinyoola et al. [160] reinforced these findings, reporting that while STC had a sensitivity of 60%, a specificity of 45%, and a PPV of 72% for detecting *S. aureus*, the overall diagnostic accuracy of STC was poor, with an overall sensitivity of 51%, specificity of 20%, and PPV of 47%.

In diagnosing PJI, STCs have been evaluated in comparison to deeper intraoperative cultures. Cuñé et al. [161] focused on acute hip and knee PJI, defining acute infection as the onset of symptoms within 15 days postoperatively and diagnosis occurring within the first month after index arthroplasty. Their study reported an 80% concordance rate between superficial swab cultures from wound drainage and deep cultures. Superficial swab cultures demonstrated high sensitivity for detecting *S. aureus* (94%) and Gram-negative bacilli (90%), highlighting their utility for identifying these pathogens in acute PJI. However, the sensitivity for other Gram-positive bacteria was lower (50%), suggesting that superficial swab cultures are less effective in detecting a wider range of pathogens.

Alternatively, Tetreault et al. [162] studied the use of superficial cultures from draining wounds or sinuses in patients who had chronic hip and knee PJI and found that these cultures were concordant with deep tissue cultures in only 47% of cases. Additionally, superficial cultures were more likely to yield polymicrobial results. Their study recommended against relying on superficial cultures in patients with draining wounds or sinuses

[5] These authors contributed to Question 5: Jakrapun Pupaibool, Rubén Arriaga Sánchez, Valérie Zeller, Al-Amin Kassam, Nilo Paner

following joint arthroplasty due to the potential for misleading diagnosis and inappropriate treatment.

Aggarwal et al. [163] compared the diagnostic effectiveness of tissue and superficial swab cultures in identifying PJI during both septic and aseptic revision arthroplasties of hips and knees. Their study revealed that tissue cultures were significantly more reliable, exhibiting superior sensitivity, specificity, and predictive values: 93, 98, 93, and 98%, respectively, compared to 70, 89, 68, and 90% for swab cultures. Additionally, swab cultures were associated with a higher incidence of both false-positive and false-negative results, underscoring their lower accuracy in diagnosing PJI.

In summary, these studies indicate that STC is not sufficiently reliable for accurate microorganism identification in chronic osteomyelitis. While STC can be useful for identifying *S. aureus*, it is generally less accurate for detecting other microorganisms. The diagnostic value is increased if deep sinus tract cultures with bone contact are obtained, and the same microorganism is isolated twice. Similarly, while superficial swab cultures may aid in diagnosing acute PJI, particularly for identifying *S. aureus* and Gram-negative bacilli, their reliability is limited in chronic PJI. Based on the available evidence, clinicians are encouraged to prioritize intraoperative tissue and bone cultures for accurate diagnosis and treatment planning.

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The Journal of Arthroplasty 41 (2025) S151–S156

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

2025 ICM: Role of Unconventional Medications

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Question 1: Is there a role for bacteriophage therapy in the treatment of orthopaedic infections?[1]

Response/Recommendation

Yes. Phage therapy demonstrates a favorable safety profile and is a reasonable therapeutic consideration for patients who have refractory bone and joint infections.

Level of Evidence: Moderate

Delegate Vote: Agree 76.5%, Disagree 13.8%, Abstain 9.7% (Strong Majority, Moderate Consensus)

Rationale

Bacteriophages (phages) are viruses that specifically infect bacteria and are being explored as a potential novel therapy for infections where antibiotics may fail, such as those involving multidrug resistance or biofilm formation. Over the past decade, there has been increasing interest in using phage therapy for bone and joint infections, with a growing body of human cases reported. In 2022, the World Health Organization (WHO) classified phages as a key component of nontraditional antibacterial agents requiring urgent development, particularly for their efficacy against priority pathogens driving the global spread of antimicrobial resistance [1].

We reviewed all documented cases of bone and joint infections treated with phage therapy in English-language publications since 2010. Our analysis includes 30 publications: one clinical trial [2], five case series [3–6], (including one involving 100 cases, 34 of which were bone and joint infections [7]), and multiple individual case reports. After removing duplicates and redundancies, the dataset encompasses 98 unique cases [6,8–32].

Phage therapy targeted a single bacterial species in 89 cases and multiple organisms in nine cases. The most commonly targeted organism was *Staphylococcus aureus* (48 cases, 49%), followed by *Pseudomonas aeruginosa* (22), coagulase-negative staphylococci (22), *Klebsiella pneumoniae* (six), *Enterococcus faecalis* (six), *Escherichia coli* (two), *Proteus mirabilis* (one), vancomycin-resistant *Enterococcus faecium* (one), *Acinetobacter baumannii* (one), and *Streptococcus agalactiae* (one). The most frequent indications for phage therapy were periprosthetic joint infection (PJI) (57 cases), diabetic foot infection (11), fracture-related infection (eight), osteomyelitis of the long bone (seven), osteomyelitis of the pelvis (seven), osteomyelitis of the foot/ankle (three), spinal infection (two), osteomyelitis of the head and neck (two), and septic polyarthritis (one).

Adverse events were not reported in three cases, while transient events occurred in 16 cases. These included transient increases in liver enzymes (eight cases) [5,15,21], transient fever (5) [2,7,9,28], localized erythema and pain at the delivery site (1) [4], and nonspecific symptoms such as exhaustion and dizziness (1) [3]. All events resolved without lasting effects. There were no adverse events noted in the remaining cases. Phage susceptibility testing was conducted in all cases. Of the 98 cases, 68 involved the use of monophage therapy. In two cases, single-phage therapy was used in a sequential manner. The remaining 30 cases employed multiple phages simultaneously, as in a cocktail. The routes of administration varied, with 69 patients receiving local delivery (11 intraoperative only, 18 local delivery outside the operating room only, and 40 both intraoperative and outside the operating room), seven receiving systemic therapy, 21 receiving combined local, and systemic delivery, and one patient receiving oral therapy [12].

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.092.

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https://doi.org/10.1016/j.arth.2025.10.092
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Conventional antibiotics were invariably given alongside phage in all cases.

Surgical intervention was common and varied by infection type. All patients with head and neck or spinal infections underwent surgery, as did 92% of those with PJIs, 88% with fracture-related infections, 71% with long bone osteomyelitis, and 57% with pelvic osteomyelitis. In contrast, only 33% of patients with foot or ankle osteomyelitis and none with diabetic foot infections underwent concurrent surgery. Overall, 88 of 98 patients (88%) achieved clinical improvement or resolution, with nine patients experiencing worsening and one showing no change. Microbiological clearance was achieved in 54 cases, was not achieved in 18, and was not assessed in 26. It must be noted that microbiological clearance was not generally assessed in patients who were doing well and for whom microbiological clearance would have required an invasive procedure. Clearance rates were higher among patients undergoing concurrent surgical intervention (64.9%) compared to those without surgery (25.0%). There was a wide range of durations of therapy (single-dose to one year), dosing intervals (daily to three times daily), and dosing concentrations (10^5 to 10^{10} PFU/mL).

Of the 10 unfavorable clinical outcomes, five occurred in osteomyelitis (three of the pelvis [7,32] and two of the foot or ankle [7]), four occurred in PJI [2,3,7,19], and one occurred in diabetic foot infection [7]. Of note, 30% of all clinical failures occurred in infections involving the foot or ankle. Among gram-positive infections, 89.4% achieved clinical improvement, while gram-negative infections achieved 95.2% improvement. Polymicrobial infections, defined here as infections where more than one bacterial species was targeted by phage, demonstrated favorable outcomes, achieving 100% clinical improvement, likely reflecting the relatively small sample size (N = nine) rather than a definitive trend. Generalizations could not be made regarding route of administration, dose, dosing interval, or duration of therapy due to heterogeneity and multiple confounding contributors for each case.

The promising outcomes reported must be interpreted cautiously due to several potential limitations. Variations in phage selection, preparation, and administration methods complicate comparisons and generalizations. The reliance on retrospective case reports and small-scale studies introduces potential publication bias, with successful cases more likely to be reported. Inconsistent microbiological and clinical outcome measures hinder accurate assessment of phage therapy's efficacy. The effects of adjunctive therapies, such as antibiotics and surgical interventions, cannot be isolated from those of phage therapy. Technical and logistical challenges also exist. Phage susceptibility testing is labor-intensive and not universally accessible. Regulatory hurdles and the need for individualized preparations further challenge scalability. In addition, the risk of bacterial resistance to phages, while less well-documented than antibiotic resistance, may be of concern. Patient-specific factors, such as immune responses and comorbid conditions, may affect outcomes [33].

In conclusion, phage therapy, particularly when combined with surgical intervention, appears to be a promising adjunctive treatment for refractory bone and joint infections. Surgical debridement and biofilm disruption, when given with conventional antibiotics, likely enhance phage efficacy. Furthermore, available evidence strongly supports the safety of phage therapy, with minimal adverse events reported across studies. This underscores the low risk associated with its use, making it a viable consideration from a safety standpoint. Although the high clinical success rates are encouraging, they must be interpreted in light of potential publication bias and other limitations. Large-scale, well-designed clinical trials are needed to validate these findings and standardize protocols. Understanding the specific contributions of phage therapy, distinct from adjunctive treatments, will be critical in optimizing its role in managing complex infections [34,35].

Question 2: Is there a role for phage lysins in the treatment of patients with orthopaedic infections?[2]

Response/Recommendation

Based on minimal clinical data, the use of phage lysins holds promise for the for the treatment of patients who have periprosthetic joint infections (PJI).

Level of Evidence: Limited

Delegate Vote: Agree 82.2%, Disagree 8.9%, Abstain 8.9% (Strong Consensus)

Rationale

Bacteriophages (phages) are natural viruses that specifically infect bacteria. Virulent phages have the ability to destroy a targeted species by replicating inside the bacterial host. This process is associated with the production of various enzymes by the virus itself during the replication process inside the bacteria. These phage-encoded enzymes are hydrolases, endolysins (also called lysins), and depolymerases [36]. Some of these enzymes, by themselves, have antibacterial and/or antibiofilm activities and are called "enzybiotics," as they are enzymes with antimicrobial activity, or "direct lytic agents" [37,38]. As a consequence, outside the use of phages, production of engineered recombinant phage enzymes is of interest because (i) from a microbiological perspective, they possess antibacterial and antibiofilm properties, with a broader spectrum in comparison with phages, (ii) from a biotech point of view, the production process and the protein itself could be patented, unlike a natural phage [36].

Of note, in 2022, the WHO categorized phages and phage-related proteins as key members of the nontraditional antibacterial agents that need to be urgently developed, especially due to their activity on priority pathogens responsible for the worldwide spread of antimicrobial resistance. These nontraditional antibacterial agents in the pipeline have been updated in the WHO 2023 report, and two lysins, called CF-301 and SAL-200, were listed [39].

We reviewed all documented cases of bone and joint infections treated with phage lysin in English-language publications since 2010. Only one article, published in 2021, was found [40]. Authors reported the use of the CF-301 lysin (exebacase), a recombinantly produced lysin, that demonstrated antibiofilm activity *in vitro* against staphylococcal species [41,42]. In this article, arthroscopic debridement and implant retention with local administration of CF-301 (Lysin DAIR procedure), followed by suppressive tedizolid as salvage therapy, were described in four elderly patients with recurrent multidrug-resistant *S. epidermidis* periprosthetic knee infection with no further surgical or antimicrobial therapeutic options. All had multiple previous prosthetic knee revisions without prosthesis loosening; three had experienced a relapse despite previous suppressive antibiotics following an open debridement, antibiotics, and implant retention (DAIR) procedure; two had clinical signs of septic arthritis; and the two others had a sinus tract. There were no adverse events that occurred during and after the treatment course. All patients received the same primary antibacterial therapy, followed by tedizolid 200 mg/day as suppressive therapy. At six months, recurrence of the sinus tract occurred in the two patients with a sinus tract at baseline. After more than 1-year follow-up, the clinical outcome was favorable in

[2] These authors contributed to Question 2: Antonia Scobie on behalf of ESGNTA, Gina A. Suh on behalf of ESGNTA, Thomas Fintan Moriarty, Francesco Falez, Willem-Jan Metsemakers, Kaspar Tootsi, Bryan Springer, Tristan Ferry on behalf of ESGNTA

the other two patients with total resolution of clinical signs of septic arthritis, even if microbiological persistence was detected in one of them. Given the severity and refractory nature of these infections, any favorable clinical outcome was unexpected.

Following this article, other patients were treated in the phage referral center for the management of complex bone and joint infections in Lyon, France, with ongoing follow-up (unpublished data). A single-center, randomized controlled trial evaluating CF-301-108 was launched in 2023, but stopped prematurely due to the bankruptcy of the sponsor.

Based on (1) the WHO report about nontraditional agents and the need to develop phages and phage-related proteins to face antimicrobial resistance; (2) the phage lysin's *in vitro* activity, and especially their lytic and antibiofilm activity; and (3) the single scientific paper available in the literature about clinical use of lysins, we concluded that phage lysins are of interest in patients with PJI. The development of phage lysins and their clinical evaluation in acute or chronic PJI needs further research for developing evidence-based recommendations about their potential adjuvant role in the management of PJI treated with a conservative approach.

Question 3: Is there a role for antimicrobial peptides as a treatment modality for patients who have orthopaedic infections?[3]

Response/Recommendation

Antimicrobial peptides (AMPs) offer a promising adjunct or alternative therapy for treating orthopaedic infections, particularly in cases of infection with antibiotic resistance or failure after conventional therapy. Early phase human trials suggest favorable safety, but further clinical research is needed to confirm their optimal use.

Level of Evidence: Moderate

Delegate Vote: Agree: 70.9%, Disagree: 14.6%, Abstain: 14.6%

Rationale

Implant-associated infections remain a major complication in orthopaedic surgery, leading to implant failure, prolonged hospital stays, and increased health care costs [43]. The causative agents often form biofilms on implant surfaces, rendering infections highly resistant to antibiotics and increasing the prevalence of multidrug-resistant pathogens [44]. Antimicrobial peptides (AMPs) offer a promising treatment alternative due to their ability to disrupt bacterial membranes, inhibit biofilm formation, and function when immobilized on implant materials [45]. Although the efficacy of AMPs in treating infection in other areas of medicine has been established [46], the role of AMPs in treating orthopaedic infections is relatively new and is currently being explored.

To answer the posed question above, we conducted a comprehensive systematic review of PubMed, Embase, and Cochrane Library from inception to August 2024 to identify studies examining the role of AMPs in treating orthopaedic-related infections. Inclusion criteria were all studies, including *in vitro*, *in vivo*, and clinical studies, examining the potential role of AMPs in treating orthopaedic-related infections. Exclusion criteria were studies investigating AMPs as a diagnostic modality, *in vitro* studies not examining AMP utilization on implant materials (titanium and magnesium), and review articles. A total of 632 studies were screened for eligibility. Of these, the full texts of 46 studies were reviewed, leaving 32 studies for final inclusion. There were two independent authors who reviewed the abstracts and full texts, and disagreements were resolved by a third independent author.

Studies examining AMPs in vitro

Various AMP coatings for implant materials, mostly titanium, have demonstrated significant bacterial load reduction, biofilm inhibition, and high biocompatibility. AMP-loaded surfaces achieved > 95% bacterial inhibition, with some eliminating colonies entirely [47–52]. Studies show that AMPs exhibit a significant bactericidal effect, reducing *S. aureus* and *P. aeruginosa* by up to 10^6-fold in 30 minutes and decreasing bacterial adhesion by 45-fold compared to titanium surfaces without AMPs [53–58]. Furthermore, AMPs have been shown to completely inhibit the growth of common pathogens such as *S. aureus*, *S. epidermidis*, and *E. coli* [59–61]. These effects likely stem from their ability to disrupt bacterial membranes and heighten the immune response by increasing cytokine release [62,63]. Several studies have shown that AMPs may have a dose-dependent effect against biofilms, demonstrating up to 90% biofilm reduction against *S. epidermidis*, *E. coli*, and *P. aeruginosa* when coating titanium surfaces with AMPs [64–67]. In addition, AMPs may outperform conventional antibiotics. Kang et al. [68], observed a greater than 4-log reduction in *S. aureus* with AMPs compared to less than 1-log reduction using conventional antibiotics (gentamicin, vancomycin, and rifampin). Against clinically isolated bacteria and multiresistant bacteria, such as methicillin-resistant *Staphylococcus aureus*, AMPs can still be effective, achieving a greater than 90% bacterial inhibition and biofilm reduction [69–72]. In a study of 17 explanted total knee arthroplasty prostheses from patients who have chronic PJI, using PLG0206 at one mg/mL for 15 minutes demonstrated a 10^4 reduction in bacterial colonies. Moreover, 59% of explants became culture negative following treatment [73].

Studies examining AMPs in vivo

In vivo studies have demonstrated the potent antibacterial, biofilm-inhibiting, and osseointegration effects of AMPs in treating orthopaedic infections. Raeder et al. [74] studied 36 Wistar rats with *S. epidermidis* bone graft infections and found that APIM-peptide combined with gentamicin eliminated bacteria in 77% of cases, compared to 38% in single-treatment groups, and led to 30% more bacterial eradication than gentamicin alone. Chen et al. [75] tested 55 New Zealand rabbits with *S. aureus*-infected implants, showing > 99% bacterial killing at 7 days with Fusion Peptide (HHC36 plus QK)-coated titanium (Ti-125FP), in addition to minimal bacterial adhesion, biofilm formation, and 1.6 times higher osseointegration than uncoated titanium at 60 days. Mandell et al. [76] used WLBU2 irrigation in six mouse PJI models and found significant biofilm reduction, with the highest efficacy at alkaline to physiological pH. Yan et al. [77] studied 67 rabbits with femoral fractures infected with *S. aureus* and found that LL-37 significantly reduced bacterial counts at two and seven days, while also lowering inflammatory markers by day seven in comparison to cefalexin or saline.

Human-based studies

A series of clinical studies have been conducted on PLG0206/zaloganan, a novel AMP with independent biofilm activity [78]. A Phase 1 single ascending dose study evaluated the safety, tolerability, and pharmacokinetics of PLG0206 when administered intravenously (IV) in 35 healthy volunteers, compared to 12 patients who received an IV placebo [79]. No serious adverse events occurred, and treatment-emergent adverse events were infrequent, with most events being mild in severity [79]. A Phase 1b open-label clinical trial is currently underway to assess PLG0206 in

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conjunction with traditional DAIR procedures for PJI treatment of the knee [80]. Preliminary data suggest that PLG0206 continues to be well tolerated and indicates a lower PJI failure rate as compared to reported literature rates [81,82], supporting the continued development of PLG0206 for PJI treatment.

Question 4: Is there a role for the use of phytochemicals in the management of patients who have orthopaedic implant-associated infections?[4]

Recommendation

Although *in vitro*, *in silico*, and limited *in vivo* animal studies have demonstrated the antimicrobial activity of several phytochemicals and their efficacy against biofilm formation, there is currently a lack of clinical studies supporting the use of phytochemicals in the management of patients who have orthopaedic implant-associated infections.

Level of Evidence: Limited

Vote Results: Agree 62.9%, Disagree 14.2%, Abstain 22.9%

Rationale

Owing to the increasing microbial resistance to conventional anti-infectives, there is a growing need for alternative antimicrobial strategies to effectively combat orthopaedic implant-associated infections. The rise of multidrug-resistant pathogens necessitates the exploration of novel therapeutic approaches that can circumvent the limitations of traditional evidence-based therapies. In this context, although known for centuries in traditional medicine, phytochemicals emerge as potentially valuable adjuncts or alternatives to conventional antimicrobial treatments. Phytochemicals are bioactive compounds derived from plants, showcasing a wide range of biological activities, including antibacterial, antifungal, and antiviral effects. Therefore, this assignment aimed to evaluate the evidence supporting the use of phytochemicals in the management of patients with orthopaedic implant-associated infections.

The database search, which included PubMed, Scopus, and Web of Science, yielded a total of 612 results. After merging 19 duplicates, 593 records remained for screening based on titles and abstracts. Following the assessment of titles and abstracts for eligibility, 49 studies advanced to the full-text screening phase. However, the full-text review revealed substantial heterogeneity among the studies, rendering them ineligible for a pooled analysis. Furthermore, no clinical studies specifically addressing this topic were identified. As a result, the assignment necessitated a narrative approach.

Several phytochemicals have been experimentally demonstrated to possess efficacy against biofilm formation and exhibit antimicrobial activity *in vitro* or *in silico*. Examples of these agents include curcumin [83], *Rosa canina* liquid extract [84], thymol [85], *Moringa oleifera* liquid extract [86], *Trifolium repens* liquid extract [87], *Cissus quadrangularis* liquid extract [88], a spectrum of essential oils [89], Manuka honey components [90], green tea extract [91], oregano oil [92], isoliquiritigenin [93], *Posidonia oceanica* liquid [94], resveratrol [95], or a variety of other flavonoids, triterpenoids, carboxylic acids, and their derivates [96]. Nevertheless, examination of the existing literature revealed a markedly limited number of animal and human studies available to investigate the *in vivo* behavior of the aforementioned agents, as their pharmacokinetics and pharmacodynamics may differ compared to experimental laboratory settings.

In addition, despite the extensive documentation of the antibacterial and antifungal properties of these phytochemicals, there remains a critical gap in evidence regarding their applicability in the context of orthopaedic implant infections. This deficiency underscores the need for further research to validate the effectiveness and safety of these agents in clinical settings. Furthermore, the spectrum of targeted bacteria and fungi is restricted to specific species, raising concerns about the generalizability to less common pathogens. Another critical area that warrants investigation is the potential synergistic effects of phytochemicals when used in conjunction with conventional therapies to enhance treatment efficacy. Although there exist experimental reports suggesting that a combination of phytochemicals with antibiotics can promote bacterial eradication [97], comprehensive clinical trials are necessary to establish the validity of these findings.

Although phytochemicals seem to be a promising preventive and treatment option, they are limited to the preclinical setting and thus lack supporting clinical data, making them only promising candidates for further research. Conclusively, given the absence of sufficient data, the applicability of phytochemicals in the management of patients with orthopedic implant-associated infections remains unclear.

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The Journal of Arthroplasty 41 (2025) S157–S163

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

General Topics

2025 ICM: Sample Collection and Agent Identification

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ARTICLE INFO

Article history:
Available online 27 October 2025

Question 1: What are the optimal sampling and processing techniques for cultures obtained during any revision surgery?[1]

Question A: How many samples should be processed for culture during any revision surgery?

Response/Recommendation: We recommend that four to six samples be submitted to the microbiology laboratory and include at least three periprosthetic tissue samples. Synovial fluid and implant sonication fluid can be sent, if available.

Question B: How should samples be processed for cultures during any revision surgery?

Response/Recommendation: Samples should be mechanically homogenized to maximize bacterial extraction and minimize contamination. Prolonged incubation in monitored blood-culture vials increases the sensitivity of culture and should be substituted for classical broth enrichment when possible.

Level of Evidence: Moderate

Delegate Vote

Question A: Agree: 93.2%, Disagree: 1.3%, Abstain: 5.5% (Unanimity, Total Consensus)

Question B: Agree 94.4%, Disagree 4.2%, Abstain 1.4% (Unanimity, Total Consensus)

Rationale

The diagnosis of periprosthetic joint infection (PJI) remains difficult, and composite clinical scores aggregating clinical, microbiological, biological, and pathological criteria are frequently used as a gold standard.

The microbiological documentation of PJI allows not only the unambiguous recognition of infection, but also optimal care through personalized antimicrobial treatment. The culture of the same microorganism from multiple samples gathered in the course of the revision surgery is commonly required for its consideration as a causative agent of infection.

The sensitivity of periprosthetic tissue culture to diagnose PJI with full microbiological documentation has been reported to range from 57 [1] to 92% [2]. Major factors governing these performance discrepancies arise at every stage of the analytical process: biopsy collection and transport, biopsy homogenization, choice of media and incubation atmosphere, automated monitoring, implant analysis, and synovial fluid culture. We acknowledge that culture-negative implant-associated infections exist. Other factors such as the formation of biofilm on the implant, prior antibiotic therapy, or infection with fastidious organisms contribute to culture-negative infections [3,4]. In these circumstances, molecular biology approaches, polymerase chain reaction-based or metagenomic, may play a role in the identification of the infective organism [5,6].

Although no specific anatomical sampling sites have been shown to provide higher diagnostic yields and should be targeted at macroscopically abnormal tissues, taking samples from deep bone [7] and the intramedullary canal [8,9] is considered best practice. The use of swabs is discouraged due to poor performance [10]. Based on recommendations of the Infectious Disease Society of North America and others, consideration should be given to refrigeration of samples if processing of the samples is expected to

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to 10.1016/j.arth.2025.08.040.

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https://doi.org/10.1016/j.arth.2025.08.040
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be more than two hours from the time of collection [11–13]. Although definitive data supporting the latter recommendation is lacking, *in vitro* evidence supports this notion [14]. Additional clinical evidence can be derived from the benefit of the addition of anaerobic media during the transport of samples to the laboratory, enhancing diagnostic performance and completeness of microbiological documentation [15,16], although a study failed to provide evidence in this regard [17]. Kaschner et al. showed that the benefit of thioglycolate broth was not related to the temperature of incubation, suggesting that the pH buffer, redox potential, cationic ions, or osmolality of the medium was providing the performance enhancement. The use of double-wrapped sterile packaging cleared for operating theaters and mechanized processing has decreased contamination rates thanks to the limitation of the sample handling steps [18].

The microbiological analysis requires the exposure of the pathogens to the culture medium to allow their growth and detection. Several methods have been reported to release bacteria from solid samples. Scalpel dissection of the samples or mortar and pestle grinding in broth were the most common techniques. Vortexes can be used with broth or saline with glass beads [19]. Mechanical homogenization has been performed with different instruments, such as a paddle blender [20], a beadmill with glass beads [18], a beadmill with steel beads [21,22], a beadmill with ceramic beads [23], and dispersion with a single-use ultra-turrax device [24]. The use of these mechanized disruption methods has allowed a substantial increase in sensitivity and has allowed the use of blood culture systems to monitor and enhance bacterial culture.

The number of samples and the number of samples positive with the same microorganism have evolved as the methods grew more standardized. As early as 1981, Kamme proposed culturing five periprosthetic tissue biopsies and claimed that a microorganism growing on two or more samples was indicative of infection. There were five to six samples with positive growth from three or more samples, which were then broadly used [25]. The less stringent breakpoint of growth of two or more identical isolates became consensual [25], with Infectious Disease Society of North America recognizing PJI with a single sample growing with a virulent species [26]. Using current microbiological methods employing mechanized sample processing and blood culture vials for monitoring of the samples, three to four periprosthetic tissue samples now appear to be optimal for sensitivity and specificity [21,27–29].

Synovial fluid has proven to be a reliable sample for culture, as well as cytological and biochemical analysis. The immediate seeding of blood-culture vials with synovial fluid has led to the improvement of culture sensitivity [30]. A sample should nevertheless be sent for cytological analysis in a vial with anticoagulants.

The retrieval of biofilms from implants using ultrasound treatment (sonication) has been initially used for immunofluorescence [31], but has been popularized by Trampuz et al. for culture [32]. The use of dithiothreitol to dislodge biofilm bacteria from implants has been advocated with contradictory results [33–35] when compared to culture or sonication. An independent meta-analysis [36] did not find a significant difference between the two methods, and further studies would be warranted to compare the performance of dithiothreitol and sonication. Extensive literature has described the increased sensitivity of implant sonication compared to tissue culture [37], but most recent publications using mechanized disruption of tissue samples achieve comparable results [38]. The combination of implant-retrieved biofilm and periprosthetic tissue cultures seems to further increase diagnostic yield [1,20].

Due to the diversity of organisms present in PJIs, aerobic, anaerobic, and carbon dioxide atmospheres should be used. Solid media in aerobic, anaerobic, and 5% carbon dioxide should be used for the culture of periprosthetic tissue samples and synovial fluid. It is unnecessary to routinely use fungal and mycobacterial growth media [39,40] and should only be performed in high-risk cases or in secondary documentation of a culture-negative PJI. Broth enrichment significantly enhances diagnostic yield over solid media [21], although discrepant studies [41,42] emphasize the benefit of larger inocula and minimizing sample handling steps with broth enrichment. The use of blood-culture vials as an enrichment broth has shown a significant improvement in sensitivity [2,20,21,43–45]. There is clear evidence that both aerobic and anaerobic media should be used [43], and the use of resin- or charcoal-free anaerobic blood-culture media is required for the culture of gram-positive anaerobes. *Cutibacterium acnes* in particular requires the combined use of solid and liquid culture media [46,47]. The recommended incubation durations for aerobic media have shown that there is no benefit to pursuing it beyond seven days [21,48], although anaerobic media should be incubated up to 14 days [21,47,49]. Using state-of-the-art tissue processing and high-volume inoculation of blood-culture bottles, a definitive diagnosis can be reached in < 48 hours in a majority of cases [21,43,44].

Question 2: Is there a role for sonication of implants obtained during revision surgery?[2]

Response/Recommendation: The use of sonication of implants retrieved during revision arthroplasty may present potential benefits in improving the detection of infective pathogens. However, further research is needed to validate the efficacy of this technique.

Level of Evidence: Moderate

Delegate Vote: Agree: 94%, Disagree: 4%, Abstain: 2% (Total Consensus, Unanimity)

Rationale

Implant-related infections, including periprosthetic joint infections (PJIs), remain a major cause of failure and morbidity after orthopedic surgeries, particularly in the context of revision procedures [50,51]. A two-stage exchange arthroplasty is the most commonly employed treatment protocol for chronic infection of total joint arthroplasties. The diagnosis of PJIs is complicated by the presence of biofilms, which protect bacteria from conventional antibiotic therapies and immune responses [52,53]. The ability to reliably identify the presence of biofilms on retrieved implants or cement (polymethyl methacrylate) spacers can tremendously impact patient management, including the decision to perform additional surgical procedures or to tailor the delivery of effective antibiotic therapy.

Sonication, which involves the use of high-frequency sound waves to dislodge adhered pathogens from surfaces, has gained attention as a potential tool for improving the detection of biofilms on implants or cement spacers [54–64]. Sonication of the implants retrieved during revision total joint arthroplasty is an option currently available as an adjunct to tissue cultures to detect the adhered microorganisms that colonize the implants [54–64]. Studies indicate that sonication of explanted implants can increase the detection of pathogens and thus predict persistent infection compared to traditional intraoperative culture methods, which may fail to detect biofilm-related infections

[2] These authors contributed to Question 2: Adam M. Gordon, Dina Raafat, Michael A. Mont, Stergios Lazarinis, Maria Eugenia Portillo, Elena De Vecchi, Li Cao

[63,65]. Multiple studies have shown that sonication is as specific as, but more sensitive than, traditional cultures in detecting pathogens on orthopedic implants [64,66–71]. In addition, sonication of removed implants from patients undergoing revision surgery increased the detection of microbial growth, particularly in cases of PJI where biofilm is attached but not identified via conventional methods [64,66–71].

The utilization of sonication as an adjunct to PJI diagnostics is reasonable [72]. Biofilm-related infections are notoriously difficult to treat due to the protection biofilms offer against antibiotics and the immune system [52,53]. An accurate method to efficiently detect microbial growth and biofilm formation on implants after revision surgery is highly desirable to avoid placing a new prosthesis in an eventually infected environment [73]. The ability to more accurately identify potential infections during revision surgery has the advantage of guiding the surgeon to a more effective and targeted treatment, possibly leading to better patient outcomes. Studies have highlighted that the combination of sonication with tissue culture could improve the identification of infections that would otherwise have been assigned to aseptic revisions, enabling a more fitting antibiotic treatment and avoiding unnecessary surgical procedures [74].

While sonication has shown promise in improving diagnostic accuracy, its role in routine clinical practice is not yet fully established [75]. In a meta-analysis of 12 studies, the pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio for detecting PJI by using sonication fluid cultures were 0.82 (confidence interval (CI), 0.76 to 0.87), 0.94 (CI, 0.85 to 0.98), 14.2 (CI, 5.4 to 37.8), and 0.19 (CI, 0.14 to 0.25), respectively, for joint arthroplasty [63]. Sonication techniques are not universally utilized and may require additional training and equipment [76]. Moreover, some studies suggest variability in its effectiveness depending on the type of implant, the pathogens involved, the specimen utilized for sonication (implant versus spacer), and the methods used for sonication. It has been reported that sonication works particularly well on detecting infections in certain types of metal implants, such as titanium or chrome cobalt, but has been less effective for others, such as ceramic, cement spacers, or other composite materials [77].

In addition, while sonication has the potential to reduce the incidence of undiagnosed infections, it does not address the underlying subsequent challenges of treating chronic biofilm-related infections. Chronic biofilm-related infections are highly resistant to standard treatments, and new therapeutic strategies, such as biofilm-disrupting agents, are needed in conjunction with better diagnostic tools like sonicatio to improve patient outcomes. Therefore, while sonication may be an initial tool for detection, the subsequent treatment of infection remains. Also, the role of sonication in aseptic revisions appears to have lower clinical value, as the sensitivity and specificity of predicting future PJI are only moderately successful [78–80].

In conclusion, sonication of explanted implants obtained during revision surgery seems to be a reasonable approach to enhance the detection of biofilms and improve the diagnosis of PJIs. While studies support its utility with a high sensitivity and specificity equal to or superior to conventional tissue cultures, further research is needed to refine and standardize protocols, address variability in effectiveness, and evaluate its impact on clinical outcomes. In addition, sonication should be considered as an adjunct rather than a sole diagnostic approach. This technique should be part of a broader approach to the management of infected implants, including improved infection prevention strategies and targeted antibiotic treatments. However, more prospective research is needed to develop standardized protocols for comparison across studies.

Question 3: How can we distinguish pathogenic microbes from normal microbiota in the musculoskeletal system?[3]

Response/Recommendation

Several methods can be utilized to distinguish pathogenic microbes from normal microbiota. Inflammatory status with reference to the International Consensus Meeting (ICM) criteria should be considered. Low diversity and predominance of a virulent microorganism in a microbiome might suggest the microbe to be a pathogen. Microorganisms with genes and traits associated with virulence could be deemed as pathogenic. Metatranscriptomics, a novel technology, might also help differentiate pathogens from commensals.

Level of Evidence: Limited

Delegate Vote: Agree: 81.7%, Disagree: 9.2%, Abstain: 9.2% **(Super Majority, Strong Consensus)**

Rationale

Conventionally, closed anatomical spaces and structures of the musculoskeletal system were believed to be sterile, and the presence of a microorganism was considered abnormal, suggesting infection. However, microorganisms not grown in culture studies could be detected nowadays due to recent advances in nucleic acid sequencing technologies like next-generation sequencing (NGS) [81]. An increasing amount of evidence suggests that microbiomes, in fact, exist in musculoskeletal spaces such as joints [81–85], muscles [86], and intervertebral discs [87,88]. Origin of these microbiomes may be attributed to translocation of organisms from other systems such as the gut, skin, and nasopharyngeal space [83,85,89].

Until now, when an organism was cultivated in a certain musculoskeletal space, a sensitive antimicrobial regimen was administered, and surgical debridement was performed if necessary for infection control. If infection is suspected clinically but, culture is negative, NGS, which is reported to be more sensitive than culture [81,90–93], can be used to identify the causative organisms. However, it is not clear against which organisms the treatment should be undertaken when a microbiome with different microorganisms is detected through NGS. Whether to diagnose the situation as a monomicrobial or polymicrobial infection and initiate antimicrobial treatment would be a crucial decision. Excessive administration of multiple antibiotic regimens would result in overtreatment, possibly imposing selective pressure promoting the emergence of multidrug-resistant organisms and causing adverse reactions to the host, while infection control would be inadequate with undertreatment. There is an unmet need for methods to differentiate a pathogen from normal microbiota in a microbiome.

Infection can be defined as the invasion and growth of a microorganism in the host, causing an inflammatory reaction. If the detected organism induces a marked inflammatory response by the host, it could be determined to be a pathogen. In the presence of a normal microbiome, the development of infection in the musculoskeletal system could also be understood as a certain organism being dominant or proliferative enough [94] among others, to break the balance in the corresponding microbiome and cause excessive inflammation. The virulence of the pathogens may result from their genomes. In this article, we propose several ways

[3] These authors contributed to Question 3: Kee Soo Kang, Nathanael Heckmann, Javad Parvizi, Emanuele Chisari, Wenming Zhang, Mohammad Ali Enayatollahi, Fernando A Lopreite, Göksel Dikmen, Chong Bum Chang

to differentiate pathogens from commensals by reviewing the literature. Although normal microbiota may sometimes become pathogenic in immunocompromised hosts, we will mainly focus on hosts who have a healthy immune system.

The International Consensus Meeting (ICM) criteria for periprosthetic joint infection (PJI) could aid in setting a threshold for inflammatory response caused by infection. In addition to the culture studies, the ICM criteria include inflammatory markers of the serum and the synovium, which reflect host inflammation caused by the organism. When it is not categorized as infection according to the ICM criteria, the aseptic loosening might be attributed to mechanical and tribological causes such as polyethylene wear, metallosis, and instability. However, since native joint has a microbiome, microbes might still be detected with NGS in the aseptic condition according to the ICM criteria. In this situation, the detected organism should not be interpreted as a pathogen unless there is supporting evidence of an inflammatory response meeting the ICM criteria.

The composition of the microbiome is reported to be markedly different between the infection- and the noninfection groups. Whereas a specific causative organism becomes dominant in the microbiome of PJI, microbiomes in aseptic loosening or non-PJI are known to be relatively balanced and have higher diversity [91,95]. Li et al. categorized periprosthetic microbiomes into four types according to the dominant species in the random forest model: *Staphylococcus*, *Pseudomonas*, *Escherichia*, and *Cutibacterium* types. They reported that more severe inflammation was observed in the *Staphylococcus* and the *Pseudomonas* types, and they were more likely to be diagnosed as PJI than the *Escherichia* and the *Cutibacterium* types. The authors insisted that the more virulent *Staphylococcus* species may be more likely to cause infection than the *Cutibacterium* species. Also, the diversity in the *Cutibacterium* type was higher than that of the *Staphylococcus* type [91]. In a study by Fernández-Rodríguez et al., *Proteobacteria* were dominant throughout the native nonosteoarthritic, osteoarthritic, and aseptic revision groups, while the relative abundance of *Staphylococcus* increased in the septic revision group, surpassing the proportion of *Proteobacteria* [83]. In a study by Torchia et al., *E. coli* was also dominant in native uninfected osteoarthritic knees. Although these studies suggest the enteric origin of the joint microbiome, geographical or hospital differences in the composition of the baseline microbiome should also be taken into account [81,83,85]. Predominance of the detected organism and disrupted diversity of the native microbiome could be indicators to decide whether it is a pathogen or not.

Similar results were reported for the microbiomes of the diabetic foot. In a study comparing skin microbiomes of diabetic feet with or without ulcers, the diabetic foot ulcer group showed lower bacterial diversity, species richness, and evenness than the group of diabetics without foot ulcers and the healthy control group. Notably, *Pseudomonas* species, which is known to cause delayed wound healing, was prevalent in the diabetic foot ulcer group [96]. The difference in the microbial composition was also observed between the feet of diabetic patients who had healed and unhealed ulcers. The presence of *Bacteroidales* and *Streptococcaceae* was observed in ulcers that did not heal, while *Actinomycetales*, which are known to secrete antimicrobial metabolites, and *Staphylococcaceae* were associated with healed ulcers [97].

Certain genes or traits could help differentiate pathogens from normal microbiota. Although there are conflicting findings that no significant correlations exist between specific genes and pathogenicity of the organism, microbes like *S. epidermidis* [94,98] and *C. acnes* [99], which are well known as normal flora, might cause infection if they have genes associated with virulence, such as antibiotic resistance and biofilm formation. These genes are known to have been transferred by the mechanism of horizontal and vertical gene transfer [100]. Sequencing types (ST) 2, ST5, and ST215 of *S. epidermidis* determined by multi-locus sequence typing were associated with PJI [98,100–102]. For example, ST2, which is the most frequent sequencing type in PJI due to *S. epidermidis*, is positive for the *ica* operon, insertion sequence IS*256*, and methicillin resistance [98]. The *ica* operon is related to polysaccharide synthesis of the extracellular polymeric substances, causing biofilm formation [102–104]. IS*256* is associated with the regulation of biofilm formation and antibiotic resistance [100]. *S. epidermidis* strains in the PJI group were more resistant to antibiotics than those of the noninfection group [98,102], multidrug resistant [100,101,104], and less susceptible to compounds used for prevention of PJI, namely, beta-lactams, aminoglycosides, and chlorhexidine [100]. Moreover, when infection and asymptomatic carriage groups were compared, elicitation of inflammation in blood reflected by serum interleukin 8 was significantly higher with *S. epidermidis* isolates from infection [94]. In contrast, *embp* and *ses* genes were more frequent in commensal than in PJI isolates of *S. epidermidis* [104]. *S. aureus* strains that strongly produced biofilms were associated with unresolved infection compared with non- or weak biofilm producers [102]. Hemolytic strains of *C. acnes* showed higher inflammatory response and clindamycin resistance than nonhemolytic strains [105]. The presence of hyaluronate lyase genes encoding enzymes for degradation of the host extracellular matrix contributed to the virulence of *C. acnes* as well [99].

Similar findings were reported for pressure ulcers and diabetic foot infections. Microorganisms causing infection in pressure ulcers after spinal cord injury showed antimicrobial resistance [106]. In polymicrobial diabetic foot infections, the chance of amputation increased if antibiotic resistance genes and genes related to biofilm formation and bacterial virulent factors were present [92]. Therefore, if the detected organism has certain types of pathogenic traits or genes, the likelihood that it is a pathogen increases. In the future, the development of a library of genes causing pathogenicity would be helpful in differentiating pathogens from normal microbiota.

Transcriptional activity may also reflect the organism's pathogenic potential. Metagenomics is the study of the structure and function of the entire nucleotide sequences investigated from all the organisms in a given space. Since metagenomics detects every DNA of the sampled community, profiles of dead or inactive organisms may also be detected. Metatranscroptomics, alternatively, can aid in detecting transcriptionally active or functional genes because it detects messenger RNA [95]. In a study comparing 16S rRNA amplicon sequencing, metagenomics, and metatranscriptomics in a PJI population, metatranscriptomics could differentiate infection from noninfection better than the 16S rRNA amplicon sequencing and the metagenomics [107]. Because there are only a few studies utilizing RNA-based sequencing in the PJI diagnosis, further studies accommodating metatranscriptomics are needed to verify the strength of this diagnostic tool.

Conclusions

Distinguishing the pathogen from normal microbiota in the musculoskeletal system is an important but unresolved question. We recommend that clinicians refer to the inflammatory status at first to decide whether the situation itself is an infection or not, with the guidance of the ICM criteria. A low-diversity microbial community composed of high-virulence organisms might suggest the detected microbes are pathogens rather than commensals. Specific genes associated with antimicrobial resistance and biofilm

formation could reflect the virulent nature of the microbe. Metatranscriptomics, which is an emerging diagnostic method, might also help find transcriptionally active organisms causing infection. We look forward to the following studies dealing with this topic.

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The Journal of Arthroplasty 41 (2025) S164–S169

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

General Topics

2025 ICM: Mycobacterium

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ARTICLE INFO

Article history:
Available online 25 October 2025

Keywords:
mycobacterial infection
periprosthetic joint infection
risk factors
antimicrobial therapy
Mycobacterium tuberculosis
nontuberculous mycobacteria

Question 1: What are the risk factors for the development of mycobacterial infections?[1]

Response/Recommendation

Patients who are immunocompromised, receiving long-term corticosteroid or immunosuppressive therapy, have multiple medical comorbidities, have a history of either pulmonary or extrapulmonary tuberculosis, or have a history of repeated surgeries are at increased risk of developing mycobacterial periprosthetic joint infection.

Level of Evidence: Limited

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to 10.1016/j.arth.2025.08.037.

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https://doi.org/10.1016/j.arth.2025.08.037
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Table 1
Summary of the Included Studies.

Author	Year	Country	Study Design	No. Of Patients	Hip/Knee PJI	Pathogens
Meyssonnier et al. [2]	2019	France	Retrospective study	9	Hip	*M. tuberculosis*
Jitmuang et al. [4]	2017	Thailand	Retrospective study	16	Hip, knee	*M. tuberculosis* and rapidly growing mycobacteria
Maimaiti et al. [6]	2023	China	Retrospective study	7	Hip, knee	Nontuberculous mycobacteria
Pring and Eckhoff [7]	1996	USA	Case report	1	Knee	*M. Chelonae*
Brown et al. [8]	2008	USA	Case report	1	Hip	*M. tuberculosis* and *M. Chelonae*
Buser et al. [23]	2019	USA	Retrospective study	9	Hip, knee	*M. goodii* and *M. fortuitum*
Cansü et al. [9]	2011	Türkiye	Case report	1	Hip	*M. tuberculosis*
Cheung and Wilson [10]	2008	Australia	Case report	1	Knee	*M. fortuitum*
Eid et al. [24]	2007	USA	Retrospective study	8	Hip, knee	Rapidly growing mycobacteria
Harwin et al. [11]	2013	USA	Case report	1	Knee	*M. tuberculosis*
Henry et al. [12]	2016	USA	Case report	2	Hip, knee	Rapidly growing mycobacteria
Kim et al. [13]	2017	South Korea	Case report	2	Knee	Rapidly growing mycobacteria
Malhotra et al. [14]	2017	India	Case report	1	Hip	*M. tuberculosis*
Marschall et al. [15]	2008	Switzerland	Case report	1	Knee	*M. tuberculosis*
McLaughlin et al. [16]	1994	USA	Case report	1	Hip	*M. avium intracellulare*
Porat and Austin [17]	2008	USA	Case report	1	Knee	*M. fortuitum*
Rodari et al. [18]	2020	Italy	Case report	1	Hip	*M. xenopi*
Saccente [19]	2006	USA	Case report	1	Knee	*M. fortuitum*
Dos Santos et al. [20]	2023	Brazil	Case report	1	Knee	*M. senegalense*
Shanbhag et al. [21]	2007	UK	Case report	1	Hip	*M. tuberculosis*
Wang et al. [22]	2007	Taiwan	Case report	1	Knee	*M. tuberculosis*
Hwang et al. [25]	2021	South Korea	Retrospective study	10	Knee	*M. tuberculosis* and *M. Fortuitum*
Peng et al. [26]	2022	Taiwan	Retrospective study	8	Hip, knee	*M. abscessus* and *M. Chelonae*

Delegate Vote: Agree: 89.9%, Disagree: 3.6%, Abstain: 6.5% (Super Majority, Strong Consensus)

Rationale

Mycobacterial infections in periprosthetic joint infection (PJI) are rare and occur infrequently [1–4]. The mycobacterial species associated with PJIs can be classified into two groups. The first is the *Mycobacterium tuberculosis* complex, a pathogen predominantly associated with late-onset chronic PJI [5]. The second group, nontuberculous mycobacterial (NTM) infections, is further subdivided into two categories. The first category, rapidly growing mycobacteria, includes *M. chelonae*, *M. abscessus*, *M. fortuitum*, *M. smegmatis*, and *M. peregrinum*, which are recognized as major pathogens in early-onset PJI. The second category, slow-growing mycobacteria, comprises species such as *M. avium intracellulare*, *M. kansasii*, and *M. gordonae* [6]. As mycobacterial infections are an uncommon cause of PJI, diagnostic investigations for their identification are not routinely performed. Nevertheless, in culture-negative PJI cases, atypical microorganisms, particularly mycobacteria, should be considered, and proper diagnosis requires submitting a sample for specialized culture [7]. Therefore, a thorough understanding of the risk factors associated with these infections is essential for accurate detection and effective management.

A systematic review was conducted with inclusion criteria restricted to English-language original articles, including case reports, case series, and retrospective or prospective clinical studies on patients who have PJI of the hip or knee caused by mycobacterial infections, specifically those that identified associated risk factors. A comprehensive literature search of the PubMed and Scopus databases retrieved 1,516 abstracts. After the initial screening, 53 studies were selected for full-text review, of which 23 met the eligibility criteria and were included in the final assessment. The total number of patients across the included studies was 85. Of these, 16 studies were case reports, comprising 18 patients [7–22], while the remaining seven were retrospective studies, involving 67 patients [2,4,6,23–26] (Table 1).

Patients who have compromised immune status are at increased risk of mycobacterial infections, particularly those who have inflammatory joint diseases or autoimmune disorders undergoing chronic corticosteroid therapy or immunosuppressive treatment [4,8,14,17]. In addition, individuals with several medical comorbidities, such as diabetes, peripheral vascular disease, chronic obstructive pulmonary disease, chronic liver disease, cirrhosis, and renal insufficiency are also at elevated risk [18–20]. Hwang et al. [25] reported that 70% of patients who had mycobacterial PJI in their series following primary total knee arthroplasty were classified as American Society of Anesthesiologists III or IV. Furthermore, systemic immunosuppression due to HIV infection is another major factor predisposing individuals to atypical infectious diseases, including mycobacterial infections [15,16,26].

A prior history of extrapulmonary or pulmonary tuberculosis may be recognized as a risk factor for PJIs caused by *M. tuberculosis*, as these infections may spread hematogenously and reactivate after a quiescent infection, particularly in individuals who have compromised immunity [2,11]. Wang et al. [22] reported a case of a patient who had a prior diagnosis of pulmonary tuberculosis one year before developing chronic knee PJI, in which cultures from debridement yielded *M. tuberculosis*. Similarly, Meyssonnier et al. [2] documented five cases of tuberculous hip PJI in patients who had a prior history of pulmonary, genitourinary, or osteoarticular tuberculosis. A systematic review by Kim and Kim [27] demonstrated that 20% of patients who had *M. tuberculosis* knee PJI in their evaluation had a history of tuberculosis infection. Moreover, some patients who have tuberculous PJI were found to have concurrent disseminated tuberculosis affecting other organs at the time of PJI diagnosis [2].

Surgical factors, particularly multiple procedures on the same joint, may increase the risk of mycobacterial infections. Cansü et al. [9] reported a case of subcutaneous abscess at the incision site following total hip arthroplasty (THA) caused by *M. tuberculosis*. The patient had previously undergone four hip surgeries for the treatment of developmental hip dislocation and later received THA before developing the infection. They hypothesized that decreased local circulation and immune response due to fibrosis from multiple prior surgeries may have contributed to the establishment of the infection. Similarly, Maimaiti et al. [6] demonstrated that, in addition to poor health status, multiple comorbidities, or immunocompromised conditions, multiple surgical interventions are major risk factors for mycobacterial PJIs following THA and total knee arthroplasty.

Question 2: What is the optimal antimicrobial treatment for patients who have orthopaedic infections caused by *Mycobacterium tuberculosis*?[2]

Response/Recommendation

Rifampin-based four-drug regimen (isoniazid, rifampicin, pyrazinamide, and ethambutol) is recommended for treating drug-susceptible musculoskeletal tuberculosis. We recommend expert consultation with an infectious disease specialist and/or a clinical microbiologist for treating drug-resistant musculoskeletal tuberculosis.

Level of Evidence: Strong

Delegate Vote: Agree: 97.4%, Disagree: 0%, Abstain: 2.6% (Total Consensus, Unanimity)

Rationale

Musculoskeletal tuberculosis accounts for approximately 10% of all extrapulmonary tuberculosis cases. The main issues in tuberculosis are its insidious onset and nonspecific presentation, which make it challenging to establish a diagnosis and thus delay the treatment.

Rifampicin-based treatment regimen for six to nine months has been recommended by several guidelines, such as the American Thoracic Society, the Centers for Disease Control and Prevention, and the World Health Organization, to treat drug-susceptible musculoskeletal (extrapulmonary) tuberculosis infection [28–30]. The four-drug regimen (isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E)) has been demonstrated by a series of randomized trials on tuberculous spondylitis management [31]. These data and those from pulmonary tuberculosis treatment have been used to develop regimen recommendations for musculoskeletal tuberculosis. The World Health Organization recommends treatment in two phases: an intensive phase for two months and a continuation phase for an additional of at least four months in musculoskeletal tuberculosis [30]. Other viable recommendations are to use a non–rifampin-based regimen for 18 months for drug-susceptible diseases [32,33].

Despite these recommendations, there are considerable variations in antituberculosis agents used among the published studies. Although some are using the recommended four-drug regimen, there are some studies that were using a three-drug regimen (HRE or HRZ) or even a two-drug regimen (HR) from the start. The possible reason behind this variability are drug-related intolerances, adherence to local/national guidelines, and drug resistance. The duration of treatment among previous studies was also varied, ranging from six to 18 months, as the optimal duration for musculoskeletal antituberculosis treatment still remains uncertain [34].

In the presence of a drug-resistant tuberculosis strain, detailed history on previous medication regimen and drug resistance profile should be obtained and considered to design a personalized regimen for the patients. Streptomycin, another first-line antituberculosis drug, may be added if the patient relapses after a full-course treatment or has a history of incomplete treatment with a first-line four-drug regimen. Drug susceptibility testing should be performed whenever available in such cases to determine the resistance profile. Levofloxacin, a second-line antituberculosis drug, was used in some cases where isoniazid resistance/toxicity occurred [35].

Periprosthetic joint infection caused by *M. tuberculosis* is an emerging problem with fewer than 200 cases reported. Studies reported were case reports and case series with a wide variability of treatments performed, including conservative (no surgery), surgical debridement, resection arthroplasty, and one- or two-staged revision. However, most of them were using the recommended rifampin-based four-drug antituberculosis regimen, and some were using a three-drug combination by excluding the ethambutol [36,37]. Few earlier cases had a successful outcome without using rifampin in their regimen; however, they needed to combine their treatment with resection arthroplasty [38–40]. The duration of treatment is still controversial; some experts recommend extending the duration of treatment to 12 to 18 months in the setting of extensive orthopaedic hardware [29,37]. A more recent study by Aunon et al. stated that nine months is the minimum breakpoint to obtain a good outcome. However, these results should be considered carefully because of the limited number of cases available [1].

Question 3: What is the optimal antimicrobial treatment for patients who have orthopaedic infections caused by nontuberculous mycobacteria (NTM)?[3]

Response/Recommendation

There is no universal optimal antimicrobial treatment for orthopedic infections caused by nontuberculous mycobacterium. We recommend expert consultation with infectious disease specialists and clinical microbiologists.

Level of Evidence: Limited

Delegate Vote: Agree: 97.8%, Disagree: 0%, Abstain: 2.2% (Total Consensus, Unanimity)

Rationale

Orthopaedic NTM infection is a rare condition and usually underdiagnosed, especially in developing countries. Diagnosis is often difficult to obtain because of the nonspecific clinical course and difficulty in isolating the pathogen [41]. The standard treatment protocol, including the recommended antimicrobial guideline, is not currently available. Therefore, the treatment recommendation is mostly extrapolated from the existing pulmonary treatment regimen/recommendation. Prolonged antimicrobial therapy, either empiric or based on susceptibility testing in combination with surgical debridement and prosthetic material removal, is recommended [42]. Among 170 mycobacterium species, over 20 species have been identified to cause infections. We proposed the treatment recommendation for some of the most prevalent NTMs in musculoskeletal infections.

Mycobacterium abscessus

Mycobacterium abscessus belongs to the rapidly growing mycobacteria subgroup of atypical mycobacterium along with *M. chelonae, M. fortuitium, M. smegmatis, and M. wolinskyi*. They typically take less than a week to grow on a standard blood agar plate and are associated with early-onset PJI, which may mimic other bacterial PJI presentations [4]. Musculoskeletal *M. abscessus* infection is mostly reported in PJI cases, which were treated with a long-term amikacin-based regimen [43–45]. These treatment guidelines are based on drug susceptibility testing results and should be continued for a minimum of six to 12 months after the last positive culture [46]. Some authors avoided long-term amikacin due to nephrotoxicity concerns and replaced it with imipenem or clarithromycin [47,48].

Mycobacterium avium

Mycobacterium avium infection is the second most common NTM infection of the upper extremity. Clarithromycin or

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azithromycin is the main component for successful treatment for most NTM, including *M. avium*. However, multidrug regimen is needed to prevent macrolide resistance in the long run. Most studies used the combination of either clarithromycin or azithromycin with ethambutol and rifampin as their antimicrobial regimen for treating musculoskeletal infections [49–52]. Quinolones were also used in several studies as an adjunct for a macrolide-based regimen [50,53]. Prolonged antimicrobial therapy for at least 12 months past the last positive culture is recommended.

Mycobacterium bovis

A three-drug combination of rifampicin, isoniazid, and ethambutol is the regimen of choice for most *Mycobacterium bovis* infections, including PJIs. For severe cases, several studies used a four-drug combination by adding moxifloxacin due to *M. bovis*' intrinsic resistance to pyrazinamide [54,55]. Duration of nine to 12 months of antituberculosis medication resulted in a good outcome in most cases.

Mycobacterium chelonae

Mycobacterium chelonae is typically associated with immunocompromised patients, and its presentation in bone has only been reported in fewer than 10 cases [56]. The antimicrobial treatment in those cases was widely varied, ranging from amikacin, clarithromycin, cefoxitin, cotrimoxazole, doxycycline, imipenem, and quinolones [56–59]. Therefore, the antimicrobial regimen should be tailored based on the patient's condition, which is usually found in an immunocompromised condition, along with drug susceptibility testing.

Mycobacterium fortutium

Mycobacterium fortutium is susceptible to agents such as amikacin, cefoxitin, imipenem, and sulfonamides, and resistant to anti-tuberculous medications [60,61]. There is a three- or four-antimicrobial combination therapy with an induction and continuation phase is recommended to prevent the development of resistance. There is no specific combination that has been determined to be optimal [46]. A combination of amikacin and cefoxitin with or without levofloxacin is usually the initial empirical treatment for *M. fortutium* for the first two to six weeks. Then it is usually followed by oral therapy of cotrimoxazole and doxycycline/levofloxacin for six to 12 months [62].

Mycobacterium kansasii

For *Mycobacterium kansasii*, rifampin susceptibility testing should be performed before initiation of treatment. Rifampicin-sensitive *M. kansasii* should be treated with rifampin, ethambutol, and isoniazid or a macrolide (clarithromycin or azithromycin). Alternatively, rifampicin-resistant *M. kansasii* should be treated by a three-drug regimen, which is guided by drug susceptibility testing results and is recommended to be treated by an expert with multidisciplinary team discussion. Duration of treatment should be continued for 12 months after culture conversion [63]. There were two cases of *M. kansasii*-related PJI that were successfully treated with revision arthroplasty and a three-drug regimen (macrolides, rifampin, and ethambutol) [64,65].

Mycobacterium marinum

Mycobacterium marinum is the most common NTM infection in the upper extremity. It is always resistant to isoniazid and frequently also to streptomycin [66]. A combination of two antimicrobials, including cyclines, macrolides (clarithromycin), ethambutol, and rifampin, is recommended for deeper infection [67]. Due to its strong bone-penetrating ability, rifampicin is usually combined with clarithromycin and ethambutol for patients with osteomyelitis or other deep infections [46,66]. The duration of treatment of deeper infections is also longer, at least 7.5 months, compared to the usual four months for skin infections [67].

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The Journal of Arthroplasty 41 (2025) S170–S176

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General Topics

2025 ICM: Use of Antibiotics for Individualized Agents

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Question 1: What is the optimal antibiotic treatment of patients who have implant-associated infections caused by *Cutibacterium acnes*?[1]

Search Method/Results

Searches were conducted in PubMed and Embase using combinations of keyword terms, including "antibiotic*," "arthroplasty," "spine implant*," "orthopedic surgery," "joint prosthesis," "periprosthetic joint infection," "PJI," "*Propionibacterium acnes*," and "*Cutibacterium acnes*." The search initially identified 706 potentially relevant studies. Titles and abstracts were screened independently by two reviewers; 54 studies were selected for an in-depth review, of which 33 were included.

Response/Recommendation

The optimal antibiotic treatment for *Cutibacterium acnes* remains unknown. We recommend expert consultation with infectious disease specialists and clinical microbiologists.

Level of Evidence: Limited.

Delegate Vote: Agree: 88.6%, Disagree: 7.7%, Abstain: 3.7% (Super Majority, Strong Consensus)

Rationale

The role of *Cutibacterium acnes* as the cause of orthopaedic implant-associated infections has been recognized for many decades [1,2]. Prospective cohort studies evaluating the microbiologic epidemiology of periprosthetic joint infections (PJIs) have found 6 to 10% of all cases to be a result of *C acnes* [3,4]. *C. acnes* has been reported to cause infections of almost all orthopaedic implants, but has a particular predilection for shoulder hardware, likely secondary to the high rates of colonization of the axilla [5]. In fact, 31 to 70% of shoulder PJIs are secondary to *C. acnes.* [5] In addition, *C. acnes* is a common cause of shoulder fracture-fixation hardware infections and infections following rotator cuff repair [6]. *C. acnes* is also a commonly encountered cause of latent spinal hardware infection, approaching 20% of cases in some series [7–10]. Despite its increasing recognition as an important pathogen in implant-related infections, the literature pertaining to the optimal antibiotic treatment of *C. acnes* implant infections is very limited; treatment recommendations are primarily guided by *in vitro* antibiotic susceptibility data and small retrospective (and largely heterogeneous) clinical studies [11].

Cutibacterium acnes is sensitive to a broad range of antibiotics, including beta-lactams (e.g., penicillin, cephalosporins, and carbapenems), glycopeptides, clindamycin, linezolid, fluoroquinolones, daptomycin, and tetracyclines [6,9,12,13]. It is intrinsically resistant to metronidazole. However, interpretation and comparison of published *C. acnes* susceptibility data are complicated by differences in or a lack of species-specific breakpoints used. The current Infectious Diseases Society of America guidelines recommend IV penicillin or ceftriaxone as first-line therapy for periprosthetic joint infections and clindamycin (IV or PO) or vancomycin as second-line therapy [14]. Guidelines of implant infections published by the Société de Pathologie Infectieuse de Langue Française (SPILF) suggest amoxicillin, cefazolin, ceftriaxone, or clindamycin [15].

There have been some concerns about changes in the prevalence of resistance to various antibiotics; for example, a large meta-analysis of 39 studies investigating the prevalence of *C. acnes* antibiotic resistance reported the following rates: co-trimoxazole: 9%, doxycycline: 8%, levofloxacin: 6%, ciprofloxacin: 5%, minocycline: 2.5%, and alarmingly, clindamycin: 31%. Major geographic variation was found, as well as temporal trends suggesting rising rates [16]. It is important to note, however, that this meta-analysis, and much of the published data regarding *C. acnes* antibiotic susceptibility, is based on isolates from dermatologic specimens, often in patients undergoing (or failing) antimicrobial treatment for *C. acnes* vulgaris. Isolates from nondermatologic specimens show much lower rates of resistance [17]. A 10-year single-center

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to doi: 10.1016/j.arth.2025.10.100.

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https://doi.org/10.1016/j.arth.2025.10.100
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study analyzing 2,497 *C. acnes* isolates from all anatomic sites, in which 51.9% of specimens were submitted by the orthopaedics department, reported all strains to be sensitive to amoxicillin, ceftriaxone, vancomycin, daptomycin, linezolid, and moxifloxacin. The study also reported that 4.1% of the strains were clindamycin-resistant – but underscoring the importance of the site of specimen acquisition, the authors noted that over half of these clindamycin-resistant strains were from dermatologic samples (and dermatologic samples only made up 21.5% of the total isolates tested), suggesting these specimens may have been impacted by treatment for *C. acne* vulgaris. In additon, 2.2% of the strains were resistant to doxycycline and 1.1% were resistant to rifampin. These findings correlate with smaller studies reporting on clinical specimens taken from infected orthopaedic implants [11,13,18,19]. Even with the lower rates of resistance, however, these studies do emphasize the need to employ antimicrobial susceptibility testing on all clinical *C. acnes* orthopaedic specimens to help guide treatment; most notably, resistance to clindamycin was still found in 2.0 to 9.0% of isolates in these studies.

The body of literature about the efficacy of specific antibiotic regimens for treating *C. acnes* orthopaedic implant infections is limited. Conducting research assessing the treatment of PJIs and other orthopaedic implant infections, regardless of their microbiologic cause, is challenging for many reasons. These uncommon infectious complications require extended follow-up to assess outcomes making it difficult to amass sufficient patients to power studies appropriately. In addition, heterogeneous presentations, variations in approach to complex surgical and antibiotic treatments, and the array of comorbidities make confounding variables challenging to control, prospectively or retrospectively. However, *C. acnes* implant infections, specifically, can be even more challenging to study secondary to both the difficulty distinguishing septic from aseptic failure and, because of its frequent isolation as a contaminant in orthopaedic specimens, the difficulty determining the clinical significance of positive culture results [20].

The available clinical studies of *C. acnes* implant infection are all retrospective in design and are typically small, single-center observational cohorts with historical controls. Only very few of these studies stratify clinical outcomes by the specific antimicrobial treatment, and there are too few to draw meaningful conclusions regarding which regimen is optimal. [21–23]. As expected, most of these studies assessed patients with *C. acnes* PJIs, primarily those of the shoulder. Studies of non-PJI *C. acnes* implant infections are even more difficult to parse, given the lack of accepted diagnostic criteria to differentiate between contaminant and infection. This issue was highlighted in a study by Tai et al. [10]. who reported retrospectively on 55 patients who had been treated for *C. acnes* spinal implant infections. Relapse rates were low, with an annual failure rate of 7.0%. However, 25% of the patients never actually received any antibiotics. A subgroup analysis within this study showed that the failure rate was only slightly higher in the untreated patients as compared to those who received antibiotic treatment; the authors suggested that this finding may indicate their diagnostic criteria, relying mainly on the presence of two or more positive cultures for *C. acnes*, may not have been sufficiently specific.

The role of adjunctive treatment with rifampin for *C. acnes* implant infections remains unclear. *C. acnes* is commonly sensitive to rifampin, but it is not reliably effective as monotherapy [24]. However, rifampin has been demonstrated in both *in vitro* studies and animal models to have excellent efficacy against *C. acnes* biofilm [25,26]. Based on these findings, the British Elbow and Shoulder Society advocated for the addition of rifampin in the setting of retained *C. acnes* hardware infections [27]. But clinical data supporting this approach are lacking. The largest study addressing rifampin-based combination therapy for *C. acnes* reported on the outcomes of 187 patients with *C. acnes* PJIs; 43.3% of the cohort was treated with rifampin-based combination therapy [28]. There were no statistically significant difference in outcomes was reported between the two groups, even after adjusting for surgical treatment (DAIR versus exchange procedure). This finding aligned with the results of several other smaller studies, all of which also showed no benefit with the addition of rifampin [11,29,30]. Of note, only a minority of the patients in these four studies underwent DAIR; most had removal of all infected hardware. Interestingly, a 2022 meta-analysis assessing the role of rifampin in the treatment of *C acnes* PJIs reported, based on the inclusion of two of these studies (Kusejo et al. [28] and Jacobs et al. [29]), that they actually did find a protective effect when rifampin was added, albeit with wide confidence intervals (0.44, 95% CI 0.22 to 0.089) [31]. In an even more recent meta-analysis assessing the effectiveness of rifampin-based combination therapy in a wide array of orthopaedic implant infections, which included all four of these studies, a subgroup analysis found that rifampin-based treatment led to higher cure rates, with an RR of 1.11 (95% CI 1.01 to 1.22, $P = 0.03$), although the authors acknowledged the certainty and quality of the evidence was low [32]. A fifth retrospective study published too recently to be included in either of these meta-analyses found no benefit to rifampin-based combination therapy in 70 patients undergoing exchange arthroplasty for chronic *C. acnes* shoulder PJIs [33].

In conclusion, based on available data, the dose, type, and route of administration of optimal antibiotics for the treatment of orthopaedic-implant infections caused by *C. acnes* remain unknown.

Question 2: What is the optimal antimicrobial treatment for patients who have orthopaedic infections caused by *Kingella kingae*?[2]

Response/Recommendation

Although the optimal antibiotic treatment for *Kingella kingae* remains unknown, the greatest clinical experience is with the use of β-lactams. We recommend expert consultation with infectious disease specialists and clinical microbiologists.

Level of Evidence: Limited (Level IV)

Delegate Vote: Agree: 89.7%, Disagree: 5.1%, Abstain: 5.1% (Super Majority, Strong Consensus)

Rationale

Skeletal infections, particularly in children, present major clinical challenges due to the potential for severe complications and long-term orthopedic disabilities if not promptly and adequately treated [34,35]. *Kingella kingae* has emerged as a dominant pathogen responsible for these infections, especially in children under six years old [36]. The management of these infections is one of the persistent orthopaedic challenges, with varying recommendations for antimicrobial treatments [37]. Previous studies have highlighted the need for effective treatment strategies. Historically, pathogens like *Staphylococcus aureus* and *Haemophilus influenzae* were considered primary culprits. However, increased vaccination coverage has reduced the incidence of infections caused by *H. influenzae*, shifting the focus to *K. kingae*. This pathogen's unique clinical presentation—characterized by a low-grade fever and mild elevation of acute-phase reactants—further complicates diagnosis and treatment decisions [38]. The treatment of these patients is still controversial [39]. Initial administration of intravenous antibiotics and switching to

[2] These authors contributed to Question 2: Arash Aali Rezaie, Ataollah Moshirabadi

oral antimicrobial drugs after improvement of clinical symptoms and reduction of inflammatory markers is the classic treatment approach for these patients [39–42], although some authors suggest just oral treatment [42–45]. Nevertheless, *K. kingae* exhibits resistance to clindamycin and vancomycin and has a high minimal inhibitory concentration for isoxazole penicillins, such as cloxacillin [46]. Given these complexities, selecting optimal antimicrobial therapy to achieve favorable clinical and functional outcomes remains a topic of ongoing discussion. Literature on the antimicrobial treatment of *K. kingae* infections is heterogeneous. Studies have reported varied outcomes based on the type and duration of antibiotic therapy [42,47–50]. By conducting a systematic review, we examined the clinical and functional outcomes, as well as the side effects, of intravenous and oral antibiotic therapy based on the type of antibiotic in patients (771 cases in 53 studies) with skeletal infections caused by *K. kingae*. Based on the results of this systematic review, except for 11 patients, the rest of the cases were reported under the age of six years (the average age of infection was 18 months). Intravenous antibiotic therapy with cephalosporin and oral amoxicillin-clavulanate was the most common antibiotic used to treat skeletal infections caused by *K. kingae* in children under six years of age. In adults infected with *K. kingae*, initial intravenous antibiotic therapy was a common approach, with agents such as cefuroxime [51,52] and ceftriaxone [53] demonstrating efficacy. In the case of multidrug-resistant strains, erythromycin and gentamicin were successfully used to treat these patients [54]. Additionally, Wensley et al. [53] highlighted the critical role of two-stage revision surgery in managing periprosthetic joint infections, while Moussadiq et al. [54] and Christensen et al. [52] reported the use of joint irrigation and arthroscopic drainage in septic arthritis cases.

Conclusions

Most of the orthopaedic infections caused by *K. kingae* occur in children younger than six years old. The most common antibiotics used to treat skeletal infections in children under six years old were intravenous cephalosporins and oral amoxicillin-clavulanate. Intravenous ceftriaxone is commonly used in older patients. The duration of intravenous antibiotic therapy is generally shorter than oral therapy. Although the studies reviewed exhibited heterogeneous results, evidence suggests that both intravenous and oral antibiotic therapies can improve clinical and functional symptoms in the short term. The rate of complications may be lower with oral antibiotic therapy. However, the evidence is still inconclusive, and it is not possible to definitively determine the superiority of one antimicrobial regimen over another for the treatment of skeletal infections caused by *K. kingae*. Prospective studies with larger sample sizes are needed to provide more accurate estimates and establish clear treatment strategies, including optimal treatment duration. All these aspects should be further examined in future research endeavors to enhance clinical decision-making and patient care.

Question 3: What is the optimal antimicrobial treatment for patients who have orthopaedic infections caused by enterococci?[3]

Response/Recommendation

The optimal antimicrobial treatment for patients with ampicillin-susceptible enterococcal infections includes ampicillin or a combination of ampicillin/ceftriaxone. For ampicillin-resistant enterococci, the available options are vancomycin, daptomycin, linezolid, or teicoplanin.

We recommend expert consultation with infectious disease specialists and clinical microbiologists.

Strength of Recommendation: Weak.

Delegate Vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Super Majority, Strong Consensus)

Rationale

Challenges in Treating Enterococcal Infections

Orthopaedic infections caused by *Enterococcus faecalis* and *Enterococcus faecium* are linked to significant morbidity due to their ability to effectively form biofilms, their intrinsic resistance to commonly used antimicrobials such as cephalosporins, and the increasing prevalence of vancomycin-resistant Enterococci (VRE). Up to 64% of *Enterococcus*-related PJIs involve other pathogens, complicating treatment [55]. Only relatively small, retrospective observational studies evaluating antimicrobial therapies for enterococcal bone and joint infection are available [56–63]. These studies are largely noncomparative, meaning that definitive evidence-based recommendations about the superiority of particular regimens cannot be made.

Ampicillin-Susceptible Enterococci (Intravenous Treatment)

Most isolates of *E. faecalis* and some *E. faecium* isolates are susceptible to intravenous ampicillin/penicillin, and these antibiotics would be considered the standard of care for most infections. However, there has been some interest in combination therapies to improve the outcomes for certain difficult-to-treat enterococcal infections, particularly in implant-related infections. The combination of ampicillin and ceftriaxone has demonstrated synergy in the treatment of ampicillin-susceptible enterococcal endocarditis and in *in vitro* checkerboard studies. This synergy is attributed to the fact that each drug had different penicillin-binding proteins (PBPs) as targets (amoxicillin, partially saturated penicillin-binding proteins 4 and 5; ceftriaxone, and penicillin-binding proteins 2 and 3), thus improving the bactericidal effect. However, this effect is likely to be attenuated significantly when the ceftriaxone minimal inhibitory concentration is high, which limits its use with penicillin [64] as well as in biofilm infections, as the synergy is seen largely in the exponential growth phase of bacteria and markedly less in the stationary phase [65]. Although good outcomes have been reported in one small study, there are no comparative studies examining the advantages of this combination therapy over ampicillin or penicillin alone [65–67].

Ampicillin combined with an aminoglycoside has historically been regarded as a beneficial regimen for treating ampicillin-susceptible enterococcal infections due to its bactericidal synergy. Ampicillin disrupts bacterial cell wall synthesis, allowing aminoglycosides to penetrate the cell and inhibit protein synthesis, leading to rapid bacterial elimination. Despite its effectiveness, the emergence of high-level aminoglycoside resistance and aminoglycoside-related nephrotoxicity and ototoxicity have markedly limited its clinical utility, particularly in patients with underlying renal dysfunction. The synergistic bactericidal activity of aminoglycosides may be highly compromised in the setting of orthopaedic infections with local purulence, acidic pH, and under anaerobic conditions [68,69].

Although clinical studies supporting the use of dual therapy are lacking, it may be considered from an *in vitro* point of view, and the relatively high relapse rates observed in enterococcal infections, particularly in the first weeks after surgical debridement, and in those patients in whom the implant will be retained.

Ampicillin-Resistant Enterococci (Intravenous Treatment)

Vancomycin remains a cornerstone in the treatment of ampicillin-resistant enterococci. Its mechanism involves inhibiting

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cell wall synthesis in Gram-positive bacteria. However, its efficacy diminishes significantly in biofilm-associated infections, where enterococci demonstrate increased tolerance [70–74]. Biofilms create a protective environment, reducing vancomycin penetration and activity, leading to suboptimal outcomes.

Daptomycin may be a good alternative option, as it demonstrates better activity within biofilm [75]. It has bactericidal action and its activity relies on disrupting bacterial cell membranes. However, clinical data to support its use in enterococcal infections are lacking, and it has not been shown to have advantages over other antimicrobials in bone and joint infections. Furthermore, EUCAST has not provided breakpoints for daptomycin in enterococcal bloodstream infections due to insufficient evidence [76], and high doses are required to achieve a probability of target attainment above 50% [77]. Thus, careful monitoring to mitigate the risk of myopathy and eosinophilic pneumonia is required [60,66,67,78].

Vancomycin-Resistant Enterococci (VRE)

The VRE strains, particularly *Enterococcus faecium*, often carry the *VanA* or *VanB* resistance genes, which confer resistance to both vancomycin and teicoplanin (especially *VanA*). While some *VanB* strains may retain susceptibility to teicoplanin, its clinical efficacy is unreliable, and it is not considered a first-line treatment for VRE infections.

Daptomycin retains activity *in vitro* against VRE and may have activity in biofilm-associated infections, even though there is a risk of emergence of resistance during therapy. Linezolid is another option for VRE infections, with the advantage of providing an oral option. Initial combination therapy may be considered [77].

Pristinamycin is an oral streptogramin antibiotic that demonstrates activity against many isolates of Enterococcus faecium, including vancomycin-resistant strains (VRE), but not *Enterococcus faecalis*. There are a limited number of studies reporting reasonable outcomes, mostly being used as chronic suppression for orthopaedic infections caused by Gram-positive organisms, including enterococci [79].

Duration of Treatment and Oral Switch

For this recommendation, we have not focused on the duration of antibiotic treatment and the timing for an oral switch. To our knowledge, there are no studies supporting a longer duration of treatment for enterococcal PJIs compared to other microorganisms. An early switch to oral antibiotics can be considered in cases in which an oral antibiotic is available with good bioavailability, which, in general, is not the case for beta-lactam antibiotics, like amoxicillin. For this reason, we recommend an IV period of at least two weeks before switching to oral, which provided that the patient has a good clinical recovery.

Oral Follow-Up

Comparative data on oral follow-up treatment are lacking. Amoxicillin and linezolid are potential options highlighted in the recent recommendations [80]. The EUCAST has not provided breakpoints for amoxicillin in bone and joint infections, as there are concerns about the probability of target attainment within the wild-type population. Based on PK modeling, a dosage of 750 mg x four is preferred [81].

Linezolid inhibits bacterial protein synthesis and has excellent oral bioavailability. However, prolonged use is limited by side effects such as cytopenias, optic neuritis, and irreversible peripheral neuropathy, the risk of which increases with cumulative dose. As there is an interindividual variability in serum levels of linezolid, it requires regular monitoring to mitigate toxicity [82]. Limited retrospective, noncomparative data show reasonable outcomes in bone and joint infections caused by *Enterococcus* [68–71,83]. Despite the challenges, linezolid remains a valuable option in the treatment arsenal for orthopedic infections caused by Enterococci.

Rifampin-Based Regimens

Rifampin is widely used in the management of staphylococcal biofilm-related orthopaedic infections due to its activity against biofilm-associated bacteria. The EUCAST has not provided breakpoints for rifampin in Enterococci, and *in vitro* data on rifampin activity when combined with other agents against biofilm-associated enterococcal infections are conflicting. There is no clinical evidence to support the addition of rifampin in the treatment of enterococcal bone and joint infections [55,75,78,84,85].

Enterococci as Part of a Polymicrobial Infection

Polymicrobial infections involving *Enterococcus* are notably challenging and are associated with significantly higher failure rates compared to monomicrobial infections. A substantial proportion of enterococcal infections, particularly in PJIs, are polymicrobial, further complicating treatment. The coexistence of multiple pathogens creates a synergistic environment that enhances biofilm formation, reducing the effectiveness of standard therapies. Consequently, accurate identification of all infecting organisms is crucial to tailor antibiotic regimens effectively and improve the likelihood of treatment success. In such complex scenarios, combination therapies are frequently necessary to address the diverse microbial population and improve the likelihood of treatment success. Definitive therapy must be guided by the susceptibility profile to optimize outcomes and combat resistance [79,82,83].

Conclusion

Optimal treatment for enterococcal PJIs demands a multidisciplinary approach integrating antibiotic regimens and surgical interventions. There is a lack of high-quality clinical evidence to recommend specific antimicrobial treatments over others, and choices should be guided by antimicrobial susceptibility testing and patient factors. Ampicillin or penicillin remains the first-line intravenous treatment option for the treatment of ampicillin-susceptible Enterococci. Initial combination therapy with ampicillin/ceftriaxone may be considered in selected situations, even though the evidence is limited. Vancomycin can be used for ampicillin-resistant Enterococci or in the setting of penicillin allergy or intolerance. Daptomycin and linezolid are valid options in the treatment of vancomycin-resistant Enterococci. Amoxicillin or linezolid may be considered for oral follow-up. Future research should prioritize the development of biofilm-disrupting therapies, innovative combination regimens, and strategies to address emerging resistance, ultimately improving patient outcomes in these challenging infections.

Question 4: What is the optimal antimicrobial treatment for patients who have orthopaedic infections caused by fungi?[4]

Response/Recommendation

For fluconazole-susceptible *Candida* species, fluconazole is currently the treatment of choice for orthopedic infections. For voriconazole-susceptible *Aspergillus* species, voriconazole is the preferred treatment for orthopaedic infections. We recommend expert consultation with infectious disease specialists and clinical microbiologists.

Level of Evidence: Moderate

Delegate Vote: Agree 91.3%, Disagree 6.0%, Abstain 2.7% (total consensus, unanimity)

[4] These authors contributed to Question 4: Danguole Vaznaisiene, Hyuk-Soo Han, Barend C. Mitton, Atsuhiro Fujie, Nicolas J. Restrepo, Al-Amin Kassam, Emmanuel Gibon

Rationale

Fungal orthopedic infections are uncommon, accounting for approximately 1.3% of periprosthetic joint infections (PJIs), with *Candida* PJIs specifically accounting for > 90% of all fungal PJIs [86]. *Candida* species, in particular *Candida albicans*, are by far the most common pathogen. Co-infection with bacterial species may occur in up to 51.3% of cases [86]. A study by Guan et al. demonstrated that the treatment success rate in nine of 19 in fungal PJI cases with bacterial co-infection, significantly lower than those without [versus 79.0% (45 of 57), $P = 0.017$] [87]. A binary logistic regression model showed that bacterial co-infection and surgical option were the two significant risk factors associated with treatment failure for fungal PJI following hip arthroplasty [87].

Risk factors for fungal PJIs include immunosuppression, systemic disease, repeated surgery, previous *Candida* infection, and extended antimicrobial therapy [86,88]. *Candida* infections are associated with biofilm formation, which plays a key role in the development of orthopaedic infections. Given the infrequency of orthopaedic infections caused by fungi, there are no standard guidelines regarding treatment. The Infectious Diseases Society of America guidelines address *Candida* infections more generally, with some emphasis on orthopedic infections requiring surgical intervention [89]. The current literature contains retrospective cohort studies, case series, case reports, and one prospective cohort study. There are no randomized clinical trials or case-control studies to guide therapeutic decisions.

The two- or one-stage revision arthroplasties are regarded to be the current standard-of-care for the surgical management of fungal PJIs. Debridement, antibiotics, and implant retention (DAIR) with the absence of prosthesis exchange was a major factor associated with failure [86]. The pooled success rate for surgical debridement, spacer implantation, resection arthroplasty, one-stage revision, and two-stage revision was four of eight, three of seven, 11 of 20, 13 of 15, and 23 of 26, respectively, with significant differences between them [87].

Systemic antifungal therapy is administered during the spacer interval between stages of surgery. Treatment options include fluconazole 400 mg (6 mg/kg) PO/IV daily, an echinocandin (caspofungin 50 to 70 mg IV daily, micafungin 100 mg IV daily, or anidulafungin 100 mg IV daily), or lipid formulation amphotericin B (3 to 5 mg/kg IV daily) [89]. Better antibiofilm activity has been demonstrated *in vitro*, but the clinical effect remains under debate. The minimum duration of antifungal therapy after resection should be six weeks, with up to 12 weeks considered in more severe cases; following revision surgery, fluconazole 400 mg IV for 14 days, followed by oral fluconazole (400 mg daily), should be continued for a minimum of six weeks, with the total duration extending up to 12 months or longer, depending on patient response and culture susceptibilities [89–91]. Voriconazole is the treatment of choice for *Aspergillus* spp. orthopaedic infections [92].

With the absence of published literature, there is no evidence to support antibiotic holidays before the second stage. Emerging evidence shows that an antibiotic holiday may, in fact, increase the rate of failure of two-stage exchange, and its role in the management of patients who have chronic PJI undergoing two-stage exchange needs to be reexamined [93,94].

The three-stage revision arthroplasty with prolonged systemic antifungal therapy [95], the addition of antibiotics, including rifampicin (even in the absence of bacterial growth) [96,97], antibiofilm antifungal treatment as initial treatment [3,10], and Amphotericin B added to cement [95,96] showed promising results in some studies but require further investigation to confirm efficacy and safety.

Conclusion

The incidence of fungal PJI is expected to rise, given the increasing amount of joint arthroplasty being performed annually. Although specific guidelines for the management of fungal PJI have yet to be established, important considerations in management include confirmation of the microbiologic diagnosis with antifungal susceptibility testing of fungal isolates, surgical options with two-stage exchange arthroplasty currently favored, the use of antifungal-eluting cement, and long-term systemic antifungal therapy.

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The Journal of Arthroplasty 41 (2025) S177–S190

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

General Topics

2025 ICM: Minimum Biofilm Eradication Concentration (MBEC) Versus Minimum Inhibitory Concentration (MIC)

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Question 1: Should antibiotic administration be targeted toward all organisms isolated by culture in patients who have polymicrobial orthopaedic infections?[1]

Response/Recommendation

We recommend that all known pathogens implicated in human orthopedic infections be targeted with antimicrobials, unless they have been treated adequately by surgery, or they were erroneously identified (i.e., culture contaminants), or a compelling reason is found that antimicrobial therapy is not necessary in specific scenarios.

Level of Evidence: Limited

Delegate Vote: Agree 88%, Disagree 9%, Abstain 3% (super majority, strong consensus)

Rationale

Orthopaedic infections of native tissues, as well as those involving prosthetic materials, are defined as polymicrobial when at least two different organisms are identified in tissue samples or fluid samples. The frequency of polymicrobial orthopedic infections can range from approximately 10 to 25% in periprosthetic joint infections (PJIs) to approximately 30% of post-traumatic osteomyelitis, to greater than 80% in diabetic foot infections (DFIs) [1].

A broad range of microbes have been reported to cause orthopedic infections, the most common and consequential of these being various genera of bacteria, including low virulence organisms (e.g., *Cutibacterium spp*., *Corynebacterium spp*., and *Enterococcus spp*.), as well as fungi [2–4]. In terms of frequency, individual reports vary, though Staphylococci and Streptococci, along with other Gram-positive bacteria, are the most frequent, followed by Gram-negative bacteria and fungi [5].

Remarkably, the otherwise heterogeneous reports on the success rates of treatment in orthopaedic infections almost uniformly cite "polymicrobial" as a major predictor of worse outcomes with or without prosthetic material involvement [6–11]. The literature is not clear on whether the likelihood of developing a polymicrobial infection is higher in less immunologically competent patients or whether there are microbial interdependencies potentiating virulence factors of individual pathogens at play. Alternatively, it is not clear whether the host characteristics, the microbiology, the selection, the pharmacokinetics, and the pharmacodynamics of the regimens used, or a combination thereof determine the causative pathway toward poorer clinical outcomes [12,13].

Importantly, due to the nature of microbiological culture techniques and their constraints, many organisms are hard to grow in cultures even without additional masking via the overgrowth of dominant populations [14]. This can lead to missed microbiological diagnoses and a lack of specific antimicrobial coverage, especially in polymicrobial infections where sub-isolation of all individual species is often technically challenging if not impossible. Not uncommonly, patients experience treatment failures of seemingly appropriate regimens, and the subsequent cultures reveal a previously unidentified pathogen. Whether the pathogen was a new infection, it represented an unidentified minority population in the original infection and is a subject of debate, though both scenarios are certainly plausible depending on the circumstances.

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.098.

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https://doi.org/10.1016/j.arth.2025.10.098
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To answer the question posed above, we conducted a comprehensive literature review based on the MeSH terms developed by our librarians and applied them to PubMed and Embase databases. The search yielded 372 articles, of which 54 were excluded as duplicates and 206 were deemed irrelevant based on abstract reviews alone. We subjected 112 articles to full-text reviews and selected only 10 for additional scrutiny, as none, including the selected 10 documents (except for a single abstract), were designed to or specifically addressed relevant comparisons of clinical success with and without antimicrobial therapy of all pathogens in polymicrobial orthopedic infections.

All reviews were performed with the assistance of Covidence software, and individual documents in each stage (i.e., abstract review, full-text review, and data extraction) were reviewed by a minimum of two investigators with a resolution of discrepant judgments regarding suitability by the group liaison (MK) [15]. (Figure 1) [16] In our review, we found only one abstract explicitly documenting that a known pathogen of human osteoarticular infections, in this case *Corynebacterium striatum*, improved in three of 12 cases of polymicrobial infections without being targeted by antimicrobials [17]. Even in this document, the authors suggest that effective surgical source control may have been the determining factor.

All other identified studies, including the 10 selected for additional scrutiny, were unfortunately unrevealing with respect to our question of interest. A study by Cordero-Ampuero et al. was the only study reporting better outcomes with polymicrobial infections than monomicrobial ones in a small cohort of patients [18]. Drexler et al. reported a fair amount of detail on antimicrobials used systemically and topically (e.g., in surgical spacers), yet

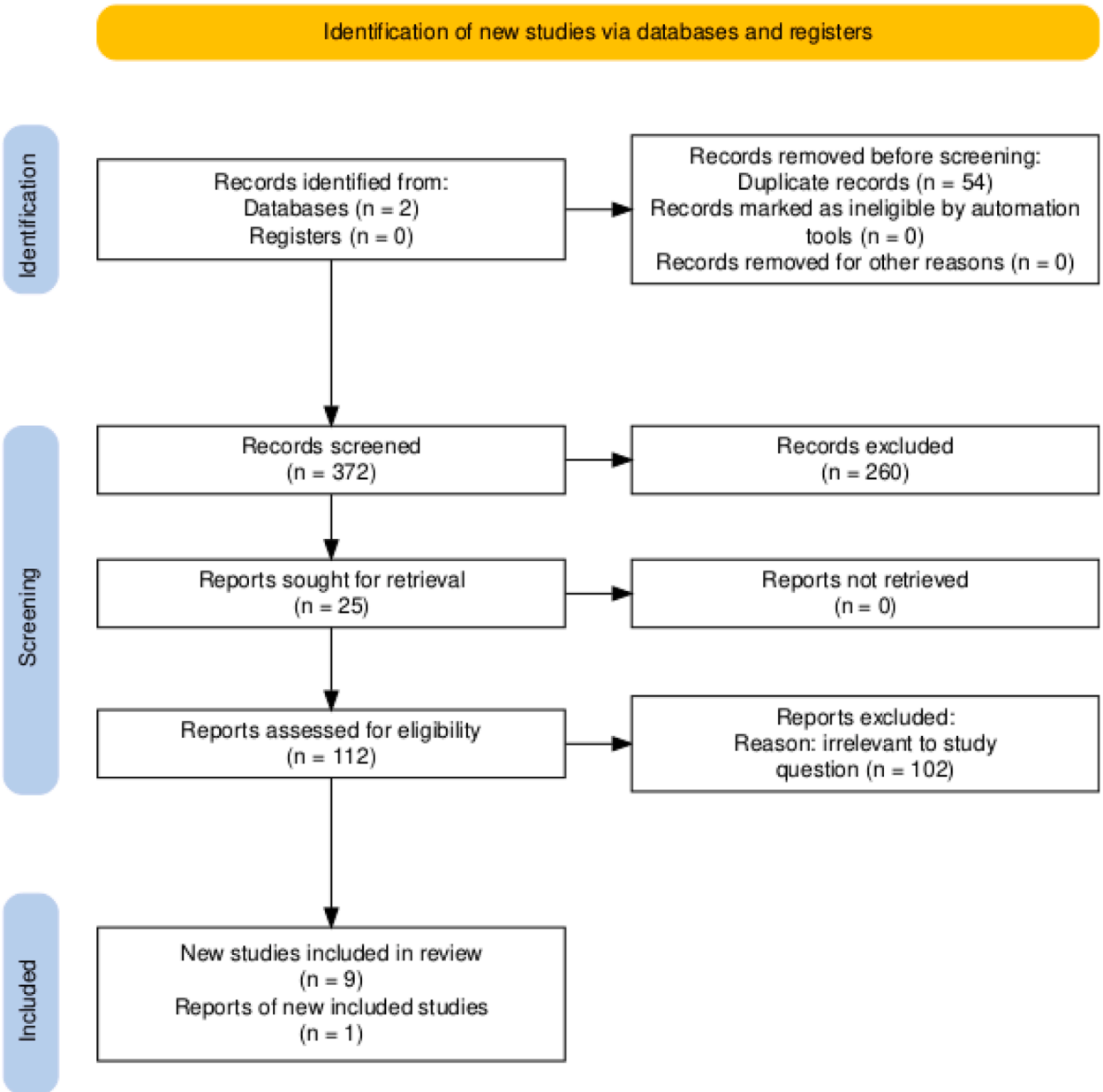

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram.

the study design and the resulting report did not reveal whether all pathogens were targeted and how that may have affected the outcomes [19]. We encountered similar problems with all the remaining studies selected for data extraction, despite the fact that these have mostly been chosen based on documenting the most amount of detail on the pathogens identified and/or on the regimens used for treatment, and some looked at different types of orthopedic infections [6–9,20–22].

In conclusion, and in the absence of concrete evidence to the contrary, we recommend that pathogens identified in an orthopedic infection be all treated with antimicrobials unless they have been treated adequately by surgery, or they were erroneously identified (i.e., culture contaminants), or a compelling reason is found that antimicrobial therapy is not necessary in specific scenarios (Figure 2).

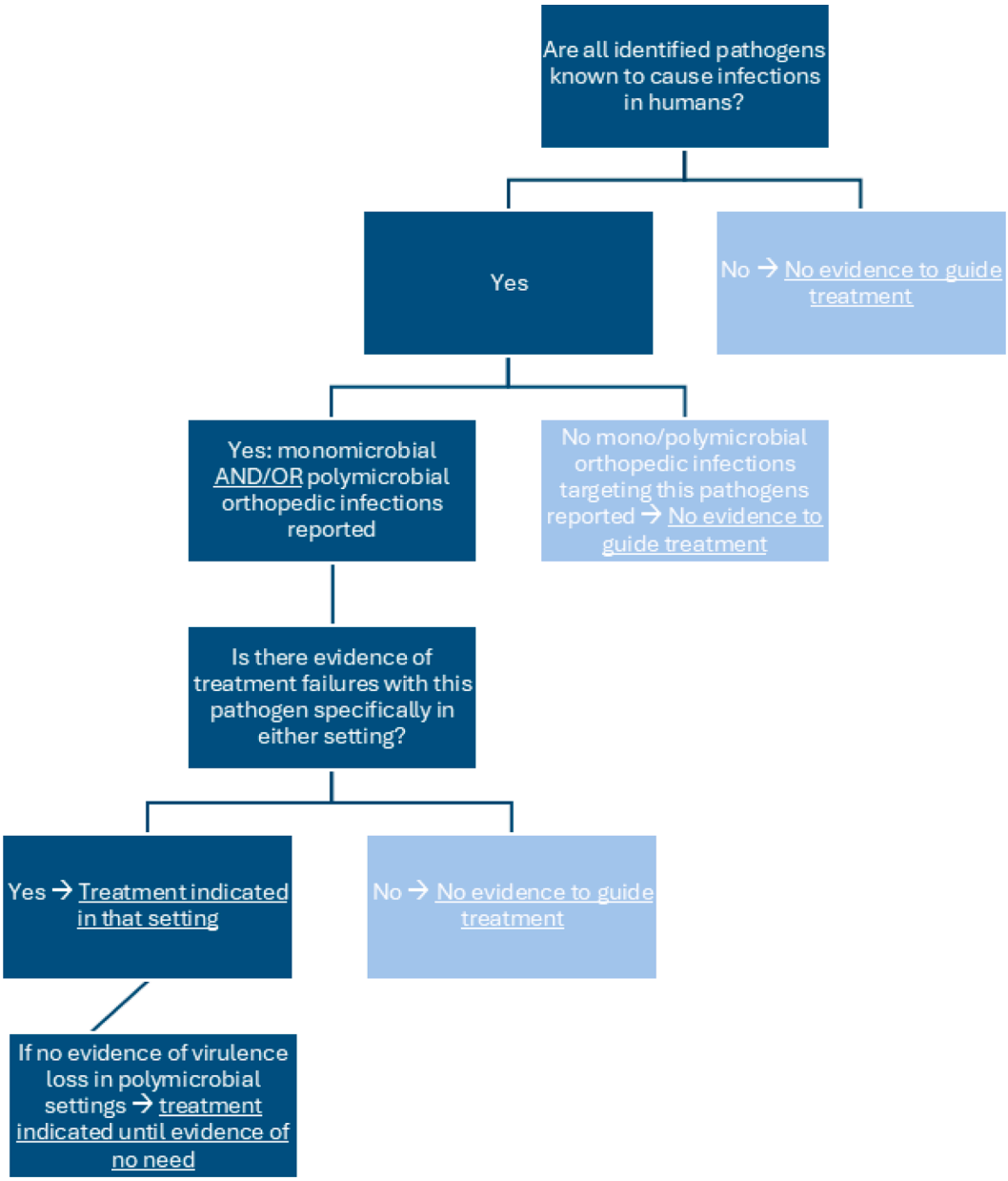

Figure 2. Decision flow diagram.

Question 2: What is the optimal antimicrobial treatment for patients who have multidrug-resistant implant-related infections?[2]

Response/Recommendation

There is no optimal antimicrobial treatment for patients who have multidrug-resistant infections. Expert consultation with infectious disease specialists and clinical microbiologists is strongly recommended.

Strength of Recommendation: Limited

Delegate Vote: 96.3% agreement, 1.9% disagreed, and 1.9% abstained (unanimity)

Rationale

Multidrug-resistant (MDR) infection has emerged as one of the most important public global health issues of the 21st century, posing serious threats to humans, animals, and the environment. Infections caused by antibiotic-resistant bacteria result in over 700,000 deaths worldwide per year. Despite many advances, management of PJI is still a complex issue. Moreover, in recent years, the problem of antimicrobial resistance has emerged as an important challenge [23]. Success rates for treatment of PJI caused by MDR pathogens are lower than those for susceptible organisms, leading to higher morbidity and costs [24]. Management of PJI is a complex process that must involve many different specialists, especially if an MDR organism appears as the cause of infection [23]. The question remains inadequately addressed in the current literature [12–22,25–59].

Methodology

The MESH terms were developed by librarians from Jefferson University to search for the question; the search was performed on PubMed and Scopus platforms. We extracted 2,095 articles; 813 duplicates were removed, 810 using Covidence, and three were removed manually. There were 1,282 articles screened, and 375 were deemed irrelevant. There were 906 full texts screened, and 56 were included. The 57th article was published later online in 2024; it was not in the extracted studies but was added for its importance following unanimous agreement from the authors (Figure 3).

Of the 57 articles deemed relevant, the majority consisted of level IV clinical series, literature reviews, and case reports. However, these studies often lacked details on the therapeutic regimens used and frequently reported treatment failures. Hence, a meta-analysis could not be performed. While numerous *in vitro* studies show promise, clinical validation is lacking.

Treatment success rates for PJI caused by resistant pathogens are lower than those for susceptible organisms, leading to higher morbidity and costs [24]. Biofilms confer relative resistance even to susceptible antimicrobials, particularly in debridement and implant retention (DAIR) cases. The selection of antimicrobial therapy should consider not only the minimum inhibitory concentration but also, in research settings, the minimum biofilm eradication concentration (MBEC) and minimum biofilm bactericidal concentration (MBBC), if available. Additional factors include patient characteristics, bone penetration, and pharmacokinetics/pharmacodynamics. The use of nontraditional approaches to combat MDR, including the development of quorum sensing (QS)–targeted therapy, nanoparticle-based therapy, anti-virulence therapy, bacteriophage therapy, and antimicrobial peptides, offers hope for future treatment strategies.

Multidrug-resistant gram-positive bacteria

A study by Walls et al. presents 15 cases of methicillin-resistant *Staphylococcus aureus* (MRSA). A total of one-third of the patients diagnosed with an surgical site infection (SSI) were successfully treated with antibiotics alone, either intravenous (IV) vancomycin or teicoplanin and oral (PO) linezolid. For those patients presenting with deep PJI, low rates of success were seen with attempted implant retention (one of five), often requiring staged revision, followed by IV vancomycin, then oral linezolid [60]. Cordero-Ampuero et al. reported on 25 cases of late total knee arthroplasty PJI infected with methicillin-resistant *Staphylococci* (MRS), including MRSA and methicillin-resistant coagulase-negative *Staphylococci* (MR-CoNS). Infection was eradicated in 22 of 25 (88%) patients, predominantly using a two-stage revision strategy, alongside antibiotic-loaded cement (16 of 25). Antibiotic combinations were administered orally for six months to all patients using one or more of the following agents: rifampin, ciprofloxacin, trimethoprim-sulfamethoxazole, fosfomycin, clindamycin, ofloxacin, linezolid, or doxycycline. After second-stage reimplantation, IV prophylactic cefazolin was administered for five days. An unsuccessful outcome (three of 25) was observed in two patients managed with antibiotic treatment alone and in one patient after two-stage revision [61]. A report by Jover Diaz et al. on 24 cases of PJI and osteomyelitis showed that linezolid is an effective, relatively safe, and well-tolerated alternative to glycopeptides for the treatment of osteoarticular infections caused by MRSA and MR-CoNS [62]. Bassetti et al. in 2014 found that linezolid is a potential option for multidrug-resistant *Staphylococci* and vancomycin-resistant *Enterococci* (VRE) for up to four weeks of duration, with prolonged courses limited due to risk of drug-related toxicity [63]. Babis et al. in 2015 reported 31 cases of late total hip arthroplasty PJI, including MRSA [64] and MRSE [65] infection. All patients were treated with a two-stage revision, antibiotic cement, and postoperative antibiotics. Intravenous options for MR bacteria included glycopeptide (vancomycin or teicoplanin) and trimethoprim-sulfamethoxazole or rifampicin. Oral antibiotic regimens consisted of ciprofloxacin and trimethoprim-sulfamethoxazole or rifampicin [66]. Ferry et al. used IV daptomycin, linezolid, or tedizolid as long-term antibiotic suppression following arthroscopic local lysin DAIR for multidrug-resistant *Staphylococcus epidermidis* (MDRSE) [67]. A retrospective study by Chang et al. treated 16 cases of MRSA and MR-CoNS PJI with either debridement or a two-stage revision, followed by IV daptomycin, with success rates of 87.5%. The study emphasizes the need for careful monitoring of potential adverse effects during daptomycin treatment [68].

Multidrug-resistant gram-negative bacteria

Ribera et al. reported 15 PJIs caused by MDR *Pseudomonas aeruginosa* and concluded that surgical treatment alongside combination therapy with β-lactams and colistin was significantly more effective than monotherapy alone. The results suggested potential synergism of colistin with β-lactams, especially against biofilm-associated infections, with the additional advantage of allowing for a lower dose of colistin, thereby reducing toxicity [69]. Frieler et al. reported 27 cases of hip and knee PJI. Infecting organisms included MRSE, *Escherichia coli* (3MRGN), *Klebsiella pneumoniae* (3MRGN), *Enterococcus faecium* (VRE), MRSA, *Klebsiella oxytoca* (3MRGN), *Pseudomonas aeruginosa* (MRGN), *Enterobacter cloacae* complex (3MRGN), *Serratia marcescens* (3MRGN), and *Proteus mirabilis* (3MRGN). Successful eradication was observed in 91% of cases following two-stage revision and postoperative antibiotics.

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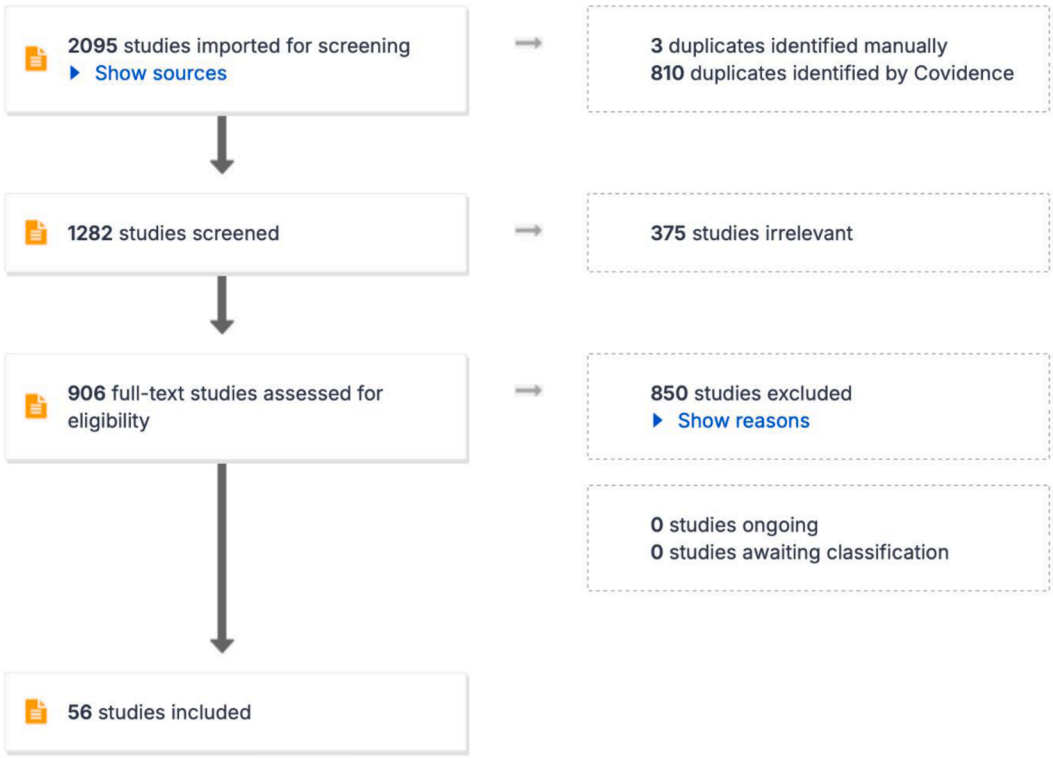

Figure 3. Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Antibiotic regimens for Gram-positive pathogens were vancomycin and meropenem, and for Gram-negative pathogens, antibiotic regimens were ceftazidime, colistin, or gentamicin [70]. Mancheño-Losa et al. also showed good outcomes with a combination of colistin and β-lactams when managing bone and joint infections by MDR Gram-negative bacteria. However, clinicians should be aware that colistin and fosfomycin have dosing challenges and may be associated with significant toxicity [61].

Failure of treatment

Rudelli et al. reported 57 cases of acute PJI of total hip arthroplasty [71] and total knee arthroplasty [72] treated with DAIR, preoperative teicoplanin, and amikacin, followed by postoperative IV teicoplanin for two weeks and four weeks of oral antibiotics. Treatment failure was observed in 55.6% of the Gram-negative MDR bacteria group, compared to 8.3% of the multidrug-sensitive bacteria group and 18.2% in the MRSA group. They concluded that DAIR may not be effective in patients with rheumatoid arthritis and acute PJI caused by MDR bacteria [73]. A review by Perez-Jorge et al. discussed the varying antibiotic options for PJI caused by MDR bacteria and concluded that individualized therapies should carefully consider the etiology, pathogenesis, and antimicrobial susceptibility. Satisfactory clinical outcomes could be further fostered by enhancing the multidisciplinary approach, with better collaboration in antibiotic selection and surgical management [23].

In Vitro studies

Many *in vitro* studies showed promising results. A study by Pistella et al., reporting seven cases of device-associated infections (including PJI), showed that vancomycin or teicoplanin in combination with fosfomycin developed bactericidal synergism at a concentration of 1x minimum inhibitory concentration [74]. Littorin et al. reported on 183 *Staphylococcus epidermidis* isolates from PJI cases and proposed that tedizolid may offer better tolerability and fewer adverse effects than linezolid. Consequently, it could be a potential treatment option for PJIs, either alone or in combination with rifampicin. [71]. Dusane et al. found that vancomycin combined with bacterial efflux pump inhibitors was effective against intracellular *Staphylococcus aureus* [75]. Pfaller et al. reported on an *in vitro* study of 1,252 isolates demonstrating sensitivity to dalbavancin. Isolates included *Staphylococcus aureus* (MRSA, MSSA), coagulase-negative *Staphylococci* (*S. epidermidis*, *S. lugdunensis*, and other CoNS), *Enterococcus faecalis*, *β-hemolytic Streptococci* (*S. agalactiae*, *S. dysgalactiae*, and *S. pyogenes*), and the viridans group *Streptococci* [76]. A narrative review by Berini et al. highlights the *in vitro* activity of nanoformulations of vancomycin, teicoplanin, and daptomycin against Gram-positive bacteria. It also includes promising findings from a limited number of animal studies and assessments of cellular toxicity [77]. A review of *in vitro* studies by Khatoon et al. focuses on quinoxaline derivatives as promising candidates to combat antimicrobial resistance. It showed that quinoxaline had a broad spectrum of activity against Gram-positive organisms (including MRSA), Gram-negative organisms (including *Acinetobacter calcoaceticus*), *Mycobacteria* (including *Mycobacterium tuberculosis*), and fungi (including *Candida* species) [78].

Conclusions

The optimal antibiotic therapy for patients who have a PJI caused by multidrug-resistant organisms remains inadequately addressed in the literature. Numerous antibiotic options are available. We provide a summary of the treatment options below:

- Quinolone-resistant *Staphylococci*: Rifampicin combinations with clindamycin or linezolid. Daptomycin plus rifampicin (according to experimental studies and some reports)
- Rifampin-resistant *Staphylococci*: Monotherapy with linezolid, clindamycin, or combinations of daptomycin alongside linezolid, fosfomycin, or beta-lactams
- MDR Gram-negative bacteria: β-lactams with or without colistin or fosfomycin or long-term β-lactam infusions.

The selection of antimicrobial therapy to treat multidrug-resistant organisms should consider patient comorbidities, mode of administration, risk of *Clostridioides difficile*-associated diarrhea, need for drug monitoring, allergy profile of the patient, intolerance, regional resistance patterns, cost, and availability. Ideally, antibiotics should also provide good bone and soft-tissue penetration and anti-biofilm activity. Currently, there is no optimal antimicrobial for MDR infections. Expert consultation with infectious disease specialists and clinical microbiologists is strongly recommended.

Question 3: Can oral antimicrobials be used for the treatment of implant-associated infection?[3]

Response/Recommendation

Yes, appropriately chosen oral antimicrobials can be effective for the treatment of implant-associated infections.

Level of Evidence: Moderate

Delegate Vote: Agree 91.2%, disagree 3.9%, abstain 5.0% (total consensus, unanimity)

Rationale

Historically, intravenous (IV) antibiotics have been considered standard for the treatment of orthopaedic infections, but this practice is not grounded in robust evidence [79]. The 2019 OVIVA multicenter randomized controlled trial (RCT) demonstrated the noninferiority of early transition to oral antibiotics compared to prolonged IV therapy for bone and joint infections, including over 200 patients treated with debridement and retention of the infected orthopedic implant (DAIR) [80]. This study also showed advantages of oral antibiotic therapy in terms of lower cost, reduced hospital lengths of stay, and fewer complications [80]. Subsequent retrospective studies have indicated that adopting the practice of treating orthopedic infections with oral antibiotics does not lead to inferior outcomes compared to IV antibiotic treatment [81–83].

Further support comes from data generated by additional randomized trials. A small RCT of patients undergoing DAIR for PJI found similar outcomes between groups switched to oral therapy at two versus six weeks [84]. Other modern RCTs evaluating antibiotic duration in PJI included early oral switch protocols and reported high cure rates [85,86]. While most data come from PJI, a recent RCT in fracture-related infections also demonstrated noninferiority of oral versus IV antibiotic therapy in the modified intention-to-treat analysis [87]. There is likewise a recent RCT in the pediatric population demonstrating noninferiority of using only oral therapy to treat bone and joint infections, although this study excluded children with orthopedic implants [88].

Observational studies have consistently associated oral antibiotics, particularly rifampin in combination with fluoroquinolones, with better outcomes following DAIR for PJI [89]. Observational studies of using oral antibiotics for PJI regardless of surgical approach have also shown good outcomes, with levofloxacin plus rifampin being the most common oral regimen [90–93]. In a systematic review and meta-analysis of IV antibiotic duration and PJI outcomes, an earlier switch to oral agents was associated with treatment success [94]. Outside of PJI, a small study of staphylococcal implant infection of the long bones or spine treated with levofloxacin plus rifampin showed modest outcomes at six months (18 of 25 patients cured) [95].

The main concern with using oral antibiotics is bioavailability, namely, if the antibiotics reach therapeutic levels in the bloodstream when taken by mouth. Studies using oral antibiotics to treat orthopedic infections, therefore, focus on antibiotics with good oral bioavailability, such as quinolones, rifampin, linezolid, trimethoprim-sulfamethoxazole, amoxicillin, clindamycin, and doxycycline. There is much less data about oral cephalosporins, particularly in the adult population. Another area of concern is patients with obesity, including those who have had bariatric surgery. The best dosing of oral antibiotics in these populations is unclear, as both obesity and bariatric surgery can affect the absorption and metabolism of antibiotics [96]. From the limited data available, quinolones and linezolid appear to be least affected by obesity and bariatric surgery [96]. Additional advances in therapeutic drug monitoring will be helpful to optimize dosing of oral antibiotics in all patients.

Overall, data support the use of oral therapy for implant-associated infections when the antimicrobial regimen is carefully selected based on pathogen susceptibility, bioavailability, and patient factors. Future research should focus on therapeutic drug monitoring to optimize dosage and determine the optimum duration of antibiotic therapy for orthopedic infections.

The use of oral antibiotics for prevention of PJI, for extended treatment after an initial prolonged IV course, and for "suppression" of suspected chronic infection is discussed in questions HK83, HK84, HK100, and HK102 and therefore is not addressed here.

Question 4: Is there a role for administration of rifampicin for patients undergoing surgical treatment for implant-associated infections?[4]

Response/Recommendation

Clinical studies examining the efficacy of rifampicin for patients undergoing surgical treatment of implant-associated infections remain conflicting, despite supportive animal data. Well-designed randomized trials are needed before a clear recommendation can be given.

Level of Evidence: Moderate

Delegate Vote: Agree 90%, disagree 9%, abstain 1% (super majority, strong consensus)

Rationale

Management of patients who have orthopedic implant-associated infections usually involves surgical debridement and a prolonged period of antimicrobial treatment [97,98]. Antimicrobial treatment is targeted toward the infective organism(s), if identified. In the last decades, there has been an interest in adding rifampicin to the antimicrobial treatment regimen for patients who have implant-associated infections caused by Gram-positive microorganisms, particularly patients undergoing a debridement, antimicrobial therapy, and implant retention (DAIR) procedure, and those infected with *Staphylococcus* spp [99].

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To answer the question posed above, we conducted a systematic review of PubMed and Embase from inception to December 2024. An initial review identified 606 studies, which were screened at the abstract level. This led to the identification of 28 studies that met the inclusion criteria for full review and data extraction. A majority of the studies reviewed related to patients undergoing a DAIR procedure. Recent systematic reviews were also evaluated.

There were two randomized trials that assessed the role of rifampicin for staphylococcal PJI. In the initial study by Zimmerli et al., 33 patients were randomized to either receive rifampicin combination therapy or ciprofloxacin monotherapy after fracture-related infection and PJI-related surgery [100]. There were 18 patients who had a PJI, of whom eight patients received rifampicin. Intention-to-treat analysis showed a nonsignificant 89 versus 60% cure rate in favor of rifampicin; significance was reached in the per-protocol analysis. The use of ciprofloxacin monotherapy as a comparator is now considered an inferior 'companion' or 'backbone' therapy for staphylococcal PJI due to the low barrier for developing resistance. Indeed, four out of the five failures in the monotherapy cohort were accompanied by ciprofloxacin resistance [100]. A more recent RCT, by Karlsen et al., on 48 patients, did not find a beneficial role for rifampicin therapy for patients who have PJI [101]. The patients in the latter study were randomized to receive rifampicin therapy, in addition to cloxacillin or vancomycin. Treatment for infection control is comparable between the rifampicin group (74%) and the beta-lactam group (72%) (relative risk (RR) 1.03, 95% confidence interval (CI) 0.73 to1.45, $P = 0.88$) [101].

A number of recent systematic reviews and meta-analyses critically evaluated the role of rifampicin therapy in patients who have orthopedic implant-associated infections. Aydin et al. published a meta-analysis in 2020 (including 13 observational studies; eight staphylococcal PJI cohorts, two *Cutibacterium acnes* PJI cohorts, and three streptococcal PJI cohorts) and did not find a positive association between the use of rifampicin and treatment success rates [102]. Scheper et al. published a systematic review and meta-analysis in 2021 that included 11 studies on patients who have staphylococcal PJI in whom rifampicin-containing regimens were compared to non-rifampicin regimens. They found a pooled risk ratio for rifampicin effectiveness of 1.10 (95% CI 1.00 to1.22) [103]. The authors highlighted the possibility of both publication and selection bias in their data synthesis. A third systematic review by Yusuf et al. was published in 2023 and included 14 studies [104]. A moderate quality of evidence was found in favor of rifampicin in patients who have staphylococcal PJI who underwent a DAIR procedure (odds ratio (OR) 2.49, 95% CI 1.93 to 3.23), but these studies were also subjected to confounding and selection bias. A major confounding factor that is present in most included observational studies is the comparison of one well-defined antimicrobial regimen (rifampicin combination treatment) with a nondefined antimicrobial regimen (nonrifampicin treatment group). The latter is likely to lead to bias in favor of the well-defined strategy and unjustified rejection of equally good alternatives within the nondefined group. Another important example of selection bias is that rifampicin is often not started in patients who have persistent wound drainage after a DAIR procedure, which may have a subsequent failure. Another major confounding variable is the marked differences in the surgical technique of a DAIR procedure between institutions and surgeons. Gerritsen et al. conducted another systematic review and meta-analysis to evaluate the outcome of DAIR for streptococcal hip and knee PJI [105]. The success rate for streptococcal PJI treated with a DAIR approach ranged from 35 to 95%, with an overall pooled estimate of 71%. The overall treatment success was 76% for knee PJI and 58% for hip PJI. The pooled relative risk ratio of success rates after administering rifampicin compared to those who did not have rifampicin was 1.15 (95% CI 0.91 to 1.45) across three observational studies, which included 425 patients.

Since the publication of the aforementioned systematic reviews, several large observational studies have been published. The findings are conflicting. Beldman et al. analyzed 669 patients who had staphylococcal PJIs in a retrospective observational cohort study and found, also after adjustment for possible confounders, a difference in failure rate of around 20% when comparing a rifampicin-based regimen (32.2%) with a nonrifampicin-based regimen (54.2%) (20 mg per kg per day) in patients who had PJIs [106]. Although Leijtens et al. reported that clindamycin and rifampicin combination therapy is effective for staphylococcal PJI [107], other authors mentioned that rifampin can reduce serum concentrations of clindamycin, and the clinical importance of this interaction remains unclear [108–116]. Also, Jacobs et al. observed no significant difference in the success between rifampicin combination therapy and other treatments for PJI caused by *C. acnes* [117].

In conclusion, the superior efficacy of rifampicin-containing regimens over other treatment regimens cannot be confirmed from the available clinical data. There is a need for larger and well-designed prospective studies with a focus on companion drug selection and timing in relation to initiation and duration of treatment. Based on the current literature, if rifampicin were to be included in the antimicrobial regimen for patients who have orthopaedic implant-associated infections, the most suitable candidates would be those undergoing a DAIR procedure and infected with Staphylococci. It appears that rifampicin–fluoroquinolone combination therapy provides better results than any other antimicrobial combinations evaluated so far.

Question 5: How can we determine that a patient who has an implant infection has received an adequate duration of antimicrobial therapy?[5]

Response/Recommendation

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) lack accuracy to independently guide discontinuation of antibiotics in orthopedic-implant infections. In the absence of any reliable marker to determine the resolution of infection, or predictive model of antibiotic course duration, the length of antimicrobial treatment needs to be decided based on infection characteristics (e.g., four to six weeks following resection arthroplasty or six to 12 weeks after implant exchange or retainment), host status and compliance, antimicrobial efficacy, and initial treatment response.

Level of Evidence: Limited

Delegate Vote: Agree 95%, disagree 2.5%, and abstain 2.5% (unanimous, strongest consensus)

Rationale

Clinical, biochemical, and radiological cues for discontinuation of antimicrobial therapy and sufficient treatment durations in various orthopedic-implant infections are insufficiently examined in high-quality studies. At the outset, expert opinion dictated 3- to 6-months or longer courses for orthopedic-implant infections, especially following debridement strategies [118,119]. Prolonged parenteral lead-in was the mainstay even in revision cohorts without apparent superiority to present-day results [120]. Current

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recommendations [121,122] are mostly based on observational studies or comparisons of predetermined treatment durations unsuited to identify determinants for customized discontinuation. Shortening courses with retained efficacy is imperative for reducing local and global antimicrobial resistance as well as toxicity and drug interactions. Conversely, treatment failure due to prematurely discontinued antibiotics increases patient suffering and health care strain and contributes to antimicrobial resistance from repeat courses.

For this narrative review, a MeSH search was undertaken in Medline, Embase, and Cochrane on reports of antibiotic treatment duration, common biomarkers (CRP, ESR, and synovial white blood cells [WBC]) for discontinuation and outcome of prosthetic joint infection (PJI), fracture-related infection (FRI), or peri-implant spinal infection (PSII), with a minimum 12-month follow-up after discontinued antibiotics. When clearly reported, only data on relapses were considered, since failure during treatment is irrelevant to the review question. There were 2,730 retrieved publications, resulting in 107 full-text reviews, ultimately yielding 55 eligible for data extraction. Despite the search strategy, most papers did not focus on clinical markers but rather on aspects indirectly informing on antibiotic treatment durations. Institutional review board approval was not required for this review (Table 1).

Certain antibiotic combinations, such as rifampicin (RIF) and fluoroquinolones (FQ), have been put forward as superior over the last decades [123,124], especially in staphylococcal (RIF plus FQ) and Gram-negative (FQ) infections [125], despite current evidence challenging this assertion [126–128]. Suzuki et al. tried to assess the effect and optimal duration of adjunctive RIF with partly conflicting results in a large (n = 4,628), but biased, cohort of *Staphylococcus aureus*-PJIs subjected to DAIR [129]. Gellert et al. reported 24-month infection-free survivals of 48 and 67% (P = 0.038) [130] in surgically similar knee-PJI cohorts on "biofilm-active" and nonbiofilm antibiotics, respectively. Although treatment durations were not clearly specified, the "nonbiofilm-active" cohort received nine to 21 weeks of oral antibiotics compared to 10 weeks in the "biofilm-active" cohort. Scheper et al. concluded from a prospective cohort that clindamycin (mean 56 days, range, 40 to 62) or flucloxacillin (mean 41 days, range, 33 to 50)-based treatment with five days of initial rifampicin was as effective as a rifampicin combination (mean 94, range, 85 to 103 days) in 200 patients (94% DAIR, 6% one-stage) [128]. Other studies report outcomes after defined treatment durations for specific antibiotics. An RCT (n = 75) comparing six weeks of daptomycin at six and eight mg/kg to a vancomycin/teicoplanin control at two-stage reimplantation for *S. aureus* PJIs demonstrated higher microbiological (50, 52, versus 38%) and clinical cure rates (58, 61 versus 38%) for the comparator [131]. There were no robust conclusions drawn from the very few publications that deal with two-dosed dalbavancin in hardware infections [132–134]. Spitzmuller et al. found no apparent benefit from more than 31 days of treatment with regimens containing an FQ (OR 1.42 (0.34 to 5.85)) and/or rifampicin (OR 1.41 (0.35 to 5.60)) in preventing relapse in an intent-to-cure case-control study of infected internal fixations [135]. Certain microbes, such as RIF- or FQ-resistant strains, Enterococci, and *Candida* spp., are considered harder to treat, and guidelines commonly recommend staged revisions but offer meager guidance on treatment duration. *S. aureus*, including MRSA [136–140] and hematogenous infection [141,142], is frequently reported as an independent risk factor for failure in DAIR, likely more influential than time on antibiotics [142]. There were two papers [143,144] that reported 68 and 67% resolution after a median of 83 days (range, 38 to 133) and 91 days (interquartile range (IQR), 58 to 171) of antibiotics for Streptococcal PJI (hematogenous in 95 and 52%) treated according to DAIR in 55 and 100%, respectively.

Furthermore, the overall likelihood of a favorable outcome is greatly influenced by host physiology and causative microbes [145,146]. Albeit varying discriminatory performance, predictive scores for PJI [147,148] may be used to predict outcomes but do not directly inform treatment duration. Interestingly, neither initial treatment response nor antimicrobial compounds are predictors in any of these models. Joulie et al. examined factors influencing resolution of *S. aureus* infections in hip and knee arthroplasties and found no significant difference in mean durations of empirical intravenous or total antibiotic treatment (7 ± 5.2 versus 7.8 ± 7.4 days and 124 ± 62 versus 117.9 ± 69 days) in resolution and failure, respectively [149]. Unfortunately, it is unclear how most of the above factors translate into the optimal duration of antibiotic treatment. Most guidelines recommend longer courses in debridement and retention of implant compared to staged revisions, which is why current evidence in support of shortened antibiotics in DAIR procedures is the most desired. Antibiotic suppression may merely postpone relapses [118], and moreover, bias results in studies where predetermined suppression (mainly DAIR) is categorized as failure. Another concern is the general compliance with prolonged peroral treatments in PJI and FRI, which is not investigated, but will influence ultimate outcomes and bias studies. In the controlled setting of the OVIVA trial, including 31.5% retained orthopaedic implants and a median of 71 (IQR 43 to 94) days of oral antibiotics, an early intravenous to oral switch did not impact 1-year failures of 18.5 and 14.2% in peroral and intravenous administration, respectively, but the study does not report on outcome differences in short versus long treatments [150]. In another study, early oral switch (less than 5 days of intravenous, mean total 80 (standard deviation (SD) 31.5) days)) in implant infections only (62% FRI, 41% retention) was not associated with failure (adjusted hazard ratio (aHR) 0.8, 95% CI 0.4 to 3.5,

Table 1
Studies Comparing Treatment Durations In Various Orthopedic Implant Infections.

Author/year	Design	N	Type	Joint/ Bone	Procedure	(No. of Weeks) Success %	(No. of Weeks) Success %
Benkabouche et al. 2019	RCT	123	PJI/FRI	Mix	Two-stage	(4) 94	(6) 95
Bernard et al. 2010	Prospective cohort	135	PJI	Hip/knee	DAIR, one-, and two-stage	(6) 89	(12) 66
Chaussade et al. 2017	Retrospective cohort	87	PJI	Hip/knee	DAIR	(6) 70.5	(12) 67.4
Chen et al. 2024	RCT	60	PJI	Hip/knee	Two-stage, second stage	(2) 96.7	(12) 96.7
Yang et al. 2020	RCT	107	PJI	Hip/knee	Two-stage, second stage	(0) 83.7	(12) 96.6
Lora-Tamayo et al. 2016	RCT	63	PJI	Hip/knee	DAIR	(8) 91.7	(12/24) 95.0
Bernard et al. 2021	RCT	410	PJI	Hip/knee	DAIR, one- and two-stage	(6) 83.4	(12) 93.1
Puhto et al. 2011	Retrospective cohort	86	PJI	Hip/knee	DAIR	(12) 87.5	(24.5) 89.5

RCT = randomized controlled trial.

$P = 0.66$). [151]. Moreover, intravenous antibiotics prolonged beyond 7 days and did not improve outcomes in early PJI subjected to DAIR. Meijer et al. reported 41.5, 44.4, and 42.1% overall failures (n = 969) in < 14, 14 to 27, and > 27 days, respectively ($P = 0.798$), possibly with the exception of highly inflammatory infection (CRP >115 mg/L), and replacement of modular components is not carried out [152].

It is well established that early surgery and complete implant removal increase the likelihood of success. Likely, this is also true for modular component exchange in DAIR, but the jury is still out regarding the degree [153]. Controlled trials on antibiotic duration in FRI are missing, and recommendations are largely extrapolated from the existing data on PJIs. However, in an RCT (n = 123). Benkabouche et al. demonstrated no difference in resolution rates after 4 and 6 weeks of antibiotics following mixed implant removals [154], including FRIs.

The PJIs were defined according to European Bone and Joint Infection Society, MusculoSkeletal Infection Society, or comparable criteria, and most relevant studies stated that antibiotic suppression was considered a failure. There are only two RCTs primarily addressing antibiotic treatment duration [155,156], and no reports that systematically analyzed strategies for determining the optimal time to discontinue treatment. There is a fair amount of knowledge regarding the role of biomarkers such as serum-CRP and ESR in orthopedic-implant infections. For example, CRP is inadequate in ruling out low-grade PJIs [157], but levels above 150 mg/L at diagnosis of late acute PJI independently correlate to early failure in DAIR [137]. Conversely, there were only a couple of studies analyzing biomarkers for deciding when to stop antibiotics. Bejon et al. performed receiver operating characteristic and time-adjusted ratios of 2,326 serum CRP measurements in 109 DAIR and 151 2-stage revisions, respectively. The authors concluded that serial CRP measurements do neither reliably detect failure within 180 days after DAIR with peroral suppression nor do they predict outcomes in staged revisions and six weeks of parenteral antibiotics (reimplantation ratio = 0.84, 95% CI 0.65 to 1.09, $P = 0.24$). Ghanem et al. assessed the prognostic value of ESR and CRP before the second stage after six weeks of parenteral antibiotics in 86 successful and 23 failed knee reimplantations and found poor area under the receiver operating characteristic curve of 0.50 and 0.55, respectively. There are numerous studies on synovial WBC measurements before second-stage revision, collectively found unreliable in predicting persisting infection [158], but synovial WBC has not been assessed as a marker for stopping antibiotics. There were two studies, however, that evaluate synovial WBCs at the end of planned antibiotics. Ascione et al. found significantly higher WBC counts (median 1,344, IQR 934 to 2,776 versus 471, IQR 290 to 804) and neutrophil percentages (61, IQR 52 to 78 versus 36, IQR 28 to 51) in failures in an 82-patient primary two-stage revision cohort receiving 8 weeks of antibiotics [159].

Cohort studies [156,160,161] comparing six to eight weeks with 10 to 12 weeks of antibiotics in implant-preserving PJI treatment indicated no additional benefit from longer courses at 12- to 24-month follow-up, but the duration of antibiotic treatment in prosthetic osteomyelitis RCT (per protocol n = 325) by Bernard et al. raised concerns by failing to demonstrate noninferiority of six weeks compared to 12 weeks, particularly in DAIR, where the risk difference for failure was 16.2% of the patients (CI 2.9 to 29.5) [155]. In a smaller (per protocol n = 44) RCT on hematogenous or early postsurgical hip and knee PJIs, Lora-Tamayo et al. offer moderate strength evidence of noninferiority in 8 versus 12 weeks of RIF plus FQ (levofloxacin) therapy [156]. Neither of the RCT was powered to significantly discriminate between hip and knee joints. Another French DAIR cohort (n = 60) appears to support that less than three months of antibiotics is independently associated (OR 20.0, CI 2.2 to 200) with failure, but the numbers were small, and 40% of failures occurred during antibiotic therapy [140]. An RCT by Karlsen et al. challenged the need for rifampicin in DAIR for early staphylococcal PJIs and allocated both groups (n = 48) to six weeks of antibiotics with 2-year cure rates of 73%, without significant group differences [127]. Indeed, examining per-protocol outcomes after removal of failures occurring during treatment, success rates increase in both long and short courses, supporting reducing durations in cases of uneventful initial treatment [128,155,156,162]. Moreover, in the large (n = 653) Prosthetic joint Infection in Australia and New Zealand Observational study PJI cohort, the duration of neither intravenous or oral antibiotics was associated with success in DAIR (OR 0.99, CI 0.97 to 1.00 and OR 1.004, CI 0.993 to 1.015) or two-stage (OR 1.009, CI 0.97 to 1.00 and OR 0.985, CI 0.970 to 1.001), respectively [139]. An observational study of shortened treatments in one-stage revision by Chieffo et al. reported a 12-month remission rate of 90% in 50 PJIs treated by one-stage and 6 weeks of various antibiotics [163]. This is reinforced by the duration of antibiotic treatment in prosthetic osteomyelitis 1-stage subgroup (risk difference 1.2% of patients, CI 4.8 to 7.1) [155]. Following the second stage, most authors suggest discontinuation of antibiotics in clinically uninfected and culture-negative cases. This was tested by Chen et al. in an RCT comparing two and 12 weeks, yielding identical outcomes at 3-year follow-up [164]. A similarly designed RCT (per protocol n = 133, mean follow-up > three years) comparing 12 and zero weeks, conversely, reported eight (13%) versus 20 (29%) failures, where 55% in the control group failed within 2.5 months [165], i.e., antibiotics provided short-term improvement in infection-free survival. There were only a few papers regarding FRI. Al Mayahi et al. concluded that more than 42 days (OR 0.1, 42 to 63 days (CI 0.1 to 2.5)) of total antibiotics did not affect outcome in a multivariate analysis of 139 patients who had mixed material FRIs, where DAIR was performed in 14% [166]. Regarding PSII, the evidence level is even weaker, but despite methodological shortcomings, there are indications that shorter treatments may be opted for. Bosch-Nicolau et al. reported in a retrospective DAIR cohort study that 8 weeks of treatment did not perform worse than 12 weeks in acute PSII (54% *Staphylococci*) [167]. Oral antibiotic choices were similar in the groups, but no beta-lactams were used. In a mixed-case cohort study, more than 42 days of total antibiotic treatment did not lead to increased healing [168]. A 1-year observational study (n = 85, 74 implants) of DAIR and six weeks of oral antibiotics in early PSII treated only seven patients who required reoperation due to infection [169], and Pull ter Gunne et al. found no relapses within one year in a PSII cohort of 132 patients after a mean of 40.8 (SD 17.0) days of mainly parenteral antibiotics. The median time to diagnosis was 15 days, and surgery was implant preserving in 73% and one-stage revision in 15% [170]. In previous observational studies, treating physicians may have opted for early discontinuation in uncomplicated cases, partly explaining why apparent short-course efficacy could not be replicated.

Optimal antibiotic treatment duration in orthopedic-implant infections is largely undefined due to the scarcity of bespoke high-quality studies, poor evaluability of [unstandardized] practices, and evolving surgical methods. Overall, the limited reports available on CRP, ESR, and synovial WBCs do not support their stand-alone use in the discontinuation of antibiotics. In pretreatment likelihood of success, even in implant-preserving procedures, it is plausible that shorter treatments than the current mainstay are equally efficacious. Knowledge of surgical, host, and microbe-specific outcome factors, and correct appraisal of initial treatment responses, may allow for shortened treatments with

retained levels of success. Evidently, there is an urgent need for well-designed site- and condition-specific studies, especially regarding implant preservation, particularly in spinal implant and fracture-related infections.

Acknowledgments

The work of this review was not supported by any external funding.

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The Journal of Arthroplasty 41 (2025) S191–S195

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

General Topics

2025 ICM: Antibiotics Usage Criteria

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Question 1: Should antimicrobial treatment target the minimum inhibitory concentration (MIC) or minimum biofilm eradication concentration (MBEC) of organisms?[1]

Response/Recommendation

Minimum inhibitory concentration (MIC) should be used to address the susceptibility of the microorganism.

The minimum biofilm eradication concentration (MBEC) value is not a clinically available metric and has not been definitively linked to any impact on treatment recommendations. Future clinical studies are needed to evaluate whether MBEC-guided treatment improves treatment success.

Level of Evidence: Limited

Delegate Vote: Agree 83.3%, disagree 5.6%, and abstain 11.1%

Rationale

The minimum biofilm eradication concentration (MBEC) is a measure that is increasingly being evaluated as an indicator of antibiotic susceptibility for *in vitro* biofilms. The growing recognition of biofilm resistance in implant- and non–implant-related infections has prompted interest in MBEC as a potential measure to guide treatment. There are currently no standardized measurement parameters (i.e., surface, age, and duration of exposure) for MBEC susceptibility testing, which is counter to the minimum inhibitory concentration (MIC), a well-established value both clinically and microbiologically. The MIC is assessed via a standard set of methods and breakpoints, such as those offered by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [1,2]. These MIC methods of susceptibility testing, although validated and reproducible, focus on the planktonic state of bacteria rather than bacteria within a biofilm state [3].

A comprehensive literature search was conducted using PubMed and Embase databases, initially identifying 535 studies. There were 519 abstracts screened, and 157 studies were assessed for eligibility as potentially relevant studies, of which 21 were selected for in-depth review.

Studies have shown that the MIC of pathogens can be achieved in surgical tissues at the time of implantation. For example, Komatsu et al. reviewed the pharmacokinetics of cefazolin in serum and hip joint capsule tissues during primary total hip arthroplasty and showed that cefazolin maintained supra-MIC levels for up to three hours [4]. The MIC values for therapeutics have been detected in antibiotic spacers during initial implantation and at the time of revision or reimplantation surgery [5–8]. Von Baum et al. and others have found that antibiotic concentrations within bone (both cancellous and cortical) can achieve MIC values for common pathogens [9,10]. Favorable clinical outcomes have been achieved with quinolones, mainly when the peak serum/MIC ratio is $\geq$ 12, resulting in good bone penetration [11]. The amount of fluoroquinolones (two to six μg/ml), cephalosporins (267 to 356 μg/mL), and amikacin (92 to 215 μg/mL) needed to achieve MIC90 of *Pseudomonas aeruginosa* biofilm from implant-related infections and was different than the same bacteria in planktonic form (fluoroquinolones 0.8 μg/mL, 19 μg/mL for cephalosporins, and amikacin three μg/ml) [12]. In a preclinical model of methicillin-resistant *Staphylococcus aureus* (*S. aureus*) osteomyelitis, intramuscular moxifloxacin has been shown to improve outcomes at levels above the MIC (43 times) but below the minimum biofilm eradication concentration (MBEC) [13]. Certain antibiotics have been found to have more effect than others in the treatment of implant-related infections. Tunney et al. found that bacteria isolated from revision hip surgery were more susceptible to vancomycin and ciprofloxacin than to gentamicin. Minimum bactericidal concentrations (MBC, 99.9% killing) were significantly higher (10 to 1,000 times) than MIC values [14,15]. Additional work by Brady et al. found that 20 staphylococcal isolates from implant infections had MBEC values higher than their MIC values and recommended MBEC testing in clinically relevant situations where implants or devices had to remain *in situ* [15]. While some antibiotics are ineffective against bacteria

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to 10.1016/j.arth.2025.08.062.

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https://doi.org/10.1016/j.arth.2025.08.062
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in biofilm [16], rifampicin has shown the lowest MBEC/MIC ratios in staphylococcal strains causing periprosthetic joint infection (PJI) [17]. The suggestion that antibiotics delivered at levels that achieve MBEC would improve clinical outcomes has been made but is not yet supported in the literature. The reporting of MBEC values can also vary based on clinical isolates, antibiotic selection, and antibiotic synergistic or antagonistic activity [18–20]. Meléndez-Carmona et al. found no relationship between antibiofilm activity (defined as biofilm-embedded cell count and crystal violet staining) of levofloxacin, rifampin, and their combination and the MBEC value when evaluating *S. aureus* isolates from patients who have PJI and had undergone debridement and retention of components [21]. Subinhibitory treatments have led to increased biofilm formation and upregulation of genes related to biofilm formation [22–25]. Additionally, the susceptibility of biofilms to antibiotics may change over time with exposure [24–27]. This variation over time could be due to changes within the biofilm or the rapid emergence of small colony variants, which can vary depending on the bacterial species, clinical isolate, or location within a biofilm [28]. Clinical isolates, when in biofilm form, may also respond differently to combinations of antibiotics and adjuvants [29,30].

Svensson Malchau et al. demonstrated that strong biofilm production is associated with increased antibiotic resistance and a higher recurrence rate of PJI [31]. Therefore, the characterization of biofilm abilities and MBEC susceptibility testing of clinical strains could serve as relevant clinical diagnostic tools to guide treatment or indicate when specific treatments are futile. The development of the MBEC, or methods to determine antimicrobial biofilm activity, has been described [15,31–34]. However, clinical studies need to verify the clinical relevance of the MBEC method [28]. A retrospective study found that in six out of seven patients who had treatment failure, staphylococcal and enterococcal strains exhibited high minimum bactericidal concentrations (MBECs) against the antibiotics used to treat osteomyelitis associated with percutaneous orthopedic implants [34]. A prospective clinical trial, where MBEC guides oral antibiotic therapy in the intervention arm, is currently underway; however, no data are yet available for review [35]. Moreover, not only the treatment success, but also the tolerability of antibiotics at the required doses to achieve MBEC will be critical, as the amount of antibiotics needed to achieve the MBEC *in vitro* is often higher than what can be safely achieved *in vivo* [36]. While *in vitro* assessment of MBEC is possible, the measurement of biofilm eradication is reliant on more variables than that of MIC testing. Before the definition of breakpoints for clinical resistance is redefined, the parameters surrounding the MBEC method should be further identified and standardized. In the future, MBEC testing will become increasingly relevant in cases where implants cannot be removed or when dealing with recalcitrant infections. In cases where the MBEC is too high, alternative treatment strategies may need to be considered.

Conclusions

Strong biofilm production is associated with increased antibiotic resistance and a higher recurrence rate of periprosthetic joint infections. The MBEC susceptibility testing could guide therapeutic treatments, though its clinical relevance needs validation. An ongoing clinical trial aiming to assess MBEC-guided therapy is currently underway. Standardizing MBEC testing parameters is crucial, and their relevance may increase in managing implant-related infections. Incorporating MBEC testing could improve treatment outcomes by providing accurate antibiotic dosing guidelines, but further research is needed to confirm its benefits.

Question 2: Do currently available products safely achieve local antibiotic concentrations above the minimum biofilm eradication concentration (MBEC) for sufficient time to achieve eradication of infection?[2]

Response/Recommendation

There is no clear evidence that the current products can safely achieve local antibiotic concentrations above minimum biofilm eradication concentration (MBEC) levels for a sufficient time to eradicate infection.

Level of Evidence: Strong

Delegate Vote: Agree 89.7%, Disagree 3.4%, Abstain 6.8% (Super Majority, Strong Consensus)

Rationale

The MBEC represents the concentration of antibiotics required to eradicate biofilms. Ceri et al. introduced the Calgary Biofilm Device in 1999, developing a novel MBEC measurement system using peg plates, and reported that MBEC requires antibiotic concentrations 100 to 1,000 times higher than the MIC [37]. Biofilm formation makes implant-associated infections (IAI) in orthopedics difficult to treat, with the MIC-MBEC disparity jeopardizing successful outcomes [38–40]. The International Consensus Meeting (ICM) in 2018 highlighted the limited utility of MIC in bacteria forming biofilms and emphasized the importance of MBEC [41]. However, achieving MBEC through systemic antibiotic administration is difficult to achieve without causing severe systemic adverse effects. Thus, there is a clear need for innovative local delivery systems or treatment strategies that can deliver high concentrations of antibiotics at the site of infection over a sustained period.

We conducted a systematic review, using specific MeSH terms developed by librarians, to identify all relevant publications in the Medline and Embase databases, covering studies published up to November 2024. Search results yielded 997 publications in English language. There were two of the authors who went through title and abstract screening, and discrepant results were reviewed by a third person. Finally, 97 full articles were reviewed, and 53 articles were referenced in this manuscript.

Antibiotic concentration and duration for MBEC vary by bacterial strain and antibiotic type [38,42]. Moreover, MBEC is influenced not only by antibiotic concentration but also by the duration of exposure [43–45]. Prolonged antibiotic administration has been shown to reduce MBEC values by promoting deeper penetration and sustained bacterial eradication. Additionally, combined antibiotic therapies can effectively lower MBEC values through synergistic mechanisms [39,46], though in some cases, a combination of antibiotics may inadvertently increase the MBEC [47]. Significant synergistic effects have also been observed when antibiotics are used in conjunction with anti-inflammatory drugs such as aspirin and ketorolac [44,48,49], essential oils [50], enzymes that degrade proteins, polysaccharides, or deoxyribonucleic acid (DNA) [51], nanoparticles [52], and antimicrobial peptides [53]. However, the challenge intensifies under *in vivo* conditions, where MBEC values for biofilm-associated infections on implants are significantly elevated compared to *in vitro* measurements [54,55]. The synergistic effect of combination therapy has the potential to reduce the MBEC to an antibiotic concentration feasible for clinical use; however, its efficacy and safety in clinical practice remain unverified.

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To achieve high local antibiotic concentrations, antibiotic-loaded bone cement (ALBC) is employed in orthopedic procedures such as single- and two-stage exchange arthroplasty [38,56]. The ALBC enables the localized delivery of high concentrations of antibiotics with sustained release over an extended period. However, this method is limited by a lack of high-quality evidence and the potential for antibiotic inactivation due to the heat generated during polymerization [57]. Moreover, randomized studies have reported that most commercially available ALBC fail to maintain intra-articular antibiotic concentrations above the MBEC, with antibiotic concentration declining rapidly [58]. The use of static or articulating antibiotic spacers with high-dose ALBC is widely recognized as an effective method for delivering high-concentration, sustained-release antibiotics directly to the infection site [38,56,59]. However, the high antibiotic concentration needed to achieve MBEC thresholds could lead to systemic toxicity and compromise the mechanical integrity of bone cement [60]. Calcium sulfate beads are also used for local antibiotic delivery, primarily in revision procedures, but have less favorable outcomes in debridement, antibiotics, and implant retention procedures, and may increase the risk of implant surface abrasion [61].

Recent studies have demonstrated the efficacy of direct antibiotic administration into the joint or intramedullary cavity via catheters or intramedullary needles, as well as the use of biodegradable carriers for localized antibiotic delivery. Roy et al. [62] reported that intra-articular administration of vancomycin resulted in sustained high local antibiotic concentrations, while Young et al. [63] demonstrated that intraosseous administration of vancomycin achieved similar results, both when compared to intravenous administration. These methods have shown potential prophylactic benefits in total knee arthroplasty and total hip arthroplasty [63–65]. Such direct delivery techniques have been shown to maintain antibiotic concentrations exceeding the MBEC locally for a sustained period, though their use is predominantly prophylactic in elective orthopedic surgeries. In spinal surgeries, topical vancomycin is frequently employed for the prevention of surgical site infections (SSIs). However, its preventive efficacy remains inconclusive [66].

Whiteside et al. investigated an intra-articular antibiotic infusion system designed for direct delivery to the infection site to disrupt biofilms in patients who have PJI [67,68]. This system achieved exceptionally high local antibiotic concentrations and demonstrated a success rate exceeding 95% in cases of PJI caused by MRSA (methicillin-resistant *Staphylococcus aureus*) or in patients who have failed two-stage revision arthroplasty. Zou et al. highlighted that incorporating intra-articular infusion in single-stage revision procedures for PJI achieved high local antibiotic concentrations, likely exceeding the MBEC [69]. Springer et al. introduced an intra-articular antibiotic irrigation system for PJI patients and evaluated its safety through a phase II prospective randomized comparative study using conventional two-stage revision arthroplasty as a control [70]. The study concluded that the intra-articular antibiotic irrigation system effectively elevated local antibiotic concentrations while minimizing systemic levels of antibiotics, with no significant increase in adverse events compared to conventional methods. The reported success rates of these intra-articular infusions are highly promising, achieving 90 to 100% in debridement, antibiotics, and implant retention, 82 to 100% in single-stage revision arthroplasty, and approximately 80% in two-stage revision arthroplasty [71]. These findings suggest that intra-articular infusion may be a viable alternative to achieve sustained local antibiotic concentrations without compromising renal function [72]. Moreover, a recent study by Semeshchenko et al. examined the ability of five different irrigation solutions to achieve MBEC and reported that only povidone-iodine and silver nitrate successfully eradicated at least 99.9% of 24-hour biofilm, suggesting the potential for nonantibiotic approaches to achieve MBEC [73].

Maruo et al. developed continuous local antibiotics perfusion, a method for treating bone and soft tissue infections by directly delivering high-dose gentamicin through an intramedullary and intra-soft tissue perfusion system while utilizing a negative pressure wound closure system to facilitate antibiotic distribution and manage dead space. The efficacy of continuous local antibiotics perfusion was first reported in managing fracture-related infections [74,75]. Additionally, its effectiveness in treating PJIs has also been documented [76,77]. Choe et al. further explored the application of this method for fungal PJIs, administering micafungin at concentrations exceeding the MBEC against *Candida albicans* without observing significant adverse effects [77]. However, concerns have been raised regarding the potential cytotoxicity of such high local concentrations of antibiotics on osteoblasts [78]. Establishing an appropriate balance between effective antibiotic concentrations and minimizing cytotoxic effects remains a critical area for future research and clinical validation in direct antibiotic delivery techniques.

Another approach for localized antibiotic delivery involves the use of biodegradable carriers. Ambrose et al. investigated a method of utilizing microspheres for antibiotic delivery by embedding antibiotics into polylactic glycolic acid to achieve homogeneous distribution, enabling steady-state release for up to 4 weeks at concentrations reaching the minimum bactericidal concentration [79–81]. These antibiotic-loaded microspheres demonstrated major efficacy in eradicating infections and promoting favorable bone defect healing in a rabbit osteomyelitis model. Furthermore, technologies incorporating antibiotics into hydrogels have been commercialized as implant coatings and have shown utility in preventing surgical site infection and PJI without significant adverse events [82,83]. Hydrogels enable the delivery of high local concentrations of antibiotics over a sustained period and have the major advantage of being biodegradable, eliminating the need for subsequent removal after their functional duration has elapsed [84–86]. Additionally, basic research is exploring methods to incorporate nanoparticles into hydrogels for more efficient localized delivery of antimicrobial agents [87]. Nanoparticles are becoming increasingly important in the treatment of biofilm-associated infections, although their clinical application has yet to be reported [88,89].

In conclusion, currently two approaches have been explored in both basic research and clinical applications to achieve local antibiotic concentrations exceeding the MBEC: the direct infusion of antibiotics to the infection site using catheters or similar devices and the use of biocompatible carriers loaded with antibiotics to release high concentrations locally. These methods have been reported to have the potential to achieve MBEC levels at the infection site. However, the concentration and duration of antibiotics required to achieve MBEC vary greatly depending on the presence of implants, the bacterial strain, and the type of antibiotic. Furthermore, no definitive evidence currently exists to confirm that MBEC can be achieved in clinical practice. A further concern is that the high concentrations of antibiotics necessary to achieve MBEC may pose cytotoxic risks to surrounding tissues. Thus, there is still no clear evidence that MBEC has been successfully and safely achieved in clinical practice, and further clinical research is needed to address this clinical question in the future.

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The Journal of Arthroplasty 41 (2025) S196–S205

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

General Topics

2025 ICM: Use of Newer Antibiotics and Fluoroquinolone-Resistance

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Question 1: Is there a role for the administration of newer and long-acting antibiotics such as dalbavancin, oritavancin, fosfomycin, or 5th-generation cephalosporins?[1]

Response/Recommendation

There may be a role for administration of newer and long-acting antibiotics as a safe and effective alternative treatment for periprosthetic joint infection (PJI). At the present time, there is more evidence around dalbavancin use than oritavancin use, but there is scant evidence regarding fosfomycin use, and unfortunately, there is no clinical data for 5th-generation cephalosporins for the treatment of PJI. Consequently, more research is needed to clarify the role of these agents in the treatment of PJI.

Level of Evidence: Limited

Delegate Vote: Agree 79.1%, Disagree 8.2%, Abstain 12.7% (Strong Majority, Moderate consensus)

Rationale

Novel antimicrobials are welcomed with excitement, particularly at a time when the emergence and spread of antimicrobial resistance are considered a global public health threat [1]. Some of these novel antibiotics, although initially approved, are used to treat complex soft-tissue and bone infections and specifically target Gram-positive bacteria, which are the most frequent pathogens in periprosthetic joint infections (PJI). Orthopedic implant-related infections require prolonged antibiotic treatment to eradicate biofilm and intracellular bacteria that are frequently involved in these infections [2].

In attempts to shorten or avoid hospitalization without increasing overall health care costs, two long-acting lipoglycopeptides, oritavancin and dalbavancin, have been approve for use in acute bacterial skin and skin structure infections (ABSSSIs). Some studies have also included complicated infections such as periprosthetic joint infections and osteomyelitis [3–6]. The use of these agents for longer courses of therapy was beneficial for resistance and would not only potentially decrease hospital admissions, but also prevent the need for prolonged intravenous catheterization, which in turn could decrease line complications [7].

The role of antibiotics such as dalbavancin, oritavancin, fosfomycin, and 5th-generation cephalosporins has been researched through a systematic review carried out by reviewing identified studies added from two databases, PubMed (274 studies) and Scopus (106 studies). The inclusion criteria were studies of clinical cases of PJIs treated with systemic newer and long-acting antibiotics. Reviews were not included. Only one study met the inclusion criteria. Therefore, we re-evaluated all available studies that included clinical applications of PJI treated with the targeted antibiotics and manually identified studies by reviewing the references of the studies. This resulted in 16 studies with clinical use of dalbavancin, oritavancin, and fosfomycin. During data extraction, PJI cases were extracted from a mixed series of other infections. Dalbavancin was the most investigated drug, with 11 clinical studies identified. Only three studies on oritavancin, two on fosfomycin, and none on 5th-generation cephalosporins were identified.

Dalbavancin

There were 11 studies, published between 2017 and 2023, that discussed the use of dalbavancin for the treatment of PJIs [1–5,8–12]. There was one study that was prospective, the rest being retrospective, with six multicenter and five single-institution studies. A total of 675 patients were treated with

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.094.

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https://doi.org/10.1016/j.arth.2025.10.094
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intravenous injection of dalbavancin, of whom 245 were for PJI. The majority of patients had hips (89 patients) and knees (63 patients), and a few had shoulders (four patients) and ankles (one patient). There were many different microorganisms treated, with the majority being Staphylococci (methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-sensitive *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), and other coagulase-negative Staphylococci), Enterococci, Streptococci, Corynebacteria, and polymicrobial as well as culture negatives. Dalbavancin was administered intravenously with different dose regimens, varying from short courses of a starting dose of 1,500 mg followed a week later with another 1,500 mg administration to longer courses starting with either 1,500 or 1,000 mg followed by 500 mg weekly. There was one regimen started with 1,500 mg followed by 1,000 mg biweekly, and another one started with 750 mg followed by 750 mg with renal adjustments of the dose. There was also a major variation in the length of treatment, from a short course of one to two doses up to three months. Surgical interventions were also not clearly identified, but included debridement, antibiotics, and implant retention (DAIR), single- or two-stage procedures, and excision arthroplasties. The results of treatment with dalbavancin were assessed based on clearance of infection, but for various periods of time in different studies. With the exception of one study [4] where there was infection clearance in eight of 17 with two PJI-related deaths, four relapses, and three antibiotic suppressions, the results of favorable outcomes ranged from 75 to 90%, but with different periods of follow-up from as short as 90 days to more than one year. Adverse drug reactions have also been reported; however, due to the small number of cases, meaningful conclusions could not be established, with the incidence of ADRs ranging from 3 to 13%, including rash, tachycardia, leukopenia, and impaired renal function.

Oritavancin

There were three studies, published between 2017 and 2020, that discussed the use of oritavancin in a small number of cases [6,7,13]. Among 576 patients receiving oritavancin, only 29 were being treated for PJI: two patients in one study [6], three in the second [7], and 24 in the third study [13]. The majority of microorganisms were *Staphylococcus aureus* with MRSA, MSSA, and one case of methicillin-resistant *Staphylococcus epidermidis* (MRSE). The dose regimens were variable, with one consisting of 1,200 mg twice every two weeks, one starting with 1,200 mg followed by 800 mg weekly, and the third 1,200 mg every 10 days. There were no specifications about the surgical intervention, except in one study where two cases were treated with a one-stage procedure. The infection clearance rate was two out of three after 30 days in one study, two out of two after six months in the second study, and 20 out of 24 (83.3%) in the third study, at three and six months. Adverse drug reactions were reported for the total group of infections, varying between 3.7 and 6.6%, but not specified among the PJI cases.

Fosfomycin

There were two studies published in 2019 discussing the use of fosfomycin in the treatment of PJI [14,15]. Among 95 PJI patients, 54 received fosfomycin in combination, mainly with vancomycin and daptomycin. There were 55 hips, 35 knees, two elbows, two shoulders, and one ankle. Isolated organisms included *Enterococcus faecalis*, *Enterococcus faecium*, and *Enterococcus casseliflavius* in one study [14], as well as *Enterobacter cloacae* in the other study [15]. The administration regimen was not identified in one study and consisted of five grams intravenously every three hours in the second study, with a mean duration of treatment of 14 days (range, three to 90). Different surgical interventions were used, including DAIR, one and two stages, with two cases of arthrodesis. Against Enterococcus species, the infection clearance was 85% (a cure rate of 95% for the group with added fosfomycin compared to an 80% cure rate for the group without fosfomycin. ($P = 0.621$). There were no specific adverse drug reactions reported for fosfomycin.

5th Generation Cephalosporin

Although ceftaroline and ceftobiprole have proven effective against both Gram-positive and Gram-negative organisms in various reports, we could not identify clinical studies addressing the treatment of PJI with 5th-generation cephalosporins.

Conclusion and remarks

Only a few studies have investigated the use of long-acting antibiotics or fosfomycin and 5th-generation cephalosporins in the treatment of PJI. Most of the current studies include retrospective small cohort studies (extracted from a mixed series of infections) and case reports. Longer-term follow-up was not available in most cases. The decision of their use, as well as the choice of surgical plan, was primarily individualized by physicians with no uniform criteria of use.

The few studies of dalbavancin suggested that its administration allowed earlier discharge, reduced hospital stay with a potential for outpatient treatment, and seemed to be safe, effective, and it can be cost-saving, and can even be used as a salvage therapy [3,4].

Regarding the very scant data on the use of oritavancin, it appeared at this juncture to be a safe and effective alternative to daily antibiotic infusions to treat complicated Gram-positive infectious disease processes.

With little available evidence, fosfomycin was found to be of value as an additive agent to other antibiotics. There is no evidence on the clinical use of 5th-generation cephalosporins that could be found in PJI patients.

Still, the current information could provide a starting point for performing new, well-structured studies evaluating these new compounds.

Question 2: Given recent warnings regarding the use of fluoroquinolones, is there a role for these antibiotics in the management of Gram-negative and staphylococcal periprosthetic joint infections treated with implant retention when other alternative antibiotic options are available?[2]

Recommendation

Based on their efficacy and the low absolute risk for serious adverse events, fluoroquinolones have a role in the management of Gram-negative and staphylococcal periprosthetic joint infections treated with DAIR.

Relevant pretreatment investigations, screening of medication lists, patient information, and careful monitoring during treatment should be considered in patients at risk for serious adverse events.

Level of Evidence: Limited

Delegate Vote: Agree 87%, Disagree 11%, Abstain 2% (Super Majority, Strong Consensus)

[2] These authors contributed to Question 2: Staffan Tevell, Craig Aboltins, Angela Hewlett, Dolors Rodriguez Pardo, Bernadette Young

Background

Fluoroquinolones (FQs) are commonly used in the oral treatment phase of periprosthetic joint infections (PJIs) caused by Gram-negative bacteria and staphylococci [16–21]. Due to reports of significant adverse events such as tendinopathy, neuropathy, dysglycemia, and aortic aneurysm, regulatory agencies have issued warnings on the use of FQs [22–27]. While these warnings do not specifically target PJIs, caution is recommended, particularly in certain patient categories. This review summarizes the risks and benefits of using FQs in PJI treatment.

Fluoroquinolone use in PJIs

Gram-negative PJIs (GNB-PJIs)

There were seven cohort studies that compared FQ-containing regimens to alternative treatments. Of these, four studies reported a benefit associated with FQs [1,6,12,13]. A pooled analysis of data from 326 patients across six studies [28–33] found a statistically significant increase in treatment success with FQ therapy (reported cure rate of 83 versus 57%, $P = 0.0001$). In contrast, a recent prospective cohort containing 100 patients did not find any significant advantage in using FQs in GNB- PJIs [34].

Staphylococcal PJIs treated with DAIR

There were 12 observational studies that compared FQ-containing antibiotic regimens to other regimens in staphylococcal PJIs treated with DAIR [29,35–45]. Most found no statistically significant difference in outcome. However, in a pooled analysis of unadjusted data from 778 patients in eight studies [29,35–41], an FQ-based regimen showed an association with improved treatment success (reported cure rate of 87 versus 75%, $P < 0.0001$).

Several studies detected a positive effect of FQs on the univariate analysis, but not the multivariate analysis [40–42]. Shabana et al. found that resistance to FQs was an independent risk factor for clinical failure in multivariate analysis [45], while Senneville et al. reported that FQ/rifampin therapy independently predicted remission [37]. A meta-analysis suggests that FQ/rifampin combinations were more effective than other rifampin-containing antibiotic strategies [46].

Review of potential adverse events during fluoroquinolone therapy

Tendinopathy

Animal models demonstrate FQ-induced tendon lesions [47], and observational studies in humans have evaluated the risk of tendon injury/rupture associated with FQ treatment [48–56]. An increased incidence of tendinopathy has been reported in connection with FQ use; in one large, population-based study, the incidence of tendinitis was 6.61 per 10^5 person-years for FQ-treated patients compared with 3.64 for controls [57–59]. An elevated risk of levofloxacin compared to ciprofloxacin or moxifloxacin was reported in several studies [32–35], but a focused systematic review did not confirm this differential risk [60]. FQ therapy with ciprofloxacin or levofloxacin within three months of surgical tendon repair for Achilles or rotator cuff injury was associated with higher revision rates within two years [48]. Various comorbidities and patient factors may increase the risk of FQ-associated tendinopathy [52–55,57,61].

QT prolongation and arrhythmia

The FQs can prolong the QT interval [62,63]. A small, uncontrolled retrospective cohort study reported that ventricular tachycardia occurred in 0.2% of patients with long QTc at baseline treated with levofloxacin [64]. While some studies link moxifloxacin to a higher risk of arrhythmia [65,66], other studies found no significant differences compared with other antibiotics [63,65–67]. Studies of levofloxacin have likewise yielded mixed results [65,66,68–70]. Large population studies, such as those by Polgreen et al. and Ellenardottir et al., did not find an excess risk of ventricular arrhythmia or out-of-hospital cardiac arrest with FQs [71,72].

Aortic aneurysm and/or dissection (AA/AD)

The FQ-induced collagen degradation is hypothesized to occur in vascular walls and may increase the risk of AA/AD [73]. However, the relationship between FQs and AA/AD remains controversial. Epidemiological studies report divergent results regarding the relationship between FQs and AA/AD [51,74,67,75–89], and only two of these reported stratified data on the different FQs [48,84]. Aortic mortality was higher in FQ users with pre-existing AA/AD [75,90]. Dong et al. demonstrated an association between infectious conditions and AA/AD [89]. The association of AA/AD to FQs with amoxicillin as a comparator initially found by Gopalakrishnan et al. did not retain significance when patients without baseline imaging were excluded [71]. There were five systematic reviews that all reported increased risk for AA after FQ use when compared to other antibiotics or no antibiotic treatment [90–94]. However, two reviews found no association with AD [92,93], and one reported no higher risk for AA/AD when compared with other broad-spectrum antibiotics [93].

Peripheral neuropathy and CNS toxicity

The FQ use has been associated with peripheral neuropathy, exacerbation of myasthenia gravis, and central nervous system (CNS) neurotoxicity [95–98]. There were three case-control studies that reported an elevated risk of peripheral neuropathy during/after FQ use compared to controls [99–101]. Morales et al. reported increased risk for peripheral neuropathy persisting up to 180 days after FQ exposure [101]. Regarding CNS toxicity, Ellis et al. reported an HR of 1.08 (95% confidence interval (CI) 1.05 to 1.11) [89].

Retinal detachment (RD)

There were 11 studies investigating whether FQ-associated collagen degeneration could lead to RD [102–112]. Etminan et al. showed an increased relative risk (RR) of 4.50 (95% CI 3.56 to 5.70) for current use of FQs and RD and found no risk with recent or past use [94], but these results could not be replicated in another setting [95]. Other studies likewise report conflicting results, including some reporting associations with multiple other antibiotics as well as FQs [92–95]. There were two systematic reviews that did not support an association between FQ use and RD [113,114].

Dysglycemia

Dysglycemia, including hypoglycemia and hyperglycemia, has been documented during FQ therapy [105–109]. This was seen particularly for patients with diabetes, where moxifloxacin [115,116] or levofloxacin [117,118] was used, increasing when combined with insulin or sulfonylurea [109]. A systematic review concluded that caution must be taken when using FQs in diabetic patients and that ciprofloxacin may be the FQ least likely to cause dysglycemia [119].

Conclusion

Available data suggest, with moderate certainty, a potential independent benefit in treating GNB-PJI managed with DAIR with FQs. For staphylococcal PJI treated with DAIR, there is some evidence for improved clinical outcomes when combining FQs and rifampin compared with other rifampin combinations and non-rifampin-based regimens. Current evidence suggests that FQ use is associated with an increased risk of tendinopathy, peripheral neuropathy, and dysglycemia in diabetics, even though the absolute risk is low. There is conflicting evidence for an association between FQs and cardiac arrhythmia, aortic aneurysm and dissection, and retinal detachment.

Acknowledgments

After requesting and receiving approval from the Executive Committee of the ICM, the authors continued and expanded the work started for ICM in order to finalize a full systematic review [120].

Funding

S.T. is supported by the Research Committee of Region Värmland (LIVFOU) and by grants from the Swedish state under the ALF agreement between the Swedish government and the county councils (Region Örebro County, Sweden OLL-967677). B.Y. is supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC).

Question 3: What antibiotics are available for patients who have implant-associated infections caused by fluoroquinolone-resistant Gram-negative organisms?[3]

Abstract

Most observational studies support the use of fluoroquinolones for prosthetic joint infections caused by Gram-negative bacilli, especially when managed with debridement, antibiotics, and implant retention. Prognosis has been observed to be worse when this class of antimicrobials cannot be used; an alternative treatment needs to be defined. However, there are no prospective comparative studies to support a given antimicrobial regimen. Among the most promising alternatives, the use of intravenous beta-lactams, with or without colistin, may provide good rates of success. The efficacy of oral co-trimoxazole is uncertain. Other treatments, such as intravenous fosfomycin or tetracyclines, need further studies to be recommended. Response/Recommendation: The use of intravenous active beta-lactams during the entire treatment duration, with or without the combination of colistin, may lead to success rates similar to those of fluoroquinolones. Co-trimoxazole may also play a role in the treatment.

Response/Recommendation

The use of intravenous active beta-lactams during the entire treatment duration, with or without the combination of colistin, may lead to success rates similar to those of fluoroquinolones. Co-trimoxazole may also play a role in the treatment.

Strength of Recommendation: weak

Delegate Vote: Agree: 90.2%; Disagree: 5.9%; Abstain: 3.9%

Methods

A database search was performed in PubMed and Scopus using a predefined strategy (see Supplementary Material). Titles were screened and abstracts reviewed using Covidence. Supplementary references from reviewed papers were added as appropriate. Overall, there were 231 articles retrieved, of which 29 were finally included in our review.

Rationale

Most observational studies consistently support the use of fluoroquinolones (mainly ciprofloxacin) as the antibiotic of choice for prosthetic joint infections (PJI) caused by Gram-negative bacilli (GNB), especially when managed with DAIR [112–115,117,121]. Notwithstanding, the incidence of GNB PJI is rising, along with an increase in the number of episodes caused by fluoroquinolone-resistant bacteria [118]. There is a scarcity of clinical publications addressing the optimal antibiotic therapy for fluoroquinolone-resistant GNB PJI, and no comparative studies have been performed to date. Based on the available observational studies, the main alternatives to fluoroquinolones are summarized below.

- Intravenous beta-lactams. While there is evidence supporting the possibility of using oral antibiotics for bone and joint infections [122,123], most beta-lactams have low bioavailability and poor bone penetration [124]. Moreover, their activity against biofilm-embedded bacteria is poor compared to other antibiotic classes [125]; thus, optimization of the pharmacokinetics may be critical to ensure sufficient anti-biofilm activity. Intuitively, if the treatment of PJI relies on active concentrations of these antibiotics at the site of infection, it may be wise to ensure high serum levels through intravenous administration [126]. Also, a pharmacokinetics-pharmacodynamics as an optimized posology and a continuous or extended infusion may be considered [127]. In this regard, Grossi et al. reported an 83% cure rate in patients with PJI caused by fluoroquinolone-resistant GNB after treatment with IV beta-lactams for a median of 90 days, including 71% success for patients managed by DAIR. Of note, the cure rate was similar to that of PJI caused by fluoroquinolone-susceptible GNB treated with ciprofloxacin [126]. Unfortunately, there are no head-to-head comparisons between different beta-lactams; hence, the choice for a specific antibiotic is usually made in accordance with standard antimicrobial susceptibility tests (i.e., minimal inhibitory concentration). The arrival of new beta-lactams with beta-lactamase inhibitors that are active against extended-spectrum beta-lactamases and carbapenemase-producing microorganisms will increase the available treatment options, although additional comparative studies are still needed.
- Colistin- or fosfomycin-based combinations. The rationale for combining colistin (polymyxin E) with a second antibiotic is based on its activity against GNB located within the inner layers of biofilms – a mechanism that is complementary to that of most antibiotics against the superficial stratum [128]. Additionally, the mechanism of action of colistin may enhance the permeability of other drugs [129]. Colistin has, in fact, demonstrated a synergistic or additive effect when combined with other antimicrobials in the biofilm experimental setting [130,131]. The two single-center retrospective studies focusing on pseudomonal osteoarticular infections (both including orthopedic-related infections and PJI) showed good results with the combination of colistin plus IV beta-lactams (cure rates of 73 and 82%) [132,133]. Furthermore, in a recent prospective multicenter study performed in patients with bone and joint infections caused by fluroquinolone-resistant GNB (n = 44, 73% with orthopedic-related infection, 34% PJI) managed with surgery plus colistin plus IV beta-lactams for a median of four weeks followed by two additional weeks of IV beta-lactams, the long-term cure rate was reported to be 82%, with good results also reported in certain subgroups of patients (e.g., cases managed by DAIR, cure 80%) [134]. One major

[3] These authors contributed to Question 3: Jaime Lora-Tamayo, Ben Clark, Tobias Siegfried Kramer, Sunil Sharma, Graham S. Goh, Joan Gómez-Junyent

downside of this antibiotic regimen is the renal toxicity of colistin (with one study reporting antibiotic withdrawal of 20%), although this was always reversible and may be foreseen by therapeutic drug monitoring (TDM) [134]. Combinations of IV fosfomycin could be an alternative to colistin [135], but dosages remain uncertain [136], and the minimal inhibitory concentration may be high for *Klebsiella* spp. and *P. aeruginosa* [137]. Also, while there is some evidence of its efficacy in the setting of bone and joint infections [132], there have been few reports in PJI management. In a recent retrospective case series of pseudomonal PJI mainly managed with exchange arthroplasty, Prié et al. reported a 90% cure rate in a subgroup of eight patients treated with beta-lactams plus fosfomycin [138].

- Co-trimoxazole has the advantage of oral administration due to its high bioavailability [139]. It is a classic alternative to fluoroquinolones for the treatment of GNB infections. However, there is a surprising lack of clinical data specifically addressing the outcome of patients treated with this antimicrobial. Moreover, previous animal models on foreign-body infection demonstrated a very low activity of co-trimoxazole [130]. In various large series of GNB PJI that included a few patients treated with co-trimoxazole, poor results were also reported [125,127]. In addition, co-trimoxazole lacks antimicrobial activity against certain GNB, such as *P. aeruginosa*. Despite these considerations, one prospective multicenter study of GNB PJI reported a 92% cure rate among 13 patients treated with co-trimoxazole (double-strength tablets, bid), although only 4% of microorganisms were fluoroquinolone-resistant [131].

It is clear that the efficacy of the above-mentioned antimicrobial strategies should be confirmed with comparative studies. Other antimicrobials could be considered given their in vitro activity, but lack significant data to support their use. In this regard, tigecycline may also play a potential role in the treatment of fluoroquinolone-resistant Enterobacterales, although experimental studies suggest poor activity against biofilms in monotherapy [135], and only anecdotal reports of its use have been published [133]. Furthermore, additional studies regarding the efficacy of local antimicrobials (administered either by intra-articular infusion [140] or by other carriers) or phage therapy [141] should be performed.

Conclusion

The optimal antibiotic treatment of PJI caused by fluoroquinolone-resistant GNB remains uncertain. Clinical data are scarce and heterogeneous. Despite this, the use of extended IV infusions of beta-lactams with *in vitro* activity against the specific GNB, alone or in combination with colistin, may provide rates of success comparable to those of fluoroquinolones. Their use must be weighed against the risk of toxicity and the drawbacks of IV therapy. The use of co-trimoxazole may be considered as a sequential oral adjunct.

Supplementary material – initial strategy search used

("arthroplasty"[MeSH Terms] OR "orthopedic procedures"[MeSH Terms] OR "arthroplast*"[Text Word] OR "artificial joint"[Text Word] OR "joint replacement*"[Text Word] OR (("joint"[Text Word] OR "orthopedic"[Text Word] OR "orthopedic"[Text Word]) AND ("implant*"[Text Word] OR "prostheses"[Text Word] OR "prosthesis"[Text Word] OR "prosthetic*"[Text Word])) OR "orthopedic operative"[Text Word] OR "orthopedic operative"[Text Word] OR "orthopedic procedure*"[Text Word] OR "orthopedic procedure*"[Text Word] OR "orthopedic surger*"[Text Word] OR "orthopedic surger*"[Text Word] OR "orthopedic surgical"[Text Word] OR "orthopedic surgical"[Text Word] OR (("spinal"[Text Word] OR "spine*"[Text Word] OR "vertebr*"[Text Word]) AND ("implant*"[Text Word] OR "prosthe*"[Text Word] OR "surg*"[Text Word]))) AND ("infections"[MeSH Terms] OR "prosthesis related infections"[MeSH Terms] OR "surgical wound infection"[MeSH Terms] OR "infection*"[Text Word] OR "PJI"[Text Word] OR "PJIS"[Text Word] OR "SSI"[Text Word] OR "SSIS"[Text Word] OR (("prosthetic*"[Text Word] OR "perioprosthetic*"[Text Word] OR "perio prosthetic*"[Text Word]) AND "joint* infect*"[Text Word])) AND ("Fluoroquinolones"[MeSH Terms] OR "Fluoroquinolones"[Text Word] OR "Ciprofloxacin"[Text Word] OR "Fleroxacin"[Text Word] OR "Enoxacin"[Text Word] OR "Enrofloxacin"[Text Word] OR "Gatifloxacin"[Text Word] OR "Gemifloxacin"[Text Word] OR "Moxifloxacin"[Text Word] OR "Norfloxacin"[Text Word] OR "Ofloxacin"[Text Word] OR "Levofloxacin"[Text Word] OR "Pefloxacin"[Text Word]) AND ("Drug Resistance"[MeSH Terms] OR "resist*"[Text Word]) AND (((1990/01/01:3000/12/12[Date - Publication] AND "english"[Language]) OR ("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract])) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]))

Question 4: Is there any antibiotic in development that has better bone penetration?[4]

Response/Recommendation

There is a new class of bone-targeted antibiotics under development for which indirect evidence of better bone penetration versus unconjugated parent antibiotics exists.

Level of Evidence:

Moderate

Delegate Vote

Agree: 88%, Disagree: 7%, Abstain: 5% (Super Majority, Strong Consensus)

Rationale

The use of systemically administered antibiotics is a key component in the prevention and treatment of bone infections [142]. The therapeutic success of antibiotic use depends on their bone penetration profile [143]. The aim of this review was to identify any antibiotics in development that have better bone penetration in a prosthetic joint infection setting.

PubMed and Scopus were searched for potentially eligible studies from data inception to December 31, 2024. The search strategy included terms such as "bone penetration" OR "bone concentration" AND "anti-bacterial agents" OR antibacterial OR antibiotic,* OR “bone-targeted antibiotic,” OR “bisphosphonate-conjugated antibiotic.” In our initial literature review, 1,217 records were retrieved. After removing 126 duplicates, the titles and abstracts of 1,091 studies were screened. A total of 229 studies were then subjected to full-text review. Ultimately, 14 studies were included in the review [144–157].

There are a number of studies on the bone penetration of new antibiotics such as dalbavancin, oritavancin, afabicin, levonadifloxacin, and cefiderocol [153–157]. These antibiotics demonstrate a bone penetration profile exceeding the minimum inhibitory concentration for a number of bone and joint infection pathogens. However, the methodological variations across the studies preclude a definitive conclusion regarding the superior penetration of

[4] These authors contributed to Question 4: Rashid M. Tikhilov, Alisagib A. Dzhavadov, Katherine A. Belden, Mats Bue, Hakan Kocaoğlu, Leibnitz J. Martinez, Mohammad Saeed, Edward Schwarz, Kenneth L. Urish

these antibiotics compared to those previously developed. These differences included sample sizes, therapeutic scenarios, species, tissue sampling methods (bone biopsy or dynamic methods such as microdialysis), analytical assays, and tissue processing techniques. In addition, the presence of various orthopedic implants, which are poorly investigated, may also influence the results of antibiotic penetration into bone.

There is also a new class of drugs referred to as "bone-targeted antibiotics" in which antibiotics are either chemically linked to known molecules with high affinity to bone, such as bisphosphonate-conjugated antibiotics (BCAs), or encapsulated in a vector that has high affinity to bone [158–166].

We reviewed five studies on various BCAs [149–153]. In their first study, Sedghizadeh et al. showed high-binding of ciprofloxacin-conjugated bisphosphonate to hydroxyapatite and its efficacy against MSSA, MRSA, *Pseudomonas aeruginosa*, and *Aggregatibacter actinomycetemcomitans in vitro* and *in vivo* in a rat model of implant-associated osteomyelitis [149]. In a follow-up study, these investigators evaluated quinolone antibiotics and several bisphosphonate-conjugated versions of these antibiotics and found that they were able to inhibit *Staphylococcus aureus* biofilms in a dose-dependent manner [150]. Adjei-Sowah et al. demonstrated the cytolytic activities of bisphosphonate and hydroxy bisphosphonate conjugates of sitafloxacin and tedizolid against MSSA and MRSA on bone wafers *in vitro* [151]. Ren et al. performed two *in vivo* studies with bisphosphonate and hydroxy bisphosphonate conjugates of sitafloxacin and demonstrated their ability to prevent and treat MRSA implant-associated osteomyelitis in murine models [161,162].

We also reviewed four studies evaluating encapsulated antibiotic treatments with bone-targeted constructs [163–166]. Cong et al. performed pioneering work with vancomycin encapsulated with micelles [163]. Lin et al. demonstrated that calcium-risedronate nanoparticles (Ca-RISNPs) can strongly bind to and penetrate human bone tissues *ex vivo* [164]. Aguilera-Correa et al. evaluated the efficacy of bone-targeted mesoporous silica nanoparticles against MRSA *in vitro* and in a rabbit model of osteomyelitis [165]. Sun et al. showed that β-cyclodextrin, modified with poly (ethylene glycol) [PEG] and aspartic acid hexapeptide (Asp6-β-CD), specifically targets the hydroxyapatite (HA) component of the bone *ex vivo* and significantly enhances accumulation of unmodified β-CD 10-fold in a nude mouse model. These investigators also showed that norfloxacin efficacy in a rat osteomyelitis model was significantly increased by loading it into the Asp6-β-CD construct [166].

Reviews by Tabit et al. [167] and Nielsen et al. [168] reported that previously developed antibiotics showed good bone penetration, reaching concentrations exceeding the minimum inhibitory concentration of common bone and joint infection pathogens. Moreover, these studies underscore that as technological advancements progress, research methodologies evolve accordingly. This development facilitates the execution of new studies, thereby enhancing the potential for obtaining novel insights regarding bone penetration characteristics.

In addition to studying the penetration of new versus clinically approved antibiotics into orthopedic tissues, it is essential to develop clear and consistent methodological protocols for these studies. This would enable comparison of the results regarding the efficacy of different antibiotics in terms of their bone penetration potential.

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The Journal of Arthroplasty 41 (2025) S206–S209

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

General Topics

2025 ICM: Immune Status

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Question 1: Should the immune status of patients who have orthopaedic infections be evaluated?[1]

Response/Recommendation

There is insufficient evidence to support routine assessment of the immune status of patients who have orthopaedic infections. However, studies to evaluate the immune status of some infected patients, such as those who have multiple failures and immunocompromised status, may be justified.

Level of Evidence: Limited

Delegate Vote: Agree: 88.9%, Disagree: 6.6%, Abstain: 4.5% (Super majority, strong consensus)

Rationale

The incidence of implant-related orthopaedic infection is increasing in concordance with the increased number of arthroplasty procedures occurring annually. This increased incidence is in part due to the aging population and advancements in modern prosthetics [1]. However, while surgical technology has advanced, we still lack definitive means by which to identify, characterize, and manage orthopaedic infection. A target for the development of better diagnostics and interventions has been host immune status [2]. Immune markers may help diagnose infection and identify offending bacteria in periprosthetic joint infection (PJI), as well as provide targets for preoperative optimization to prevent infection after primary arthroplasty. We reviewed 17 studies that assess how immune markers behave in the setting of orthopaedic infection.

There is no gold standard for diagnosing PJI. Scoring systems like the Musculoskeletal Infection Society criteria and Infectious Diseases Society of America can sometimes yield ambiguous results, potentially leading to inappropriate or substandard treatment [1,3,4]. These current diagnostic tools rely upon culture, serum markers (CRP, ESR), and imaging. However, some of these tests lack precision and may be expensive [3]. Using these extant diagnostic systems, complications following total joint arthroplasty, such as PJI and noninfectious arthroplasty failures, can be difficult to distinguish [1,3]. Inclusion of immune biomarkers and synovial proteomic analysis could improve diagnostic yield in these settings. For example, Fisher et al. demonstrated that PJI can be distinguished from noninfectious arthroplasty failure via the levels of antimicrobial inflammatory proteins in the serum. Additionally, there are several checkpoint molecules (BTLA, PD-1, CTLA-4) that are markedly different between the aspirates of PJI patients and those who have aseptic implant failures. Further studies demonstrate that certain serum marker combinations, such as the albumin/globulin ratio and CRP-albumin ratio, offer a highly sensitive way to differentiate between high- and low-grade PJI [5]. Gedbjerg et al. [6] demonstrated that supplementing CRP testing with anti-Gmd IgG titers can improve diagnostic sensitivity among Staphylococcus species and identify methicillin-resistant *Staphylococcus aureus* even in culture-negative cases. Using immunoassays to measure IgG levels has also shown promise in differentiating between types of orthopaedic complications, such as osteomyelitis and PJI. These measurements could be used for diagnosis, but also for monitoring a patient's ability to clear an infection [7,8]. These examples underscore the potential for adding immune marker testing to improve diagnostic precision and treatment plans for orthopaedic complications.

Biofilms play a critical role in the formation of implant-associated infections. The most common pathogens are Staphylococcus and Streptococcus species. Certain strains of *S. epidermidis* and *S. aureus* have greater biofilm-forming capacity than other strains [2,9]. Biofilms can disrupt cell-mediated immunity and modify neutrophil function in favor of their formation. Many studies have demonstrated that biofilms decrease CD3+ T cells, CD4+ T helpers, and CD8+ T suppressors [2,4,9,10]. Additionally, biofilms may induce monocyte myeloid–derived suppressor cells (MDSCs), which are increased in PJI patients. Since these cells have an immunosuppressive role, medically targeting them may have a therapeutic role in the future.

Al-Ishaq et al. [11] postulated that immune markers such as C5a may be useful in distinguishing between types of biofilms in PJI. Some biofilms require polysaccharide intercellular adhesin (PIA) to

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.097.

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https://doi.org/10.1016/j.arth.2025.10.097
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grow on prosthetics. This is important because some PIA-expressing biofilms are more effective in immunosuppressed patients. It was found that C5a levels may be able to differentiate between PIA-dependent and independent biofilms, potentially leading to improved diagnostics and treatment specificity. Understanding how biofilms impact immunity underscores the importance of immune surveillance for future diagnostic or therapeutic studies.

Many host conditions, such as rheumatoid arthritis, seronegative arthropathies, and HIV, lead to immune dysregulation and increased PJI risk [2]. In addition to screening for common immune-modulating illnesses, Conway et al. recommend assessing for immunoglobulin deficiencies preoperatively, as low immunoglobulins were strongly associated with reinfection risk [12]. There is also a suggested association between vitamin D deficiency and PJI [13,14]. It is well known that vitamin D plays a major role in bone health, but it has also been shown to modulate the immune system in favor of preventing infections. This suggests that testing vitamin D levels before elective orthopaedic procedures could potentially help identify patients at risk of developing infection. Further randomized controlled trials need to be conducted, as causality cannot be established by the extant literature.

Evaluating a patient's thyroid function may also prove to be efficacious, as hypothyroidism is linked to impaired immune function. It is suggested that addressing thyroid imbalances before surgery may help prevent future PJI [15]. Similarly, it may also be worth assessing a patient's nutritional status via albumin to determine a patient's ability to fight infection before undergoing orthopaedic surgery [16].

Overall, more research is needed to determine the best way to evaluate a patient's risk for PJI; this testing may include genetic testing for alleles linked to increased PJI susceptibility [17]. Drawbacks to immune system profiling include high cost and logistical challenges. Limited access to advanced tests may impede the ability to develop universal protocols. Also, identifying patients who would benefit from additional preoperative testing remains a challenge.

Conclusion

Patients' immune status may impact the diagnostic accuracy and risk of developing PJI. Unfortunately, of the extant studies, there are limited prospective analyses, and therefore, no clinical consensus can be made as to the best immunologic markers for assessing infection. Surgeons should consider the immune status of patients before indicating primary total joint arthroplasty to minimize the risk of infection.

Question 2: Is there a role for immunotherapy in patients who have orthopaedic implant-associated infections?[2]

Response/Recommendation

Preclinical models are promising in multiple areas of immunotherapy, so while the potential is high, human clinical studies are still needed to elucidate the role of immunotherapy in the management of orthopedic infections.

Level of Evidence: Moderate

Delegate Vote: Agree: 91%, Disagree: 4.5%, Abstain: 4.5% (Total Consensus, Unanimity)

Rationale

With the recent boom in biomedical implants due to an aging population, implant-associated infection (IAI) has become a widespread threat [18,19]. Humans possess powerful armament in their own immune system. The immune system can respond rapidly and specifically to pathogens; however, its function is affected by the implanted biomaterials [18,20]. Immunotherapy for IAI can broadly be grouped into three categories: immunization/vaccination, implant immunomodulation, and antimicrobial peptides (AMPs).

The most studied immunotherapy technique in medicine broadly is immunization/vaccination. The role of vaccination has been heavily studied, particularly focusing on *S. aureus* for obvious reasons as a major health care–acquired infection [21,22]. One immunization utilized the SA4Ag vaccine, which demonstrated a great immune response and overall success in preclinical trials [23]; however, Hassanzadeh et al. failed to show a difference in infection rates between the SA4Ag and placebo groups in elective spine surgery [21]. Importantly, despite the same infection rates, there was evidence of an immune memory response to antigens in the vaccination group [21]. Fowler et al. utilized another *S. aureus* vaccine, the V710 vaccine, in a full-scale clinical trial for median sternotomy patients after the vaccine demonstrated preclinical and early clinical successes [24–28,29]. Unfortunately, the trial was stopped early due to lack of efficacy with slightly poorer clinical outcomes in the vaccinated group despite evidence of an immune response [22]. Therefore, to date, preclinical successes have not translated to full-scale phase 2 to 3b trial success in reducing infection rates, even while eliciting strong immune responses for the vaccine candidates that have progressed to those stages. Despite previous failures, immunization/vaccination continues to be an important area of research due to the potential impact that success would achieve in orthopaedic infections and beyond.

Implant immunomodulation is another promising area of immunotherapy in the field of orthopaedics. Most current biomaterials are identified as foreign by the immune system and targeted for destruction, leading to a reduction of immune cells available to combat bacteria [18]. This targeting leads to chronic inflammation, reducing wound healing as well [18]. Neutrophils (polymorphonuclear neutrophils) are the predominant immune cell present immediately after invasion and utilize various strategies to clear pathogens [18,30,31]. Macrophages follow neutrophils in the immune response and come in two main subpopulations: proinflammatory and anti-inflammatory [18,32]. Proinflammatory macrophages aid by phagocytosing remaining pathogens and secreting inflammatory cytokines such as IL-12 and TNF-α, while anti-inflammatory macrophages promote wound healing and reduce antibacterial activity by producing markers such as IL-10 and arginine [18,33]. Another population of cells, MDSCs, possesses a unique ability to suppress T cells, and several studies have illustrated increased MDSCs surrounding an IAI, playing a role in biofilm formation by bacteria [21,22,33]. Emerging evidence indicates T cells and B cells may play a role in IAI; however, this role has not been fully elucidated [18,33].

Historically, traditional biomaterials lacking antibacterial activity have been used, necessitating antibiotic administration [18,34]. Furthermore, many bacteria form biofilms, which increase resistance to antibiotics, promoting bacterial proliferation and reducing the efficacy of the immune system [35]. The traditional biomaterials, such as titanium, have been shown to break down in response to IAI and promote inflammation, reducing osseous integration and wound healing [36]. Nonmetallic biomedical implants have been developed; however, these face similar challenges regarding implant failure, predilection for infection via biofilms, and the ability to create sustained inflammation that impedes the ability of the immune system to fight off pathogens [18,37,38]. Given the susceptibility to infection and growing

[2] These authors contributed to Question 2: Austin Helton, Humaid Al Farli, Jeremy Gililland, Aree Tanavalee, Kyle H. Cichos

antibiotic resistance of bacteria, newer strategies to prevent IAI have begun focusing on manipulating the immune system instead of solely focusing on direct antibacterial activity. There were two main strategies that evolved: passive and active immunomodulation [18,33,39].

Passive immunomodulation relies on changing surface morphology to deter biofilm formation and stimulate autoimmunity [33,39,40]. To further complement passive strategies, bioactive molecules such as host defense peptides, metal nanoparticles, and gasotransmitters are loaded onto the biomaterial [18,33,41]. Promising results have arrived from many animal and *in vitro* studies. Regarding metal ions [41–45], Whu et al. demonstrated enhanced phagocytosis of bacteria by loading Cu-Sr onto a titanium alloy [41]. Guo et al. [43] demonstrated the ability of $CuFe_5O_8$ nanocubes to induce proinflammatory polarization and enhanced phagocytosis. However, this was only achieved with disrupted biofilms. Xiao et al. [43] created a Cu^{2+} dressing that promoted proinflammatory polarization while simultaneously exerting direct antibacterial effects in rat models. Raza et al. [44] found that small spherical-shaped Ag nanoparticles demonstrated strong antibacterial effects *in vitro*. All are very promising but remain largely in the preclinical stage.

Host defense peptides are proposed to contain antibacterial and immunomodulatory effects [18,46–48]. The IDR-1, an innate defensin, modulated genetic transcription leading to a controlled inflammatory environment that resulted in enhanced bacterial clearance *in vitro* and in mice [46]. Qu et al. [47] loaded LL-37 plasmid onto a scaffold and illustrated extracellular and intracellular antimicrobial effects, along with continued production of LL-37 by incorporating the gene into neighboring cells to facilitate continual effects, including inflammation control. Wang et al. [48] utilized DJK-5 to promote direct antimicrobial killing, along with promoting enhanced macrophage phagocytosis and inhibiting potentially harmful inflammatory cytokines such as IL-6 and TNF-α.

Other strategies include manipulating topography along with embedding metal ions/nanoparticles [49,50]. Fisher et al. [49] created a diamond nanocone surface mimicking cicada wings, which demonstrated bactericidal activity *in vitro* despite adhesion to the surfaces, with less uniform surfaces having higher activity. Liu et al. [50] fabricated a porous surface that effectively trapped bacteria, allowing the embedded copper to exert antibacterial effects *in vitro* and in animal models along with proinflammatory macrophage promotion. Recently, attention has turned to innate molecules such as beta-defensin-2 and other similar molecules secreted by the immune system. Borysowski et al. [51,52] recently used *E. coli* phages to induce expression of beta-defensin-2 along with other cytokines, suggesting the ability to modulate the immune system via phages. Su et al. utilized an acidity-activated metal-organic framework to release H_2S that stimulated cytokine production by anti-inflammatory macrophages to promote wound healing, along with direct antibacterial effects [29].

Also, AMPs are naturally occurring antimicrobials with broad-spectrum activity [53,54]. AMPs exhibit a low likelihood of drug resistance [38]. Systemic administration has been met with toxicity and fickle activity due to pH and ion concentration sensitivity [53,54]. However, two new synthetic AMPs have promising early results. Huang et al. engineered a synthetic AMP, PLG0206, to combat toxicity and recently had a successful phase 1 trial in humans [37]. PLG0206 is currently undergoing a phase 1b trial for outcome and safety profile in debridement, antibiotics, and implant retention patients, with results expected in the near future. Pennone et al. [54] created LL-37 segmental analogs to balance antimicrobial activity and toxicity. These analogs demonstrated effectiveness against 18 bacterial strains and *S. epidermidis* biofilms at safe levels during *in vitro* trials with human cells [54], with in vivo studies and eventual clinical trials to follow [54].

Given the many broad and unique strategies employed for immunotherapy in IAI, trends are beginning to emerge for possible strategies. Most implant immunomodulation studies utilized methods to promote proinflammatory and anti-inflammatory macrophages at specific time points during IAI. The metal ion–based and hypertensive disorders of pregnancy studies typically utilized the direct and indirect antibacterial effects inherent to the metal ion and hypertensive disorders of pregnancy. The appearance of the theme of dual action, both direct antibacterial and indirect via stimulation of the immune system, may be the most promising course of action preclinically. Immunization/vaccination has been promising until the point of full-scale clinical trials, which have been less successful to date. Antimicrobial peptides have been equally promising in the preclinical stages but are still awaiting large clinical trial results. Thus, while early results of numerous immunotherapy candidates have been promising, there have been few studies performed in humans, with most targets having only in vitro or animal models to date. Future human clinical studies are necessary to identify the true role of immunotherapy in IAI prevention/management.

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The Journal of Arthroplasty 41 (2025) S210–S221

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

General Topics

2025 ICM: Epidemiology, Mortality, Registries, Public Reporting, Specialized Treatment Centers, and Physical and Psychological Impact

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Question 1: Is the epidemiology of orthopaedic implant-associated infections changing?[1]

Response/Recommendation

Yes. The number and population incidence of periprosthetic joint infections (PJIs) is rapidly increasing, driven by an increased number of arthroplasty operations, an increase in cumulative incidence of early infections (particularly in hips), as well as an increased prevalence of people living with joint arthroplasties, who are at risk for late PJI.

Level of Evidence: Low

Delegate Vote: Yes: 94%, No: 4.0%, Abstain: 2.0%

Rationale

The incidence of arthroplasty procedures is increasing. In Organisation for Economic Co-operation and Development countries, the annual incidence of hip and knee arthroplasty operations is 174 and 134 per 100,000 population, respectively [1]. With aging populations, this is set to increase rapidly in both high- and middle-income countries in the coming decades. In parallel with the increase in total numbers and incidence of arthroplasty procedures, and due to improvements in the durability of implants, the prevalence of people living with at least one implant in the population is also increasing. As an example, in Australia, the prevalence of joint arthroplasty is increasing in all age groups but was highest among older Australians, with an overall prevalence of 22.5 and 13.3% in those aged > 85 years and 65 to 84 years, respectively. The prevalence of people living with multiple joint arthroplasties is increasing more rapidly than patients who have undergone only one joint arthroplasty procedure [2].

Understanding the relationship between the incidence of new arthroplasty procedures and the prevalence of joint arthroplasties in a population is an important consideration for the epidemiology of periprosthetic joint infection (PJI); the former represents infections acquired during the initial operation and is manifested by PJI occurring early in the postoperative period. Most PJIs occur within a few months of index surgery, but chronic failures may occur for some years. By contrast, late-acute PJIs can occur at any time from hematogenous seeding of the prosthesis. In this context, the population at risk is people living with a joint arthroplasty, reflected by the prevalence of joint replacements in the population.

We performed a systematic review to evaluate whether the epidemiology of implant infections is changing. PubMed and Embase databases were searched (Figure 1) from January 1, 1990 to December 31, 2024. Studies were limited to humans and in English. After being imported into COVIDENCE (Veritas Health Innovation, Melbourne, Australia; Available at www.covidence.org) and after deduplication, titles and abstracts were reviewed. Publications were included if they reported hip or knee PJI and any of (i) total numbers of PJI over time, (ii)

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to doi: 10.1016/j.arth.2025.10.111.

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https://doi.org/10.1016/j.arth.2025.10.111
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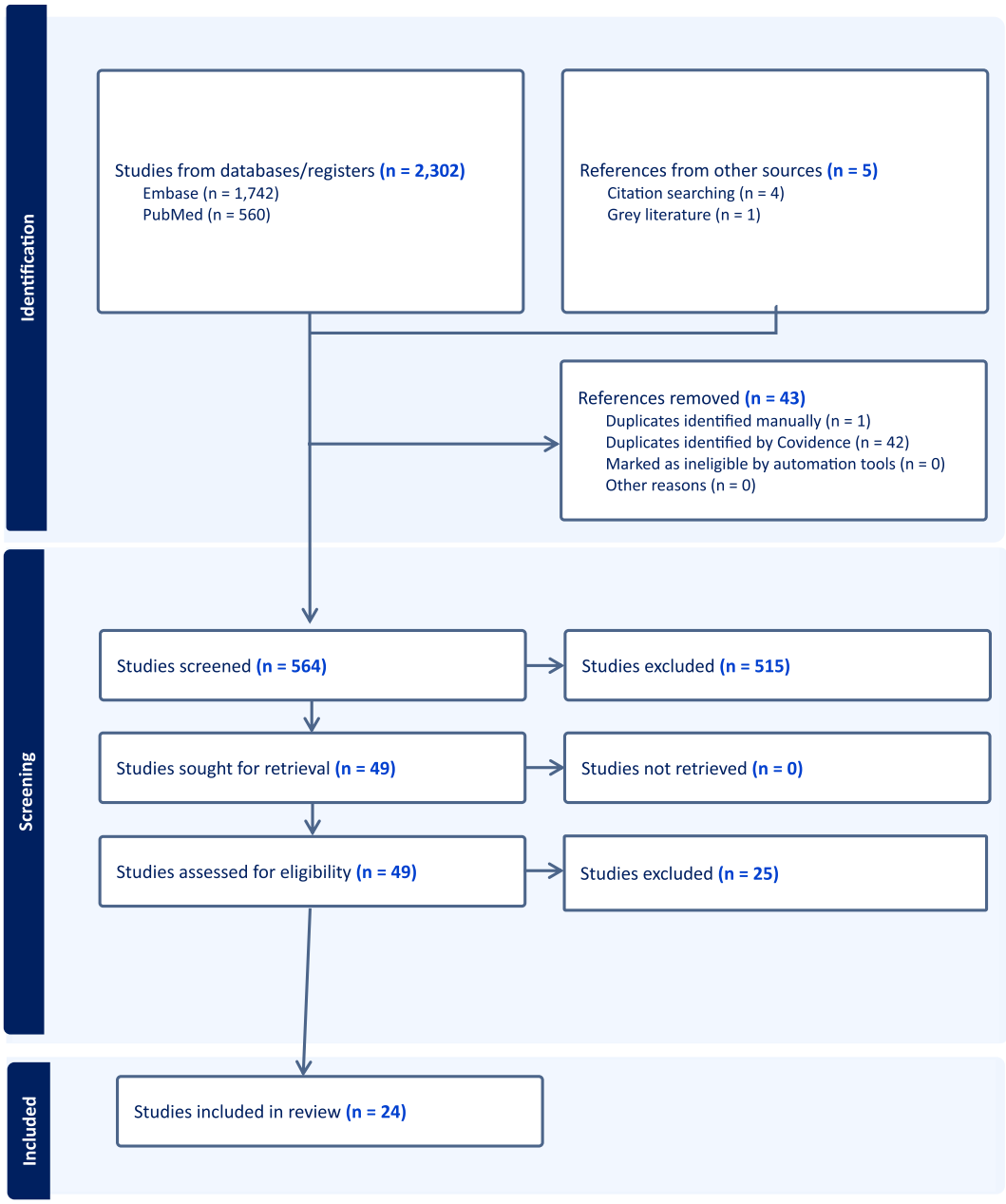

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram.

incidence (per year) as a denominator of the total population, (iii) cumulative incidence as a denominator of procedures or intravenous, and (iv) the proportion of confirmed PJIs that were early/chronic compared with late-acute or hematogenous PJIs. Citations within these papers and the "gray literature" were also searched. There were 24 publications included in the final narrative synthesis (Figure 1). Due to variation in reporting metrics, no quantitative synthesis was performed. One systematic review of the incidence of hip PJI was identified, which included 16 studies [3]. Interestingly, only one of these studies was identified in our systematic review. Similarly, a systematic review of deep surgical site infections (synonymous with PJI) identified 15, 22, and 24 studies for all, knee, and hip arthroplasty operations, respectively, without overlap with the studies identified in the present review [4]. Taken together, the lack of overlap suggests shortcomings with the search strategy employed here. Studies from the United States (n = seven), the United Kingdom (n = three), Australia (n = three), Canada, China, Taiwan, Korea, India, France, Denmark, Sweden, and Italy (one each) were identified.

The total burden of PJIs is rapidly increasing across most settings. There were eight studies reporting the total numbers of PJI over time, usually presented as a proportion of infections as the indication for joint arthroplasty revision. In Taiwan, PJI (both hips and knees) increased rapidly between 2004 and 2013, with projections of a 5-fold increase until 2035 [5]. Similarly, in the United States, knee and hip PJI have more than doubled between 2003 and 2006 [6–8]. Projections suggest ongoing rapid increases in PJI numbers until 2030 [8]. Likewise, Australian data demonstrate a 5-fold increase from 2002 to 2020 [9].

As a proportion of the total population, PJIs are also increasing. Using administrative data from the United Kingdom collected between 2006 and 2019, PJIs of knees have increased from 0.9 to 2.7 and hips from 0.8 to 2.3 per 100,000 adults [10,11].

Data reporting the cumulative incidence of PJI vary according to the time from the primary arthroplasty, affected joint, and study type [3]. Systematic under-reporting of the indication for revision to national joint registries may also impact estimates of cumulative incidence compared with administrative data [12,13]. Most studies report 12-month cumulative incidence, but 3-month, 2-year, and 10-year outcomes were also reported. The systematic review of hip PJI reported an overall incidence of 0.34 to 2.23% with a pooled estimate of 1.05% (95% confidence interval [CI]: 0.75 to 1.46), but with high heterogeneity. Interestingly, the pooled estimate in studies of PJI occurring within 90 days was 1.43% (95% CI: 0.81 to 2.52), which was higher than the 1-year cumulative incidence (0.49% [95% CI: 0.22 to 1.10]). In a meta-regression, there was no association with publication date (a surrogate for time period) and PJI incidence [3]. In Sweden, the 2-year incidence of hip PJI appeared to increase between 2005 and 8 (0.9 [95% CI: 0.8 to 1.0] and 2012 and 2014 (1.2 [95% CI: 1.1 to 1.3]) despite the implementation of a bundle of interventions to prevent infection [14]. Using administrative and Australian joint registry data, the 90-day revision rates for PJI are increasing over time for hip but not knee arthroplasty [13]. By contrast, the 1-year incidence (0.53 and 0.57%) of hip PJI in Denmark did not increase over time [15].

Beyond two years, the cumulative incidence of PJI continues to increase up to and beyond 10 years, but at a slower annual rate [9,16,17]. The proportion of late-acute infections as a total of all PJI may be increasing, but data supporting this are limited to three studies only, with different study designs. Reported estimates of late-acute PJI range from 4% (2006 to 8) [18], 10% (2011 to 16) [19], and 45% (2014 to 17) in a large prospective observational study [20].

In conclusion, notwithstanding the potential limitations of the search strategy and variability in how "PJI epidemiology" is presented, key themes have emerged from this literature review. The total PJI numbers have rapidly increased across most settings and are projected to increase further into the future. A rising incidence at a population level is also in accordance with this. The cumulative incidence of early PJI (within 90 days and up to one year) may be increasing over time, particularly following hip arthroplasty. There is no consistent, comparable evidence following knee arthroplasty. Also, the proportion of late-acute PJI as a total of all PJI may also be increasing. If confirmed in future studies, this is likely a consequence of a rapidly increasing prevalence of people living with joint arthroplasties who are at risk of hematogenous seeding during bloodstream infections.

Question 2: Is mortality increased in patients with orthopaedic implant-associated infections?[2]

Response/Recommendation

Yes. There is an increased mortality rate following orthopaedic implant-associated infections.

Level of Evidence: Strong

Delegate Vote: 90.4%: Agree, 4.8%: Disagree, 4.8%: Abstain.

Rationale

Total joint arthroplasty, spine surgery, and treatment of hip fractures are associated with large improvements in quality of life, and patients have a reduced mortality compared to the general population during the first decade following surgery [21–23]. [21] However, periprosthetic joint infection (PJI) and surgical site infection (SSI), which can occur in 1 to 2% of patients [24,25], adversely impact function and quality of life. Orthopaedic-related infections are associated with prolonged hospitalization, multiple revision surgeries, and prolonged courses of antibiotics.

In order to answer the question posed above, we conducted a comprehensive review of PubMed and Embase databases to identify all eligible publications. The initial search resulted in 513 potential studies. The abstracts of the latter studies were reviewed to identify 37 studies for full-text review, of which, 27 studies were included in the final analysis. This systematic review identified 27 studies that included 1,034,897 cases (148,875 infected) assessing the impact of orthopaedic-related infections on mortality.

The analysis of data revealed that patients suffering orthopaedic-related infections had increased in-hospital mortality (1.8% [2,327 of 127,972] versus 0.6% [4,597 of 727,874]; $P < 0.001$). These differences persist with increased follow-up (Table 1). In the fields of arthroplasty (hip, knee, and shoulder), patients who have prosthetic joint infection have an elevated risk of mortality at all time points (inpatient to 20-year follow-up) relative to patients undergoing aseptic revision arthroplasty, even when controlling for confounding variables. Elevated mortality risk is also seen in patients who have an SSI following spine or hip fracture surgery in comparison to similar patients who do not develop infections. In patients with orthopaedic implant infections, increased age, severity of comorbidities, and infecting organism have been consistently associated with mortality. Efforts to mitigate early mortality following orthopedic implant-associated infections have unknown efficacy and require further investigation.

HIP and Knee Arthroplasty

Much of the available literature on mortality and orthopaedic-related infections focuses on PJI in the hip and knee (99.3% of the included cases in our systematic review were for hip and knee arthroplasty, and 21 of the 27 included studies). Taken together, patients suffering PJI had a mortality rate of 4.6% (6,867 of 148,251) at a weighted average follow-up of 0.97 years compared to 3.4% (29,897 of 879,723; $P < 0.0001$) for patients without infections. At every time point in this analysis, patients suffering from PJI had greater rates of death than patients undergoing primary or aseptic revision total hip or knee arthroplasty. This includes differences in inpatient deaths [22,25] and an increased rate of mortality at 20-year follow-up [26]. Furthermore, these findings persist across different study designs: cohort studies, case-control studies from a single institution, and case-control studies from large registries or administrative databases.

Consistently, these studies identified increasing age [24,27–32] and comorbidities [24,27–36] as factors associated with early mortality in patients with PJI. Given that increased comorbidities are associated with the development of PJI, it can be difficult to determine if PJI is truly an independent risk factor for death. However, studies employing techniques to control for confounding variables (such as indexes of comorbidities) through matching or multivariate analysis consistently found PJI to be a factor independently associated with early mortality [24,27,30,34]. Other factors associated with early mortality were polymicrobial infections [30], Enterococci infections [32,37], men [24,32], and suboptimal weight (underweight or obese) [24,36]. Kurtz et al. and Ng et al. identified a small, but statistically significantly decreased risk of mortality following PJI as time has progressed [24,35]. This may be a sign of improving patient care, and therefore decreased mortality, in lower extremity PJI.

[2] These authors contributed to Question 2: Benjamin Zmistowski, David Campbell, Gabriele Tucci, Per Gundtoft, Robert Hube, Seper Ekhtiari, Jaime Lora-Tamayo, Jeppe Lange, Ferdinando Iannotti

Table 1
Mortality Rate for Patients Suffering From Orthopaedic-Related Infection Versus Those Without.

Category	Minimum Follow-up					
	All Follow-up	60 days	1 year	5 years	10 years	20 years
Infected						
Total	148,875	18,670	13,733	7,610	2,522	894
Deceased at follow-up	6,983	4,633	4,543	2,413	1,113	724
Mortality rate (%)	4.7	24.8	33.1	31.7	44.1	81.0
Not infected						
Total	886,022	136,880	117,192	97,262	50,537	3,637
Deceased at follow-up	31,215	26,480	26,395	20,570	16,032	2,728
Mortality rate (%)	3.5	19.3	22.5	21.1	31.7	75.0
P-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0002

Shoulder Arthroplasty

A systematic review for this analysis provided three papers [38–40] (1,588 patients [348 infections]) that analyzed the association between shoulder PJI and early mortality. Combined, these papers found a mortality rate of 14.6% (51 of 348) in infected patients compared to 9.2% (114 of 1240; $P = 0.003$) in aseptic patients at a median study follow-up of 4.7 years. The largest of these papers, Austin et al., [38] found that patients with shoulder PJI had increased rates of mortality if they were older, had increased Charlson Comorbidity Index (sicker), and had methicillin-resistant *Staphylococcus aureus* infections. Specifically, *Cutibacterium acnes* infections were associated with decreased mortality rates in the shoulder PJI group [38,39].

Hip Fracture

There were two studies [41,42] identified that assessed the impact of SSI on mortality following treatment for hip fracture with arthroplasty or operative fixation. At 1-year median follow-up, patients suffering from SSI after treatment for hip fracture had a significantly greater likelihood of death (43.2%; 35 of 81) than those who did not have an SSI (26.5%; 1,184 of 4,474; $P = 0.0007$). Duckworth et al. [33] identified dementia and *S aureus* infections as factors associated with early mortality.

Spine

To our knowledge, there is only a single study directly evaluating the impact of spine SSIs on early mortality. Casper et al. [43] assessed identified 195 patients undergoing reoperation for SSI and matched these patients 1:3 for age, sex, body mass index, year of surgery, Charlson Comorbidity Index, spine region, and approach. At all time points, patients with SSI had a greater rate of death, culminating in a 5-year mortality rate of 7.7% compared to 2.25% ($P = 0.001$). Mortality in the infected cohort was associated with increased age and the Charlson Comorbidity Index.

In conclusion, our review of the literature revealed that patients with PJI of the hip, knee, and shoulder have an elevated risk of mortality at all time points (inpatient to 20-year follow-up) relative to patients undergoing aseptic revision arthroplasty, even when controlling for confounding variables. Elevated mortality risk is also seen in patients who had SSI following spine or hip fracture surgery in comparison to similar patients who do not develop infections. In patients with orthopedic implant infections, increased age, severity of comorbidities, and infecting organism have been consistently associated with mortality. Efforts to mitigate early mortality following orthopaedic implant-associated infections have unknown efficacy and require further investigation.

Question 3: Can registries be used to conduct research on orthopaedic infections?[3]

Response/Recommendation

Registries can be used to conduct research on orthopaedic infections. However, factors such as data completeness, validation processes, and the consistency of infection definition should be described when data from registries are used.

Level of Evidence: Moderate

Delegate Vote: Agree: 94%, Disagree: 2%, Abstain: 4%.

Rationale

Infections in orthopaedics, particularly periprosthetic joint infections (PJIs), represent a significant challenge due to their impact on patient outcomes and health care resources [44,45]. Understanding infection trends and outcomes through robust data collection, such as registries, is critical for improving prevention and treatment strategies.

To investigate whether registries can be used to conduct research on orthopaedic infections, a systematic review was conducted. Using the appropriate MESH terms developed by librarians, we conducted a search in Medline, Embase, Cochrane Library, and Scopus. We identified 696 relevant studies from inception to November 2024. After screening and removing 99 duplicates, 24 studies met our criteria for full review and data extraction. We also performed a multinational survey of 21 member registries of the International Society of Arthroplasty Registers.

The studies reviewed demonstrate varying degrees of success in identifying PJI and related metrics, underscoring both the strengths and limitations of different registries. The completeness of data varies significantly among registries. For instance, the Danish Hip Arthroplasty Register demonstrated 67% completeness for PJIs when using registry data alone, which improved to 90.3% when microbiology databases were integrated [46]. However, underreporting remains a common issue, as seen in the Dutch Arthroplasty Register, which captured only 43% of total hip arthroplasty infections and 59% of total knee arthroplasty infections within one year [47].

[3] These authors contributed to Question 3: Spyridon Hadjispyrou, Muhanned Ali, Dirk Jan F. Moojen, Koen Bos, Per Gundtoft, Tim Petheram, Christopher Kandel, Richard de Steiger, Wierd Zijlstra, Maziar Mohaddes

Several studies employed multilevel validation methods, such as cross-referencing registry data with microbiology databases, clinical records, or prescription data. For example, the National Joint Registry (UK) validated its data against electronic patient records and microbiology reports [48]. Similarly, the Danish Knee Arthroplasty Register and Healthcare-Associated Infections Database combined surgeon-reported data with microbiological evidence [49], and the Australian Joint Registry linked data with a dedicated PJI prospective study database [50]. These validation efforts improved accuracy but also highlighted discrepancies due to nonreporting and misclassification [51].

Definitions of infection varied across studies, which affected comparability. Many registries relied on surgeon-reported diagnoses, such as "deep infection," or coding systems like International Classification of Diseases (ICD)-9/ICD-10 (e.g., T84.5) [52,53]. More rigorous definitions, such as those from the Musculoskeletal Infection Society, were employed in some studies [54,55] but not consistently across all registries.

The 1-year PJI incidence rates ranged from 0.4 to 1.9%, depending on the registry and the definition of infection used [55,56]. Studies utilizing algorithms that integrated multiple data sources reported higher and more accurate PJI rates compared to single registry sources [57].

The findings from a recent multinational survey of 21 member registries of the International Society of Arthroplasty further highlight these trends. Among the surveyed registries, four out of 21 reported comprehensive infection-related data collection, while 10 out of 21 collected partial data, often limited to revisions for infections. Only nine systematically recorded microbiological results and treatment outcomes. Validation studies were conducted by 10 out of 21 registries, with methods including linkage to national surveillance systems and hospital discharge records. Data linkage capabilities were present in 13 of the registries, though challenges such as privacy regulations and resource limitations hinder broader integration. Suggested improvements included expanding data collection to include microbiological results and antibiotic use, enhancing linkage with external databases, and developing standardized protocols for infection-related end points.

Despite these strengths, limitations persist. Nonreporting and misclassification are significant barriers. For example, 80% of false negatives in the Danish Knee Registry were due to nonreporting rather than misclassification [49]. Similarly, the New Zealand Joint Registry failed to capture a proportion of PJI cases identified through medical audits [50]. In a study by Lindgren et al., 67% of all infections were captured in the Swedish Hip Arthroplasty Register [51].

The strengths of registries lie in their large sample sizes, long-term follow-up, and higher degree of generalizability, making them invaluable for studying rare events like PJIs [52,58]. Furthermore, data linkage, such as combining registry data with microbiology databases, significantly enhances accuracy and completeness [46,48].

New registries focusing on orthopaedic infection may offer useful tools to conduct research on orthopaedic infection. The UK Bone And Joint Infection Registry (www.bajir.org) is an example of such a registry. It captures data on orthopaedic surgeries, microbiology, and antibiotic management, and it captures patient outcomes in the form of patient-reported outcomes measures and surgical outcomes, as well as mortality. The registry uses a consistent definition of infection but allows modifications, as long as the criteria used in future definitions are already captured in the dataset. Dedicated infection registries address the challenges of linking orthopaedic and microbiology data by collecting both aspects in one registry. The challenge lies in compliance and high levels of data entry.

In conclusion, registries are a valuable tool for conducting research on orthopaedic infections. However, their reliability depends on robust data validation processes, consistent infection definitions, and efforts to address underreporting and misclassification. Linkage with external databases and improved standardization can enhance their utility in infection research. While challenges remain, the evidence supports the use of data from registries (if validated) as an essential component of orthopaedic infection research.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT 4.0 for proofreading. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Question 4: Does public reporting of surgical site infection (SSI) rates for institutions contribute toward prevention of SSI?[4]

Response/Recommendation

Public reporting of institutional surgical site infection (SSI) rates can be a strategy to improve transparency, foster accountability, and drive adherence to infection prevention measures.

Strength of Recommendation: Moderate

Delegate Vote: 77.4%: Agree, 11.3%: Disagree, 11.3%: Abstain.

Rationale

Surgical site infections (SSIs) are among the most common health care–associated infections, contributing to major patient morbidity, mortality, and increased health care costs [59]. Preventing SSIs is a critical goal for health care systems worldwide. Public reporting of institutional SSI rates has been proposed as a strategy to improve transparency, foster accountability, and drive adherence to evidence-based infection prevention measures [60]. Despite its theoretical benefits, the effectiveness of public reporting remains controversial due to challenges such as variability in surveillance methodologies, disparities in resources, and inadequate risk adjustment [61–67]. This systematic review synthesizes evidence from 25 studies to evaluate whether public reporting contributes meaningfully to SSI prevention.

Public reporting improved institutional compliance with evidence-based practices such as timely antibiotic prophylaxis and adherence to Surgical Care Improvement Project measures [68–71]. These measures were associated with reductions in SSI rates, driven by heightened accountability among health care providers [72]. Despite these improvements, differences in surveillance methodologies led to inconsistent SSI rates, complicating inter-institutional comparisons. Facilities with more rigorous surveillance methods reported higher rates, likely due to improved detection rather than poorer quality of care. These variations highlight the need for standardized surveillance practices to ensure accurate and fair comparisons across institutions [73,74].

Social and institutional disparities further complicated the impact of public reporting. Hospitals serving disadvantaged populations often reported higher SSI rates, partly due to limited resources and the influence of social determinants [75]. These disparities underscored the inadequacy of existing risk adjustment models, which failed to account for institutional challenges, potentially penalizing safety-net hospitals. Public reporting also

[4] These authors contributed to Question 4: Priscila R Oliveira, Humaid Al Farii, Amir H Hoveidaei, Richard de Steiger, Henry Fu

incentivized systemic improvements in infection control and heightened awareness among health care professionals. However, the benefits were more pronounced in resource-rich settings, where facilities could invest in infrastructure and staff training to meet reporting benchmarks [76–78].

This review demonstrates that public reporting contributes to SSI prevention by promoting transparency and fostering institutional accountability [79,80]. However, several challenges limit its broader impact. Methodological variability in surveillance and reporting practices undermines the comparability of SSI rates between institutions [81]. Without standardized methods, the reliability of reported data is compromised. Risk adjustment models are often insufficient, failing to adequately account for social and institutional disparities [82]. These shortcomings disproportionately affect safety-net hospitals, potentially exacerbating health care inequities [83]. Additionally, resource limitations in underfunded facilities hinder their ability to achieve benchmarks set by public reporting systems, further limiting their effectiveness [61,64]. To maximize the impact of public reporting, several policy changes are necessary. Standardized surveillance methods must be implemented to ensure the reliability and comparability of SSI rates [66,72]. Risk adjustment models should incorporate social determinants and institutional factors to create a more equitable evaluation framework [71]. Additionally, resource-limited facilities require targeted support to meet infection prevention standards, ensuring that public reporting drives improvement across all health care settings [73,77].

Conclusions

Public reporting of SSI rates enhances institutional transparency and promotes adherence to preventive measures, contributing to SSI prevention. Addressing methodological limitations and ensuring equitable resource distribution are critical to maximizing its impact.

Question 5: Should implant-associated orthopaedic infections be treated in specialized centers?[5]

Response/Recommendation

Treating implant-associated orthopaedic infections in specialized centers with a dedicated multidisciplinary service could potentially lead to improved clinical outcomes, antibiotic therapy compliance, and lower reinfection rates.

Level of Evidence: Limited

Delegate Vote: Agree: 92.9%, Disagree: 4.8%, Abstain: 2.4% **(Total consensus, Unanimity)**

Rationale

While the incidence of hip and knee periprosthetic joint infection (PJI) remains stable, its prevalence continues to rise due to the increasing volume of primary procedures being performed [84–87]. For this reason, adopting new strategies to improve and streamline infection control and quality of life outcomes is imperative. Due to the high disease burden and treatment failure rates, patients often require comprehensive and specialized medical treatment, similar to oncology patients [88–91]. Consequently, various referral centers for PJI have transitioned to centralized patient care through a multidisciplinary approach, aiming to become specialized centers for PJI treatment. While there is no universal definition for these specialized centers, they are typically characterized by the following elements: (1) available surgeon and nursing staff specialized in PJI cases; (2) at least one infectious disease (ID) specialist and plastic surgeon; (3) multidisciplinary meetings, academic discussions, and case conferences; (4) combined orthopaedic and ID clinics; (5) standardized antibiotic protocols; (6) elective surgery with fast-track protocols; (7) communication with smaller centers; and (8) patient-reported outcomes collection [92]. We performed a literature review and found that 11 of 289 articles matched the previous description for specialized centers.

An example of specialized centers is the network of referral centers for bone and joint infections (BJI) used to treat osteomyelitis and septic arthritis [92]. Besnard et al. described a reduction of failure rates from 42.9 to 11.8% ($P = 0.03$) of arthroscopic treatment of septic knee and shoulder arthritis after the implementation of a BJI center with a multidisciplinary team of orthopaedic surgeons and ID specialists [93]. However, the use of multidisciplinary teams extends beyond the management of osteomyelitis and native septic arthritis, proving equally valuable in the treatment of implant-associated orthopaedic infections. Vuorinen et al. described the outcomes of PJI patients at a single hospital after the implementation of a multidisciplinary team with ID and plastic surgeon specialists. They reported a 36.2% ($P = 0.004$) decrease in two-stage procedures, a 46.8% ($P < 0.001$) increase in debridement antibiotics and implant retention (DAIR) procedures, and an increase in DAIR success rates from 55.6 to 85.2% ($P = 0.077$) [94]. One way to ensure a multidisciplinary approach is through weekly conferences with physicians from other surgical and nonsurgical specialties involved in patient care. Biddle et al. explored the effect of implementing multidisciplinary weekly meetings with ID specialists and microbiologists. They found that in the postintervention cohort, the mean time to microbiology advice decreased by five days ($P < 0.001$) and failure rates decreased from 41.4 to 3.45% ($P < 0.001$) [95]. These findings align with the ones reported by Ntalos et al. who found that holding a weekly infection conference with a pathologist and microbiologist to discuss operative treatment and postoperative course led to a decrease in the mean lengths of stay (62 ± 43 days versus 29 ± 14 days; $P < 0.001$) as well and decreased number of surgical procedures (5.1 ± 4.3 versus 1.8 ± 1; $P < 0.001$) and mean number of antibiotics administered (4.2 ± 2 vs 2.8 ± 1.2; $P = 0.008$) [96]. Likewise, Bauer et al. found that a weekly meeting with an ID specialist, microbiologist, and pharmacist led to a more accurate antibiotic therapy selection and length, based on antibiogram results ($P < 0.005$), but no significant differences in reinfection rates (preintervention 25 versus 18% postintervention; $P = 0.75$) [97].

Moreover, combined orthopaedics and ID clinics could help centralize patient care, decreasing treatment fragmentation. In the study by Carlson et al., implementing a combined ID and arthroplasty clinic led to a decrease in the incidence of missed ID appointments from 40.6% (three of 32) to 25% (three of 24) [98]. In a similar study, Karczewski et al. studied the impact on patient outcomes after establishing an interdisciplinary service specialized in PJI, composed by a surgery, microbiology, and pathology teams. They found that, using a standardized treatment protocol, a significant decrease in the time between staged procedures (66.6 versus 80.7 days; $P < 0.001$) and reinfection rates (3.1 versus 10.4%; $P = 0.048$) was achieved [99]. A relevant benefit of a PJI referral center is the prevention of treatment fragmentation, which has been associated with worse postoperative outcomes. Garceau et al. compared the outcomes of two-stage exchange arthroplasty procedures for patients who had both surgeries performed at one center to patients explanted at a general orthopaedic hospital and transferred to a specialized center during the interstage period for reimplantation. They found that patients who received continued

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Table 2
Regional and National Hospital Networks for Treating PJI.

Author	Year	Country	Intervention	Population	Results/Outcomes
Kamp [18]	2019	Netherlands	Combined diagnostic and treatment protocol for acute PJI (DAIR) in nine regional hospitals.	Patients undergoing DAIR for acute PJI N = 236	87% success rate at 1 year and 3% mortality within the first year. Better adherence to regional protocol over time.
Zijlstra [19]	2022	Netherlands	Northern Infection Network for Joint Arthroplasty (NINJA). Development of mutual diagnostic and treatment protocol for PJI across four hospitals.	N/A	Descriptive study describing the treatment protocol used in such centers.
Ferry [20]	2019	France	Bone and joint infections national network. There were nine main centers (CRIOAcs) and 15 corresponding centers.	N/A	Study describes the characteristics of a national BJI network, which has allowed for the creation of PJI-focused academic programs and research.
Dombrowsky [21]	2024	USA	Regional referral center for the treatment of PJI.	Chronic PJI patients referred from external institution undergoing two-stage exchange. N = 182	3.9% 1-year mortality rate. 90% of the patients were successfully reimplanted. Patients referred >90 days after the diagnosis of chronic PJI have higher failure rates.

PJI, periprosthetic joint infection; BJI, bone and joint infections.

care had lower rates of recurrent infection (53.6 versus 13.4%; $P < 0.001$) and soft tissue complications (31.3 versus 14.3%; $P = 0.030$) compared to their counterparts [100]. Of note, the aforementioned studies represent retrospective cohorts with a before-after design, rather than a prospective comparative design, which limits the generalizability of their findings. Although the use of regional and national hospital networks for treating PJI appears promising (Table 2), the current literature consists primarily of descriptive studies without any comparison groups for reference [101–104].

The low number of studies surrounding this topic could be explained by the lack of a standardized definition for specialized centers, as many institutions might have a dedicated BJI or PJI units. Anticipating the increase in PJI-related scientific literature, we encourage researchers to describe the institutional characteristics and interdisciplinary collaborations to achieve a more objective measurement of the impact of specialized centers for PJI.

Conclusions

Treating implant-associated orthopaedic infections in specialized centers with a dedicated PJI service could potentially lead to improved clinical outcomes, antibiotic therapy compliance, and lower reinfection rates.

Question 6: How can we capture the physical and psychological impact of orthopaedic infections on patients?[6]

Response/Recommendation

There are no standard outcome measures to capture the physical and psychological impact of orthopaedic infections. Currently, both general and disease-specific measures are used depending on the anatomical location and subspecialty practice preferences. Until universal outcome measures are adopted, providers should use outcome measures recommended by their respective societies.

Level of Evidence: Limited

Delegate Vote: Agree: 90.9%, Disagree: 2.4%, Abstain: 6.8% (Super Majority, Strong Consensu).

[6] These authors contributed to Question 6: Allison M Lastinger, Ryan Blake, Ran Schwarzkopf, Lincoln Liow, James Slover, Peter Sculco, Janet Conway, Amir Hoveidaei, Benjamin Ricciardi, Meghan Whitmarsh-Brown

Rationale

Infections are a devastating complication of orthopaedic surgery. Examples of common orthopaedic infections include periprosthetic joint infection (PJI), fracture-related infection (FRI), and spine infection, to name a few. The goal of treating a patient who has an orthopaedic infection is to maximize the patient's physical and psychological health by selecting the best surgery and treatment course for that patient. Without specific outcome instruments to measure the impact of a surgery on patients' physical and psychological health, care teams are left without evidence-based metrics to guide care.

Patient-reported outcome measurements are used by orthopaedic surgeons to monitor the impact of specific musculoskeletal procedures on patients' overall health and functional outcomes. Some examples of these include the Hip Disability and Osteoarthritis Outcome Score (HOOS) and Knee Disability and Osteoarthritis Outcome Score, Joint Replacement (KOOS JR) scores and the Oswestry Disability Index (ODI). Unfortunately, there are no standardized metrics to capture the physical and psychological impact of orthopaedic infections on patients, but providers who care for these patients recognize the enormous burden such infections impose on patients and their families. If there were standardized metrics to compare physical and psychological outcomes, orthopaedic surgeons could make better evidence-based recommendations for the patient.

A review of articles from 2007 to 2024 was performed. A total of 34 studies met the search criteria. Of the 34 studies, 26 focused on PJI, three studies examined spine infections, one study compared spine infections and PJI, one study examined FRI alone, and one study compared FRI and PJI. The majority of the PJI studies sought to determine which surgical strategy results in better physical and/or psychological outcomes for patients (Table 3).

Multiple outcome measures were used, including physical, psychological, and overall quality of life outcome measures. Of note, many of the quality-of-life outcome measures included both physical and psychological components, so there was overlap. The most common physical outcome measures examined were Western Ontario and McMaster Universities Osteoarthritis Index (four studies), Oxford Hip Score and/or Oxford Knee Score (five studies), visual analog score (VAS) (three studies), HOOS and/or KOOS JR (four studies), and Knee Society Score (two studies). Psychological outcome measures included Hospital Anxiety and Depression Scale-A and Hospital Anxiety and Depression Scale-D (two studies), ICD-10 Symptom Rating score (two studies), Patient Health Questionnaire 4 (one study), and Fear of Progression Score

Table 3
Summary of Studies Used.

Author	Year	Outcome Measure			Design	Population
		Physical	Psychological	Quality of Life		
Ghanem [105]	2007	WOMAC	-	SF-36	Prospective	PJI
Boettner [106]	2011	HHS	-	RAND-36 (same as SF-36)	Retrospective	PJI (2-stage)
Petilon [107]	2012	ODI, NRS	-	SF-36	Case-control	Spine
Kim [108]	2012	UCLA Activity Scale, KSS Pain and Function	-	-	Retrospective	PJI (2-stage)
Chen [109]	2012	-	-	SF-12	Retrospective	PJI (fusion, amputation)
Aboltins [110]	2013	HHS	-	SF-12	Case-control	PJI (DAIR)
Nunez [111]	2015	WOMAC	-	SF-36	Prospective	PJI
Helito [112]	2015	Ability to walk	-	SF-36	Case series	PJI (amputation)
Rohner [113]	2015	VAS, KOOS	-	SF-36	Retrospective	PJI (fusion)
Lee [114]	2016	VAS	HADS-A, HADS-D	SF-36	Retrospective	PJI (2-stage)
Aboltins [115]	2016		-	SF-12	Retrospective	PJI (DAIR)
Beaupre [116]	2017	WOMAC	-	RAND-36 (same as SF-36)	Prospective	PJI (2-stage)
Grammatopoulos [117]	2017	OHS	-	-	Case-control	PJI
Gelhorn [118]	2018	PROMIS-PF	-	-	Qualitative	PJI and spine
Poulsen [119]	2018	OHS	-	EQ-5D	Cross-sectional	PJI (2-stage)
Vincenten [120]	2019	-	-	WHOQOL-BREF, EQ-5D-3L	Cross-sectional	PJI (Girdlestone)
Knebel [121]	2020	-	PHQ-4, PAF-F-KF	SF-12, FLZ Herschbach, and Henrich Score	Prospective	PJI (2-stage)
Golgelioglu [122]	2020	KSS	-	SF-36	Retrospective	PJI (2-stage)
Walter [123]	2021	-	ISR score	SF-36, EQ-5D	Retrospective	PJI
Wildeman [124]	2021	OHS	-	EQ-5D-5L	Retrospective	PJI
Goh [125]	2021	KSS, OKS	-	SF-36	Retrospective	PJI
Lueck [126]	2022	-	HADS	SF-36, FLZ	Prospective	PJI (2-stage)
Karamian [127]	2022	ODI, VAS Back and Leg	-	SF-12	Case-control	Spine
Walter [128]	2022	-	-	SF-36, EQ-5D, Expectation Questionnaire	Case series	PJI and FRI (fusion)
Bohle [129]	2022	VAS, Modified Lysholm, WOMAC	-	SF-36	Retrospective	PJI (amputation)
Wixted [130]	2023	PEQ	-	PROMIS	Retrospective	PJI (Girdlestone)
Shichman [131]	2023	-	-	PROMIS (modified version)	Retrospective	PJI
Abboud [132]	2023	ODI, SF-WAI	-	SF-36, SF-MPQ	Retrospective	Spine
Conway [133]	2023	KOOS	-	SF-36	Retrospective	PJI (fusion)
Lastinger [134]	2023	HOOS JR, KOOS JR	-	Adapted DT	Retrospective	PJI
Gitajn [135]	2024	BPI	-	VR-12	Retrospective	FRI
Van Engen [136]	2024	KOOS JR	-	PROMIS-10	Retrospective	PJI (DAIR)
Walter [137]	2024	-	ISR score	SF-36, EQ-5D	Prospective	PJI
Manning [138]	2024	OHS, OKS	-	-	Prospective	PJI

PJI, periprosthetic joint infection; FRI, fracture-related infection.
Physical Outcome Measures: BPI, Brief Pain Inventory; HHS, Harris Hip Score; HOOS JR, Hip Disability and Osteoarthritis Outcome Score, Joint Replacement; KOOS JR, Knee Disability and Osteoarthritis Outcome Score, Joint Replacement; KSS, Knee Society Score; Modified Lysholm; NRS, Numerical Pain Rating Scale; ODI, Oswestry Disability Index; OHS, Oxford Hip Score; OKS, Oxford Knee Score; PEQ, Prosthesis Evaluation Questionnaire; PROMIS-PF, Patient-Reported Outcomes Measurement Information System-Physical Function.
UCLA Activity Scale: VAS, visual analog score; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; UCLA, University of California, Los Angeles.
Psychological Outcome Measures: HADS, Hospital Anxiety and Depression Scale; ISR, ICD-10 Symptom Rating; PA-F-KF, Fear of Progression Score; PHQ-4, Patient Health Questionnaire 4; Quality of Life Outcome Measures; DT adapted, Distress Thermometer adapted; EQ-5D, EuroQol-5D; FLZ, Questionnaire on life satisfaction; PROMIS, Patient-Reported Outcomes Measurement Information System Global-10 Short Form; SF-36, Short Form 36; SF-12, Short Form 12; WHOQOL-BREF, World Health Organization Quality of Life-BREF; SF-MPQ, McGill Pain Questionnaire; SF-WAI, Working Alliance Inventory; VR-12, Veterans RAND 12 item health survey.

(one study). Quality of life measures included Short Form (SF)-36 (17 studies), SF-12 (five studies), EuroQol-5D (EQ-5D) (five studies), Questionnaire on life satisfaction (two studies), Patient-Reported Outcomes Measurement Information System (one study), Distress Thermometer modified (one study), and World Health Organization Quality of Life- BREF (one study).

Since there are currently no standardized physical and psychological outcome measures specific to the management of patients who have orthopaedic infections, we must rely on the metrics used in orthopaedics in general. Each specialty within orthopaedics uses its own outcome measures. In total joint arthroplasty, the recommendation from the American Association of Hip and Knee Surgeons is to use either the Patient-Reported Outcomes Measurement Information System 10 or VR-12 instruments to assess general health and the KOOS JR or HOOS JR to assess joint-specific health [139]. The Orthopaedic Trauma Association does not currently recommend specific outcome measures within the subspecialty. However, the most prevalent general measures reported are the VAS, EQ-5D, SF-36, and SF-12, with the use of specialized outcomes of Disability of Arm, Shoulder and Hand Score, ODI, and Harris Hip Score for traumatic orthopaedic injuries specific to the upper extremity, lower back, and hip, respectively [140]. Spine surgery as a specialty also does not have a standard recommendation or consensus for outcome measures.

The Neck Disability Index [141], ODI [19–104,139–155], Modified Japanese Orthopaedic Association [141,154], and Rolland-Morris Disability Questionnaire [141,155] are the most common disease-specific tools involving pathology of the spine. General outcome measures within the specialty are reported most frequently using the SF-36 [155], VAS [154], and EQ-5D [155], with the VAS measurement appearing at an increasing rate in the literature compared to the others. In general, orthopaedic spine and trauma surgery use a combination of disease-specific outcome measures while utilizing general measures as well. The VAS, EQ-5D, and SF-36 appear to have the most generalizability to assess the physical function and quality of life measures for patients undergoing either orthopaedic trauma or spine surgery.

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The Journal of Arthroplasty 41 (2025) S222–S228

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General Topics

ICM 2025: New Technologies like Artificial Intelligence, Robotics, and Anti-Biofilm

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ARTICLE INFO

Article history:
Available online 27 October 2025

Question 1: Is there a role for employing artificial intelligence and/or machine learning in the management of orthopaedic infections?[1]

Response/Recommendation

Artificial intelligence may soon be used to manage orthopaedic infections. Its main advantages are data mining and systematic information collection, which allow the creation of predictive, diagnostic, or treatment modules. Alas, it still struggles with external validation and generalizability issues.

Level of Evidence: Limited

Delegate Vote: Agree 85.3%, Disagree 7.4%, Abstain 7.3% (Super Majority, Strong Consensus)

Rationale

The integration of artificial intelligence (AI), machine learning (ML), or natural language processing into health care has opened new avenues for managing complex conditions [1], including orthopaedic infections. These technologies offer potential enhancements to several stages of bone and joint infection management by analyzing vast datasets to identify patterns not readily apparent through traditional methods [2]. Patient usage of this technology is also expected to increase, with some studies examining the quality of the information provided by free-to-use chatbots with satisfactory results [3,4].

Current research into AI in orthopaedic infections can be broadly categorized into five main areas: prediction, prevention, diagnosis, treatment, and prognosis.

Prediction models using AI or ML are the most researched subject in the literature. Artificial intelligence (AI)—based prediction models have been applied to forecast infections, with promising results in several orthopaedic and surgical contexts, such as predicting surgical site infections (SSIs) in lumbar spinal surgery and orthopaedic trauma [5–7]. These models often integrate clinical, laboratory, and operative variables, demonstrating robust predictive capabilities.

Studies like Chen et al. reported an exceptional performance of an ML model for SSI prediction in lumbar spinal surgery, using variables like hemoglobin, glucose levels, and modic changes [8]. Similarly, Ying et al. employed ensemble ML models to predict infections following tibial fracture fixation, with diabetes and procedural duration identified as key predictors [5]. Despite these findings, retrospective, single-center studies and external validation limitations underscore the necessity for multicenter, prospective trials. All studies advocate using AI in infection prediction to complement clinical expertise.

As part of a preventive strategy, AI was also applied to ensure compliance with surgical antimicrobial prophylaxis bundles, identify clinical risks, and optimize preoperative planning. For example, artificial neural network models have demonstrated the ability to predict SSIs based on variables like preoperative white blood cell count and surgical antimicrobial prophylaxis

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to 10.1016/j.arth.2025.08.041.

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https://doi.org/10.1016/j.arth.2025.08.041
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compliance, with compliant patients showing a significantly lower SSI rate [9]. The AI's potential to enhance clinical risk management by identifying at-risk patients, optimizing perioperative conditions, and improving incident reporting processes has also been demonstrated [10,11]. Moreover, ML has shown promise in preventing periprosthetic joint infections (PJIs) by aiding in preoperative optimization, surgical planning, diagnosis, and antibiotic selection [12–14].

Regarding diagnosis, Fu et al. used natural language processing to extract data from electronic medical records, demonstrating strong correlations with the Musculoskeletal Infection Society criteria, particularly regarding the growth of cultured organisms [15]. Similarly, Kuo et al. compared an in-house ML system with the International Consensus Meeting criteria, concluding that ML is feasible and competitive for diagnosing PJIs [16].

Other studies have targeted specific diagnostic elements, such as laboratory data, pathology, and medical imaging. Paranjape et al. (2023) employed ML to analyze synovial fluid biomarkers, achieving an exceptional area under curve of 0.99 compared to ICM criteria [17]. Tao et al. applied deep learning to frozen pathological sections, achieving an area under curve of 0.8 [18], while Nie et al. used AI with dynamic bone scintigraphy in 449 patients, reporting diagnostic accuracies of 86% for knee and hip infections [19].

Using AI to treat infections directly is the least researched area. It has been shown that AI engines are a good option for extracting structured information (e.g., occurrence of complications) from unstructured data sources like free text. This technology was applied in the automated surveillance of SSIs requiring reoperation within 90 days following lumbar discectomy, with a higher successful identification rate when compared with current procedural terminology and International Classification of Diseases codes [20]. The AI also has major potential in wound management. The AI-powered digital wound assessment tools, leveraging ML algorithms, can enhance the classification of wounds and provide detailed analyses of parameters such as size, depth, color, texture, granulation tissue, and signs of infection [21]. Additionally, AI, combined with the analysis of electronic health records, can identify patients at higher risk of developing SSIs and facilitate monitoring and tracking, indirectly assisting in the patient's treatment [21].

Still, regarding ML coadjuvants for patient treatment, Chen et al. have proposed an ML-based model for predicting vancomycin trough concentration in adult PJI patients. This random forest regression algorithm, with a relative accuracy of 82.8% and an absolute accuracy of 67.2%, might reduce the need for further blood testing and invasive procedures [22].

Concerning prognosis, studies focus on identifying high-risk patients and anticipating treatment failure. Shohat et al. developed a tool to predict failure after irrigation and debridement of infected hip and knee arthroplasties. This study identified prognostic markers such as elevated serum C-reactive protein and positive blood cultures, supporting its utility for decision-making [23]. Wouthuyzen-Bakker et al. complemented this by integrating risk scores and ML to enhance predictions of treatment failure in acute PJIs managed with conventional DAIR [24]. Further investigations by Klemt et al. for recurring infections following revision arthroplasties showed possible improvements in early detection of high-risk patients [25]. The same author also investigated AI in PJI following aseptic revision, affirming that the excellent results advocate AI aiding surgeons in patient-specific risk stratification and assisting in preoperative counseling and clinical decision-making [26].

In conclusion, most studies show the importance of prognostic tools for improved risk stratification and individualized treatments in managing PJIs. Nevertheless, the main advantage of using AI for infection in orthopaedics is for data mining and the systematic collection of information. Following this, decision-making may become easily tailored for each patient and their specific characteristics. Despite these advancements, the field remains in its early stages, characterized by promising developments and inherent challenges, such as the "black box" nature of ML models. This research area's novelty implies limited evidence, necessitating cautious optimism. As the field evolves, rigorous validation and integration into clinical practice will be essential to fully realize the benefits of AI and/or ML in managing orthopaedic infections.

Question 2: Are patients undergoing robotic-assisted orthopaedic procedures at higher risk of subsequent surgical site infections/periprosthetic joint infections?[2]

Response/Recommendation: No. At present, there is no definitive evidence to suggest that the rates of SSI/PJI are increased in robotic-assisted orthopaedic procedures.

Level of Evidence: Limited

Delegate Vote: Agree 75.6%, Disagree 13.2%, Abstain 11.2% **(Strong Majority, Moderate Consensus)**

Rationale

The introduction of robotic-assisted technology in orthopaedic surgery has attracted major attention in recent years, especially in spinal surgery, hip, and knee arthroplasty. Initially introduced in the 1980s to enhance implant positioning accuracy and alignment while reducing complications compared to manual techniques, robotic systems have evolved considerably. Despite these advancements, concerns persist regarding prolonged operative times, increased surgical site complexity, and the potential impact on rates of surgical site infections (SSIs) and periprosthetic joint infections (PJIs).

This systematic review was conducted to evaluate whether patients undergoing robotic-assisted orthopaedic procedures are at a higher risk of subsequent SSI/PJI. Searches of PubMed and SCOPUS databases were performed in October 2024 using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. From 268 identified articles, 69 studies were included following full-text screening. Notably, 50% of the included studies were published in 2023 and 2024, underscoring the contemporaneity of the evidence.

The majority of studies evaluating robotic-assisted orthopaedic procedures predominantly focus on radiological and functional outcomes, with only a limited number examining the incidence of SSI/PJI. Among the studies analyzed, only three had a minimum follow-up period of 10 years. In 2020, Kim et al. published a randomized controlled trial (RCT) with the longest follow-up period of 13 years, reporting no statistically significant differences in infection or complication rates between robotic-assisted and manual total knee arthroplasty (TKA) [27]. Similarly, retrospective studies by Jeon et al. and Lee et al. supported these findings, demonstrating comparable PJI rates across surgical techniques [28,29]. These findings emphasize that, at least in the limited literature available to date, long-term outcomes, including infection rates, remain comparable between robotic-assisted and conventional surgical techniques. In 2023, Alrajeb et al. published a systematic review and meta-analysis of RCTs comparing robotic-assisted and conventional knee arthroplasties. This important

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study analyzed seven RCTs encompassing 1,942 knees. The findings indicated that both clinical and functional outcomes, as well as complication rates, including infections, were statistically similar between robotic-assisted and conventional knee arthroplasties [30]. All other included studies, RCTs, prospective and retrospective, had shorter follow-up periods but consistently reported no significant differences in infection rates between robotic-assisted and conventional arthroplasty surgery [31–46]. In 2024, Burgio et al. published a retrospective study focused exclusively on PJI in the context of robotic-assisted TKA without comparison to manual TKA. It was the only study that clearly defined the criteria used for diagnosing PJI, highlighting the importance of standardizing criteria and definitions for PJI [47]. Certain studies highlighted procedural aspects unique to robotic-assisted surgeries that could influence infection risks. Honl et al. observed that prolonged surgical durations associated with robotic TKA were initially linked to SSI. However, the increased rate of early complications diminished as surgeons overcame the learning curve associated with the technology [31]. Li et al. reported comparable PJI rates between robotic and conventional TKA groups, despite robotic-assisted procedures having increased operative times [48,49]. Other publications from LaValva et al. emphasized potential concerns related to equipment use. While pin-site complications were infrequent, they, along with increased operating room traffic and extended operative times, were identified as potential contributors to contamination risk [50,51]. Several retrospective studies, including those by O'Rourke et al., Aggarwal et al., Katzman et al., and Khanna et al., reported lower rates of PJI in robotic-assisted surgeries when compared to conventional techniques [52–55]. However, the unknown follow-up periods in these studies limit the interpretability of their findings. While the results suggest a potential advantage of robotic systems in minimizing infection risks, the absence of robust longitudinal data prevents drawing definitive conclusions about their long-term effectiveness. In contrast with those studies, in 2024, Piple et al. published that robotic-assisted total hip arthroplasty was associated with increased rates of medical complications, including PJI [56]. Despite these complexities, most studies suggest that robotic-assisted joint arthroplasty does not inherently increase the risk of PJI compared to conventional approaches. Factors such as learning curve improvements and advancements in robotic technology appear to address earlier concerns, as reflected in the findings of St Mart et al. These studies reported higher infection rates with earlier robotic systems, attributing them to technical and procedural limitations rather than inherent flaws in robotic technology [57,58]. The heterogeneity in study designs, follow-up periods, and definitions of infection, combined with the limited number of long-term studies, underscores the need for further research with standardized methodologies to validate these findings.

In spinal surgery, the impact of robotic assistance on infection risks and surgical outcomes has been variable across studies. Yang et al. reported an increased risk of complications, including SSIs, associated with robot-assisted lumbar spinal fusion compared to conventional techniques [59]. However, other studies have highlighted major benefits of robotics in spinal procedures. Keric et al. demonstrated that robotic systems reduced infection rates in minimally invasive spine surgery, particularly in high-risk populations, suggesting that the precision and minimally invasive approach afforded by robotics may contribute to better outcomes [60]. Interestingly, unlike joint arthroplasties, robotics in spinal surgery has been associated with reduced operative time, which may play a critical role in minimizing intraoperative contamination risks [61–63]. Zawar et al. similarly found that robotic-guided open spine surgeries achieved lower infection rates compared to conventional open procedures, further supporting the notion that robotics can enhance overall outcomes in spinal surgery [64]. While there are differences in infection-related outcomes reported in the literature, the growing evidence suggests that robotic assistance in spinal surgery may offer distinct advantages, particularly in terms of procedural efficiency and reduced operative times. These benefits contrast with findings in joint arthroplasties, where robotic procedures often prolong surgical time. The divergence underscores the importance of tailoring robotic applications to the unique demands of specific surgical fields to optimize their potential benefits.

Conclusions

At present, there is no definitive evidence to suggest that the rates of SSI/PJI are increased in robotic-assisted orthopaedic procedures. Robotic joint arthroplasty may have longer operative times and increased operating room traffic, which are well-established risk factors for contamination events; however, these potential risks have not yet been demonstrated to have an effect on rates of PJI. Future studies with a longer follow-up period, preferably a minimum of 10 years, are necessary to assess complications and revision rates. Furthermore, most of the included studies were not RCTs and had small sample sizes, increasing the possibility of publication bias. Despite these limitations, robotic-assisted techniques continue to evolve. As robotic technology becomes more prevalent, rigorous long-term studies are essential to substantiate its clinical benefits.

Question 3: Are there any effective anti-biofilm technologies that can be used in clinical practice to treat orthopaedic infections?[3]

Response/Recommendation: Yes. A number of anti-biofilm technologies, including antiseptics, antimicrobial peptides, mechanical disruption, bacteriophages, bioactive glass, and implant surface modification or coatings, are in development or available for clinical use in some countries.

Level of Evidence: Limited

Delegate Vote: Agree 80.6%, Disagree 8.3%, Abstain 11.1% **(Super Majority, Strong Consensus)**

Rationale

To address the question, we conducted a comprehensive systematic review. There were two databases, PubMed and Scopus, which were searched for potentially eligible studies from inception to October 31, 2024. The search strategy was based on relevant MeSH terms developed by the librarians. Our initial review yielded 1,179 studies. After the removal of 503 duplicates, the titles and abstracts of 676 studies were screened, and 240 studies were then subjected to full-text review and data extraction.

Bacteriophage Therapy

Bacteriophage therapy continues to be explored as a possible treatment for periprosthetic joint infection (PJI) with early limited case series [65–69]. Bacteriophages have demonstrated the ability to degrade biofilms as well as target and kill bacteria. Phage therapy has demonstrated the ability to eradicate biofilms [70,71]. In addition, phage therapy can be personalized to target a specific strain of bacteria [72]. Bacteriophages with antibiotics *in vitro* or *in vivo* confirm earlier reports of the synergistic effect of these agents in improving biofilm removal. Studies on the application of

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phage-derived lysins *in vitro, ex vivo*, or *in vivo* against biofilm-related infections are encouraging [73].

Implant Coatings/Material Science

Carbon-infiltrated nanotubes demonstrated a 2.5-fold reduction in adherent bacteria [74]. Tantalum–Titanium lattice structures have been shown to reduce biofilm adhesion [75]. Silver nanoparticles and nanostructures have demonstrated anti-biofilm properties *in vitro* [76,77]. Anesthetic-doped ultra–high-molecular-weight polyethylene has demonstrated antibiotic effects, which may prove clinically utility [78]. Recently, the Federal Drug Administration completed a *de novo* approval of antibacterial-coated arthroplasty implants (DEN210058). A proprietary coating model of methacryloyloxydodecyl pyridinium bromide has reported a 5-log kill rate with *in vitro* testing of bacteria commonly found in the operating room environment [79]. For these technologies, further clinical studies are needed.

Novel Antibiotics/Antimicrobial Agents

Antibiotics remain a mainstay of treatment and have been demonstrated to improve outcomes and survivorship [80]. Novel antibiotics such as dalbavancin, among others, have demonstrated good bony penetration, cement elution, and pharmacokinetics similar to vancomycin [81]. A new class of Clp proteases has biofilm activity that includes acyldepsipeptides and ureadepsipeptides that remain in preclinical development [82,83]. Antimicrobial peptides have also yielded a demonstrable reduction in biofilm bacterial counts [84]. Antibiotic delivery systems via hydrogels have demonstrated biofilm reduction, but the burden of proof so far remains unpersuasive [85].

There are potential limitations with the use of antibiotics in the treatment of PJI, as biofilm is antibiotic-tolerant [86,87]. Biofilms are composed of a subpopulation of persistent cells that survive exposure to bactericidal concentrations of antibiotics [88–90]. A new class of broad-spectrum antimicrobials, PLG0206 (WLBU2), has demonstrated *in vitro* and *in vivo* activity against biofilm. This would be the first class of antibiotics with independent biofilm activity [91,92]. Regulatory clinical studies have demonstrated safety and tolerability in a single ascending dose clinical study, and efficacy studies are pending [93].

Iodophor exposure demonstrated a 3-log decrease in *Staphylococcus aureus* colony forming units *in vitro* after a 5-minute exposure at a concentration of 0.5% [94]. Clinical studies using povidone-iodine solutions in PJI treatment and prevention have had mixed results and did not directly look at biofilm activity [95–97]. In contrast, hydrogen peroxide, povidone-iodine, and chlorhexidine had a decrease in *S. aureus* biofilm, but had more activity on planktonic bacteria [98]. Monoclonal antibody therapy has been shown to reduce biofilm burden in an *in vitro* mouse model [99]. Intraoperative use of a hyaluronan-derivative coating in the form of a gel, loaded with antibiotics to prevent PJI, has gained interest as a prophylactic measure [100]. Lytic agents such as exebacase offer a potential novel mechanism to reduce the infectious burden and potentiate activities of the immune system and traditional antibiotics [101].

Mechanical Disruption

In vitro, both alternating/pulsed magnetic fields [95,96], extracorporeal shock wave therapy [97], and ultrasound-based therapies have demonstrated disruption of biofilms [102]. Piezoelectric ultrasound-based tools exist, which have demonstrated improved reduction in biofilm colony forming units compared to pulsatile lavage [103]. Methylene blue photodynamic therapy effectively eradicated common PJI pathogens on arthroplasty materials without damage to underlying materials [104].

Bioactive Glass

Bioactive glasses are a group of surface-reactive glass-ceramic biomaterials. Implanted in the body, it will react with the surrounding fluids, exchange ions between the glass and fluid hydrogen ions, and create an alkaline microenvironment with increased osmotic pressure. These combined effects inhibit bacterial adherence and biofilm formation [105,106]. Studies have found that S53P4 bioactive glass granules are effective against a multitude of bacterial strains, such as methicillin-resistant *S. aureus* [107]. Translational studies need to be completed.

Induction Heating

Non-contact induction heating (NCIH) is a noninvasive treatment modality that can potentially be used to cause thermal damage to the bacteria within the biofilm on the metal implant surface [108,109]. The NCIH uses pulsed electromagnetic fields to induce so-called 'eddy currents' within metal objects, such as joint implants. This heats the material while avoiding thermal necrosis on the surrounding tissue [108,109]. Several *in vitro* studies have shown the effect of NCIH on metal implants in reducing bacterial load within biofilms [109–111]. Translational studies need to be completed.

In conclusion, a number of novel technologies are being explored that hold potential to prevent the formation of biofilm or destroy mature biofilm on orthopaedic implants. Some of these novel agents are already in clinical use in some countries, while others are being explored at the preclinical level or are in the process of regulatory evaluation.

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The Journal of Arthroplasty 41 (2025) S229–S237

Contents lists available at ScienceDirect

The Journal of Arthroplasty

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Hip and Knee

2025 ICM: Previous Procedures and Risk of Surgical Site Infection/ Periprosthetic Joint Infection

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Question 1: Do intra-articular injections before primary joint arthroplasty increase the risk of surgical site infection (SSI)/ periprosthetic joint infection (PJI)?[1]

Response/Recommendation

Yes. There is an increased risk of SSI/PJI when intra-articular injection is performed within three months of primary hip and knee arthroplasty.

Level of Evidence: Moderate

Delegate Vote: Agree 86.6%, Disagree 6.7%, Abstain 6.7% (Super Majority, Strong Consensus)

Rationale

Intra-articular injections (IAIs) remain a highly utilized nonoperative treatment for patients who have knee and hip osteoarthritis, with almost 50 and 25% of patients receiving intra-articular corticosteroid (CS) injections within one year of primary knee and hip arthroplasty, respectively [1,2]. Hyaluronic acid (HA) injections are also commonly used [3,4]. There remains debate as to whether the use of IAIs before primary arthroplasty increases the risk of postoperative infection.

We conducted a comprehensive systematic review to identify studies that examine this possible correlation. There were 14 included studies that assessed IAIs before knee arthroplasty, with eight only assessing CS, two combining CS and HA, and five separately assessing CS and HA results. There appears to be a relative dichotomy with regard to sample size and study conclusion: five of six studies with populations of $\geq$ 5,000 patients found a significant association between preoperative injection and periprosthetic joint infection (PJI), while only one of eight studies with populations < 5,000 found a significant association between preoperative injection and PJI [3,5–17]. It is possible that this finding is due to the relatively low incidence of PJI after primary knee arthroplasty, approximating 1 to 2%, making it difficult for smaller, single-center studies to have sufficient power to detect a significant difference between the two groups [18,19]. Muffly et al. performed a review using the IBM MarketScan database, identifying 81,645 patients who underwent primary total knee arthroplasty (TKA), 3,445 of whom underwent a CS injection within one year before arthroplasty. The PJI prevalence was higher in the injection group compared to the control group (0.84 versus 0.36%, odds ratio (OR) 2.40) [16]. Cancienne et al. conducted a similar analysis of 35,890 patients within the PearlDiver database: 5,313 patients received a CS injection within three months of TKA and had higher rates of PJI at both three and six months postoperatively compared to controls (three months: 2.6 versus 1.3%, OR 2.0; six months: 3.4 versus 2.3%, OR 1.5) [14].

When assessing injections before total hip arthroplasty (THA), a similar trend appeared in the 13 studies included, of which 10 assessed CS, two combined CS and HA, and one assessed HA individually. All five studies with populations $\geq$ 5,000 demonstrated a significant association between preoperative injection and PJI, compared to only four of eight studies with populations < 5,000 [2,4,20–30]. Using state-level ambulatory surgery and inpatient databases for Florida and California, Schairer et al. assessed 173,958 patients undergoing primary THA, with 5,421 receiving a preoperative hip injection of CS or HA within one year of THA. The PJI incidence was significantly increased at three months (1.58 versus 1.04%), six months (1.76 versus 1.21%), and one year (2.04 versus 1.47%) postoperatively in patients who had an injection zero to three months before surgery [29]. Prkić et al.

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.093.

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https://doi.org/10.1016/j.arth.2025.10.093
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performed a large single-center, retrospective cohort study of 5,909 THAs stratified by timing of CS injection before THA: 2.8% of patients in the zero to 3-month injection group developed PJI at 1 year compared to 1.0% of patients who had no injection (hazard ratio (HR) 2.63, $P = 0.018$) [2].

The timing of preoperative IAIs appears to play a critical role. Of the 12 studies that found a significant association between injection and PJI and also considered time from injection to arthroplasty, 11 cited a specific interval within which IAI increases infection risk [2,3,6,13–16,24,27–30]. Bains et al. reported an OR of 1.84 (95% confidence interval (CI) 1.31 to 2.58) for CS injections zero to four weeks preoperatively and 1.4 (95% CI 0.98 to 2.02) for CS injections four to six weeks preoperatively when assessing two years PJI [13]. Bhattacharjee et al. stratified patients into biweekly cohorts, reporting increased infection risk in the zero- to 2-week cohort (OR 2.89) [15]. There were four large studies that specifically stratified patients receiving injections into three cohorts: < three months, three to six months, and > six months before TKA or THA. All four studies reported increased PJI risk in patients within the < 3-month cohort, while patients receiving injections at > three months preoperatively were at equivalent risk to controls [2,14,27,29].

Several meta-analyses and systematic reviews have been performed investigating IAI and postoperative infection. A 2022 meta-analysis by Lai et al. demonstrated equivalent overall odds of PJI between control and injection groups, although subgroup analysis revealed a higher OR of 1.39 for postoperative PJI with IAI into the hip or knee within three months of surgery [31]. There were four other meta-analyses performed by Yang et al., Kim et al., Baums et al., and Avila et al. that demonstrated highly similar findings: each reported odds/risk ratios of 1.26, 1.26, 1.52, and 1.23 for PJI in subgroups who received an IAI within three months of primary arthroplasty [32–35]. Saracco et al. found an increased risk of PJI both in the overall injection group (relative risk 1.38, 95% CI 1.01 to 2.72) as well as in the zero-to-three-month subgroup (relative risk 1.64, 95% CI 1.44 to 1.86) [36].

It remains unclear whether the number of preoperative injections impacts infection risk. Despite finding increased infection risk for injections within three months of TKA, Richardson et al. found no difference in odds of PJI when comparing patients in a multiple injection cohort to a single injection cohort of HA or CS (OR 0.98, 0.83) [3]. Khan et al. performed a retrospective cohort study investigating whether cumulative injections given more than 90 days before TKA increased infection risk, excluding all patients who had received an injection within 90 days of surgery. They reported no significant association between the cumulative amount of CS or HA injections, concluding that multiple IAI can be safely administered before TKA [37]. Investigating the number of injections in the 3-month preoperative window, Forlenza et al. demonstrated a dose-dependent relationship between hip CS injections and PJI risk. They found that one, two, and ≥ three injections within the 3-month window had escalating ORs: 1.45 (1.28 to 1.64), 2.08 (1.44 to 2.89), and 3.59 (1.52 to 7.10). This same trend was found for surgical site infection (SSI) [28].

The currently available literature indicates that increased infection risk can occur with both CS and HA injections. There was one study that specifically investigated HA injections < six months before THA in 118 patients, finding increased risk for both SSI (8.5 versus 2.8%) and PJI (4.2 versus 0%) compared to the control group [4]. Richardson et al. conducted a review of the PearlDiver database, including 58,337 patients who underwent primary TKA, 19,905 of whom underwent a CS or HA injection ≤ one year before arthroplasty. They found increased PJI risk for both HA (OR 1.55) and CS (OR 1.21) injections within three months of surgery, while a direct comparison of HA to CS revealed no difference in infection odds based on medication type (OR 1.24, 95% CI 0.80 to 1.85).

In conclusion, most large-scale studies demonstrate an increased risk of postoperative SSI/PJI for both primary hip and knee arthroplasty following IAIs. There were several studies for both THA and TKA that found no increase in risk; however, these tended to have small sample sizes, and many were not able to stratify patients by injection timing. Therefore, three months before surgery appears to be the time period within which injections increase risk, supported by multiple meta-analyses. It remains unclear how the number of injections impacts infection risk. Both CS and HA injections have been associated with increased infection risk; however, further studies comparing infection risk between different medications should be performed.

Question 2: Does prior hip arthroscopy increase the risk of a subsequent infection in patients undergoing elective hip arthroplasty?[2]

Response/Recommendation

Based on available data, there is no evidence suggesting a clinically meaningful increase in the risk of postoperative infection following total hip arthroplasty (THA) in patients who have a history of ipsilateral hip arthroscopy (HA).

Strength of Recommendation: Strong consensus (Agreement 84.2%)

Rationale

Hip arthroscopy (HA) is a relatively uncommon orthopaedic procedure, but has been growing steadily over the past few decades [38]. It was first described in 1931, with the indications for HA evolving over time [39]. The most common indications include repair of traumatic labral tears, femoroacetabular impingement (FAI), chondral flap lesions, and removal of loose or foreign bodies [40]. Conversion rates to THA following HA have been found to be variable, extending from 9.5 to 50% [41–43]. However, the effect of prior HA on infection rates following THA remains controversial.

Several studies have utilized the PearlDiver database to investigate this question; the majority of these investigations suggest there is no increased risk of infection following THA in patients who have a history of HA. In a propensity score-matched study comparing 1,940 patients who underwent THA with prior HA to a control group, no significant difference was found in prosthetic infection rates within one year of surgery. Infection rates remained nonsignificant when the authors conducted an analysis of patients undergoing THA within one year of HA compared to no prior HA [44]. Another PearlDiver study, including 110 patients who received THA with prior HA for FAI between 2005 and 2014, reported no difference in surgical site infections within three years of surgery [45]. In a study involving 3,156 patients, Ross et al. found that those who had HA before THA showed a significantly lower rate of prosthetic joint infection one year postoperatively (0.6 versus 1.3%; odds ratio [OR] 0.50; $P = 0.01$) [46]. However, one manuscript demonstrated that osteoarthritis patients who underwent HA before THA were at an increased risk of periprosthetic joint infection (OR 1.87; $P = 0.01$). Notably, 82% of patients in this

[2] These authors contributed to Question 2: Matthew L. Magruder, Pedro Dantas, Søren Overgaard, Dario E. Garin, Mattia Alessio Mazzola, Magaly Iñiguez, Abdullah Hammad, Hofstätter Jochen, Yoshi Pratama Djaja, Michael A. Mont

cohort were over 65 years old, representing a distinct subset compared to the younger population typically undergoing HA for FAI [47].

A study utilizing the Swedish Hip Arthroplasty registry compared 135 patients who underwent THA following HA for FAI to 540 matched controls. They found one deep infection in the HA group and eight in the control, which is a nominally larger percentage in the control group, but was not significant (0.7 versus 1.4%; $P = 0.25$) [48].

There have also been multiple single-institution studies on this topic. A large academic medical center conducted a retrospective analysis including 95 patients who had conversions to THA following HA compared to 95 matched controls. The authors found a higher rate of wound complications in the conversion group, although there was no increased risk of deep infection. Furthermore, when comparing time to conversion of zero to six months, six to 12 months, 12 to 18 months, and > 18 months, no significant differences were found in the complications and infection rate [49]. Another academic center conducted a study with 39 patients who underwent THA after a previous HA for FAI. They found similar results, with no statistically significant difference in the postoperative superficial or deep periprosthetic infection [50]. In another single-institution propensity match-controlled study with 35 patients who had prior arthroscopy, infection rates were nominally higher in the arthroscopy group than in controls, though this difference was not statistically significant [51]. Additionally, Jain et al. reported no differences in the incidence of infection between a group of 18 patients who required conversion to THA after HA and a control group [52]. These studies did not find significant differences in infection rates; however, it is important to note that they are almost certainly underpowered to identify significant differences in prosthetic joint infection.

A 2019 systematic review including 305 hips that underwent THA following a prior HA compared to 502 matched control hips reported infections in five patients (2.82%) in the prior HA group and one patient (0.35%) in the control group. There was a trend toward a higher risk of infection in the prior arthroscopy group, but the paucity of data limits this finding [53]. Another systematic review with 235 patients who had a history of HA and 374 matched controls showed no statistically significant differences in the incidence of postoperative superficial or deep periprosthetic joint infection [54]. However, Liu et al. conducted a systematic review and meta-analysis of the effect of prior arthroscopy on outcomes following arthroplasty, combining both hip and knee data together [55]. They demonstrate a significantly increased risk of infection in the prior arthroscopy group compared with controls (OR 1.83; $P < 0.001$).

Conclusion

Most studies have shown no significant increase in the postoperative superficial or deep infection risk following THA after previous HA compared with controls. Small sample size was a major limitation of many studies; however, those including a greater number of patients also do not generally indicate an increased infection risk in THA after HA. There may be a difference in infection risk based on underlying hip pathology, with one study demonstrating increased risk in osteoarthritis patients and multiple studies demonstrating no increased risk in FAI. However, there are insufficient data to determine whether this is related to the underlying pathology or to the confounding age of onset (FAI patients tended to be younger than osteoarthritis patients).

Question 3: Does prior knee arthroscopy increase the risk of a subsequent infection in patients undergoing elective arthroplasty?[3]

Response/Recommendation

Based on available data, there is a clinically relevant increased risk of postoperative infection following total knee arthroplasty (TKA) in patients who have a history of ipsilateral knee arthroscopy within six months.

Strength of Recommendation: Strong consensus (Agreement 83.8%)

Rationale

Knee arthroscopy (KA) is one of the most common orthopaedic surgeries, with an estimated one million procedures performed per year [56]. Well-established indications include removal of loose bodies, partial meniscectomies, arthroscopic irrigation and debridement for infection, ligament reconstructions, and more [57,58]. Other, more controversial, indications include pain control in elderly patients who do not want arthroplasty and in patients who want to delay total knee arthroplasty (TKA) [59–61]. Furthermore, it has historically been used as a diagnostic tool in patients who have presumed unicompartmental arthritis to confirm the diagnosis before unicondylar knee arthroplasty [62]. A KA is very common before TKA; it has been estimated that 10% of patients who undergo KA will receive a TKA within one year and 33% in nine years [63,64]. Nevertheless, whether KA before TKA increases the risk of postoperative infection remains debated.

Three groups have evaluated this patient population using single-institution retrospective cohort studies. Piedade et al. conducted a retrospective review of patients undergoing TKA and compared patients who had a history of KA (n = 60) to those who did not (n = 1,119) [65]. The authors demonstrated that there was a nonsignificant trend toward increased infections (1.25 versus 3%; P = NS). However, the 10 years survival of TKA implants that have a history of KA was 86.8%, compared with 98.1% for those without. Barton et al. conducted a retrospective cohort study using a prospectively collected database at a large academic institution [66]. When comparing patients who had ipsilateral KA within 12 months of primary TKA (n = 187) to those who did not have a history of KA (n = 1,708), multivariate regression analyses demonstrated that KA within six months of TKA increased the risk of needing a revision (odds ratio (OR) 3.85; $P = 0.004$). While indications for revision included infection, there were not enough patients to conduct a separate analysis for infections alone. In addition, a retrospective analysis of 87 patients who had a history of KA before TKA and 174 controls was conducted to evaluate the risk of postoperative complications [67]. The authors demonstrated a significantly higher rate of infection in the KA (4 versus 0%; $P < 0.001$).

Single-institution studies tended to have small sample sizes and provide limited insight into this question; however, multiple large national databases have more recently been evaluated. There were two studies that have used the PearlDiver Patient Records Database. Werner et al. conducted a study that evaluated patients who had received a KA in three different timeframes before TKA and compared them to age-matched controls who had not received a KA [68]. The authors demonstrated that the cohort who received a KA within six months had a significantly increased risk of postoperative infection (OR 2.0; $P = 0.004$). Gu et al. conducted a

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similar study comparing patients who had a history of KA within two years of TKA to age- and comorbidity-matched controls [69]. They found that the experimental cohort had a higher rate of PJI than controls (2.65 versus 1.83%; $P = 0.022$). The same group conducted a similar study, comparing patients who received KA before TKA to matched controls at time points zero to 15 weeks, 16 to 35 weeks, 36 to 43 weeks, and 44 to 52 weeks [70]. Multivariate analysis demonstrated that patients had an increased risk of PJI in the zero to 15-week (OR 1.79; $P < 0.001$) and 16- to 35-week (OR 1.20; $P = 0.035$) cohorts. Additionally, an investigation using the IBM Watson Health MarketScan (IBM Watson Health, Ann Arbor, MI) database evaluated incidence and risk of postoperative complications in patients who had undergone ipsilateral KA within one year of TKA [71]. They demonstrate there was no increased risk of postoperative PJI compared to controls (OR 1.08; $P = 0.739$). Moreover, Tayton et al. evaluated the New Zealand Joint Registry database to determine risk factors for PJI within 12 months following TKA [72]. They demonstrated that a history of ligament reconstruction was an independent risk factor for PJI (OR 1.84; $P = 0.28$), but did not provide specifics on what ligament reconstructions were included. Interestingly, a history of meniscectomy trended toward being protective against PJI.

There were three studies that evaluated this question and found no difference in postoperative infection between groups. Issa et al. compared patients who had a history of at least two prior KAs (n = 62) to those without any history of KA (n = 438) with a minimum of 2-year follow-up [73]. The authors demonstrated that there was no difference in implant survival or postoperative complications between cohorts. Sax et al. conducted a retrospective time-based analysis, evaluating patients who underwent KA at different intervals before TKA (< 12, 12 to 16, 16 to 20, and 20 to 24 months) [74]. There was no difference in septic revisions at six months, one year, and two years following TKA ($P > 0.476$). Furthermore, Viste et al. conducted a retrospective review of a prospectively collected database and compared patients who had a history of KA (n = 160) to matched controls (n = 320) [63]. The prior KA cohort had two PJIs, and the control had three, but the difference was not statistically significant. Furthermore, they demonstrated that the 10-year event-free rate of infection was statistically similar when comparing cohorts who had a history of arthroscopy less than 1 year before TKA and those greater than one year.

There were two recent systematic reviews and meta-analyses that have demonstrated an increased risk of infection in patients who have a history of arthroscopy following lower-extremity arthroplasty. The first one evaluated arthroscopy and arthroplasty of both hip and knee, of which nine of the 23 studies reporting on TKA only [75]. There were 10 studies (n = 6,771) reported on the risk of infection at an average follow-up of one to six years following surgery and demonstrated a statistically significant increase in risk of infection in the arthroscopy group compared with controls (OR 1.83; $P < 0.001$) with low heterogeneity. The second meta-analysis evaluated patients who received TKA with and without a history of KA [76]. They demonstrate a greater than 50% increased odds of postoperative infection in the KA before TKA group ($Z = 3.54$; $P = 0.0004$).

Conclusion

Most studies reviewed (eight out of 11 individual studies and two out of two systematic reviews and meta-analyses) demonstrate a statistically and clinically relevant increase in risk of postoperative SSI/PJI following TKA in patients who had a history of KA. However, all studies used retrospective analyses, including both single-institution databases with prospectively collected data and national databases. It is important to note that three studies demonstrate no increased risk, but those tended to have small sample sizes in the KA cohorts. Furthermore, the data suggest that there may be a greater risk of postoperative infection for patients as the time interval between the two procedures decreases. Based on available data, orthopaedic surgeons who are considering a TKA for a patient who has a history of a KA should consider waiting at least six months to minimize the risk of infection.

Question 4: Does prior surgery and insertion of hardware increase the risk of subsequent periprosthetic joint infection in patients undergoing conversion total joint arthroplasty?[4]

Response/Recommendation

While clinically the infection rate in conversion total joint arthroplasty (TJA) is higher than in primary TJA, there is no significant difference between them. Therefore, additional studies with larger sample sizes are needed to draw more definitive conclusions.

Level of Evidence: Moderate

Delegate Vote: Agree 84.2%, Disagree 10.5%, Abstain 5.3% (Super Majority, Strong Consensus)

Rationale

Periprosthetic joint infection (PJI) is considered a catastrophic complication and an unfavorable factor contributing to the failure after TJA [77,78]. The optimal management of pre-existing hardware during TJA remains a challenging issue in orthopaedic surgery. The presence of hardware from previous surgeries can complicate subsequent arthroplasty procedures, potentially increasing the risk of complications such as PJIs [79,80]. The incidence of PJIs in primary TJA typically ranges from 0.5 to 2%; however, higher infection rates have been reported in patients who have residual hardware from prior procedures, such as high tibial osteotomies, fracture fixations, or ligament reconstructions [81,82]. In a recently published review, the authors found no significant difference in perioperative complications, specifically PJI, between staged and concurrent hardware removal during conversion TJA [83]. In this study, we aimed to investigate the total incidence of PJI following conversion to TJA (with or without hardware removal). Additionally, we compared the PJI rates between conversion TJA and primary TJA in case-control studies.

A random effects model with random intercept logistic regressions was used [84]. Heterogeneity was evaluated using the I^2 statistic and the *Chi*-square tests.

Our analysis included 37 studies [79,80,82,85–118] with a total sample size of 35,696 (19,866 conversion and 15,830 primary), comprising 17 studies conducted in the Americas (N = 34,377, conversion = 18,792, primary = 15,585), four in Asia (N = 313, conversion = 265, primary = 48), 15 in Europe (N = 994, conversion = 797, primary = 197), and one in Africa (N = 12, conversion = 12, primary = 0). There was a significant variation in sample sizes across studies, ranging from as few as six samples [93] to as many as 18,245 samples [82]. The reported PJI rates ranged from 0 to 23.81%. Overall, our analysis revealed a mean PJI rate of 1.92% (95% confidence interval (CI): 1.05 to 3.50) in patients who underwent conversion TJA.

When analyzing based on joint type, 19 studies focused on hips, 17 on knees, and one on shoulders. A total of 6,595, 13,243, and 28 samples underwent conversion to THA, total knee arthroplasty (TKA), and total shoulder arthroplasty, respectively. Additionally, 207 and 15,623 samples underwent primary THA and TKA,

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respectively. The mean PJI rate was 1.18% (95% CI: 0.37 to 3.64) for THA, 3.13% (95% CI: 1.60 to 6.02) for TKA, and 0% (95% CI: 0 to 12.34) for total shoulder arthroplasty. The test for subgroup differences did not show a significant difference between the groups (*Chi*-square: 2.45, degrees of freedom (df) = 2, $P = 0.29$).

When comparing PJI rates between conversion TJA and primary TJA in case–control studies, 11 studies were selected, involving 3,953 samples in the conversion group and 15,830 samples in the primary group. The PJI rate was 1.05% (95% CI: 0.21 to 5.06) in the conversion group and 0.54% (95% CI: 0.11 to 2.61) in the primary group. However, the test for subgroup differences did not show a significant difference in PJI rates between these groups (*Chi*-square 0.43, df = 1, $P = 0.51$). Additionally, we calculated the odds ratio (OR) between the two groups and found an OR of 3.71 (95% CI: 2.88 to 4.79). However, in many studies, the ORs exhibited a wide range, with some confidence intervals, including one study, indicating no difference.

Conclusion

In this study, we identified the rate of PJI in conversion TJA to be 1.92%. We found no significant difference in PJI rates between hip and knee arthroplasty. Additionally, although the infection rate in conversion TJA is higher than primary TJA (1.05 versus 0.54%), there is no significant difference between them. However, there was a substantial discrepancy in sample sizes between studies conducted in the USA and those from other parts of the world, with over 90% of the samples coming from the United States. This highlights the need for more studies in other regions to gain a more comprehensive perspective.

Question 5: Is the rate of periprosthetic joint infection higher in patients who have prior unicompartmental knee arthroplasty and are undergoing conversion to total knee arthroplasty?[5]

Response/Recommendation

While conversion total knee arthroplasty (TKA) surgery may be associated with increased periprosthetic joint infection (PJI) rates, it is inconclusive based on limited evidence that conversion from UKA to TKA has higher PJI rates. The increased need for the use of augments and stems at the time of surgery makes the conversion of unicompartmental knee arthroplasty (UKA) to TKA a more complex procedure and potentially at risk of higher complications, including infection.

Level of Evidence: Limited

Delegate Vote: Agree 75.6%, Disagree 19.7%, Abstain 4.8%. (moderate consensus)

Rationale

Unicompartmental knee arthroplasty (UKA) is a viable alternative to TKA in patients who have end-stage, symptomatic osteoarthritis affecting a single compartment. Potential advantages of UKA over TKA include faster recovery, improved proprioception, reduced pain, better function, improved range of motion, and reduced infection and manipulation rates [119–122]. However, some registry data show a higher revision rate of UKA compared to TKA [123]. To date, it remains unclear if the surgical site infection (SSI) or PJI rates are higher in patients who have a prior UKA undergoing conversion to TKA with a primary or revision TKA.

Overall, 1,088 studies were identified using the search terms supplied across EMBASE, SCOPUS, and PubMed. After the title and abstract review, 61 full-text reviews were performed, reducing the full data extraction to 18 studies. There were 17 practice registry studies and one database study, eight level 3 evidence studies, and the remainder were level 4 evidence studies. There were two studies that looked at patellofemoral arthroplasty (PFA) conversions; 11 looked at medial conversion, while the remainder included all UKAs or did not list the type of UKA. There were seven studies with a comparison group of primary TKA, with one also comparing to revision TKA and one comparing high tibial osteotomy to TKA, totaling 1,172 in the practice registry and 13,257 including the database study.

The studies consisted of 1,377 patients undergoing conversion to TKA from UKA. The average age was 65.7 years [95% confidence interval (CI) 63.7 to 67.7]; the women's rate was 65.3% [95% CI 57.9 to 72.7]; the body mass index was 28 to 33, with an average weighted follow-up of 57.1 months [95% CI 43.9 to 70.3]. The average time from UKA to conversion TKA ranged from 28 to 108 months, with an average of 63 months.

Of the 1,377 patients undergoing conversion TKA, 28 (2.0%) developed SSI/PJI during the follow-up period. There were four studies that included a comparator group of 159 primary TKAs that had 15 (3.0%) SSI/PJI [124–127]. When performing a meta-analysis for the difference in proportions of SSI/PJI in UKA to TKA conversions versus their comparators, there was no significant difference between the groups, OR 0.353 [95% CI: 0.769 to 1.48]. While there was no difference in the odds ratio of infection between UKA conversion to TKA and primary TKA, more UKA conversions required additional fixation. There were 230 (16.7%) patients who required augments, 404 (29.3%) patients required stems during the time of surgery, and 96 (7.7%) required another reoperation for reasons other than SSI/PJI. Although the overall reoperation rate was higher, a meta-analysis of three studies comparing reoperation rates found no significant difference between the UKA conversion group (7.7%) and the comparator group (3.6%), with an odds ratio of OR 1.42 [95% CI 0.548 to 2.29], $P = 0.68$ [125–127].

The rate of SSI/PJI for patients undergoing UKA conversion to TKA was not elevated compared to their TKA comparator group, and the SSI/PJI rate appears to be in accordance with previous studies on primary TKA and historical controls [128]. This may be explained by the low SSI/PJI absolute number reported in the studies. Additionally, nearly all of the studies are practice registries, which may suggest a high expertise level bias from high-volume centers and technical skill [129]. Database studies, which may be more generalizable and may include lower-volume centers, may have findings different than ours.

Although infection episodes were overall low, the use of revision components, stems, and augments was much higher. Nearly all studies reported the use of stems and augments to improve fixation and replace lost bone. Studies have reported the use of increased thickness of the polyethylene bearing, usually a surrogate for tibia bony resection, resulting in a higher likelihood of stem and augment use [130]. For PFA conversion, the use of stems and augments would be expected to be much lower due to the location of the bone loss, and this is what was seen in the review. Anatone et al. reported on a combined 82 PFAs undergoing conversion to TKA, with only three (3.6%) patients requiring stemmed implants and zero patients requiring any augments [127,131]. Importantly, the orthopaedic surgeon should strongly consider the use of additional reconstruction options if deemed appropriate intraoperatively. Lewis et al. reported that the use of tibial stems during UKA-to-TKA conversion had a lower revision risk than conversions without the use of stems, suggesting that the use of these modes of fixation may be beneficial [132].

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Although not statistically different, the reoperation rates were higher in UKA-to-TKA conversions compared to historical controls. Besides infection, the main causes for reoperation included aseptic loosening, instability, extensor mechanism failure, hematoma, and arthrofibrosis. Both studies investigating PFA conversion to TKA reported arthrofibrosis requiring manipulation under anesthesia and lysis of adhesions in some patients as a complication [127,131]. This potential complication is something the surgeon should be aware of when revising these.

There are several potential limitations of this systematic review and meta-analysis. English-only articles can limit the number of reports in European and Asian countries. Since the studies were primarily practice registries and not large database studies, centers that specialize in UKA may have expertise bias and therefore lower rates of infection and complications than a more generalizable population of surgeon experience. Additionally, underreporting or low numbers of UKA to TKA SSI/PJI and failures can skew the data, and capturing this specific patient population in database studies can be challenging due to a lack of TKA conversion coding. Also, masking of other adjunctive procedures was not considered a failure and could also underreport the reoperation rate and skew data. We were also unable to determine differences in SSI/PJI between types of UKAs, such as fixed bearing versus mobile bearing or PFA, due to low numbers available.

In conclusion, conversion to TKA following UKA failure is associated with a relatively low SSI/PJI rate, but a higher need for revision components and a higher reoperation rate compared to primary TKA. Further database research is warranted to confirm these findings and explore strategies to minimize complications and improve long-term outcomes.

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The Journal of Arthroplasty 41 (2025) S238–S242

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Hip and Knee

2025 ICM: Use of Antibiotic-Impregnated Polymethyl Methacrylate Cement

Ernesto Guerra-Farfán, Mustafa Akkaya, Atthakorn Jarusriwanna, Khalil Amri, Levent Bayam, Thiago Sampaio Busato, Frank Buttacavoli, Wei Chai, Keerati Chareancholvanich, Cheng-Fong Chen, Julian Costantini, Ronald E. Delanois, Michael Dunbar, Seper Ekhtiari, Ismet Gavrankapetanović, Sérgio Gonçalves, André Grenho, Matteo Innocenti, Jean-Yves Jenny, Ianiv Klaber, Stergios Lazarinis, Brett R. Levine, Elysia Masters, Pablo Sanz-Ruiz, Aasis Unnanuntana

Question 1: Does the use of antibiotic-impregnated polymethyl methacrylate cement reduce the incidence of infection in patients undergoing primary joint arthroplasty?[1]

Response/Recommendation

The evidence among low-level comparative studies is mixed, with some studies suggesting that antibiotic-impregnated cement reduces the risk of infection in patients undergoing primary joint arthroplasty. However, pooling of the available Level 1 evidence, as well as pooled registry data, does not support a reduction in infection risk in primary total joint arthroplasty.

Level of Evidence: Moderate

Delegate Vote: Agree 75.5%, Disagree 18.5%, Abstain 6.0% (Strong Majority, Moderate Consensus)

Rationale

A total of 32 comparative studies were identified and published between 1990 and 2024 across 21 different countries [1–31]. Nearly five million patients were included in total (4,943,801 joints in 4,943,768 patients). Of the studies reporting sex distribution, 37.3% were women. There were six randomized controlled trials (RCTs), one prospective cohort study, 22 retrospective cohort studies, one case-control study, and one economic Markov model analysis. There was one study that was a long-term follow-up of an earlier published RCT [8].

The majority of studies included only total knee arthroplasty (TKA) cases, while six studies included hip arthroplasty cases. Data from four RCTs comparing antibiotic-loaded bone cement (ALBC) versus plain cement in primary TKA revealed no significant difference in infection rates between the ALBC group and the plain cement group.

The evidence among low-level comparative studies was mixed. There were 12 studies that demonstrated no significant difference between ALBC and plain cement in primary hip and knee arthroplasties [3,12,15,18–21,23–25,28,29], while seven studies demonstrated a significant reduction in infection rates with the use of ALBC [10,11,14,16,17,22,31]. Only one study found an increased risk of infection with the use of ALBC [27].

It is worth highlighting the findings from various registries and large database studies as well. A report utilizing data from the United Kingdom's National Joint Registry [17], as well as one from a large national insurance registry in the United States [10], found significant benefits in terms of infection prevention with the use of ALBC. However, three other registry-based studies did not find a difference between ALBC and plain cement [12,19,23]. Importantly, one of these studies combined data from 14 different high-quality national or regional arthroplasty registries, with a sample size of over two million TKA patients [23].

The evidence regarding the economics of antibiotic-impregnated cement is also mixed. Of the two studies evaluating the economics of routine ALBC use, one found that routine antibiotic cement use was not cost-effective [26], while the other found that it was only potentially cost-effective if the antibiotics were added by the surgeon rather than commercially available premixes [27].

Overall, there is a lack of evidence to support the routine use of ALBC in primary total joint arthroplasty. Data for total hip arthroplasty are relatively limited, while there are more studies available on total knee arthroplasty, including some high-quality RCT and registry data. The overall conclusion, whether based on pooling of data or an overall qualitative synthesis of the available literature, does not provide convincing evidence of the efficacy of ALBC in preventing infection in primary total hip and knee arthroplasties. The caveat that must be kept in mind is that with

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.073.

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https://doi.org/10.1016/j.arth.2025.10.073
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the overall rarity of prosthetic joint infection and the very large sample sizes required to answer this question directly (i.e., via RCT); many studies are likely underpowered to definitively answer the question.

Question 2: Does the use of antibiotic-impregnated polymethyl methacrylate cement reduce the incidence of infection in patients undergoing aseptic revision arthroplasty?[2]

Response/Recommendation

Based on available low-level data, the use of antibiotic-impregnated PMMA cement in aseptic revision arthroplasty leads to a clinically relevant reduction in the risk of postoperative infection, regardless of whether a single or dual antibiotic-loaded cement is used.

Level of Evidence: Moderate

Delegate Vote: Agree 73%, Disagree 24.3%, Abstain 2.7% (Strong Majority, Moderate Consensus)

Rationale

Primary total joint arthroplasty (pTJA) has achieved great success in patients who have arthrosis, leading to major improvements in daily quality of life as well as functional abilities. This has rendered pTJA the most commonly performed orthopaedic surgical procedure, with the increasing number of patients undergoing pTJA over time [32–34]. As a result, there has been a marked increase in the number of revision total joint arthroplasties (rTJA), wherein projections for the near future foresee more than a 100% increase in the number of rTJAs performed [35,36].

Although the literature provides varying rates, one of the most common causes of rTJA is aseptic implant loosening [37,38]. Moreover, despite all the preventive and protective measures, periprosthetic joint infection (PJI) remains a major risk during rTJA performed for aseptic reasons [39,40], with a higher incidence rate (3 to 7.5%) compared to primary PJI [41,42].

The concept of antibiotic-loaded polymethyl methacrylate (AL-PMMA) was first introduced in the literature following a scientific study in 1977 [43] and has since been widely studied, particularly for its role in preventing and mitigating the risk of prosthetic and bone infections. It is widely used, particularly in infected rTJA cases. However, the current literature does not provide evidence that clearly supports the use of AL-PPMA for reducing the risk of pTJA PJI or lowering early revision rates [44–47]. Moreover, the impact of using AL-PMMA on the risk of PJI in aseptic rTJA is still a subject of ongoing debate.

The first study that provided important data on this topic is a retrospective study of 1,154 patients undergoing aseptic revision TKA (rTKA) conducted by Bini et al. in 2015 [48]. Overall, 114 (10%) of the 1,154 patients underwent re-revision within a mean period of 3.6 years, and 30% of these re-revisions were performed for an infection (34 of 114). In the study, AL-PMMA was used in 308 of the 1,154 patients undergoing aseptic rTKA, wherein only 12% (n = 14) of these patients required re-revision during follow-up. This study shows that the use of AL-PMMA was linked to a 50% reduction in the risk of all-cause re-revision.

Another relevant study is the AL-PMMA review conducted by Gandhi et al. in 2018 [49]. The study included both pTJA and rTJA cases and reported that the routine use of AL-PMMA in aseptic revision TJA could be regarded as the standard of care, offering advantages in terms of infection rates and all-cause re-revision. In routine practice, aminoglycosides (gentamicin or tobramycin) were preferred for inclusion in cement, whereas vancomycin or daptomycin can also be added in case of clinical requirement, although this may have a negative impact on the strength of cement [50,51].

In a study by Abdelaziz et al., conducted with 32 patients in 2019, a combination of clindamycin and gentamicin was added to PMMA, wherein 18 patients constituted the PJI group and 14 patients constituted the aseptic rTJA group during a 5-year follow-up [52]. At the end of follow-up, none of the patients had required re-revision, and the PMMA loaded with the antibiotic combination had achieved a high level of success in infection prevention and eradication in septic and aseptic rTJA cases. In another study published by Sanz-Ruiz et al. in 2020, the effects of AL-PMMA combinations on PJI were compared in a case series of 246 patients who underwent aseptic rTKA, wherein 143 patients received low-dose single AL-PMMA (PALACOS R plus G, gentamicin 0.5 g (g)), and the remaining 103 patients received high-dose dual AL-PMMA (COPAL G plus C, gentamicin one g plus clindamycin one g) [53]. The patients were evaluated after a minimum follow-up of one year, and it was found that the use of dual AL-PMMA was more effective in PJI prevention in rTKA while also demonstrating a cost-effective profile in all cost calculation models used.

Another recent study on this topic was conducted by Blersch et al. in 2023 with 403 patients who underwent aseptic rTKA with dual AL-PMMA. The patients were retrospectively analyzed with a minimum follow-up of 5 years [54]. There were five patients (1.24%) who were diagnosed with PJI (one acute, four chronic) and underwent re-revision. In conclusion, 98.2% of patients who underwent aseptic rTKA with dual AL-PMMA (Copal G and C) exhibited PJI-free survival throughout the 5-year follow-up.

In an article published by Bos et al. in 2023, data from the Dutch Arthroplasty Register were used to analyze 2,529 patients who underwent aseptic revision total hip arthroplasty (rTHA) and 7,124 patients who underwent aseptic rTKA between 2007 and 2018 in terms of single or dual AL-PMMA use [55]. Among patients who underwent rTHA, single AL-PMMA was used in 1,669 patients, 53 of whom required re-revision for PJI. In addition, dual AL-PMMA was used in 860 patients, wherein 24 patients also required re-revision for PJI. Considering the patients who underwent rTKA, single AL-PMMA was used in 5,270 and dual AL-PMMA in 1,854 patients, 97 and 46 of whom needed re-revision due to PJI, respectively. From the statistical point of view, single or dual AL-PMMA was not found to be superior to one another in rTJA practices.

According to a study by Hamoudi et al. carried out in 2024, 290 patients who underwent aseptic rTJA were evaluated in terms of PJI risk, wherein 145 patients received single and 145 patients received dual AL-PMMA [56]. Overall, 24-month follow-up results revealed no statistical superiority between single and dual AL-PMMA in terms of PJI in aseptic rTJA.

Conclusions

Most of the reviewed studies show that the use of AL-PMMA leads to a statistically and clinically relevant reduction in postoperative PJI risk in patients undergoing aseptic rTJA. This is also supported by a study found in the national registry involving nearly 10,000 patients. There were two recent studies indicated that the use of single and dual AL-PMMA was comparable in terms of their impact on PJI prevention in aseptic rTJA, wherein both led to a decreased risk of PJI. However, all studies have a retrospective design. Therefore, conducting prospective studies on this topic is a scientific necessity. Based on available data, the use of AL-PMMA is recommended to minimize the risk of PJI in aseptic rTJA cases, regardless of whether single or dual AL-PMMA is used.

[2] These authors contributed to Question 2: Mustafa Akkaya, Cheng-Fong Chen, Jean-Yves Jenny, Stergios Lazarinis, Pablo Sanz-Ruiz, Julian Costantini, Khalil Amri, Ismet Gavrankapetanović, Matteo Innocenti

Question 3: Does the use of antibiotic-impregnated polymethyl methacrylate cement reduce the incidence of infection in patients undergoing reimplantation for periprosthetic joint infection?[3]

Response/Recommendation

Unknown. While some studies have reported high success with the use of antibiotic-impregnated polymethyl methacrylate (PMMA) cement in reimplantation, others show limited infection control. In addition, the use of uncemented implants during reimplantation has also demonstrated favorable outcomes.

Level of Evidence: Moderate

Delegate Vote: Agree 73.7%, Disagree 20.5%, Abstain 5.8% (Strong Majority, Moderate Consensus)

Rationale

The use of antibiotic-impregnated polymethyl methacrylate (PMMA) cement in reimplantation for PJI has been proposed as an adjunctive strategy for local antibiotic delivery, aiming to enhance infection eradication while minimizing systemic toxicity [57]. However, the concentration of antibiotics such as vancomycin, gentamicin, tobramycin, or erythromycin in antibiotic-loaded bone cement (ALBC) may not reach and remain at the minimum inhibitory concentration (MIC) and the minimum biofilm eradication concentration (MBEC) over a prolonged period [58]. This raises questions about whether the use of antibiotic-impregnated PMMA cement effectively reduces the incidence of infection in patients undergoing reimplantation for PJI.

To answer the question posed above, a comprehensive systematic review was conducted with inclusion criteria restricted to English-language original articles reporting prospective or retrospective clinical studies on patients who underwent single- or two-stage rTJA for PJI. The review included studies evaluating the use of ALBC or no ALBC in rTKA and cementless or cemented techniques with or without ALBC in revision THA). A comprehensive literature search of the PubMed and Scopus databases yielded 813 abstracts. After the initial screening, 74 studies were selected for full-text review, and 25 were included in the final evaluation. The total number of patients across all included studies was 2,192. There were 15 studies that focused on two-stage revision [59–73], eight studies examined single-stage revision [74–81], and the remaining two studies reported on both single- and two-stage revisions [82,83]. Most two-stage revisions utilized antibiotic cement spacers or beads between stages [59–73,82]. An ALBC was used during reimplantation in 13 studies, covering 990 patients. In contrast, another 14 studies, including two that assessed both ALBC and non-ALBC patients, reported 1,202 patients who did not receive ALBC during reimplantation.

The infection control rate, defined as a successful revision of TJA without recurrence or new infection in patients who received antibiotic-impregnated PMMA cement during reimplantation, ranged from 75 to 100%, with an average follow-up duration from 22.3 months to 10.5 years [67,80]. Hsieh et al. [66] reported on 24 patients who underwent two-stage revision THA for PJI with massive bone loss. They used a cemented polyethylene cup within a metal cage for patients who have acetabular deficiencies and a cemented allograft prosthesis composite for those who have segmental femoral bone loss. Their ALBC protocol during reimplantation involved adding two grams of antibiotics (mostly vancomycin) per 40 grams pack of cement. After a follow-up period of 4.2 years (range, two to seven), no patients experienced recurrent infection. However, two cases of fractures of the cement femoral stem and one case of dislocation occurred, though these complications were unrelated to infection. Another study by Kuo et al. [69] investigated 10 knee and 12 hip PJI cases caused by methicillin-resistant *Staphylococci*. They performed two-stage revisions using one gram of daptomycin per 40 grams pack of bone cement during reimplantation in the second stage. Their treatment protocol achieved a 100% success rate, with no recurrence of infection during a mean follow-up of 33.7 months (range, 24 to 57). However, a study by Leijtens et al. [71] reported an unsatisfactory success rate in 10 patients who had a late infection of a cemented THA treated with two-stage revision while retaining the original well-fixed femoral cement mantle. During the second-stage revision, they implanted a cemented polyethylene cup on the acetabular side and performed a cement-within-cement revision on the femoral side. The ALBC consisted of bone cement mixed with 500 mg of erythromycin and 3,000,000 international units of colistin. After a mean follow-up of 26 months (range, five to 54), the primary microorganism was successfully eradicated in only two patients (20%).

In studies that did not use antibiotic-impregnated PMMA cement during reimplantation, whether in cemented revision THA or TKA or cementless revision THA, the success rate without reinfection ranged from 83 to 100%. The mean follow-up duration for these patients varied between 35 months and 10.4 years [64,68]. There were four studies that reported a 100% success rate with no relapse or new episodes of infection. Born et al. [82] found that all 21 single-stage revision THAs with a cementless stem had no infection failure over a mean follow-up of seven years. Another three studies performed a two-stage revision THA using a cementless prosthesis during the second-stage revision and found no reinfection following surgical intervention [64,72,73]. Similarly, several other studies reported high infection control rates despite not using antibiotic-impregnated PMMA cement [59–61,65,68,74,76,77,80].

While antibiotics in cement may help protect the implant-bone interface during the early postoperative period, infection eradication and successful treatment appear to depend more on meticulous surgical debridement, optimized systemic antibiotic therapy, and the host immune response.

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The Journal of Arthroplasty 41 (2025) S243–S247

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Hip and Knee

2025 ICM: Diagnosis of Surgical Site Infection (SSI)/Periprosthetic Joint Infection (PJI) With Samples From the Wound and Clinical Signs

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Question 1: In doubtful cases for periprosthetic joint infection (PJI), what is the best intraoperative test to confirm or refute the diagnosis?[1]

Response/Recommendation

Based on its diagnostic accuracy, availability, and rapid turnaround time, leukocyte esterase currently represents the best intraoperative test for confirming or excluding PJI. Despite limitations related to availability and/or processing time, other intraoperative tests, including synovial fluid analysis, frozen section histology, alpha-defensin, and calprotectin, also demonstrated favorable diagnostic performance and can be considered reliable adjuncts in the intraoperative diagnostic workup of PJI.

Level of Evidence: Moderate

Delegate Vote: Agree: 66.5%, Disagree: 16.7%, Abstain: 16.7% (Strong Majority, Moderate Consensus)

Rationale

Reliable intraoperative diagnostic tests are essential for guiding appropriate treatment, minimizing unnecessary procedures, and improving patient outcomes, particularly in preoperative unclear cases. Diagnosis of PJI relies on a combination of tests on serum and synovial fluid as well as tissue samples. Because of the lack of a single absolute test for the diagnosis of PJI, the combination of these tests provides some degree of certainty related to the presence or absence of PJI in a painful prosthetic joint. However, despite performing these tests occasionally, preoperative diagnosis of PJI is not possible, or an unexpected finding during revision surgery prompts surgeons to seek additional data to confirm or refute the diagnosis of PJI during the operation. The question posed above is seeking tests that can easily be performed during surgery to provide additional data.

To answer the above question, a comprehensive systematic review was conducted. Using the Medical Subject Headings terms developed by librarians, the Medline, Scopus, Web of Science, and Embase databases were searched to identify relevant studies. A total of 964 potentially eligible studies were identified. After screening by two observers, 887 were excluded, leaving 77 studies for inclusion in this review (Table 1). Only studies that evaluated the diagnostic tests in the intraoperative setting were included.

Based on our analyses of the studies, the tests that can be performed during surgery, both from the perspective of time and logistics, were included in the final recommendation.

Alpha-Defensin

Alpha-defensin demonstrates high specificity (96.3%) and good sensitivity (85.8%), with the advantage of being performed intraoperatively using lateral flow devices for rapid results and reduced operator dependency compared to histopathology [1–15]. However, its use is limited by the high cost of commercial test kits and the potential for false positives in cases of metallosis or inflammatory arthropathies, though these occurrences are rare.

Histopathology and Frozen Section

Frozen section is a traditional and widely used intraoperative method that allows direct visualization of polymorphonuclear leukocytes in tissue, providing additional valuable diagnostic insights (wear, arthrofibrosis, etc.) [6,9,16–40]. However, it is operator-dependent, requires an experienced pathologist, and has moderate sensitivity (71.5%) with a risk of sampling error.

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to 10.1016/j.arth.2025.10.107.

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https://doi.org/10.1016/j.arth.2025.10.107
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Table 1
Summary of Pooled Diagnostic Accuracy Metrics for Intraoperative Tests Used in the Detection of Periprosthetic Joint Infection.

Test	Number of Studies	Total Patients	Number of PJI Cases	Pooled Sensitivity (%)	Pooled Specificity (%)	Pooled LR+	Pooled LR-	DOR	Availability	Time to Results	Cost
Alpha-defensin	15	1,259	333	85.8	96.3	18.6	0.11	119.3	Limited	<15 minutes	High
Frozen section	27	3,755	649	71.5	93.9	9.2	0.28	34.0	Moderately available	30 to 60 minutes	Moderate
Calprotectin	11	786	262	90.1	89.8	7.3	0.11	73.8	Limited	<15 minutes	Moderate
Leukocyte esterase	14	1,368	384	82.5	93.8	8.0	0.15	54.8	Widely available	<15 minutes	Low
Synovial fluid analysis	6	636	200	79.4	85.6	5.3	0.21	26.4	Moderately available	15 minutes to 1 hour	Low
PCR – synovial fluid	4	341	161	67.4	88.7	-	-	-	Limited	>1 hour	High
PCR – tissue samples	6	381	209	83.7	98.7	16.9	0.12	144.0	Limited	>1 hour	High
PCR – sonication fluid	3	228	107	63.2	84.1	-	-	-	Limited	>1 hour	High
D-lactic acid	2	258	86	(83 to 86)	(82 to 100)	-	-	-	Moderately available	15 minutes to 1 hour	Moderate
NGAL	1	86	23	92	83	-	-	-	Limited	15 minutes to 1 hour	High
IL-6 lateral flow	1	26	-	46.9	97.6	-	-	-	Limited	<15 minutes	High

PJI, periprosthetic joint infection; PCR, polymerase chain reaction; IL-6, interleukin; LR, likelihood ratio; DOR, diagnostic odds ratio; NGAL, neutrophil gelatinase-associated lipocalin.

Calprotectin

Calprotectin offers high sensitivity (90.1%) and good specificity (89.8%), with lateral flow test kits enabling rapid intraoperative results like alpha-defensin [41–51]. However, its use is limited by less available data compared to alpha-defensin, potential issues with cost and availability depending on the setting, and the potential for false positives in cases of metallosis or inflammatory arthropathies.

Leukocyte Esterase

Leukocyte esterase is a rapid and inexpensive diagnostic option for PJI, utilizing a readily available urine dipstick test with reasonable specificity (93.8%) and sensitivity (82.5%) [22,27,52–63]. However, its subjective colorimetric interpretation can lead to errors, and its sensitivity is limited for detecting low-grade infections. In addition, it can also be influenced by metallosis or inflammatory arthropathies.

Synovial Fluid Analysis

Synovial fluid aspiration and evaluation of white blood cell and polymorphonuclear leukocytes counts were suggested as a diagnostic tool for PJI. The pooled sensitivity and specificity of the synovial fluid analysis were 79.4 and 85.6%, based on the results of six studies [1,43,51,52,59,64]. However, its accuracy may be affected by the presence of metallosis or underlying inflammatory arthropathies.

Polymerase Chain Reaction

Polymerase chain reaction on tissue samples offers the highest diagnostic accuracy, with excellent specificity (98.7%) and good sensitivity (83.7%), making it especially valuable for identifying difficult-to-culture and low-virulence pathogens [5,7,11,35,65–75]. However, its use is limited by the need for specialized molecular biology facilities, higher costs, and limited availability as a rapid intraoperative test.

Other Tests

D-lactic acid, neutrophil gelatinase-associated lipocalin, and interleukin 6 lateral flow have limited evidence or practical constraints that restrict their routine use in diagnosing PJI [5,52,53,76,77]. D-lactic acid shows promise as a biochemical marker, but lacks robust studies and is not widely available intraoperatively. Neutrophil gelatinase-associated lipocalin demonstrates high sensitivity (92%) in a single study but lacks validation across cohorts. Interleukin 6 lateral flow offers rapid point-of-care testing with high specificity (97.6%), but suffers from very low sensitivity (46.9%) and limited supporting evidence, reducing its standalone utility.

Composite Evaluation of Intraoperative Tests Using Diagnostic Utility Index

While the diagnostic odds ratio offers insight into a test's diagnostic accuracy by amalgamating its sensitivity and specificity, it fails to account for critical logistical and economic factors, including availability, cost, and turnaround time, which are essential in intraoperative contexts. To bridge this gap, we have developed a Diagnostic Utility Index (DUI)—a composite scoring model that harmonizes diagnostic strength with operational feasibility. This approach is consistent with principles from health technology assessment and decision-analytic frameworks like Multi-Criteria Decision Analysis, adapted here for enhanced simplicity and clinical relevance [78–80].

The DUI was calculated using the following formula:

$$\mathrm{DUI} = \frac{DOR \times A \times T}{C}$$

- **Diagnostic odds ratio** is the diagnostic odds ratio obtained from pooled meta-analysis.
- **A** represents a scaled ordinal score for **availability**.
- **T** denotes the **time-to-result** score.
- **C** reflects **cost**, which is inversely scaled to penalize more expensive tests.

Each of the qualitative factors (A, T, and C) was scored on a 3-point ordinal scale based on literature evidence and real-world accessibility.

Factor	Score = 0.5	Score = 1.0	Score = 1.5
Availability	Limited	Moderately available	Widely available
Time to result	>1 hour	15 to 60 minutes	<15 minutes
Cost	Low	Moderate	High

Test	DOR	Availability (A)	Time (T)	Cost (C)	DUI Calculation	DUI Value
Leukocyte esterase	54.8	1.5	1.5	0.5	(54.82 × 1.5 × 1.5) ÷ 0.5	**246.7**
Synovial fluid analysis	26.4	1.5	1.0	0.5	(26.36 × 1.5 × 1.0) ÷ 0.5	**79.1**
Alpha-defensin	119.3	0.5	1.5	1.5	(119.25 × 0.5 × 1.5) ÷ 1.5	**59.6**
Calprotectin	73.8	0.5	1.5	1.0	(73.84 × 0.5 × 1.5) ÷ 1.0	**55.4**
Frozen section	34.0	1.0	1.0	1.0	(33.97 × 1.0 × 1.0) ÷ 1.0	**34.0**
PCR – tissue	144.0	0.5	0.5	1.5	(143.98 × 0.5 × 0.5) ÷ 1.5	**24.0**

For tests where DOR was not available (e.g., PCR–synovial, NGAL, D-lactic acid), they were excluded from the DUI calculation due to insufficient quantitative metrics.
DUI, Diagnostic Utility Index; PCR, polymerase chain reaction; DOR, diagnostic odds ratio; NGAL, neutrophil gelatinase-associated lipocalin.

Question 2: What clinical signs have the highest diagnostic accuracy in differentiating seroma from surgical site infection/periprosthetic infection (SSI/PJI)?[2]

Response/Recommendation

Based on the available data, apart from witnessing frank purulent discharge, there are no specific clinical signs that are indicative of SSI/PJI and can differentiate it from seroma or hematoma. Thus, SSI/PJI should be suspected in any patient presenting with an abnormal fluid collection.

Strength of Recommendation: Limited

Delegate Vote: Total Consensus (Agree: 94.4%, Disagree: 5.6%)

Rationale

The postoperative fluid collection remains one of the most common complications after primary or revision arthroplasty surgery. Seromas and hematomas remain the most commonly encountered fluid collections, especially in the early postoperative period. However, PJI or SSI poses the most fearful differential diagnosis of this condition. A high index of suspicion is required to diagnose these three conditions—seroma/hematoma/early infection—either to prevent bacterial seeding of the sterile fluids or to clear out the infection before going into chronicity [81]. Since the clinical examination is the first and simplest step in the diagnosis journey, defining the specific clinical signs to differentiate sterile from septic fluid collection is crucial.

To answer this question, we systematically reviewed the relevant literature across two search engines, Scopus and PubMed. We imported 513 studies for screening, excluding 16 duplicates, resulting in 497 studies screened against the title and abstract. We defined the inclusion criteria, including human case series and randomized control trials published after the year 2010, reporting on patients older than 18 years who have a PJI and/or SSI and/or clinical signs of seroma and/or wound complications after hip and/or knee joint arthroplasty surgery. We excluded animal studies, case reports, narrative reviews of literature, studies on children, or reports on nonarthroplasty surgery and skin diseases before 2010. This excluded 495 studies, ending with 12 studies assessed for full-text eligibility [82–93].

The results of our research were not decisive. We were not able to find a clear answer to this question. Most papers reported the number of patients complicated with seromas/hematomas/PJI/SSI without referring to the clinical signs or symptoms detected and used for the diagnosis [82–93]. We attribute this to the previous successful work done by several bodies to define the specific diagnostic criteria used to detect the PJI. Recent papers rely on these diagnostic criteria owing to their high sensitivity and specificity. However, apart from seeing the pus or purulent discharge, the clinical criteria reported are of poor specificity. Constitutional manifestations such as fever and pain, and local signs and symptoms such as erythema, warmth, and tenderness, are all suggestive and should not be relied on [94–99].

Conclusions

Available literature could not provide definitive evidence for a clinical sign that can help clinicians differentiate between postoperative sterile fluid collection, such as seroma, and fluid collection, resulting from infection. Relying on previous diagnostic criteria defined by different bodies, we still recommend that clinical signs, apart from witnessing a frank purulent discharge, be considered suggestive and not confirmatory. Confirmation should be made based on further aspiration and fluid analysis.

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The Journal of Arthroplasty 41 (2025) S248–S260

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The Journal of Arthroplasty

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Hip and Knee

2025 ICM: Serological Diagnosis of Surgical Site Infection (SSI)/Periprosthetic Joint Infection (PJI)

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Question 1: Is there a role for joint-specific (hip versus knee) cutoffs for serological tests in the diagnosis of periprosthetic joint infection?[1]

Response/Recommendation

No. There is no compelling evidence to support the need for separate cutoff thresholds for C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in diagnosing periprosthetic joint infection (PJI) between the hip and knee. The current thresholds for serum CRP and ESR are appropriate for use in both hip and knee PJI. The evidence for other serologic markers beyond CRP and ESR in distinguishing hip versus knee PJI remains limited. While further research may refine these approaches, a unified cutoff threshold remains a reasonable and effective approach.

Level of Evidence: Moderate

Delegate Vote: Agree: 86.5%, Disagree: 5.4%, Abstain: 8.1% (Super Majority, Strong Consensus)

Rationale

Diagnosing PJI based on serologic markers is challenging due to the retrospective nature of most studies, which often combine data from hip and knee PJI, complicating joint-specific conclusions. Serum CRP and ESR have been routinely used as part of the diagnostic workup for PJI with the thresholds of 10 mg/L (one mg/dL) for CRP and 30 mm/hour (mm/h) for ESR, as recommended by the Musculoskeletal Infection Society (MSIS) [1] and the International Consensus Meeting (ICM) [2]. However, some studies suggested that these thresholds were too high, leading to false negatives, and proposed lower cutoffs [3,4]. Notably, the 2021 European Bone and Joint Infection Society PJI definition [5] removed ESR from the diagnostic criteria. It is important to note that these thresholds were set arbitrarily, and their clinical utility should always be considered alongside other clinical and laboratory findings for an accurate diagnosis.

The 2010 meta-analysis by Berbari et al. [6] found that CRP had higher diagnostic accuracy than ESR for identifying hip and knee PJI, but neither marker was sufficient alone, recommending a combination of tests with clinical evaluation. In 2017, a meta-analysis by Huerfano et al. [7] further evaluated the diagnostic accuracy of CRP and ESR using the thresholds recommended by MSIS/ICM in hip PJI. The study found that CRP had 87% sensitivity and 79% specificity, while ESR had 86% sensitivity and 72% specificity, indicating moderate diagnostic accuracy for both tests. A prospective study in 2024 by Tarabichi et al. [8] evaluated the same thresholds for hip and knee PJI and found that CRP had 90% sensitivity and 70% specificity, while ESR had 74% sensitivity and 85% specificity. In addition, a meta-analysis in 2022 by Tang H et al. [9], which included 216 studies, found that the optimal CRP thresholds for chronic hip and knee PJI were 13.5 mg/L (sensitivity 84%, specificity 83%), slightly higher than MSIS/ICM recommendations, while the ESR threshold of 30 mm/hour remained optimal (sensitivity 79%, specificity 78%).

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.102.

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https://doi.org/10.1016/j.arth.2025.10.102
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Table 1
Mean ± SD of CRP and ESR for Patients Diagnosed With PJI and Aseptic Joint.

Study, Y	Design	Knee				Hip			
		CRP (mg/L)		ESR (mm/hour)		CRP (mg/L)		ESR (mm/hour)	
		PJI (n)	Aseptic (n)	PJI (n)	Aseptic (n)	PJI (n)	Aseptic (n)	PJI (n)	Aseptic (n)
Schwartz et al., 2012 [24]	R	76 ± 87.25 (22)[a,b]	3.8 ± 57.5 (126)[a,b]	45 ± 33.3 (22)[a,b]	8 ± 30.8 (126)[a,b]	N/A	N/A	N/A	N/A
Balato et al., 2023 [25]	P	16.2 ± 23.7 (146)[a,b]	4.29 ± 6.4 (115)[a,b]	32.5 ± 24.4 (146)[a,b]	19.5 ± 19.4 (115)[a,b]	N/A	N/A	N/A	N/A
Balato et al., 2018 [26]	R	22 ± 30.1 (31)[a,b]	3.7 ± 1.93 (136)[a,b]	65 ± 26.7 (31)[a,b]	23 ± 9.3 (136)[a,b]	N/A	N/A	N/A	N/A
Cohen-Levy et al., 2022 [27]	R	152.3 ± 141.4 (20)	5.8 ± 5.1 (26)	60.2 ± 28.7 (19)	19.1 ± 14.9 (29)	N/A	N/A	N/A	N/A
Denyer et al., 2023 [28]	R	25.3 ± 43.3 (124)	3.2 ± 9.04 (162)	72.7 ± 33.6 (124)	21.8 ± 21.5 (162)	22.9 ± 48.1 (122)	3.3 ± 7.76 (167)	67.4 ± 33.4 (122)	26.75 ± 24.09 (167)
Ghanem et al., 2008 [29]	R	14.5 ± 10.1 (161)[a,b]	2.2 ± 2.7 (268)[a,b]	72 ± 34.5 (161)[a,b]	25 ± 21.5 (268)[a,b]	N/A	N/A	N/A	N/A
Gallo et al., 2018 [32]	P	107 ± 108.5 (59)[a,b]	3.5 ± 37.8 (57)[a,b]	61 ± 29.8 (59)[a,b]	14.5 ± 23.3 (57)[a,b]	50 ± 96.5 (34)[a,b]	3 ± 11.5 (90)[a,b]	55 ± 27.5 (34)[a,b]	17 ± 18.5 (90)[a,b]
Schiffner et al., 2020 [30]	R	78.5 ± 33.5 (32)[b]	4.5 ± 4.1 (117)[b]	N/A	N/A	N/A	N/A	N/A	N/A
Schinsky et al. 2008 [31]	P	N/A	N/A	N/A	N/A	52.4 ± 86.1 (55)	7.8 ± 21.2 (146)	55.4 ± 24.5 (55)	26.2 ± 17 (146)

[a] median.
[b] SD calculated from range or interquartile range; R, retrospective; P, prospective; N/A, not applicable; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PJI, prosthetic joint infection.

The accuracy and optimal thresholds of CRP and ESR in diagnosing PJI vary across studies due to factors such as pathogen virulence [10–12], chronicity [12,13], time since surgery [14], type of arthroplasty (e.g., hemiarthroplasty) [15], inflammatory conditions [16], obesity [17], age [18], and sex [19]. For instance, ESR was found to increase with age, particularly in women and African Americans, while CRP showed a slightly positive trend with age [18]. Unter Ecker et al. [11] found that the optimal CRP threshold was 8.9 mg/L for hip and 9.9 mg/L for knee PJI. Kim et al. [20] found that a CRP threshold of 34.9 mg/L had the best diagnostic performance for acute knee PJI (within three weeks of arthroplasty). Alijanipour et al. [14] evaluated the thresholds for early postoperative hip and knee PJI (within 4 weeks of arthroplasty); the optimal thresholds were 23.5 mg/L for CRP and 54.5 mm/hour for ESR. Salimy et al. [15] identified different thresholds for hip hemiarthroplasty, with 40 mg/L for CRP and 52 mm/hour for ESR. In inflammatory arthritis with chronic PJI, Cipriano et al. [16] recommended a CRP threshold of 17 mg/L and an ESR threshold of 30 mm/hour. In addition, obesity, which is associated with a proinflammatory state, can lead to elevated baseline CRP. Liu et al. [17] found that a higher CRP threshold of 36 mg/L was more accurate in diagnosing knee PJI in obese patients. Ghanem et al. [21] published a retrospective study focusing on hip PJI and found a CRP threshold of 20.5 mg/L and an ESR threshold of 30 mm/hour. For chronic knee PJI, a prospective study by Greidanus et al. [22] identified optimal thresholds of 13.5 mg/L for CRP and 22.5 mm/hour for ESR. However, none of these studies addressed the CRP and ESR cutoffs for knee versus hip PJI within the same analysis. These variations highlight how patient demographics and comorbidities impact the accuracy of CRP and ESR in diagnosing PJI.

We reviewed the evidence on whether joint type (hip versus knee) is another factor that influences the CRP and ESR thresholds in PJI diagnosis. The data evaluating separate cutoff thresholds of other serologic markers (such as interleukin-6 and D-dimer) for hip versus knee PJI are much less established. Only two studies have specifically aimed to evaluate distinct ESR and CRP thresholds for hip versus knee PJIs within the same study [14,23]. The retrospective study by Piper et al. [23] reported the optimal CRP thresholds of 10.3 mg/L for hip PJI and 14.5 mg/L for knee PJI. The optimal ESR thresholds for hip and knee PJI were 13 and 19 mm/hour, respectively. A large retrospective study by Alijanipour et al. [14] analyzed 1,962 patients and found that, for chronic PJI, the optimal CRP thresholds were 13.5 mg/L for hips and 23.5 mg/L for knees, with ESR thresholds of 48.5 mm/hour for hips and 46.5 mm/hour for knees. When comparing the findings from Piper et al. [23] and Alijanipour et al. [14], several differences and similarities emerge in the optimal thresholds for CRP and ESR in diagnosing chronic PJI. For CRP, the thresholds for knee PJI tend to be higher than hip PJI, while for ESR there is substantial variation between the two studies.

Other studies we reviewed did not specifically aim to evaluate the differing thresholds of CRP and ESR for hip versus knee PJIs, but they provided data that we were able to extract and analyze in our systematic review and meta-analysis. A total of nine studies were included in the final analysis [24–32]. The meta-analysis was performed using a random-effects model to assess the effect sizes of mean values of CRP and ESR between total knee arthroplasty (TKA) and total hip arthroplasty (THA) in the setting of PJI. Further analysis was performed to evaluate the mean values of CRP and ESR between PJI and aseptic patients in both the settings of TKA and THA. Subgroup differences were tested using Dixon Q-test, and mean differences with 95% confidence intervals (CIs) were calculated (Table 1).

For CRP, there were 595 TKA PJI, 211 THA PJI, 1,007 aseptic TKA, and 403 aseptic THA. As expected, the mean difference in CRP between THA PJI and aseptic THA was significantly different (34.1

[95% CI: 12.5 to 55.66]; $P = 0.002$). Similarly, there was a significant mean difference when comparing CRP of TKA PJI and aseptic TKA (52.7 [95% CI: 21.1 to 84.2]; $P < 0.001$). However, the mean difference of CRP between THA PJI and TKA PJI was not significant (18.0 [95% CI: −20.1 to 56.1]; $P = 0.35$).

For ESR, there were 562 TKA PJI, 211 THA PJI, 893 aseptic TKA, and 403 aseptic THA. As expected, the mean difference in ESR was significantly different between THA PJI and aseptic THA (36.3 [95% CI: 25.9 to 46.6]; $P < 0.001$). A significant mean difference was also observed when comparing ESR of TKA PJI and aseptic TKA (39.4 [95% CI: 27.3 to 51.4]; $P < 0.001$). However, ESR was similar when comparing THA PJI to TKA PJI (1.2 [95% CI: 12.9 to 15.1]; $P = 0.87$).

Question 2: Which serological screening tests should be obtained for patients undergoing revision arthroplasty?[2]

Response/Recommendation

A C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) should be obtained in all patients undergoing revision total joint arthroplasty (TJA), regardless of the presenting complaint. Furthermore, D-dimer may be a useful tool in cases of diagnostic uncertainty.

Level of Evidence: Strong

Delegate Vote: Agree: 91.0%, Disagree: 6.7%, Abstain: 2.3% (Total Consensus, Unanimity)

Rationale

Periprosthetic joint infection (PJI) is a devastating complication and a major cause of morbidity and mortality following primary and revision TJA [33]. To date, the orthopedic community has yet to identify a single absolute test for the diagnosis of PJI [34]. As such, the diagnosis of PJI can be challenging to make and relies on a combination of tests [35].

Due to their high negative predictive value, low cost, and widespread availability, serological markers are commonly utilized to rule out chronic infection in patients undergoing revision TJA [36,37]. At this time, clinical practice guidelines endorse the use of serum CRP and ESR as first-line tests in this setting [38]. Although a range of diagnostic thresholds has been proposed for CRP and ESR within the arthroplasty literature, a cutoff of 10 mg/L for CRP and 30 mm/hour for ESR has been shown to have the best overall accuracy for chronic PJI (Table 2). However, the vast majority of existing studies on the diagnostic utility of serological markers utilized statistical analyses that maximized both sensitivity and specificity when selecting the optimal cutoffs for these tests. Hence, it is not surprising that a growing body of evidence has demonstrated that serology is normal (i.e., below the above-stated thresholds) in a number of PJI patients, especially in cases caused by slow-growing organisms such as *Cutibacterium acnes* and coagulase-negative *Staphylococci* [53,54]. More recently, in an effort to identify the optimal cutoffs of serological markers for use as screening tests, Bingham et al. demonstrated that a CRP and ESR cutoff of five mg/L and 10 mm/hour, respectively, had a sensitivity of 95% for the diagnosis of PJI, minimizing the potential for false-negative results when using these tests [45]. Furthermore, there have been data to suggest that the combination of CRP and ESR improves overall diagnostic confidence in this setting, highlighting the importance of routinely ordering both tests when working up patients undergoing revision TJA (Table 3). In one study, the authors found that the combination of CRP and ESR at a cutoff of five mg/L and 10 mm/hour, respectively, had a sensitivity of 100% and a specificity of 55% [45].

A D-dimer test has garnered attention as a potential serum marker of infection in view of reports demonstrating its ability to identify outcomes in patients who have bacteremia [56]. The utility of D-dimer in the diagnosis of PJI has since been established in the orthopedic literature [57–59], culminating in its inclusion in the 2018 International Consensus Meeting definition of PJI [60]. Although the 2018 International Consensus Meeting definition utilized a D-dimer threshold of 860 ng/mL, there remains a lack of consensus on the optimal cutoff for D-dimer in the diagnosis of PJI, precluding it from universal adoption in this setting (Table 4). However, it is important to recognize that there are certain clinical scenarios where D-dimer may provide additional diagnostic information. In one study, D-dimer was found to have the highest

Table 2
Diagnostic Utility of Serum C-Reactive Protein and Erythrocyte Sedimentation Rate as Demonstrated in the Literature

Study and Publication Year	Definition of Infection	Cutoff	Sensitivity (%)	Specificity (%)
C-reactive protein		mg/L		
Glehr et al., 2013 [39]	2011 MSIS	10.2	91	72
Alijanipour et al., 2013 [40]	2011 MSIS	10.0	97	70
Shahi et al., 2017 [41]	2013 ICM	10.0	79	80
Klim et al., 2018 [42]	2011 MSIS	10.3	90	67
Fu et al., 2019 [43]	2011 ICM	10.0	80	80
Wu et al., 2020 [44]	2013 ICM	10.8	73	95
Bingham et al., 2020 [45]	2013 ICM	10.0	85	67
Bingham et al., 2020 [45]	2013 ICM	5.0	95	63
Erythrocyte sedimentation rate		mm/h		
Bottner et al., 2007 [46]	(+) Histology or ≥ 2 (+) cultures	32	81	89
Ghanem et al., 2009 [47]	Sinus tract or ≥ 2 (+) cultures	31	94.5	72.2
Xiong et al., 2019 [48]	2011 MSIS	30	73	100
Bin et al., 2020 [49]	2011 MSIS	31	77	97
Huang et al., 2020 [50]	2013 MSIS	30	81	88
Yang et al., 2021 [51]	2018 ICM	36.5	70	86
Tarabichi et al., 2024 [52]	2018 ICM	41	74	85

MSIS, Musculoskeletal Infection Society; ICM, International Consensus Meeting.

[2] These authors contributed to Question 2: Saad Tarabichi, Jens T. Verhey, Jesse W.P. Kuiper, Ernesto Muñoz-Mahamud, Colin M. Baker, Ran Schwarzkopf, Viktor E. Krebs, Juan D. Lizcano, Xianzhe Liu, Hamad Alenezi, Mark J. Spangehl, Joshua S. Bingham

Table 3
Diagnostic Utility of the Combination of C-Reactive Protein and Erythrocyte Sedimentation Rate as Demonstrated in the Literature.

Study and Publication Year	Definition of Infection	CRP Cutoff (mg/L)	ESR Cutoff (mm/h)	Sensitivity (%)	Specificity (%)
Ghanem et al., 2009 [47]	Sinus tract or ≥ 2 (+) cultures	30	10	87.8	88.1
[a]Alijanipour et al., 2013 [40]	2011 MSIS	13.5	48.5	85.7	60.6
[b]Alijanipour et al., 2013 [40]	2011 MSIS	23.5	46.5	95.6	54.0
Shahi et al., 2017 [41]	2013 ICM	10	30	84	47
Bingham et al., 2020 [45]	2013 ICM	10	30	88.8	71.7
Bingham et al., 2020 [45]	2013 ICM	5	10	100	54.7
[a]Yu et al., 2023 [55]	2011 MSIS	30	10	70.1	88.8
[b]Yu et al., 2023 [55]	2011 MSIS	30	10	78.3	88.8
Tarabichi et al., 2024 [52]	2018 ICM	7	51	82.4	84.1

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MSIS, Musculoskeletal Infection Society; ICM, International Consensus Meeting.
[a] Hips only.
[b] Knees only.

sensitivity for PJI caused by "low virulence" organisms at 93.8%, when compared to CRP (sensitivity 74.0%) and ESR (sensitivity 78.8%) [65]. Similarly, in another study, the authors demonstrated that when evaluating the performance of different serological markers as screening tests (maximizing sensitivity to 100%), D-dimer demonstrated a specificity of 40.2%, outperforming both ESR and CRP [52]. Notwithstanding, D-dimer is a nonspecific test that has been shown to be elevated in patients who have certain medical conditions, including cancer, systemic inflammatory diseases, a history of venous thromboembolism, and recent trauma, reducing its diagnostic utility in these patient populations [66,67].

Serum interleukin-6 (IL-6) is a cytokine that stimulates the release of acute-phase reactants from the liver [68]. In the orthopaedic literature, there is a growing body of evidence to suggest that IL-6 has excellent utility for the diagnosis of PJI. In a recent meta-analysis by Berbari et al., serum IL-6 was found to have a pooled sensitivity and specificity of 97 and 87%, respectively, for the diagnosis of PJI [69]. Similarly, in a separate study, Xie et al. demonstrated that serum IL-6 had a sensitivity and specificity of 72 and 91%, respectively, in the diagnosis of PJI [70]. However, it is important to recognize that although the use of serum IL-6 in this patient population was endorsed by the American Academy of Orthopaedic Surgeons clinical practice guidelines, the limited availability and relatively high cost of this test have prevented it from being universally adopted [38]. Furthermore, there remains a lack of consensus within the orthopedic literature on the optimal cutoff of this marker for the diagnosis of PJI [71].

In patients undergoing revision TJA, there is substantial evidence to support the routine use of CRP and ESR to help rule out infection in cases of low pretest probability. Furthermore, a growing body of evidence has demonstrated that there may be a role for measuring D-dimer levels in cases of diagnostic uncertainty. Notwithstanding, it is important to recognize that when traditional thresholds are used, serology can be negative in a relatively large proportion of PJI patients. Therefore, physicians must employ a high index of suspicion for infection and have a low threshold for arthrocentesis in all patients undergoing revision TJA.

Question 3: Is there a role for fibrinolytic serological markers, such as fibrinogen and D-dimer, in the diagnosis of periprosthetic joint infection (PJI)?[3]

Response/Recommendation

Yes. Fibrinolytic serological markers, such as fibrinogen and D-dimer, have demonstrated utility in the diagnosis of PJI. D-dimer is recognized for its sensitivity, and fibrinogen for its specificity.

Level of Evidence: Strong

Delegate Vote: Agree: 66.5%, Disagree: 23.1%, Abstain: 10.4%

Rationale

The D-dimer levels are elevated in cases of infection due to the inflammation of the synovium and the robust fibrin production. As the synovium becomes inflamed, it releases proinflammatory cytokines that activate the coagulation cascade, leading to increased fibrin formation and subsequent degradation. This process results in elevated circulating levels of D-dimer, which serves as a marker

Table 4
Diagnostic Utility of D-Dimer as Demonstrated in the Literature.

Study and Publication Year	Definition of Infection	Cutoff (ng/mL)	Sensitivity (%)	Specificity (%)
Shahi et al., 2017 [41]	2013 ICM	850	89	93
Li et al., 2019 [61]	2013 ICM	1,250	64.5	65.0
Pannu et al., 2020 [62]	2013 ICM	850	96	32
Xu et al., 2021 [63]	2013 ICM	800	85.7	47.8
Muñoz-Mahamud et al., 2022 [64]	2018 ICM	950	91	64
Tarabichi et al., 2023 [65]	2018 ICM	664	81.3	81.7

ICM, International Consensus Meeting.

[3] These authors contributed to Question 3: Alisina Shahi, Ruben Arriaga Sánchez, Charles Davis, Saul Martinez, Laia Boadas Girones, Aldo Riesgo, Huang Wei, Rocco Papalia, Kenneth Mathis

of systemic fibrinolysis and inflammation. Shahi et al. [72] introduced this mechanism as a key reason why D-dimer has diagnostic utility in identifying PJI. Since then, several studies have explored the utility of serum D-dimer in detecting PJI. However, their diagnostic accuracy has varied, likely because of differences in the threshold, inclusion criteria, measurement methods, and study designs. Reported pooled sensitivity is approximately 0.73 to 0.81 and specificity of 0.74 to 0.78 for D-dimer, using thresholds between 756 and 1,250 ng/mL [73–80].

Diagnostic performance of D-dimer

D-dimer, a fibrin degradation product, reflects the fibrinolytic activity associated with inflammation and infection. A meta-analysis of studies on D-dimer in PJI reported pooled sensitivity and specificity values of 0.81 (95% confidence interval (CI): 0.71 to 0.88) and 0.74 (95% CI: 0.61 to 0.84) [81], respectively. Notably, Shahi et al. [72] identified a sensitivity of 0.89 and a specificity of 0.93 for serum D-dimer when a threshold of 850 ng/mL was applied. Similarly, studies such as those by Wang et al. and Hu et al. reported consistent findings, with Wang et al. [82] demonstrating an area under the curve of 0.85 and Hu et al. [83] identifying a sensitivity of 0.88 and specificity of 0.89 at a threshold of 995 ng/mL. These findings suggest that D-dimer is a highly sensitive marker, making it useful for screening purposes. Furthermore, its diagnostic utility has been validated in diverse patient populations, including those with low-grade infections, where traditional markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) may fail to provide conclusive results. In a study by Pannu et al. [84], the authors found that D-dimer has high sensitivity (97.5%) and NPV (95.4%) in PJIs caused by low-virulent organisms. However, D-dimer's specificity can be limited by confounding factors such as systemic inflammatory conditions, malignancies, or recent surgical interventions. Thus, integrating D-dimer with other diagnostic markers, such as fibrinogen, CRP, and synovial fluid analysis, can enhance its overall diagnostic accuracy and clinical applicability.

Diagnostic performance of Fibrinogen

Plasma fibrinogen, a coagulation-related protein, has emerged as a robust marker with higher specificity compared to D-dimer. Studies have reported fibrinogen's specificity to range from 0.85 to 0.90, with sensitivity values around 0.86 [73,85]. Its diagnostic accuracy, reflected in an area under the curve of 0.916, supports its use as a confirmatory test [86]. The cost-effectiveness and wide availability of fibrinogen further enhance its clinical applicability. In addition, fibrinogen may provide added value in differentiating infectious from aseptic failure in complex cases [87]. Recent findings, such as those by Huang et al. [85], highlight the potential of fibrinogen to outperform D-dimer in diagnostic precision, particularly in distinguishing PJI from aseptic loosening. Their study noted a sensitivity of 0.78 and specificity of 0.88 for fibrinogen at a threshold of 4.01 μg/mL, which was comparable to conventional markers such as CRP and ESR but with enhanced specificity in certain clinical scenarios. The robust performance of fibrinogen underlines its utility as an adjunct in diagnosing PJI, especially in low-grade or indolent infections where traditional inflammatory markers might falter. It is crucial to recognize that fibrinogen and D-dimer share a physiological relationship, as fibrinogen is converted to fibrin, which subsequently degrades into D-dimer. This dynamic means that elevations in fibrinogen and D-dimer often occur in parallel, providing complementary insights into the coagulation and fibrinolytic processes. As such, fibrinogen should be considered following and synonymous with D-dimer, with both markers collectively reflecting the coagulation cascade's activity in inflammatory and infectious states [88,89].

While conventional markers such as CRP and ESR remain integral to the diagnosis of PJI, both markers exhibit limitations in cases of low-grade infections or those caused by indolent organisms like *Cutibacterium* acnes. D-dimer and fibrinogen, by reflecting different pathophysiological mechanisms, complement these traditional markers and improve diagnostic yield.

Both fibrinolytic markers are minimally invasive and widely available, making them accessible tools for clinical practice. However, variations in thresholds, sampling methods (serum versus plasma), and patient comorbidities must be considered to optimize their diagnostic accuracy. Standardization of these factors will be essential for broader clinical adoption.

Several systematic reviews and meta-analyses underscore the importance of these markers. For instance, Wang et al. [79] demonstrated that D-dimer and fibrinogen are valuable additions to the diagnostic algorithm, particularly in ambiguous cases. Prospective studies with standardized protocols will further elucidate their roles and establish robust guidelines for their application.

Conclusions

The integration of fibrinolytic markers such as D-dimer and fibrinogen into the diagnostic framework for PJI enhances diagnostic accuracy and complements traditional methods. D-dimer is recommended for its high sensitivity and suitability as a screening tool, particularly excelling in the detection of low-virulence organisms, which are often challenging to diagnose with traditional markers. Fibrinogen, with its superior specificity, serves as an effective confirmatory test, especially in distinguishing infectious from aseptic failures. Both markers, being physiologically linked—as fibrinogen is converted to fibrin and subsequently degrades into D-dimer—often exhibit parallel elevations, further highlighting their diagnostic synergy. These properties underline their potential to transform the diagnostic landscape for PJI. Future research should focus on standardizing thresholds, optimizing clinical algorithms, and validating these findings across diverse patient populations and clinical settings to refine their application and improve patient outcomes.

Question 4: Is the accuracy of serum and/or synovial biomarkers for the diagnosis of periprosthetic joint infection (PJI) affected by the presence of inflammatory conditions?[4]

Response/Recommendation

Unknown. It remains unclear whether the presence of inflammatory conditions affects the accuracy of serum and/or synovial biomarkers for the diagnosis of PJI. However, current evidence suggests that synovial biomarkers such as synovial white blood cell (WBC) and alpha-defensin offer greater diagnostic accuracy for PJI than serum biomarkers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in this population.

Level of Evidence: Limited

Delegate Vote: Agree: 80.7%, Disagree: 14.5%, Abstain: 4.8% (Super Majority, Strong Consensus)

Rationale

Periprosthetic joint infection is a devastating complication after arthroplasty and results in major morbidity to the patient as

[4] These authors contributed to Question 4: Alexander Linton, Hernan Prieto, Wael Samir Osman, Artit Laoruengthana, Danielle Ponzio, Hesham Abdelbary, Karan Goswami

well as a considerable economic burden [90,91]. The PJI rates vary with patient age, comorbidities, and social factors, but are estimated to range from approximately 0.5 to 2% for primary total knee arthroplasty and 0.5 to 1% for total hip arthroplasty [92–94]. Patients who have inflammatory arthritis (IA), such as rheumatoid arthritis (RA), are particularly at risk, with a higher incidence of PJI observed in this population compared to patients who undergo arthroplasty for osteoarthritis (OA) [95,96]. Diagnosis of PJI in this population of patients who have concomitant inflammatory conditions may be challenging, due in part to the heterogeneity of inflammatory diseases and various treatments, including immunosuppressants, as well as different phases of disease activity [97]. Similar to serum cytokines such as ESR/CRP, synovial fluid cytokines may be affected by systemic inflammatory disease [98]. The utility of serum and synovial biomarkers for PJI diagnosis in patients who have IA remains unclear. This review aimed to evaluate whether serum and synovial biomarkers commonly used for PJI diagnosis are affected by the presence of inflammatory conditions.

There were 12 studies that were included in the final analysis, eight of which separated IA and non-inflammatory arthritis (NIA) patients, while three studies included only IA patients, and one study compiled both IA and NIA patients [97,99–109]. There were four studies that specifically investigated RA, while eight included patients who have RA and other conditions, including ankylosing spondylitis (AS), psoriatic arthritis, systemic lupus erythematosus, Sjögren syndrome, and juvenile RA. Results within the included studies were highly divided: six of 12 studies found no change in diagnostic accuracy or optimal thresholds between IA and NIA patients, while six of 12 studies noted changes in either sensitivity/specificity or optimal diagnostic thresholds for the biomarkers assessed.

There were three studies performed by Cipriano et al., Wang et al., and Shohat et al. that directly compared results between IA and NIA patients for serum ESR, CRP, and synovial fluid WBC count and polymorphonuclear cell (PMN%) [99,102,107]. Zhao et al. conducted a similar analysis without assessing synovial fluid biomarkers [108]. Individually reported diagnostic thresholds, sensitivities, specificities, and receiver operating curve area under the curve (AUC) data are reported in Table 5. Cipriano et al. compared 810 NIA and 61 IA patients who have RA, juvenile RA, or AS undergoing revision hip and knee arthroplasty, finding similar optimal diagnostic thresholds for PJI diagnosis between the IA and NIA groups. Despite a trend toward lower specificities in the IA group, no significant differences were found among sensitivity, specificity, and receiver operating curve AUC when directly comparing IA versus NIA patients, although this may have been influenced by wide confidence intervals within the IA group. Shohat et al. conducted a review of 55 IA and 512 NIA patients who have PJI, concluding that both serum and synovial fluid biomarkers had comparable accuracy in PJI diagnosis for IA and NIA patients at similar thresholds, despite baseline elevation of serum CRP in the IA group [102]. Conversely, Wang et al. found significantly higher optimal diagnostic thresholds for both serum ESR/CRP and synovial WBC/PMN% in RA patients compared to NIA patients. Sensitivity, specificity, and AUC values were all lower in the RA-PJI group than the OA-PJI group, although the authors noted that synovial fluid WBC performed the best in RA patients who have 94.4% specificity and an AUC of 0.916 [107]. Zhao et al. reported a 10-fold higher incidence of PJI at five years in patients who have RA compared to OA (6.92 versus 0.67%). Similar to Wang et al., they found significantly higher optimal thresholds in addition to lower sensitivity and specificity for serum ESR and CRP in PJI diagnosis for RA patients [108]. These results help highlight the discordant nature of the currently available literature.

Several other studies found that diagnostic accuracy was affected by inflammatory conditions. Ren et al. investigated the diagnostic accuracy of multiple serum and synovial biomarkers in acute PJI diagnosis for RA patients, noting poor results for serum CRP, synovial WBC count, and PMN%, with specificities of 39, 36, and 9.3%, respectively [109]. A prospective cohort study by Qin et al. compared several synovial/serum biomarkers in 35 patients who had chronic PJI to those seen in 30 patients who had active rheumatoid flares, attempting to explore whether normal biomarker thresholds were able to differentiate between RA flares and PJI. They reported poor ability of several serum biomarkers to distinguish active RA from chronic PJI, including serum CRP, ESR, D-dimer, and interleukin 6, with reported specificities of 3.33, 26.67, 40.00, and 6.67%, respectively. Interestingly, they reported promising results with the synovial CD64 index (threshold 0.87, sensitivity 82.9%, specificity 93.3%, AUC 0.930) and synovial fluid interleukin 6 (threshold 4,817.38 pg/mL, sensitivity 91.4%, specificity 86.7%, AUC 0.875) [105].

Plasma fibrinogen has been investigated several times in patients who have IA. Li et al. [103] reported poor overall diagnostic accuracy of 0.524 in a subgroup of 42 patients who have

Table 5
Cipriano, Wang, Shohat, and Zhao Outcomes Summary [99,102,107,108].

Test/Study	Optimal Diagnostic Threshold		Sensitivity (%)		Specificity (%)		AUC	
ESR (mm/h)	IA	NIA	IA	NIA	IA	NIA	IA	NIA
Cipriano, 2012	30	32	94.4	87.2	59.4	67.1	0.85	0.849
Wang, 2023	39	31	81.7	77.9	52.5	97.1	0.709	0.929
Shohat, 2018	32	31.5	84.9	83.2	80.7	82.8	0.89	0.88
Zhao, 2024	33.02	22.95	62.2	80.9	60.4	84.4	0.613	0.905
CRP (mg/L)								
Cipriano	17	15	93.8	85.8	70.3	83.4	0.851	0.885
Wang	12.5	8.2	86.7	83.7	53.7	96.2	0.757	0.938
Shohat	13	11	84.6	88.2	86.2	81.3	0.92	0.88
Zhao	13.85	5.74	67.6	85.4	74.7	86.6	0.676	0.92
SF WBC count (cells/uL)								
Cipriano	3,444	3,450	88.2	91	80	93	0.938	0.945
Wang	3,654	2,673	80.5	89.9	94.4	96.4	0.916	0.966
Shohat	2,533	2,683	91.2	83.4	78.6	93.3	0.93	0.8
SF PMN %								
Cipriano	75	78	100	95.5	81.8	87.3	0.936	0.95
Wang	65.9	62	85.4	92.8	77.8	92.9	0.855	0.968
Shohat	73	72	100	86.8	82.7	89.9	0.91	0.89

IA, inflammatory arthritis; NIA, non-inflammatory arthritis; AUC, area under curve; SF WBC count, synovial fluid white blood cell count; SF PMN%, synovial fluid polymorphonuclear cell %; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

autoimmune diseases, including RA, AS, gout, sicca syndrome, and anaphylactoid purpura, although a low sample size limited any important conclusions regarding its utility. A retrospective cohort study of 62 patients who have inflammatory disease by Xu et al. found more promising results, finding a serum fibrinogen cutoff of 4.04 g/L to be 72.4% sensitive and 81.2% specific with an AUC of 0.795. They also concluded that combining biomarkers may help produce improved accuracy for PJI diagnosis in patients who have inflammatory disease: the combination of serum CRP, ESR, fibrinogen, and neutrophil/lymphocyte ratio showed 86.2% sensitivity and 84.4% specificity [106].

There were three studies that investigated alpha-defensin specifically in patients who have inflammatory disease, reporting excellent diagnostic utility with sensitivities of 92 to 100% and specificities of 98 to 100% [97,102,110]. Miyamae et al. conducted a retrospective cohort study in a population of 41 patients who have RA, psoriatic arthritis, polymyalgia rheumatica, sarcoidosis, polymyositis, systemic lupus erythematosus, and systemic sclerosis who underwent revision arthroplasty for PJI, reporting an accuracy and a positive predictive value (PPV) of 97 and 100%, respectively. They concluded that alpha-defensin had high accuracy for PJI diagnosis even in patients who have inflammatory disease [110]. Deirmengian et al. [100] investigated the combination of alpha-defensin and synovial CRP, reporting a sensitivity of 97% and specificity of 100% for PJI diagnosis in a patient population with a 23% rate of systemic inflammatory disease. An additional prospective, multicenter study demonstrated excellent sensitivity (92.3%), specificity (96.3%), PPV (85.7%), and NPV (98.1%) using alpha-defensin for PJI diagnosis in an inflammatory disease subgroup [111]. Goodman et al. [112] conducted a cross-sectional study examining the performance of serum and synovial fluid tests for differentiating PJI from flares and reported that, while all tests appear to be affected by reduced specificity, alpha-defensin was the most accurate (PPV 100.0% and NPV 78.3%). Ding et al. [113] also evaluated the performance of the alpha-defensin lateral flow test for diagnosing PJI in an Asian population and found that systemic inflammatory joint disease was not significantly associated with a positive alpha-defensin test result ($P = 0.33$), although the study was limited by a sample size of 19 PJI cases and incomplete data for accurate Musculoskeletal Infection Society classification of patients.

In conclusion, literature assessing the diagnostic accuracy of serum/synovial biomarkers in the IA/disease population is sparse. The wide spectrum of inflammatory diseases, treatments, and different phases of disease activity creates significant heterogeneity within study populations. In addition, the multitude of available biomarkers and various methods for assessing optimal diagnostic thresholds make comparison of data among studies difficult. From the literature that is available, conclusions vary widely, with no true consensus concerning whether inflammatory diseases affect the accuracy of different biomarkers for the diagnosis of PJI. Synovial fluid biomarkers such as synovial WBC and alpha-defensin appear to produce superior results to serum biomarkers in the inflammatory disease population; however, further systematic evaluation with larger study populations is needed.

Question 5: Is there a role for serum procalcitonin (PCT) for the diagnosis of periprosthetic joint infection (PJI)?[5]

Response/Recommendation

There is no role for the use of serum PCT for the diagnosis of PJI.

Level of Evidence: Strong

Delegate Vote: Agree: 90%, Disagree: 7.5%, Abstain: 2.5% (Total consensus: Unanimity)

Rationale

Procalcitonin is a precursor of calcitonin. While serum PCT in healthy, uninfected individuals is very low, increased serum levels have been noted in systemic bacterial infection [114,115]. Procalcitonin has been proposed as an alternative biomarker for diagnosing PJI, particularly in some cases where traditional serum and synovial biomarkers show lower accuracy. These include early postoperative infection and chronic, deep, or low-grade infection, which elicit a less pronounced systemic inflammatory response [116], as well as some cases of noninfectious causes of C-reactive protein (CRP) elevation, such as inflammatory arthritis and obesity [117]. While many studies reported high diagnostic accuracy for PCT in systemic bacterial infection [118], the reported results for PCT in PJI have been highly variable.

The aim of this comprehensive systematic review and meta-analysis was to evaluate the diagnostic accuracy of PCT in PJI. The systematic literature search was conducted by two independent reviewers using the PubMed/MEDLINE, Web of Science, and Cochrane databases based on selected MeSH terms related to PJI and serum PCT. We included clinical studies on PJI exploring the diagnostic accuracy of serum PCT as a biological marker. A standardized data extraction form was created and pilot-tested to collect study characteristics and outcomes. Risk of bias of the included studies was assessed using the QUADAS-2 tool [119].

There were 14 studies included in the final analysis, enrolling a total of 993 patients. Among them, 561 cases involved the hip, 465 the knee, and seven the shoulder.

The optimal PCT cutoff varied across the studies. There were three studies [120–122] that identified 0.5 ng/mL as the optimal cutoff, while two studies [123,124] reported 0.1 ng/mL. Additional cutoffs reported were 0.3 ng/mL [125], 0.35 ng/mL [126], 0.05 ng/mL [127], 0.081 ng/mL [128], 2.29 ng/mL [129], and 46 ng/mL [130]. There were two studies [131,132] that did not specify the optimal cutoff, and one study [133] identified 0.025 ng/mL as the optimal threshold for detecting low-grade infections. There were eight studies [123,124,126–130,133] that used the Musculoskeletal Infection Society criteria [134] for PJI diagnosis, one study [121] used International Consensus Meeting definition 2013 [135], one study [120] used the International Consensus Meeting definition 2018 [136], three studies [122,125,131] relied on culture and histological examination without using a specific definition, and one study [132] did not mention their criteria for PJI diagnosis.

The pooled sensitivity of PCT for diagnosing PJI was 0.47 (95% confidence interval (CI): 0.42 to 0.51), and the pooled specificity was 0.84 (95% CI: 0.80 to 0.87) (Figures 1 and 2). The pooled positive likelihood ratio was 4.02 (95% CI: 2.11 to 7.66), suggesting that PCT is moderately useful for ruling in PJI. However, the pooled negative likelihood ratio was 0.62 (95% CI: 0.50 to 0.77), reflecting limited ability to rule out PJI effectively. The pooled diagnostic odds ratio was 7.91 (95% CI: 4.18 to 14.98), and the area under SROC (the pooled AUC) was 0.7916 (Figure 3). This indicates that PCT has moderate diagnostic efficacy in distinguishing between septic and aseptic cases. This means that while PCT can provide some diagnostic value, its moderate accuracy limits its reliability, particularly in scenarios requiring high precision, such as detecting low-grade infections.

Bottner et al. [125] reported a low sensitivity of 33% for PCT. However, they claimed that PCT is highly specific for the diagnosis of PJI (98%). They suggested that PCT could serve as a useful confirmatory tool in patients with positive CRP or elevated levels of interleukin-6. Similarly, Randau et al. [130] reported a low sensitivity (12.9%) and high specificity (100%) of PCT. Conversely,

[5] These authors contributed to Question 5: Mohammad Kamal Abdelnasser, Levent Bayam, Sasheela Ponnampalavanar, Imelda Lumban-Gaol, Muhammad Amin Chinoy, Rares-Mircea Birlutiu, Ahmed Abdelazim Hassan, Thorsten M. Seyler

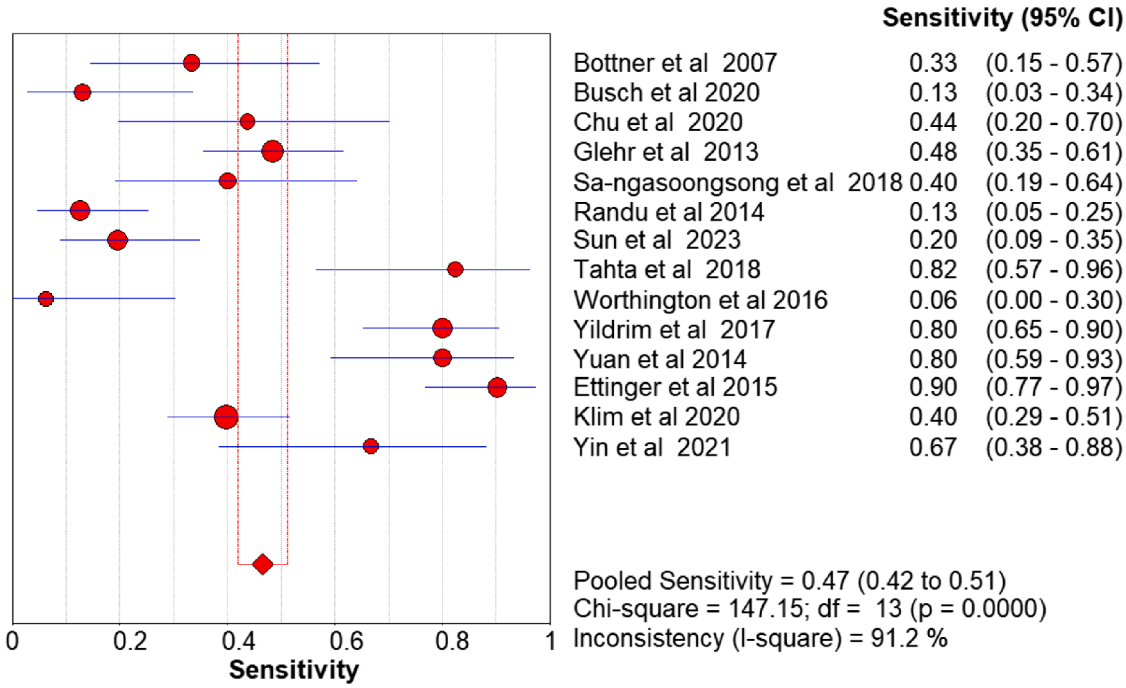

Figure 1. Pooled sensitivity. CI, confidence interval.

Glehr et al. [126] reported that PCT is a sensitive but less specific marker for PJI. With a sensitivity of 90% and specificity of 67%, Glehr et al. reported that PCT is a useful marker for PJI. Tahta et al. [123] demonstrated that PCT, when combined with other markers, is a useful biomarker for PJI, particularly in patients who have inflammatory joint disease. Busch et al. [120] reported that PCT is a specific, but less sensitive marker for PJI; however, they concluded that PCT is not a reliable marker to differentiate between PJI and aseptic loosening. They did not recommend a single use of PCT to rule out PJI. Similarly, Worthington et al. [131] reported that PCT could not differentiate septic and aseptic causes of THA loosening. All patients who had aseptic loosening and 94% who had septic loosening had a PCT level < 0.5 ng/mL. Only one case of septic loosening had levels > two ng/mL. Ettinger et al. [133] concluded that PCT cannot be used to distinguish aseptic loosening from low-grade infection. Sun et al. [127] reported that PCT is not a reliable

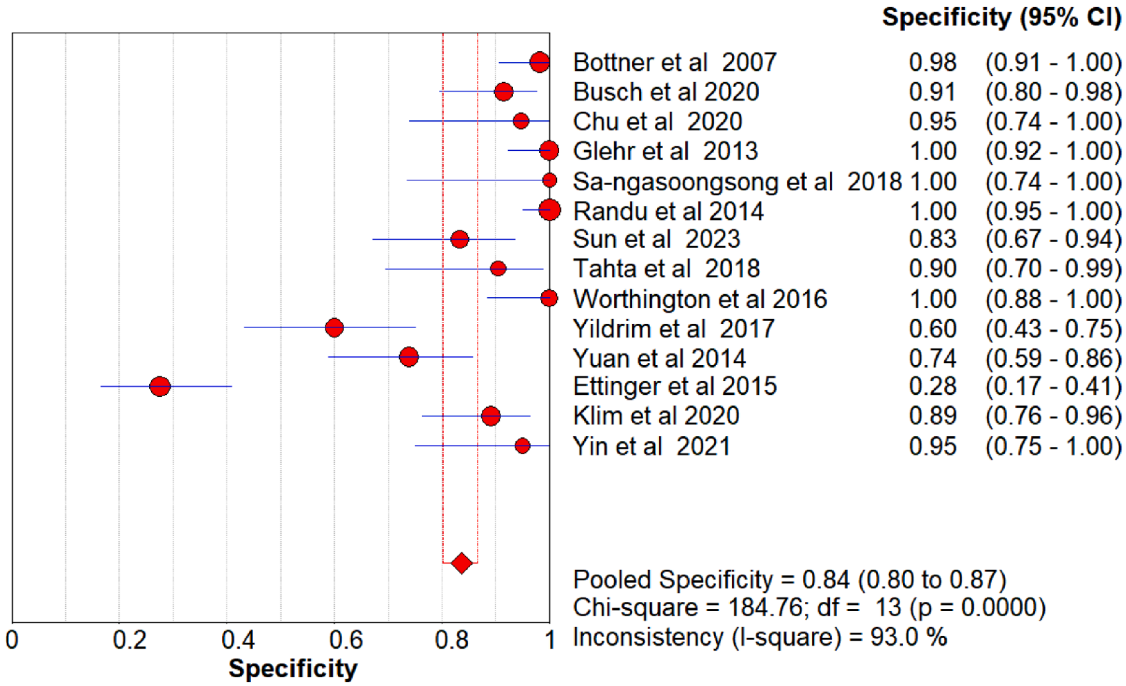

Figure 2. Pooled specificity.CI, confidence interval

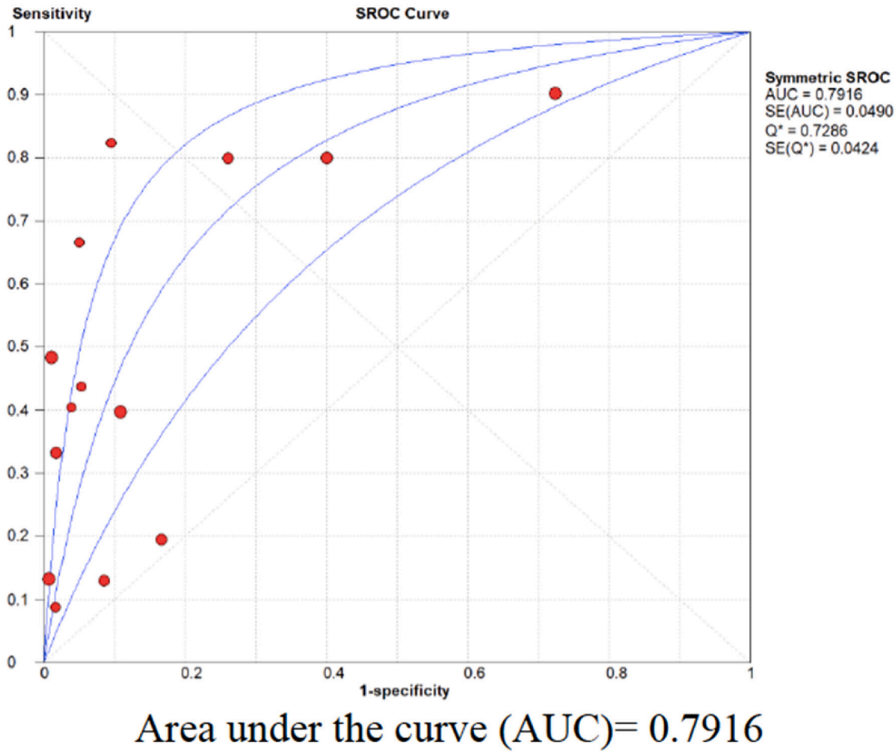

Figure 3. Pooled AUC. AUC, area under the curve.

marker for PJI. They compared PCT with ESR, CRP, fibrinogen, and platelets. The PCT had the lowest diagnostic accuracy. Adding PCT to other markers, such as CRP, improved the diagnostic accuracy. Similarly, Yuan et al. [122] demonstrated that PCT did not offer an advantage over CRP for the diagnosis of PJI. Several meta-analyses confirmed the inferior performance of PCT as a marker for PJI.Sun et al. [137], in a recent meta-analysis, confirmed the poor diagnostic accuracy of PCT, recommending against its use for ruling in/out PJI. Yoon et al. [138], in their meta-analysis, did not recommend the use of PCT to rule out PJI. Moreover, Xie et al. [139] reported a low sensitivity for PCT, which limits the clinical application of PCT.

There are many explanations for such inferior diagnostic performance of PCT. The PCT is released in response to bacteremia, which is not essentially present in PJI [140]. Infection with slow-growing organisms does not elicit much of a physiological response and release of PCT [120]. Transient bacteremia, even in healthy individuals, can induce PCT release [141]. Moreover, renal disease can cause PCT retention, resulting in higher PCT levels than in normal individuals [142,143].

Conclusions

The evaluation of available literature revealed that serum PCT has little to no role in the diagnosis of PJI.

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The Journal of Arthroplasty 41 (2025) S261–S266

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Hip and Knee

2025 ICM: Joint Aspiration

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Question 1: Should joint aspiration be performed in patients undergoing revision arthroplasty for presumed aseptic failure?[1]

Response/Recommendation

All joints undergoing revision arthroplasty for assumed aseptic failure should be aspirated, whenever possible.

Level of Evidence: Moderate

Delegate Vote: Agree 74.4%, Disagree 23.1%, Abstain 2.6% (Strong Majority, Moderate Consensus)

Rationale

We reviewed the available evidence on the utility of routine preoperative aspiration before total joint arthroplasty (TJA) revisions. However, robust studies directly comparing patients who undergo routine preoperative aspiration to those who do not are currently unavailable. Therefore, we present the working group's statement, reflecting a consensus-based belief in the value of this practice.

Although clinical presentations and radiographic findings often lead to a presumptive diagnosis of aseptic failure in patients requiring revision arthroplasty, definitively excluding periprosthetic joint infection (PJI) before a revision surgery is crucial but may not always be feasible. The failure to identify an underlying infection can result in severe consequences, including persistent pain, implant failure, further revision surgeries, and even life-threatening systemic complications [1]. A large proportion of patients undergoing revision arthroplasty for presumed aseptic reasons are, in fact, infected [2,3]. Reported rates of unexpected intraoperative positive cultures in patients who have a preoperative diagnosis of aseptic failure range from 6.9 to 28% [2,3]. These high rates of misdiagnosis are attributed to the difficulty in distinguishing aseptic failure from PJI [4].

In patients who do not have apparent symptoms of PJI, such as fistula, erythema, or warmth, or a previous history, the second step is often to check serum levels of C-reactive protein (CRP) and erythrocyte sedimentation rate to exclude septic failure. However, normal serum markers do not reliably rule out infection. Some studies indicate that serum CRP and/or erythrocyte sedimentation rate levels can be within normal ranges in about 15% of patients who have septic failure [2]. Considering the relatively high rates of unexpected intraoperative positive cultures after presumed aseptic revisions and the impact of undiagnosed PJI on the outcomes of revision TJA, we emphasize that some patients do not get investigated thoroughly. Joint aspiration, a relatively simple procedure, provides an opportunity to obtain synovial fluid analysis for more accurate diagnosis and should be part of a routine preoperative workup before revision surgery. It is particularly useful for identifying low-grade infections that may not be detected through other diagnostic methods because they often do not present with typical signs of inflammation [5,6].

Synovial fluid analysis plays a key role in the diagnosis of PJI according to the criteria of the Musculoskeletal Infection Society and International Consensus Meeting (ICM)-2018 [7]. Based on these guidelines, aspirated synovial fluid should be analyzed for cultures, synovial white blood cells, synovial polymorphonuclear percentage, leukocyte esterase, and alpha-defensin. Beyond those validated tests, numerous synovial biomarkers have been investigated, and some of them are available, such as synovial CRP and synovial calprotectin [5,8–10].

Besides decreasing the rate of misdiagnosed failures as a result of infection, identifying the causative pathogen is essential for developing an appropriate surgical plan and initiating targeted antibiotic

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.091.

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https://doi.org/10.1016/j.arth.2025.10.091
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therapy [6,11]. In recent years, the role of nonculture molecular methods (next-generation sequencing, second-generation multiplex polymerase chain reaction, and so on.) has been explored in the identification of pathogens in culture-negative PJI or early failure of TJA that may be a result of the pathogen's difficulty in culturing or occult infection [12–17].

In conclusion, since the combination of clinical examination and serum serological markers may be insufficient to rule out PJI, surgeons should ensure thorough preoperative evaluation, including synovial fluid analysis. Joint aspiration is a simple, safe, cost-effective, and highly informative procedure that plays a vital role in managing patients undergoing revision arthroplasty for presumed aseptic failure. Given its important advantages and minimal risks, joint aspiration should be considered an indispensable part of the preoperative or intraoperative evaluation of each patient undergoing revision arthroplasty for presumed aseptic failure.

Question 2: In patients who have a periprosthetic joint infection (PJI) of one joint, is there a role for aspiration of other joints that have prostheses in place?[2]

Response/Recommendation

We recommend that when a patient develops a periprosthetic joint infection (PJI) in one joint, all other artificial joints should be examined clinically, and if clinical suspicion for PJI exists, then other joints should be aspirated.

Level of Evidence: Low (few retrospective studies)

Delegate Vote: Agree 71.8%, Disagree 25.5%, Abstain 2.7% (Moderate Consensus)

Rationale

The number of joint arthroplasties implanted and the population with more than one joint in place are constantly increasing. Subsequently, the risk of having another prosthetic joint in place when a PJI occurs is continuously increasing. In the literature, the occurrence rate of metachronous or synchronous infection ranges from 6.3 to 20% [18–20]. The issue of having a PJI in more than one joint was initially evaluated and highlighted by Murray et al. [21]. Managing those patients is extremely challenging since a possible second infection can complicate an already tough situation. Another burden is that no established guidelines exist on how to evaluate and treat these patients, who can be severely affected by higher mortality and reoperation rates [22]. Few studies exist about optimal management and workouts in patients who have more than one arthroplasty and develop a second PJI on another joint.

We attempted to answer the question by identifying all studies dealing with patients who have multiple arthroplasties in place and suffer from an initial PJI. Those patients may be at risk for developing another infection, which can be either synchronous (occurring at the same time) or metachronous (occurring at a later stage). We performed an extensive review of the literature utilizing specific search terms in three different databases (PubMed, Scopus, and Cochrane). Using the Covidence database for systematic reviews, we scanned all the available manuscripts and finally ended up with 11 relevant studies (Figure 1). Data extraction was performed using an Excel spreadsheet.

As aforementioned, the first to describe this problem was Murray et al. back in 1991 [21]. Luessenhop et al. were the first to attempt to identify risk factors for subsequent prosthetic infections and identified rheumatoid arthritis and major nonprosthetic infection (sepsis) as those [20]. Jafari et al. demonstrated a substantially increased risk of a second PJI (20%), underscoring the potential for hematogenous spread between prosthetic joints, with the risk being elevated in immunocompromised patients having chronic or delayed PJI [19]. Haverstock et al. showed a decreased prevalence of multiple PJIs of 6.3%, emphasizing that better management of the initial PJI could lower the risk of another joint being infected and, therefore, may lower the necessity for aspiration [23]. On the contrary, a study of the same period highlighted the importance of a multidisciplinary approach to those patients [24]. They proposed that those patients should be clinically evaluated, and a low threshold for aspiration should exist, especially when radiographic findings are suggestive of infection (periosteal reaction) or bacteremia exists. The presence of bacteremia as a predisposing factor for developing another PJI was also identified by Abblitt et al. [25].

In the last five years, more studies have strived to delve into this subject and highlight the role of aspiration and optimal management of this specific population. Thiesen et al [26]. directly investigated the need for all artificial joints to be aspirated routinely in the setting of synchronous PJIs [27]. They recommended aspirating all prosthetic joints when a PJI is present, especially when a history of neoplasia, immunomodulating therapy, and the presence of systemic inflammatory responses or sepsis coexist. Interestingly, even taking into account a suspicious clinical presentation and a history of neoplasia, eight of 26 synchronous PJI cases in their cohort would have gone undetected unless aspirated. Similarly, Komnos et al. also focused on what should be done with the other prosthetic joints in the establishment of a PJI [18]. This study addressed the potential role of aspiration in women and patients who have an initial PJI with methicillin-resistant *Staphylococcus aureus* (MRSA) and patients who have rheumatoid arthritis and bacteremia. Other risk factors recognized by Lee et al. include systemic inflammatory response and multiple previous surgeries [27]. Gausden et al. examined patients who have synchronous infections, noting the high risks associated with them, including major mortality and reoperation rates [22]. They suggest careful monitoring and possibly proactive measures such as aspiration in patients who have bacteremia and multiple arthroplasties, as well as immunocompromised patients.

There are two recent studies that dealt with the question of whether ipsilateral prosthetic joints are at elevated risk for subsequent PJI, with conflicting results [28,29]. Akkaya et al. showed that the ipsilateral metachronous PJI group had a shorter stem-to-stem distance, shorter empty native bone distance, and a higher risk of cement restrictor failure, suggesting these as high-risk factors increasing the likelihood of subsequent PJI in the neighboring joint [28]. According to this study, proximity is a concern, and preventive measures, including possibly preemptive aspiration, should be considered in tightly spaced joint arthroplasties. However, on the contrary, another study demonstrated that an infected ipsilateral joint does not substantially increase the risk of infection in another joint within the same extremity compared to contralateral joint infections [29]. Therefore, aspiration of other joints might not be necessary unless there are additional risk factors such as the use of immunosuppressants.

Potential limitations of this review include the high heterogeneity of the included studies, the fact that all available studies until now are retrospective studies, and the different protocols regarding the management of these patients that exist in various institutions. Another issue is that not all studies evaluate the role of aspiration, and although most of them refer mainly to hip and

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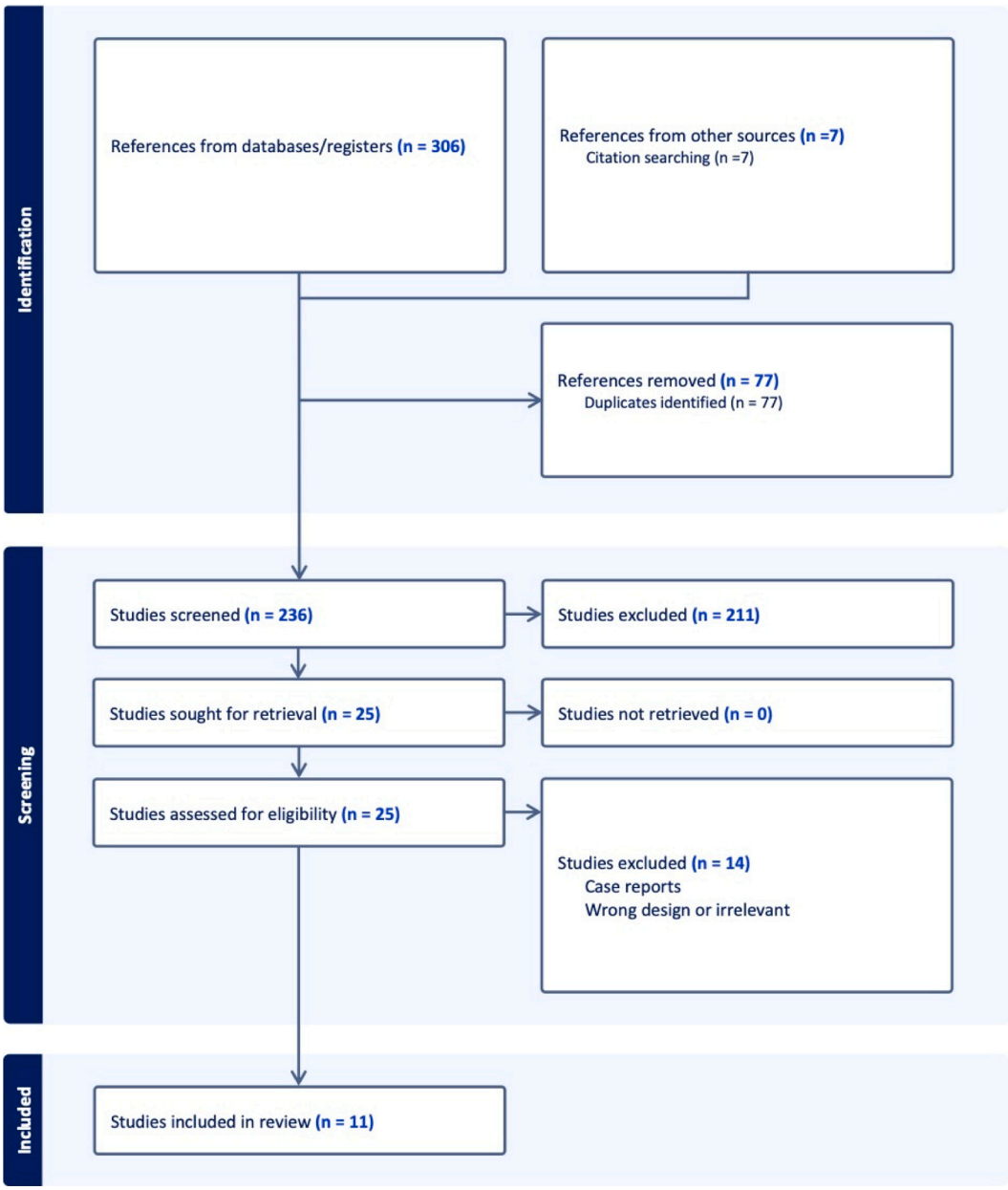

Figure 1. Flowchart of the review.

knee arthroplasties, there are sporadic references and the inclusion of a few shoulder and elbow arthroplasties.

Interpretation of available data shows that diagnosing early a second periprosthetic joint infection is extremely challenging, and aspiration can be one of the most important pillars. Although aspiration is widely accepted as a successful and relatively reliable means of diagnosing PJI, considerations against its utilization still exist. These mainly consist of the fact that it can be a traumatic experience for the patient, especially in the hip; that they also carry a risk of causing PJI themselves; and that widespread use of anticoagulants can complicate it with severe bleeding. Nevertheless, in the development of a PJI in patients who have multiple prosthetic joints, investigation of other prosthetic joints should always be performed, starting with a thorough clinical evaluation. If symptoms are present, further investigation is needed. The most reliable method seems to be the aspiration of the other joints, especially when risk factors such as immunosuppression, sepsis, bacteremia, rheumatoid arthritis, women patients, and methicillin-resistant *Staphylococcus aureus* as the isolated pathogen coexist.

Question 3: Should saline be injected into a joint during a dry aspiration (tap)?[3]

Response/Recommendation

Routine saline instillation following a dry tap in suspected periprosthetic joint infection cannot be recommended due to

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limited evidence. The technique remains nonstandardized, and there is a known risk of contamination. Although some studies suggest potential benefits, large-scale investigations are needed to establish its diagnostic efficacy and safety before considering widespread clinical application.

Level of Evidence: Moderate

Delegate Vote: Agree 90.5%, Disagree 7.2%, Abstain 2.4%

Rationale

Dry taps, characterized by insufficient synovial fluid on aspiration, occur in up to 35% of cases, as noted by Mirzaei et al. (2018) [30] and other authors. This can be produced either by technical issues or by anatomical barriers [31]. Saline injection (also referred to as saline lavage) after a dry tap has been explored as a method to improve diagnostic accuracy in PJI by increasing the fluid available for cytological and microbiological tests.

Saline injection enhances sensitivity and specificity in diagnosing PJI, as reported in three of the studies [32–34]. Heckmann et al. found that while saline lavage significantly lowered synovial white blood cell (WBC) counts, the percentage of polymorphonuclear cells (%PMN) remained similar, providing reasonable sensitivity for detecting PJI [32]. Sensitivity for saline lavage ranged from 75 to 88.2% throughout our research, with specificity reaching up to 100% in some cases [34].

Partridge et al. [34] demonstrated that saline lavage improved culture yield compared to direct aspiration, particularly in dry tap cases where insufficient fluid was obtained initially.

Other studies [35] highlighted the role of saline lavage in achieving a culture sensitivity of 79.5% and specificity of 95.7%, reinforcing its diagnostic value. Although these studies suggest that saline lavage can facilitate additional fluid recovery, especially in scenarios where synovial fluid is scarce, most investigations included in this systematic review were retrospective, and the overall evidence is limited by small sample sizes and inconsistencies in protocols.

Percutaneous interface biopsy, as evaluated by Corona et al. [33], showed high sensitivity (88.2%) and specificity (100%), making it a reliable alternative, particularly in chronic PJI cases. However, its invasive nature limits its standardized applicability.

Meanwhile, ultrasound-guided aspiration demonstrated sensitivity of 95.7% and specificity of 74.1%, providing a noninvasive alternative for predicting dry taps and guiding reaspiration. In this study, ultrasound-guided aspiration was used in the hip joint for the diagnosis of PJI [30].

Although saline injection may increase diagnostic accuracy, studies such as Li et al. [35] and Christensen et al. [36] highlighted the risk of contamination associated with the procedure. Also, Li et al. demonstrated that saline lavage and reaspiration for culture in cases of insufficient synovial fluid can be a feasible method for diagnosing PJI, with good sensitivity and specificity. Standardized protocols are necessary to mitigate this risk [37].

Xu et al. [38] emphasized the importance of adjunct diagnostic tools like serological markers to complement saline lavage and reduce false positives or negatives.

Some authors, such as Treu et al. [39], underscored that dry taps are not inherently reassuring and require further diagnostic workup, often benefiting from saline lavage to increase fluid retrieval and culture sensitivity.

This systematic review presents varying levels of evidence. With only one of eight studies being prospective, the reliability of retrospective data requires further analysis. Some studies indicate that preoperative lavage accuracy varies, with inconsistent concordance rates between preoperative and intraoperative cultures in the absence of standardized methods. This underscores the need for further evidence to clarify its diagnostic reliability [35].

Question 4: Is aspiration of the joint necessary before reimplantation?[4]

Response/Recommendation

Aspiration of a joint before reimplantation can identify patients with persistent infections, considering synovial fluid cell count and relative neutrophil percentage. Aspiration should be individualized based on the type of joint, type of infection, and clinical course of treatment.

Level of Evidence: Limited

Delegate Vote: Agree 86.1%, Disagree 8.5%, Abstain 5.4% (Strong Majority)

Rationale

Management of PJI continues to challenge the orthopaedic community. In patients undergoing two-stage exchange arthroplasty, determining the optimal timing of reimplantation remains challenging, as there are no specific metrics to guide one in this respect. It can be difficult to confirm whether the resection arthroplasty, insertion of an antibiotic spacer, and administration of antibiotics have effectively treated PJI or if the infection persists. In order to assess the presence or absence of infection in a patient who has a spacer *in situ*, aspiration of the joint and analysis for various parameters and culture remain an option. In managing PJI, standard protocols for joint aspiration before reimplantation have been the subject of considerable debate. The sensitivity and specificity of diagnostic tests play a crucial role in determining the reliability of joint aspiration.

The question posed above is whether the routine aspiration of a joint before reimplantation is justified. In order to answer this question, we performed a comprehensive systematic review using MeSH terms to identify pertinent literature from three databases (PubMed, Web of Science, and Scopus). We identified a total of 374 studies. After screening these articles, 340 studies were excluded. The remaining 34 full articles were reviewed in detail. An additional 24 publications were excluded due to insufficient data, wrong study design, wrong patient population, wrong evaluated parameters, or ineligible article types such as meta-analyses or reviews. The final systematic review included 10 studies, with no studies categorized as ongoing or awaiting classification. All included studies were retrospective, encompassing 986 patients. The majority of studies focused on both the hip and the knee (five studies) [40–43], three focused on only the hips [44–46], and two focused only on the knees [47,48].

Synovial fluid cultures were evaluated in seven studies [40,41,43,44,46–48] and exhibited low sensitivity (0 to 56.6%) but high specificity (84.6 to 100%). Multiple factors can exacerbate the challenges faced by synovial fluid cultures, particularly their low sensitivity. The presence of biofilms on spacers can shield microorganisms, leading to false negatives on culture results[48]. Factors such as prior antibiotic therapy also contribute to reduced microbial yield, as ongoing treatment can diminish bacterial viability [40]. Interestingly, despite these limitations, synovial fluid cultures often maintain high specificity, leading to a clinical conundrum where positive results confirm infection, but fail to detect it consistently. These intricacies necessitate reevaluating current diagnostic strategies, focusing on complementary methods to enhance sensitivity and accuracy [42].

White blood cell counts and the percentage of PMN% in synovial fluid were evaluated in five studies [42,44,45,48] and exhibited better sensitivity (21 to 88%) and specificity (75 to 96.9%) rates.

[4] These authors contributed to Question 4: Pedro Ivo de Carvalho, Alaina Ritter, Emilio Freitas, Gwo-Chin Lee, Jeffrey Stambough, Mahmoud Abdel Karim, Marcos Giordano, Tiziana Ascione, Osamu de Sandes Kimura

Several factors contribute to the low sensitivity and specificity; one major factor is the timing of antibiotic administration, often resulting in high false-negative rates due to biofilm presence on implants [43]. In addition, the defined thresholds for WBC and PMN percentage may lack robustness; for instance, studies propose varied optimal cutoff values that affect diagnostic performance, ranging from 1,166 to 4,450/μL, leading to inconsistencies in clinical practice [44,47,48]. Variability in patient populations, including comorbid conditions and the duration of infection, further complicates these diagnostic tests, as evidenced by differing sensitivities observed in knee versus hip infections [41,42].

In conclusion, although joint aspiration prior to reimplantation plays a critical role in the management of patients undergoing two-stage exchange arthroplasty for the treatment of chronic PJI, we found that there is no evidence to suggest that this practice should be routinely performed. The low sensitivity, but high specificity of synovial fluid culture, white blood cell count, and percentage of polymorphonuclear neutrophils pose a difficulty in interpreting the results obtained with joint aspiration before reimplantation.

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Hip and Knee

2025 ICM: Synovial Analysis

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Question 1: Is there a role for joint-specific (hip versus knee) cutoffs for synovial tests in the diagnosis of periprosthetic joint infection (PJI)?[1]

Response/Recommendation

Synovial C-reactive protein (CRP), white blood cell (WBC) count, and polymorphonuclear percentage values were similar between PJI following total hip arthroplasty (THA) and total knee arthroplasty (TKA). Therefore, the use of differential values for hip and knee PJI is not recommended.

Level of Evidence: Limited

Delegate Vote: Agree: 97.9%, Disagree: 0%, Abstain: 2.1% (Total consensus: Unanimity)

Rationale

Periprosthetic joint infections (PJIs) are the most common cause for revision after THA and TKA and represent a major morbidity burden to patients [1–3]. Multiple serological, synovial, and intraoperative criteria have been proposed for the diagnosis of PJI [4–7]. Based on the current International Consensus Meeting (ICM) 2018 recommendations, a synovial WBC > 3,000 cells/μL and a synovial fluid polymorphonuclear cell percentage (PMN%) > 70% are indicative of PJI [4]. The ICM 2018 validation study also included synovial CRP > 6.9 mg/L as an indicator for PJI [5]. However, there has been no evaluation of differential synovial marker cutoffs between hip and knee PJI. This study assessed whether the use of joint-specific (hip versus knee) synovial marker values is warranted to diagnose PJI based on available literature.

Methods

A systematic review was performed to identify studies that reported synovial fluid markers for hip and knee PJI separately. A total of 375 studies were identified from PubMed and 273 studies

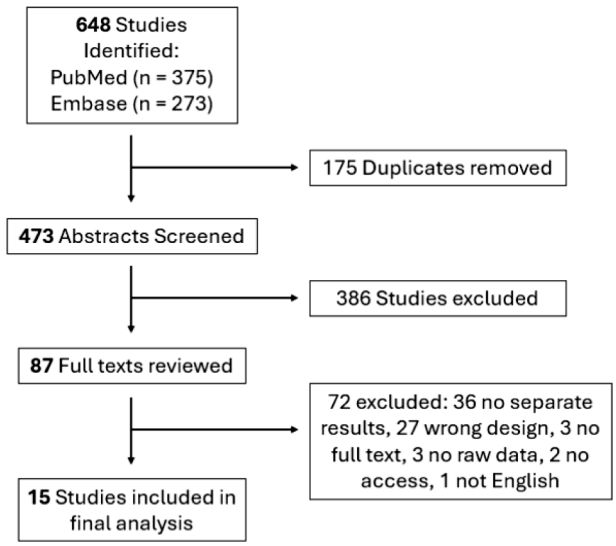

Figure 1. Manuscript inclusion flowchart.

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to DOI: 10.1016/j.arth.2025.10.080.

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https://doi.org/10.1016/j.arth.2025.10.080
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Table 1
Mean and Standard Deviation of Synovial WBC, Polymorphonuclear Cell Percentage (PMN%), and CRP for Patients Diagnosed With Periprosthetic Joint Infection and Aseptic Joint Infection.

Study, Years	Design	Knee						Hip					
		WBC		PMN%		CRP Mg/L		WBC		PMN%		CRP Mg/L	
		PJI (n)	Aseptic (n)	PJI (n)	Aseptic (n)	PJI (n)	Aseptic (n)	PJI (n)	Aseptic (n)	PJI (n)	Aseptic (n)	PJI (n)	Aseptic (n)
Ghanem et al., 2008	R	58,027 ± 17,372 (161)[a,b]	549 ± 1,894 (268)[a,b]	85 ± 23.3 (161)[a,b]	25 ± 22.8 (268)[a,b]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Klemt et al., 2023	R	N/A	N/A	N/A	N/A	N/A	N/A	26,421 ± 19,329 (191)	812 ± 953 (273)	88.5 ± 11.4 (191)	16.1 ± 9.4 (273)	N/A	N/A
Denyer et al., 2023	R	60,612 ± 77,916 (124)	788 ± 1,145 (159)	88.7 ± 13 (124)	27 ± 22 (159)	N/A	N/A	64,782 ± 92,807 (122)	3,949 ± 8,980 (167)	85.8 ± 21 (122)	54.5 ± 33.1 (167)	N/A	N/A
Balato et al., 2018	R	7,892 ± 18,124 (31)[a,b]	808 ± 1,032 (136)[a,b]	84 ± 6.7 (31)[a,b]	47 ± 22.8 (136)[a,b]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Warren et al., 2021	P	57,803 ± 66,595 (53)	735 ± 856 (70)	89 ± 13 (5)	21 ± 24 (70)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kim et al., 2017	R	50,825 ± 38,903 (12)	2,141 ± 2,837 (185)	93.3 ± 2.5 (12)	70.7 ± 24.9 (185)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Karlidag et al., 2024	R	32,496 ± 38,156 (50)	2,350 ± 8,230 (94)	86.4 ± 20.4 (50)	39.2 ± 25 (94)	N/A	N/A	43,995 ± 53,621 (59)	6,397 ± 22,194 (57)	88.4 ± 15 (59)	36.8 ± 26.2 (57)	N/A	N/A
Vanderstappen et al., 2013	R	N/A	N/A	N/A	N/A	11.98 ± 9.65 (11)	1.08 ± 1.14 (33)	N/A	N/A	N/A	N/A	N/A	N/A
Schinsky et al., 2008	P	N/A	N/A	N/A	N/A	N/A	N/A	61,336 ± 84,268 (55)	1,721 ± 4,722 (146)	86.1 ± 20.3 (55)	51.3 ± 29.3 (146)	N/A	N/A
Omar at el, 2015	P	N/A	N/A	N/A	N/A	N/A	N/A	20,253 (10,574 to 29,932) (21)[c]	1,592 (784 to 2,399) (59)[c]	85 (79 to 91) (21)[c]	35 (28 to 41) (59)[c]	15.5 (17 to 21) (21)[c]	1.2 (0 to 2) (59)[c]
Higuera et al., 2017	R	N/A	N/A	N/A	N/A	N/A	N/A	42,794 (27,891 to 57,697) (79)[c]	1,890 (1,247 to 2,533) (374)[c]	89.7 (87 to 92.4) (76)[c]	44.6 (41.6 to 47.7) (339)[c]	N/A	N/A
Trampuz et al., 2004	P	18,900 ± 44,425 (34)[a,b]	300 ± 3,975 (99)[a,b]	92 ± 11.3 (34)[a,b]	7 ± 19.8 (99)[a,b]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Yi et al., 2013	R	N/A	N/A	N/A	N/A	N/A	N/A	84,954 ± 108,948 (36)	2,391 ± 2,640 (37)	91 ± 7 (36)	63 ± 23 (37)	N/A	N/A
Choi et al., 2016	R	N/A	N/A	N/A	N/A	N/A	N/A	75,974 ± 24,539 (50)	849.6 ± 315 (88)	88.2 ± 0 (50)	39.2 ± 0 (88)	N/A	N/A
Bedair et al., 2010	R	92,600 ± 127,000 (19)	4,200 ± 5,700 (127)	89.6 ± 20.6 (19)	76.9 ± 21.2 (127)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

WBC, white blood cell; CRP, C-reactive protein; PJI, periprosthetic joint infection; R, retrospective; P, prospective.
[a] Value given as median.
[b] SD approximated from range, interquartile range.
[c] Confidence interval; R, retrospective; P, prospective.

Table 2
Comparison of Synovial WBC Count Between Hip (THA) and Knee (TKA) PJI.

Variable	THA (n = 613)	TKA (n = 484)	*P*-Value[a]
Mean WBC (95% CI)	50,486 cells/uL (34,693 to 66,280)	43,241 cells/uL (26,854 to 59,628)	0.55

WBC, white blood cell; THA, total hip arthroplasty; TKA, total knee arthroplasty; PJI, periprosthetic joint infection; CI, confidence interval.
[a] *P*-value for the mean difference between PJI THA and PJI TKA.

from Embase using appropriate Medical Subject Headings (MeSH) terms and keywords developed by librarians. Following the removal of 175 duplicates, 473 study abstracts were screened for relevance. Abstract review led to 386 study exclusions. The full texts of the remaining 87 abstracts were reviewed, and 72 publications were excluded for the following reasons: 36 did not separate results into THA and TKA, 27 studies had the wrong study design, three studies were abstracts only without full text, three studies did not report raw data for analysis, two full-text manuscripts were not accessible, and one publication was not in the English language (Figure 1). The final analysis included 15 studies, which provided values for synovial fluid WBC, PMN%, and/or CRP (Table 1) [8–22].

A review of the included studies revealed 3,183 joints, including: 495 PJI TKA, 1,171 aseptic TKA, 613 PJI THA, and 1,201 aseptic THA. Synovial fluid markers, including WBC, CRP, and PMN %, were assessed, and many patients had various combinations of the three endpoints reported. In studies that reported median rather than mean, a Gaussian distribution was assumed to be able to equate mean to median values. In studies that did not report SDs or 95% confidence intervals (CIs), but rather ranges (R) or interquartile ranges (IQRs), a Gaussian distribution was assumed so SD could be estimated through the following formula: SD = R/4 and SD = IQR/1.35.

A subgroup meta-analysis was performed using a random-effects model to assess effect sizes of mean values of synovial

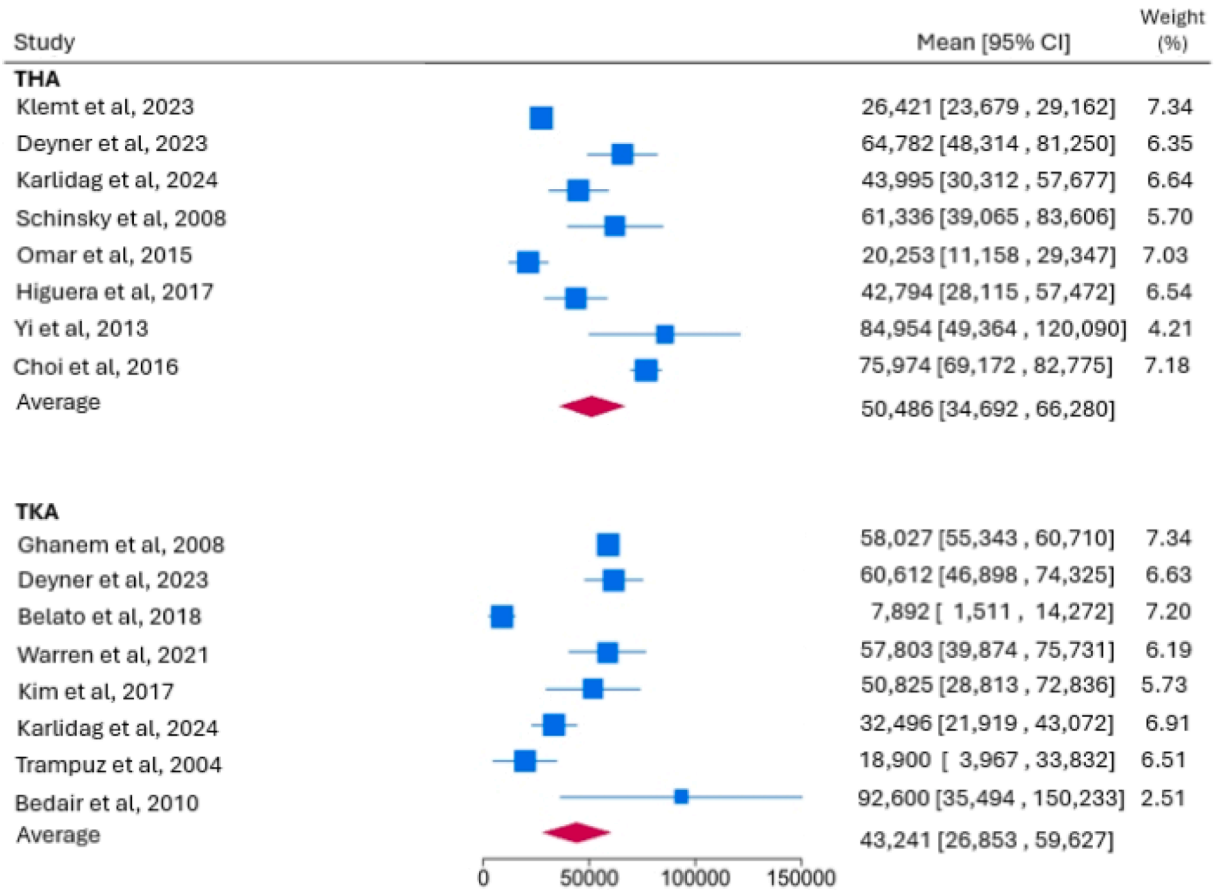

Figure 2. Forest plot of hip (THA) and knee (TKA) white blood cell counts in periprosthetic joint infection. THA, total hip arthroplasty; TKA, total knee arthroplasty; CI, confidence interval.

Table 3
Comparison of Synovial Polymorphonuclear Cell Percentage (PMN%) Between Hip (THA) and Knee (TKA) PJI.

TKA (n = 436)
88.5 (85.7 to 91.3)

P-value for mean difference between PJI THA and PJI TKA.
THA, total hip arthroplasty; TKA, total knee arthroplasty; PJI, periprosthetic joint infection; CI, confidence interval.

CRP, WBC, and PMN% between TKA and THA in the setting of PJI. Further analysis was performed to evaluate the mean values of synovial CRP, WBC, and PMN% between PJI and aseptic patients in both the settings of TKA and THA. Subgroup differences were tested using Dixon's Q-test, and mean differences with 95% CIs were calculated to evaluate statistical significance. Significance was set to $P < 0.05$.

Results

The corresponding manuscripts and their reported values for synovial CRP, WBC, and PMN% within PJI and aseptic joints for both hips and knees are reported in Table 1.

Synovial White Blood Cell

The analysis of synovial WBC included 14 studies with 484 TKA PJI, 1,138 aseptic TKA, 613 THA PJI, and 1,201 aseptic THA [8–14,16–22]. There was a significant difference in mean synovial WBC between TKA PJI (43,241 WBC [95% CI: 26,854 to 59,628]) and aseptic TKA (1,407 WBC [95% CI: 531 to 2,282], $P < 0.01$). This difference was again found between the mean synovial WBC of THA PJI (50,486 WBC [95% CI: 34,693 to 66,280]) compared to

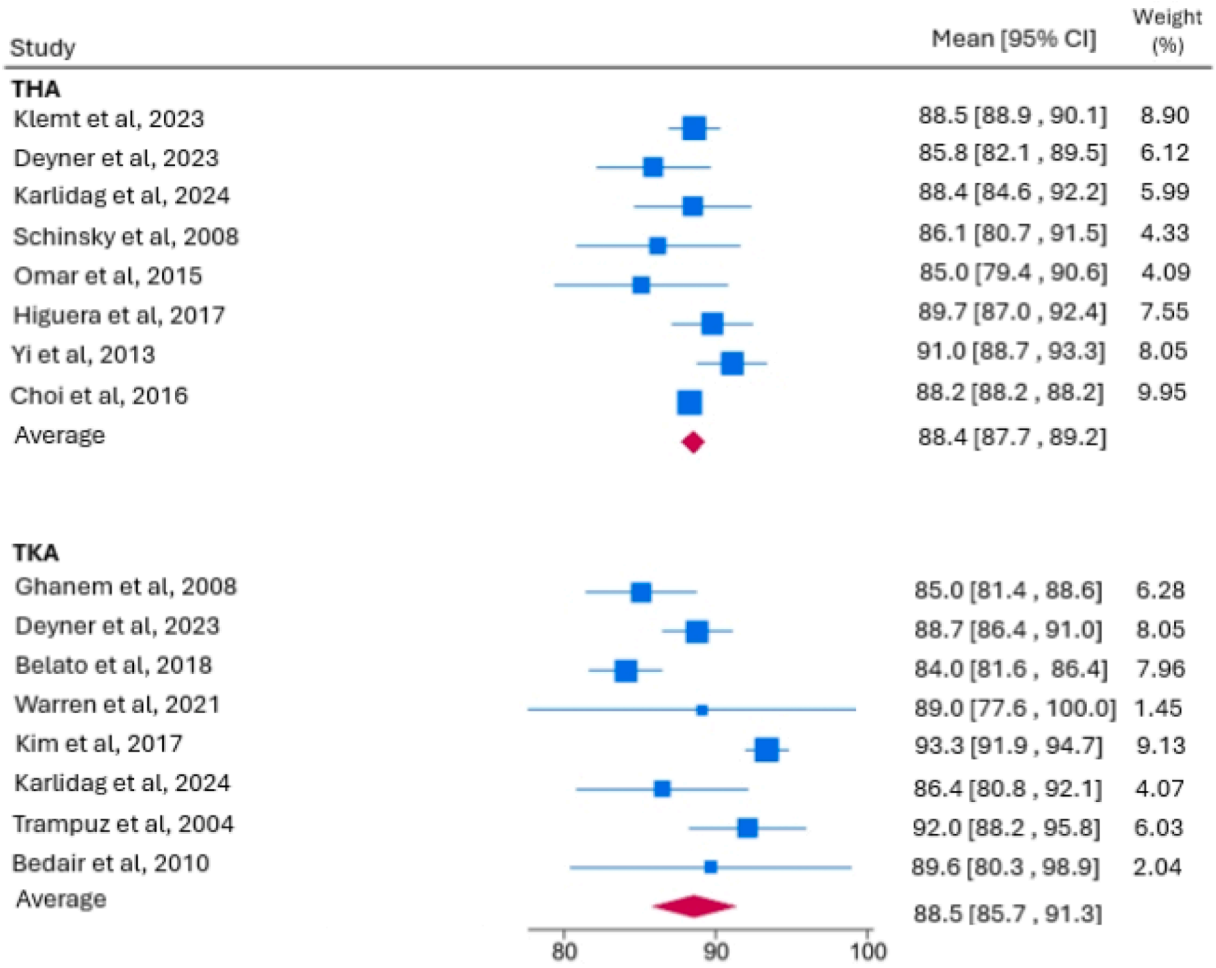

Figure 3. Forest plot of hip (THA) and knee (TKA) polymorphonuclear cell percentage in periprosthetic joint infection. THA, total hip arthroplasty; TKA, total knee arthroplasty; CI, confidence interval.

Table 4
Comparison of Synovial CRP Between THA and Knee (Knee) PJI.

Variable	THA (n = 21)	TKA (n = 11)	*P*-Value[a]
Mean CRP (95% CI)	15.5 mg/L (8.9 to 22.1)	12.0 mg/L (6.3 to 17.7)	0.24

CRP, C-reactive protein; THA, total hip arthroplasty; PJI, periprosthetic joint infection; CI, confidence interval.
[a] *P*-value for mean difference between PJI THA and PJI TKA.

aseptic THA (1,817 WBC [95% CI: 1,110 to 2,523], $P < 0.01$). However, the difference in mean synovial WBC between TKA PJI and THA PJI showed they were similar (7,245 [95% CI: −15,516 to 30,007], $P = 0.53$) (Table 2 and Figure 2).

Synovial PMN%

For synovial PMN%, 14 studies were included with 436 TKA PJI, 1,138 aseptic TKA, 610 THA PJI, and 1,166 aseptic THA [8–14,16–22]. The difference in PMN% between TKA PJI (88.5% [95% CI: 85.7 to 91.3]) and aseptic TKA (39.2% [95% CI: 22.3 to 56.2]) was significant ($P < 0.01$). Similarly, THA PJI had a significantly higher PMN% (88.4% [95% CI: 87.7 to 89.2]) compared with aseptic THA (42.4% [95% CI: 32.4 to 52.4], $P < 0.01$). The mean difference of PMN% showed no difference between TKA PJI and THA PJI (0.1% [95% CI: −3.0 to 2.9], $P = 0.97$) (Table 3 and Figure 3).

Synovial C-Reactive Protein

The evaluation of synovial CRP included two studies with 11 TKA PJI, 33 aseptic TKA, 21 THA PJI, and 59 aseptic THA [15,17]. Synovial CRP in TKA PJI (12.0 mg/dL [95% CI: 6.3 to 17.7]) was significantly greater compared to aseptic TKA (1.1 mg/dL [95% CI: 0.7 to 1.5], $P < 0.01$). Synovial CRP was also significantly higher in THA PJI (15.5 mg/dL [95% CI: 8.9 to 22.1]) compared with aseptic THA (1.2 mg/dL [95% CI: 0.2 to 2.2], $P < 0.01$). However, once again, the mean difference of synovial CRP between TKA PJI and THA PJI was not significantly different (3.5 [95% CI: −5.2 to 12.2] $P = 0.43$) (Table 4 and Figure 4).

Discussion

This systematic review of the current literature was unable to find a significant difference between synovial WBC, PMN%, and CRP of THA PJI compared to TKA PJI based on information found in the included manuscripts. These data from multiple institutions, in multiple countries, at different time points make the recommendation generalizable and appropriate for the ICM. It is impactful, as it supports the current ICM 2018 guidelines, which do not make a distinction between synovial markers in PJI of the hip and knee. However, this recommendation comes with limitations, noting that many studies were excluded because they did not separate THA PJI from TKA PJI, which limited the available number of cases for the statistical analysis. As a result, the evaluation of synovial CRP included only two studies [15,17]. Vanderstappen et al. evaluated synovial CRP limited to the knees, while Omar et al. only evaluated the hips. Therefore, a direct comparison of synovial CRP within one study cohort was not available, limiting its meaningfulness.

There were further potential limitations of this study. There were three studies that reported values as median rather than mean, so a Gaussian distribution was assumed to be able to equate mean to median values. In addition, three studies did not give a SD, but rather a range or IQR for synovial values, which was approximated to a SD as previously mentioned. Assuming a Gaussian distribution limits our results, as we do not know the true distribution of patients in any of the studies included. Furthermore, studies used different definitions to determine the presence of PJI, including Musculoskeletal Infection Society criteria, Infection Diseases Society of America criteria, American Academy of Orthopaedic Surgeons criteria, and ICM criteria. While all having overlapping criteria, their differences make comparing between them limited in its efficacy.

In conclusion, synovial CRP, WBC, and PMN% values were similar between THA and TKA PJI, and the use of differential values

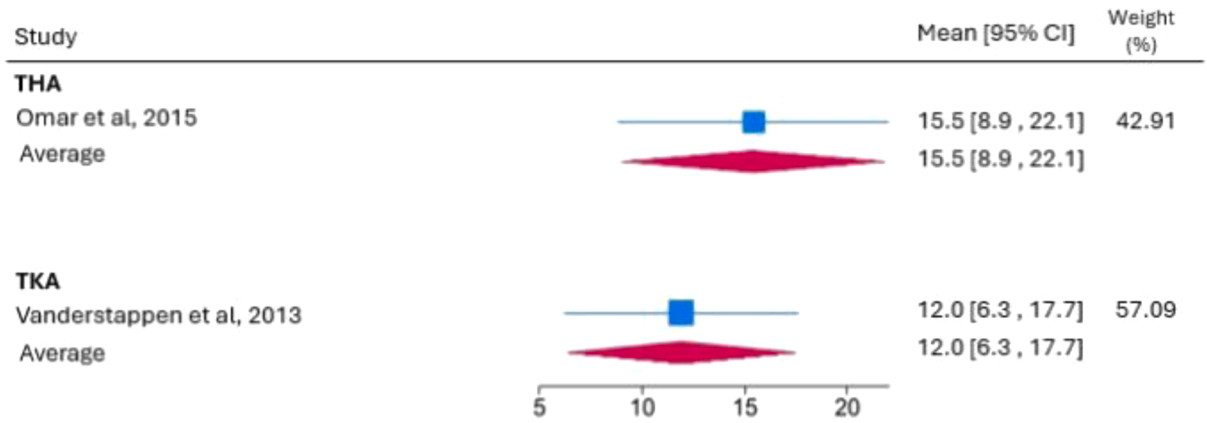

Figure 4. Forest plot of hip (THA) and knee (TKA) C-reactive protein in periprosthetic joint infection. THA, total hip arthroplasty; TKA, total knee arthroplasty; CI, confidence interval.

is not recommended based on the available data from a systematic review. Future studies evaluating synovial markers for PJI should report values for TKA and THA separately.

Question 2: Is there a role for synovial calprotectin in the diagnosis of periprosthetic joint infection (PJI)?[2]

Response/Recommendation

Yes. Synovial calprotectin (CLP) serves as a promising biomarker for diagnosing chronic PJI of the hip and the knee.

Level of Evidence: Moderate

Delegate Vote: Agree: 76.6%, Disagree: 16.3%, Abstain: 7.1% (Strong Majority, Moderate Consensus)

Rationale

Calprotectin (CLP) is a zinc- and calcium-binding heterodimer produced primarily by granulocytes and monocytes [23]. The CLP is released by these cells at the site of inflammation or infection. The role of this marker in the diagnosis of PJI has been explored [24–26]. Generally, there are two available methods for quantifying CLP in synovial fluid. The CLP enzyme-linked immunosorbent assay (ELISA) immunoassay is based on colorimetric detection using monoclonal and polyclonal antibodies against CLP. In contrast, the CLP lateral flow test (LFT) is a quantitative detection of synovial CLP, which has the advantage of immediate availability of results, making it useful for prompt intraoperative diagnosis of PJI. Recently, five meta-analyses evaluated the accuracy of CLP for diagnosing PJI and collectively concluded that CLP exhibits a high level of diagnostic sensitivity and specificity, confirming its potential utility as a reliable biomarker in the clinical assessment of PJI [26–30].

This systematic literature review was conducted independently by two researchers using the PubMed/Medline and Scopus databases. A total of 15 original studies were included based on the selected MeSH terms related to CLP and the diagnosis of PJI. Among these, six studies investigated laboratory methods, including five utilizing the ELISA [31–35] and one employing the immunoturbidimetric method [36]. The LFTs were investigated in 11 studies, including six studies dedicated to chronic PJI (Lyfstone Calprotectin) [34,37–41] and five studies for off-label use on synovial fluid samples [25,31,42–44]. For the diagnosis of PJI, eight studies referenced the 2018 International Consensus Meeting (ICM) criteria [45], three adhered to the European Bone and Joint Society 2021 criteria [46], and four studies utilized older diagnostic criteria.

A comprehensive analysis was conducted utilizing pooled data from 1,161 patients, as sourced from the original studies. The joint samples included 372 hips, 722 knees, and 12 samples from shoulder joints. Notably, one study did not specify the joint distribution [43]. Among these, 399 were diagnosed with PJI, 749 experienced aseptic failures, and in 13 cases, the diagnosis was inconclusive. Subsequent analyses included only four studies with groups larger than 100 patients [34,39,41,42]. The cutoff values for definitive positive PJI diagnosis varied among the studies and the applied quantification method, ranging from 1.5 to 173 mg/L (area under the curve [AUC] ranging between 0.71 and 0.996). The most frequently used threshold across seven studies was 50 mg/L (AUC = 0.926 to 0.996) [25,31,32,34,41,42,44]. Across all cohorts, sensitivity varied from 60 to 100%, specificity from 61 to 100%, positive predictive value from 40 to 100%, and negative predictive value from 78 to 100%. The LFT presented sensitivity from 60 to 100% and specificity from 61 to 98.5%, comparable with the ELISA method (87.5 to 100% and 76.9 to 100%, respectively).

Warren et al. reported 98.2% sensitivity and 98.5% specificity using a dedicated LFT [41], applying a threshold proposed by the test manufacturer (50 mg/L) and the ICM 2018 diagnostic standard, although only including total knee arthroplasty PJIs. Conversely, a smaller study by Lazic et al. analyzing patients who have implant loosening revealed sensitivity and specificity of 60 and 61%, respectively [38]. Despite using the European Bone and Joint Society diagnostic standard, they could not establish a correlation between the extent of osteolysis and the test performance. Furthermore, the same group showed that CLP has a favorable diagnostic performance when other causes of intra-articular inflammation are present, for example, in the early postoperative phase. However, larger studies are required to define accurate threshold values in such circumstances. Concerning LFT dedicated to diagnosing PJI, there is a need to remember that for reading the result, a smartphone application is required. Lighting conditions, different resolutions, and camera parameters can influence the obtained results.

Several authors evaluated different point of care tests with specific analyzers dedicated to fecal samples, with off-label use in synovial fluid samples with excellent results. Wouthuyzen-Bakker et al. used the Quantum Blue fCAL assay on 61 synovial fluid samples from patients to exclude PJI, achieving 89% sensitivity and 90% specificity [25]. A similar test was employed by Bottagisio et al. [43] and Alkadhem et al. [42], with comparable accuracy. However, it is essential to note that these tests are validated for solid samples rather than liquids, necessitating a recalibration of results from μg/g to mg/L.

The potential limitations of laboratory methods include higher costs, reduced availability, and longer turnaround times due to the need for sample delivery to the laboratory. Salari et al. demonstrated excellent accuracy in their study of 76 patients, categorizing them into PJI and aseptic groups according to the ICM 2018 definition [32]. With a cutoff of 50 mg/L (AUC = 0.996), they achieved 100% sensitivity and 95% specificity. Warren et al. investigated lateral flow and ELISA tests on the same cohorts [34]. They received the same results of sensitivity (98.1%) and specificity (95.7%) for both methods. Similar results were obtained by Grassi et al., with the results of sensitivity and specificity for the LFT (97.4 and 94%, respectively), and for the ELISA method (92 and 100%, respectively) [31]. The only study comparing different laboratory methods was conducted by Grzelecki et al. [36]. They used the immunoturbidimetric technique and found sensitivities and specificities of 95.6 and 96%, respectively, and the results were equivalent to the ELISA method. Finally, the results of the meta-analysis of Festa et al., which consisted of fourteen currently available studies, revealed a pooled 92% sensitivity and 93% specificity, confirming that CLP may provide very high accuracy for diagnosing PJI that stays in accordance with the results of this review [29].

Both laboratory and LFT methods dedicated to the detection of CLP in synovial fluid are promising for diagnosing chronic PJIs. Despite some limitations emphasized by prior studies, such as the concern with small sample size, application of different diagnostic standards, the influence of blood contamination on the obtained results, and the need for validation when synovial

[2] These authors contributed to Question 2: Dariusz Grzelecki, Piotr Sypień, Rares Mircea Birlutiu, Mohammad Kamal Abdelnasser, Mats Bue, Rüdiger von Eisenhart-Rothe, Imelda Lumban Gaol, Carlos Higuera Rueda, Giovanni Balato

fluid samples are used, the excellent accuracy of this biomarker encourages its use in clinical practice.

Question 3: Does the pH of infected synovial fluid vary from that of uninfected synovial fluid?[3]

Response/Recommendation

No. The pH in the synovial joint has been reported to range from acidic to alkalotic, regardless of infectious status. The pH is a diagnostic parameter of interest. Much work is needed to disentangle host-microbial interactions in synovial structures and their impact on pH. We, therefore, recommend that the current knowledge is insufficient to support pH as a diagnostic biomarker to differentiate between septic and aseptic synovial fluid.

Level of Evidence: Limited

Delegate Vote: Agree: 82.0%, Disagree: 10.4%, Abstain: 7.7% (Super Majority, Strong Consensus)

Rationale

The pH scale is used to determine the acidity or alkalinity of a solution; a lower pH is consistent with increased acidity. Studies regarding the pH of synovial fluid date back to 1959, when Jebens et al. demonstrated the average pH of synovial fluid to be significantly higher than that of serum (7.7 ± 0.04 versus 7.38 ± 0.01) and that the pH of synovial fluid is lower in the setting of joint trauma (7.56 ± 0.03) and osteoarthritis (7.55 ± 0.04) [47]. A 1975 study of human synovial fluid revealed a direct correlation between increased synovial fluid white blood cell count and decreased pH in human synovial fluid [48]. Additional studies underscored the relationship between increasing inflammation and synovial fluid acidity: synovial fluid in inflammatory conditions such as rheumatoid arthritis has lower pH values than osteoarthritis [49].

The pH of infected synovial fluid is lower than that of noninfected synovial fluid [48,50–52]. This is most likely due to increased inflammation and lactic acid production in the setting of an infection [51]. Treuhaft et al. demonstrated that the pH of synovial fluid correlates strongly with the presence of lactate and with increasing severity of clinical inflammation in the setting of inflammatory arthritis [49]. Recent studies have revealed decreased pH in the setting of both native and periprosthetic joint infections (PJIs) of the hip and knee [52–54]. Judl et al. reported that patients who have a PJI of the hip and knee had a significantly lower synovial fluid pH (6.98 ± 0.48) than noninfected hip and knee arthroplasties (7.82 ± 0.29) and that a threshold pH of 7.4 had a sensitivity of 88.6% and specificity of 95.5% for the diagnosis of PJI [54]. Conversely, while Theil et al. also demonstrated synovial fluid pH to have reasonable specificity (89% at a threshold of $pH = 7.11$), the authors report poor sensitivity (53%) of synovial pH for the diagnosis of chronic PJI of the hip and knee [52].

In order to answer the above question, we conducted a comprehensive systematic literature review consistent with the Preferred Reporting Items for Systematic Reviews and Meta-analyses. This study was exempt from requiring approval by the institutional review board. MeSH terms were utilized to identify relevant studies. The primary databases used were PubMed and Scopus, with Web of Science being utilized to ensure all possible citations were identified. Of the literature reviewed, only articles containing original research for the direct measurement of synovial fluid pH were included for analysis. Species included for review were humans and clinically relevant animal species, including equine, porcine, and canine. The pH data were either reported as recorded or calculated for normal joints, septic conditions, osteoarthritis, and arthroplasty. Conditions such as gout, rheumatoid arthritis, and traumatic and soft tissue injury were excluded.

The initial search generated 2,959 studies across all three databases. Of these, 20 studies met the inclusion criteria. Species distribution was 15 humans, five equine, one canine, and one porcine. There were nine papers published after 2010. There were 50% of the papers that included a direct measurement of pH for normal synovial fluid. There were five papers that included a direct measurement of pH in conditions relating to septic arthritis. There were ten papers that included a direct measurement of pH in osteoarthritic conditions. There were four papers that reported pH for cases of septic arthroplasty, and five papers included pH for cases of aseptic arthroplasty. There were two papers that included the causative organism with pH, and two papers mentioned the use of antibiotics with pH. The methodologies of measuring pH varied greatly from digital pH meters to commercial blood gas analyzers to pH papers. Overall, the rigor of preserving sample integrity from collection to analysis was low and varied substantially. Furthermore, there is a concern for pH changes as a function of time, as well as the temperature at which it is stored, if samples are not fresh when analyzed.

There is some consensus that the pH of synovial fluid is lower in the setting of an infection. In addition, the low pH of synovial fluid in infection may explain why certain antibiotics (such as aminoglycosides) are rendered less effective when used for gram-negative infections [48]. White blood cells, metabolic products, and inflammatory mediators have been shown to influence the pH of synovial fluid, which may explain why infected synovial fluid has a different pH than noninfected fluid [48,55]. The impact of nonsteroidal anti-inflammatory drugs and/or systemic or local antimicrobials on the synovial milieu is not well defined. Only two studies mentioned the use of antimicrobials, both of which considered the impact of specific antimicrobials on the joint environment. There is very little published data addressing the impact of antimicrobials on the *in vivo* environment when measuring pH, and vice versa. The causative organism in septic conditions may also affect the degree to which pH shifts, especially when comparing organisms of different phyla. There were two studies that measured the pH of the infectious organism; however, both papers used experimentally induced models of septic arthritis. The other papers that listed causative organisms in the clinical population did not correlate those organisms with pH. Also, the environment created by arthroplasty is unique and understudied and may have a direct impact on pH. Metal ions in the joint fluid were shown to have a buffering effect in a physiologic simulation study [56]. Metallosis, synovectomy, and arthrotomy have all been reported to change the pH of the native joint to favor a more alkalotic environment [56]. Advanced age may also have an impact on synovial fluid pH. Milosev et al. demonstrated synovial fluid pH to be higher in octogenarian patients who have native osteoarthritis of the hip and knee, as well as a revision for the aseptic failure of hip and knee arthroplasties compared to those aged 40 to 49 years [56]. There were no studies that interrogated pH in the immediate postoperative surgical wound milieu.

Conclusions

The current systematic review revealed that the pH of synovial fluid in the setting of infection differs from that of noninfected joints. However, there are multiple factors that can affect the synovial fluid environment, such as inflammation, renal failure, metallosis, and the administration of drugs like nonsteroidal anti-inflammatory drugs. Therefore, pH is not a reliable stand-alone diagnostic metric for PJI. Synovial fluid pH shows promise as an adjunctive measure for the diagnosis of PJI, but its role as a

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Table 5
Studies in the Literature Report Concordance Between Preoperative Synovial Fluid Culture Results and Intraoperative Tissue Sample Results.

Study and Publication Year	Definition of Infection	Concordance Rate (%)	Synovial Fluid Positive Culture (%)	Periarticular Tissue Positive Culture (%)
Shanmugasundaram et al. (2014) [76]	Surgeon discretion	75 (THA) 78.6 (TKA)	44.4 THA 45.2 TKA	85 THA 79.3 TKA
Lindberg-Larsen et al. (2017) [77]	Surgeon discretion	66		
Declerq et al. (2020) [78]	Sinus tract or 2+ cultures	68.2	77.6	87
Rockov et al. (2020) [79]	MSIS 2011	78.1		
Boyle et al. (2021) [69]	MSIS 2011	76.6		
Schulz et al. (2021) [74]	MSIS based	52.1		

THA, total hip arthroplasty; TKA, total knee arthroplasty; MSIS, Musculoskeletal Infection Society.

diagnostic measure and potential to guide antibiotic selection need to be further refined. Original *in vivo* research of high translational fidelity and/or clinical research using standardized analytical methods is needed to better understand host-microbial interactions and their impact on the environments created in different states of joint pathology.

Question 4: Is there a difference in the diagnostic yield of synovial fluid (SF) versus periarticular tissues for isolation of infective organisms causing periprosthetic joint infection (PJI)?[4]

Response/Recommendation

Yes. Periarticular tissues have a higher yield for the isolation of infective organisms and should be obtained in all cases.

Level of Evidence: Moderate

Delegate Vote: Agree: 95.4%, Disagree: 2.3%, Abstain: 2.3% (Unanimity, Total Consensus)

Rationale

Identification of the causative organism(s) in the setting of PJI is crucial for both diagnosis and treatment. Accurate organism identification is necessary for targeted antibiotic therapy and impacts treatment outcomes [57–62]. Despite various recently proposed techniques and advanced technologies, conventional culture techniques of SF and/or intraoperative periarticular tissue samples remain the most widely used method for organism isolation in PJI.

It is inherently difficult to provide evidence-based recommendations regarding the yield of SF and tissue sample culture results, as there is major heterogeneity within the literature regarding how PJI was defined, study protocols, and statistical analysis. Many institutions have wide variability among culture techniques, sample handling, and sampling protocols. Synovial fluid samples are generally sent for one culture, while periarticular tissues are often sent in multiples. Conventional wisdom proposes that combining multiple tissue samples will improve sensitivity and decrease specificity. Given this, combining multiple tissue samples will improve the culture yield and provide a greater opportunity for a positive result. In addition, it has been demonstrated that SF samples culture planktonic bacteria more commonly present in acute infections or in PJI secondary to high-virulence organisms, whereas tissue or sonication cultures, which are more likely to capture sessile and biofilm-protected organisms [63,64].

A review of the literature suggests that periprosthetic tissue cultures appear to have greater diagnostic sensitivity (65 to 94%) compared to SF (45 to 75%) [65–68]; however, there are conflicting reports. A recent study by Boyle et al. examined 363 PJI patients, as defined by the most recent International Consensus Meeting criteria, and found 76.8% concordance between preoperative SF samples and intraoperative tissue culture at the time of revision surgery. Only seven (1.9%) SF samples were polymicrobial compared to 35 (9.6%) intraoperative tissue samples. These findings highlight the importance of tissue culture for identifying causative organisms, particularly in the setting of polymicrobial PJI. Organism type did play a role in the concordance rate, with Methicillin-sensitive *Staphylococcus aureus* and Methicillin-resistant *Staphylococcus aureus* being most likely to be identified with SF samples, while *C. acnes* and polymicrobial infections were more likely to be identified with periarticular tissue sampling [69].

In the setting of chronic or indolent PJI, SF samples alone are less likely to identify the causative organism and can often provide false-negative results [70]. This is supported by recent literature indicating that SF culture poorly identifies slow-growing gram-positive anaerobic bacteria such as *C. acnes* [71,72]. Interestingly, Font-Viscarra et al. examined 87 PJIs and compared the frequency of positive cultures between SF samples with periprosthetic tissue and swab samples. They found SF samples to be culture-positive in 90% of cases compared to 82% of tissue samples. The authors partially attributed this to the use of SF sample incubation in blood culture flasks, a notion supported in the literature [73].

Conversely, Schulz et al. [74] evaluated 167 PJI patients who had either a preoperative SF sample or an intraoperative tissue sample with a positive culture. In this study, 66% of SF cultures identified the causative organism. This was found to be significantly lower compared to intraoperative cultures, identifying an organism in 92% of cases. As expected, intraoperative specimens were more likely to identify polymicrobial infections. Chronic infections were more likely to have an organism detected from intraoperative tissue samples rather than SF, again a common theme seen in the literature. Bjerkan et al. [75] evaluated 18 PJI cases, with SF culture positive in 12, while tissue specimens were culture positive in 16 of the samples ($P = 0.008$), indicating the improved yield of periarticular tissue sampling.

Several studies have evaluated concordance rates between preoperative SF samples and intraoperative samples (Table 5). Tetreault et al. [80] performed a randomized controlled trial of 65 PJI patients who had preoperative culture-positive aspirations and provided prophylactic preincisional antibiotics to one group, while the other group received antibiotics after tissue samples were collected. The concordance rates between preoperative and intraoperative cultures were 82 and 81% in the preincision antibiotic and postsample antibiotic groups, respectively. Though this highlights that antibiotic use may not impact yield, there is still a difference in organism identification from SF alone and intraoperative tissue. Barker et al. [81] similarly aimed to identify the accuracy of SF aspirations in the

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setting of PJI. The authors concluded that the post-test probability of SF culture was not reliable, again highlighting the need for multiple tissue samples.

Also, Huang et al. evaluated 49 PJI patients. They found that SF identified an organism via culture in 61.2% of PJI cases. However, 79.6% of these cases yielded a positive culture when combining synovial tissue and sonicate fluid samples. This again highlights the importance of sampling periarticular tissues for organism identification. Interestingly, next-generation sequencing, a novel technique that is gaining traction in the world of PJI, identified an organism in 95.6% of PJI patients [82]. These findings are similar to those reported in other next-generation sequencing–related PJI studies, indicating the possible utility of this technology in identifying organisms from both SF and tissue samples in PJI patients [83–86].

In conclusion, both SF and tissue specimens are helpful in identifying infective organisms in the setting of PJI. Combining multiple periarticular tissues with SF obtained intraoperatively provides an increased yield overall and is helpful with organism identification in patients who have PJI, particularly in cases of slow-growing organisms and polymicrobial infections. More novel techniques, such as tissue and implant sonication, as well as metagenomic sequencing, may provide additional utility in identifying causative pathogens; however, the limited availability and lack of consensus limit their use at this time.

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The Journal of Arthroplasty 41 (2025) S277–S284

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Hip and Knee

2025 ICM: Samples for Culture

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Question 1: When taking the culture of a joint, how many samples should be taken?[1]

Response/Recommendation

When taking samples for routine culture from a hip or knee joint, it is recommended to obtain four to six samples. This number may be reduced to three when using blood culture bottles. However, there is limited evidence on the optimal number of samples required for culturing acid-fast bacilli or fungi from a hip or knee joint.

Level of Evidence: Moderate

Delegate Vote: Agree: 93%, Disagree: 5%, Abstain: 2% (Total consensus, Unanimity)

Rationale

Regarding the identification of microorganisms in large joints, including hips and knees, earlier studies suggested that five or more samples should be collected [1,2]. However, these studies lacked hypothesis-driven analyses to specifically support this recommendation. Recent studies have aimed to validate the optimal number of samples required to identify microorganisms in knee and hip joints [3–6].

Bémer et al. conducted a multicenter, prospective, cross-sectional study involving 215 patients who had periprosthetic joint infections (PJIs) diagnosed using the IDSA criteria [7]. The overall positive culture rate was 89.3%. There were five intraoperative samples collected from each patient. Subsets of two, three, and four samples were randomly selected to assess agreement with the full microbiological dataset. Results demonstrated that four samples were sufficient to diagnose PJI, achieving a percentage of agreement of 98.1 and 99.7% with the bacteriological and overall IDSA criteria, respectively [4]. Gandhi et al. retrospectively analyzed 74 patients infected with total hip arthroplasty (THA) or total knee arthroplasty (TKA) diagnosed according to the Musculoskeletal Infection Society (MSIS) criteria [8]. The overall positive culture rate was 85.1%. A receiver operating characteristic curve analysis was performed to determine the optimal number of cultures required for a positive result. The analysis revealed an area under the curve of 0.708 (95% confidence interval: 0.554 to 0.861, $P = 0.019$). A threshold of four samples demonstrated an optimized sensitivity and specificity of 0.63 and 0.61, respectively. Notably, increasing the number of culture samples was associated with improved sensitivity [3]. Peel et al. retrospectively reviewed 499 patients who underwent revision total joint arthroplasty, of whom 22% (N = 111) met the MSIS criteria for PJI [9]. The majority of these cases involved revision TKA and THA procedures (83.2%, N = 415). The overall positive culture rate among PJI patients was 80.2%. For conventional culture techniques, including synovial and sonicate fluid cultures, Bayesian latent class modeling demonstrated the highest accuracy (95%) with a sensitivity of 97% and specificity of 91% when five samples were collected. When using blood culture bottles, the optimal number of samples decreased to three, achieving an accuracy of 93% (sensitivity: 92%, specificity: 93%) [6]. Kheir et al. conducted a single-center, retrospective study involving 622 PJI patients, with a total of 2,290 cultures collected from hips and knees. The diagnosis was made based on the MSIS criteria [10]. For each patient, three to five tissue and fluid samples were generally

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.103.

[1] These authors contributed to Question 1: Shang-Wen Tsai, Truong Nguyen Khanh Hung, Dirk Jan F Moojen, Dao Thanh Tu, Goh Ohji, Manuel Suyon Paniccia, Alexander L Neuwirth

https://doi.org/10.1016/j.arth.2025.10.103
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collected for bacterial cultures. The overall positive culture rate was 62.6% (N = 1,433 out of 2,290 cultures). On average, four samples were required to obtain a minimum of two positive cultures, with variations observed among different microorganisms. Collecting five samples yielded the highest number of positive cultures, with a mean of 3.74 positive results, compared to other sample numbers, which ranged from one to more than nine [5].

The incidence of positive acid-fast bacilli or fungal cultures is very rare, ranging from 0 to 0.6% among 446 acid-fast bacilli and 486 fungal cultures performed during 253 orthopedic procedures over a 2-year study period, primarily involving TKA and THA procedures. Therefore, routine testing might not be necessary unless there is a high clinical suspicion [11]. Because of the rarity of such cases, most studies—typically case reports or small series—have not validated the number of cultures required to obtain positive results for acid-fast bacilli or fungi [12–18]. Repeated joint aspiration using selective culture media or molecular diagnostic techniques may improve the yield of organism detection for these types of pathogens [19].

Current evidence recommends collecting four to six samples for bacterial cultures from a hip or knee joint to achieve a positive yield and diagnose PJI. When using blood culture bottles, this number might be reduced to three. However, evidence regarding the optimal number of samples needed to culture acid-fast bacilli or fungi from a hip or knee joint remains limited.

Question 2: What is the optimal duration for holding cultures in patients with periprosthetic joint infection (PJI)?[2]

Response/Recommendation

In view of recent data suggesting that certain slow-growing microorganisms, such as *Cutibacterium acnes (C. acnes)*, require prolonged incubation times in order to be isolated on culture, we recommend routine holding of cultures for a duration of 14 days in patients with an established diagnosis of PJI. If fungal or mycobacterial PJI is suspected, samples should be inoculated on special media and held for at least four to six weeks.

Level of Evidence: Strong

Delegate Vote: Agree: 86.9%, Disagree: 11.5%, Abstain: 1.6% (Super Majority, Strong Consensus)

Rationale

Periprosthetic joint infection is a devastating complication and one of the leading causes of failure in patients undergoing total joint arthroplasty [20]. Concurrently, the economic burden of PJI in the United States is projected to reach an all-time high of $1.85 billion per year by 2030 [21]. Furthermore, as the annual volume of primary and revision total joint arthroplasty procedures continues to rise, the overall prevalence of PJI is also expected to increase [22].

The most important consideration in the management of patients with an established diagnosis of PJI is the prompt and accurate identification of the infecting organism [23]. This allows for the administration of targeted antibiotic therapy, which has been shown to markedly increase the odds of treatment success [24]. Although there have been promising reports on the utility of newer diagnostic techniques for microbial identification, conventional culture remains the modality of choice for pathogen isolation in patients diagnosed with PJI [25]. In a recent meta-analysis, culture was found to have a pooled sensitivity and specificity of 70 and 97%, respectively, in the diagnosis of PJI [26]. However, it is important to recognize that there are data to suggest that the rate of culture-negative infection in this patient population is on the rise [27]. In one study, Bejon et al. found that bacterial culture was negative in 45% of patients undergoing two-stage exchange arthroplasty [28]. As such, given that the administration of antimicrobial therapy has been shown to reduce the rate of positive cultures, physicians must obtain a detailed history in order to ensure that patients are not receiving antibiotics before performing arthrocentesis [29].

In an effort to maximize diagnostic yield, several studies in the orthopedic literature have examined the efficacy of different culture techniques that have been popularized in recent years [30,31]. As a result, there is now a growing body of evidence to support the implementation of strategies that have been shown to increase the rate of culture positivity, such as obtaining a minimum of three intraoperative samples and the use of blood culture bottles [32–34]. In cases of PJI suspected to be caused by fungal and mycobacterial pathogens, it is well established that samples should be inoculated on special media and held for four to six weeks [35]. Conversely, although a number of prior investigations have evaluated the impact of extending incubation times on the overall culture positivity rate in patients with PJI, the optimal duration for holding aerobic and anaerobic cultures in this setting remains a contentious issue [36–40].

While it was previously believed that an incubation time of three to five days was sufficient to capture the majority of infecting organisms, we now know that this may lead to a relatively high rate of false-negative culture results in this patient population [41]. In a study of 711 PJI patients, Kheir et al. showed that the culture positivity rate increased from 42 to 95% when prolonging the incubation time from three to eight days, respectively [42]. Similarly, Schafer et al. found that holding cultures for 13 days resulted in a 100% culture positivity rate in patients with an established diagnosis of PJI [43]. Moreover, in another study, Tarabichi et al. demonstrated that routine holding of cultures for 14 days was necessary in order to capture cases of PJI caused by atypical pathogens [44]. Furthermore, in light of recent data suggesting that a minimum duration of 10.2 days is required in order to isolate *C. acnes*, it is evident that prolonging incubation time to 14 days is paramount to maximizing the sensitivity of culture for slow-growing organisms that are not uncommon in this setting [42,45].

Despite its well-established limitations, culture remains the preferred option for the isolation of infecting pathogens in patients diagnosed with PJI. Although it was previously believed that holding cultures for three to five days is sufficient, there is now substantial evidence to suggest that a prolonged incubation time is necessary in order to maximize diagnostic yield and reduce the overall false-negative rate of culture. Based on recent literature, we recommend routine holding of aerobic and anaerobic cultures for 14 days. In cases of suspected fungal or mycobacterial infection, samples should be inoculated on special media and held for four to 6 weeks.

Question 3: What is the optimal duration for holding cultures in patients undergoing revision for presumed aseptic failure?[3]

Response/Recommendation

For patients who have presumed aseptic failure undergoing revision arthroplasty, the culture incubation period should be extended to 14 days to enhance the detection of slow-growing organisms.

[2] These authors contributed to Question 2: Saad Tarabichi, Jens T. Verhey, Jacem Saadana, Juan D. Lizcano, Jaime Esteban, Lorenzo Drago, Hernan A. Prieto, Ashok Rajgopal, Omer Faruk Bilgen, Emmanuel Thienpont, Mark J. Spangehl, Joshua S. Bingham

[3] These authors contributed to Question 3: Edward M Vasarhelyi, Sebastian Braun, Ashok Rajgopal, Fidel Dobarganes, Darren Tay, Thananjeyen Srirangarajan

Level of Evidence: Limited

Delegate Vote: Agree: 92.6%, Disagree: 5.7%, Abstain: 1.7% (Total Consensus, Unanimity)

Rationale

The number of total joint arthroplasty procedures continues to rise annually, leading to an increasing volume of revision surgeries [46]. According to joint registry data, aseptic failure remains the leading cause of revision hip and knee arthroplasty, with periprosthetic joint infection (PJI) being the second most common cause [47,48]. The Musculoskeletal Infection Society and International Consensus Meeting have established internationally accepted criteria for the diagnosis of PJI [49,50].

A missed diagnosis of PJI can be devastating, resulting in recurrent operations, poor clinical outcomes, and the need for lifelong treatment. To mitigate this risk, it is considered good practice to obtain tissue and fluid cultures during revision surgery, even when the cause of failure is considered to be aseptic. However, no standardized guidance exists for culture incubation duration, which often varies between institutions, typically ranging from seven to 14 days. Extended culture durations increase the detection of low-virulence organisms such as *Cutibacterium acnes (C. acnes)* and coagulase-negative *Staphylococci* [51]. However, the clinical relevance of single positive cultures remains debated, as they may lead to unnecessary interventions and re-revision surgery [52].

The role of atypical pathogens, such as acid-fast bacilli (AFB) and fungi, in failed revisions is also a critical concern. Routine use of extended culture protocols, which may require up to 45 days of incubation, is controversial due to the major cost implications and questionable diagnostic yield. Selective use of these cultures in cases of high clinical suspicion is recommended [53].

There is limited literature specifically addressing the optimal duration for culture incubation in aseptic revision cases. Most studies focus on identifying the prevalence of positive cultures in presumed aseptic revisions. The culture duration in these studies varies from seven to 15 days for standard cultures, with an average PJI detection rate of 14.1% in hip and knee revision surgeries undergoing single-stage procedures for presumed aseptic failure [51,54–57].

Schwarze et al. investigated unsuspected positive cultures (UPCs) after 14 days of culture incubation in single-stage hip and knee revisions for aseptic failure. Among 434 cases, 160 (39.9%) demonstrated UPC, with *C. acnes* and coagulase-negative *Staphylococci* being the most common isolates. Of these, 44 cases (27.5%) subsequently developed PJI, with 31 of 44 (70.5%) requiring further staged revision surgery. Risk factors associated with UPC included men, obesity, and a preoperative C-reactive protein > 10, suggesting a subgroup in which prolonged cultures may be particularly beneficial [51].

Khalid et al. conducted a similar study reviewing 72 hip and knee revision cases for aseptic failure using cultures incubated for up to 15 days. They identified PJI in five cases (7%), with two cases detected on extended cultures at 10 days. The authors emphasized the importance of clinical suspicion and patient-specific risk factors in determining the need for extended cultures [54].

Tokarski et al. explored the role of atypical cultures in 1,717 hip and knee revisions for presumed aseptic failure. Acid-fast bacilli cultures (held for 50 days) and fungal cultures (held for 32 d) yielded positivity rates of 0.5 and 1.7%, respectively. However, AFB cultures were 100% false-positive, and fungal cultures demonstrated a 73.3% false-positive rate. Given the high cost and limited diagnostic value, the authors recommended strict criteria for the selective use of atypical cultures [53].

Portillo et al. evaluated 63 hip and knee revisions for aseptic failure and identified single UPC in 13% of cases, with *Staphylococcus* species and *C. acnes* being the predominant isolates. Anaerobic cultures were held for 14 days, while aerobic cultures were incubated for seven days. The study found no statistically significant difference in the rate of re-revision surgery at a median follow-up of 2.1 years between patients who have and who do not have UPCs, suggesting that single positive cultures may often represent contamination rather than true infection [52].

In contrast, Ribera et al. analyzed 89 hip and knee revisions with cultures held for 10 days, reporting a 13.5% PJI detection rate and a 24.7% rate of single positive cultures. The authors emphasized that single positive cultures may represent indolent infections, which could contribute to early implant failure. They proposed the use of sonication to aid in distinguishing contaminants from true infections [57].

Conclusions

The optimal duration for culture incubation in presumed aseptic revision hip and knee arthroplasty remains an area of debate. While extending culture duration to 14 days improves the detection of low-virulence organisms, the clinical relevance of single positive cultures requires careful consideration to avoid overtreatment. Atypical cultures for fungal or AFB pathogens should be selectively used in cases with high clinical suspicion, given their low diagnostic yield and high false-positive rates. Future research should aim to standardize culture protocols, assess cost-effectiveness, and integrate advanced diagnostic tools to refine the approach to detecting occult infections in revision arthroplasty.

Question 4: Should intraoperative culture be obtained in all patients undergoing revision arthroplasty?[4]

Response/Recommendation

Yes. Samples for culture should be obtained in all revision arthroplasty cases.

Level of Evidence: Moderate

Delegate Vote: Agree: 90.3%, Disagree: 8.1%, Abstain: 1.6% (Unanimity, Total Consensus)

Rationale

Surgeons should employ a high index of suspicion for periprosthetic joint infection (PJI) in any patient who is undergoing revision total joint arthroplasty [58–61]. When there is diagnostic ambiguity, intraoperative cultures are often performed, and these cultures may influence the postoperative care of these patients, sometimes resulting in more surgery or the use of extended courses of parenteral antibiotics.

This is important because unnecessary treatment with antibiotics due to a false-positive test can result in major emotional and financial hardship on patients, morbidity, and the development of antibiotic resistance. However, not treating an infected patient due to a false-negative result can have even more devastating consequences.

A multitude of factors can lead to an arthroplasty revision surgery, with the specific causes varying from patient to patient and depending on the joint affected. Instability, aseptic loosening, periprosthetic fractures, and chronic, unexplained pain are frequently cited as reasons for revision. However, PJI after arthroplasty is always a concern. The problem is that there are occasional cases of occult infection that are difficult to detect preoperatively with the use of conventional microbiologic culture

[4] These authors contributed to Question 4: Saadana Jacem, Rottman Martin, Murylev Valeriy, Tarabichi Saad, Muldoon Eavan, Abid Hichem

techniques [62,63]. It is also important to note that multiple causes for failure can exist. Thus, having a reason for revision does not mean that infection cannot exist in a given patient who has a discrete cause of failure.

The necessity of intraoperative sampling in prosthetic revision surgery raises an important clinical question. When PJI is either suspected or confirmed based on clinical, laboratory, and radiological findings, intraoperative sampling is unequivocally mandatory [64], irrespective of the anatomical location (hip, knee, and shoulder). This practice is crucial because the microbiological data obtained directly influence the optimal treatment strategy for the patient, even if the infective organism is previously identified by aspiration [65], and increase the odds of treatment success [66].

We realize that the decision to take intraoperative samples during revision surgery for presumed aseptic reasons is complex and controversial. There is an ongoing debate in the orthopedic community about the necessity of this practice. The incidence of occult PJI justifies systematic intraoperative sampling [67]. Anagnostakos et al. demonstrated that approximately one out of 11 aseptic revision arthroplasties had positive intraoperative cultures. The incidence of positive findings was 9.3% (14 out of 151 cases) for the hip and 7.8% for the knee joint (six out of 77 cases).

Infection is one of the most common reasons for revision total hip arthroplasty (THA) in the USA (15%). Close to 50,000 revisions are performed per year, with PJI being one of the most frequently cited reasons for revision in the first five years following the primary procedure [67]. In the study by Renard et al., the causes of revision in 523 THA were instability (42%), aseptic loosening (25%), periprosthetic fracture (19%), unexplained pain (6%), and others (8%) [67]. Among all revisions for instability, 16% (n = 15) met the infection criteria. When assessing only the early dislocations (before three months), this percentage increased to 23%. This incidence of infection was 12% among periprosthetic fractures, 3.2% among cases of aseptic loosening, and 2.8% in cases of polyethylene wear/osteolysis [67,68].

A short time between primary THA and revision or an early postoperative dislocation are some examples of signs that are concerning for infection [67]. Patients undergoing conversion THA from prior hip or acetabular fracture have a high rate of positive intraoperative cultures [69]. In revisions of THA involving the acetabulum, the proportion of patients who have one or more positive intraoperative cultures (PIC) was 15% (39 of 260). Of the 260 patients who underwent a cup revision, 85% had no PICs (221 of 260), 8% had one PIC (21 of 260), and 7% had two or more PICs (18 of 260) [70].

Shoulder surgeons need to maintain a high index of suspicion for periprosthetic infections after shoulder arthroplasty, as many of the conventional clinical and laboratory markers may be negative. At this time, multiple cultures taken at the time of revision surgery have been shown to have the highest diagnostic utility for PJI [71]. Surgeons need to balance the cost and morbidity of a potential missed diagnosis of a PJI with those of potentially overtreating an aseptic revision shoulder arthroplasty.

Ahmadi et al. found that 169 of the 537 surgeries (31.5%) had positive intraoperative cultures [71], Positive culture results, however, must be viewed in the context of the overall clinical picture as well as the appearance of the tissues at the time of revision surgery [70,71]. Intraoperative tissue culture should be in accordance with clinical and preoperative findings. Causative microorganisms are also an important factor.

Given the therapeutic implications of intraoperative culture results obtained during prosthesis revision surgery, and regardless of the clinical, biological, or radiological factors prompting the revision, obtaining intraoperative samples enables the detection of occult infections where the diagnosis may be solely microbiological.

Question 5: Should fungal and acid-fast bacilli (AFB) cultures be done in all culture samples taken from joints?[5]

Response/Recommendation

Routine culture for AFB and (non-*Candida*) fungi in all culture samples taken from the joint is not needed, except in endemic regions.

Level of Evidence: Limited

Delegate Vote: Agree: 93%, Disagree: 4.1%, Abstain: 2.9% (Total consensus: Unanimity)

Rationale

Periprosthetic joint infection (PJI) can be caused by a range of pathogens, including fungi and mycobacteria [72,73]. However, these etiologies remain relatively rare. However, in some settings reported prevalence of PJI can reach up to 6.5% [74].

The majority of fungal PJIs are caused by a variety of *Candida* spp. [75,76]. This finding is likely influenced by routine laboratory practices, including the use of standard culture media, incubation conditions, and duration, which favor the detection of yeasts [77,78]. Consequently, the true prevalence of nonyeast fungal PJI may be underestimated, as these organisms require specialized culture media, alternative incubation conditions, and prolonged incubation times. Despite this limitation, reports of nonyeast fungal PJIs exist in the literature [79], with certain fungal species, including *Coccidiomycosis* [80], *Zygomycosis* [81], *Histoplasma capsulatum* [82–84], *Trichospora spp.* [85], and *Peudallescheria boydii* [86], being implicated in isolated case reports and small case series. Typically, these infections occur in immunocompromised patients with significant underlying conditions [87–90].

In cases of mycobacterial PJI, a variety of species have been implicated. Detection of PJI due to *M. tuberculosis* complex remains relatively rare [91]. Risk factors for mycobacterial infection include, but are not limited to, prior therapy with *Bacillus Calmette-Guérin* in cases of urothelial carcinoma [92–94], treatment with biologic immunosuppressive agents [95–98], and exposure in endemic regions with high prevalence rates. Both active and latent infections may be reactivated under immunosuppressive conditions [99,100]. For the detection of *M. tuberculosis* complex and nontuberculous mycobacteria, specialized diagnostic approaches, including specialized culture and polymerase chain reaction, are necessary. Although rapidly growing nontuberculous mycobacteria may occasionally be detected using conventional bacterial culture methods, the identification of slow-growing mycobacteria remains challenging [101].

Despite the clinical importance of fungal and mycobacterial PJI, few studies have evaluated the utility of routine testing for these pathogens. Lee et al. similarly identified cases of fungal and mycobacterial PJI only when specific diagnostic testing was requested [78]. In their retrospective cohort, all fungal PJIs were detected using standard bacterial culture media. In addition, mycobacterial cultures were ordered in more than 96% of cases; however, only five of 186 cases were confirmed to be caused by mycobacteria. Similarly, Golden et al. reported that among 97 patients undergoing PJI diagnostic workup with mycobacterial cultures, only one case was identified as mycobacterial in origin [102].

[5] These authors contributed to Question 5: Tobias Siegfried Kramer, Roberto Rostagno, Talha Riaz, Toshibumi Taniguchi, GOH Ohji, Manuel Suyon, Gholam Hossain Shahcheragi

A retrospective study by Tai et al. analyzed test positivity rates in a cohort of 2,067 PJI cases, in which fungal and/or mycobacterial cultures were performed in 1,157 cases (56%) [101]. The test positivity rates for fungal and mycobacterial cultures were 5% (n = 179) and 1.2% (n = 34), respectively. Notably, the additional use of blood culture bottles for sample incubation yielded a 90% sensitivity rate for diagnosing fungal PJI and a 100% sensitivity rate for detecting rapidly growing mycobacteria.

Few studies have assessed the clinical utility of routine mycobacterial cultures in PJI. Yates et al. reported a number needed to test of 1,623 in a low-prevalence setting, indicating that routine mycobacterial testing may not be cost-effective in such regions [103]. Furthermore, even blood culture bottles specifically designed for mycobacterial growth failed to detect slow-growing mycobacteria when compared to sequencing-based approaches [104].

According to the current scientific literature reviewed, we would like to further specify the suggested criteria for testing [73]:

Testing for mycobacteria or fungi (non-*Candida*) in suspected cases of surgical site infection/PJI should be limited to only those patients with an increased risk of atypical infections, which include the following:

(a) Severely immunocompromised host.
(b) Previous history of or high suspicion for atypical infection.
(c) Culture-negative PJI with clinical or diagnostic signs or an elevated risk for such an atypical infection (e.g., prior *Bacillus Calmette-Guérin* treatment for bladder cancer).

In conclusion, while fungal and mycobacterial PJIs remain rare, their identification requires targeted diagnostic strategies. Routine culturing for these pathogens may have limited value, particularly in low-prevalence settings. The use of enhanced culture techniques, including prolonged incubation and molecular diagnostics, may improve detection rates, particularly for slow-growing organisms. Further research is needed to optimize diagnostic workflows and determine the clinical and cost-effectiveness of routine fungal and mycobacterial testing in PJI cases.

Question 6: Is there a role for a specialized diagnostic algorithm in patients who have culture-negative periprosthetic joint infection (CN PJI)?[6]

Response/Recommendation

Yes. There is a definite need and role for a specialized diagnostic algorithm for patients with CN PJI, especially in the so-called "inconclusive" according to the Infection Consensus Meeting (ICM) (2018) or the "infection likely" category according to EBJIS (2021) category.

Level of Evidence: Moderate

Delegate Vote: Agree: 93.9%, Disagree: 3.1%, Abstain: 3.1% (Total consensus, Unanimity)

Rationale:

There has been a recognition that no single diagnostic test can reliably identify or rule out PJI [105]. A PJI can present with a wide range of clinical features or just pain at any point after prosthesis implantation. Although PJI is an inflammatory condition, patients vary in the degree of their inflammatory response, making the use of serum biomarkers more challenging for diagnosis [106].

The difficulty in diagnosis is further complicated by the presence of CN infection, which may be present in 20 to 30% of some series, particularly in chronic late-presenting cases [106].

There is currently no gold standard for diagnosing a CN-PJI. It is important to differentiate whether a CN-PJI is a true negative (i.e., aseptic failure) or a false negative result (diagnostic tests have failed to identify an organism, but there is a PJI) [107].

A major concern about the early definitions was that they presented a bimodal clinical decision (infected or not) based on tests that are neither 100% sensitive nor 100% specific. This was partly addressed in the ICM (2018) definition, which allowed an 'inconclusive' group that had some minor criteria present but did not reach the score required for a definitive PJI diagnosis. The EBJIS PJI definition defines three distinct groups (infection unlikely, infection likely, and infection confirmed). This new concept of the definition includes a middle group where the presence of at least two positive tests suggests that the joint is more likely to be infected than not, but with no confirmation of PJI diagnosis [106]. This recent realization highlights the so-called "inconclusive or likely" group, in which the different diagnostic tests fail to confirm or refute the presence or absence of PJI. Such a group of patients is probably where the presence of a specific diagnostic algorithm may be of paramount importance to help clinicians decide about the next area of investigation to either reach a definite diagnosis before intervention or proceed in choosing the appropriate intervention, but with the indefinite diagnosis in mind, whereby further investigation is tailored within the procedure, without either risking ignoring a PJI with the major risk of an early failure with infection recurrence or exposing a case of aseptic failure to unwarranted, risky, and costly additional procedures.

To answer the question about the role of a specialized diagnostic algorithm for CN-PJIs, we conducted a systematic review search on Covidence by adding two databases from PubMed and Scopus, where 797 studies were identified. Sixteen duplicates were removed, with 781 studies screened, followed by reviewing 196 studies in full text, ending up with 14 studies included for data extraction. There were two more studies removed, leaving 12 studies with an algorithm to study and extract data from. Studies included were chosen based on the presence of a suggested diagnostic algorithm in the case of PJI, with clear recommendations about cases of CN-PJIs.

Out of the 12 studies that were included for analysis with some diagnostic algorithm, eight were found to have some clear recommendations of how to proceed in the event of a CN result after synovial aspiration.

In a study by Walker et al., the algorithm suggested steps based on the presence of high or low clinical suspicion with ESR and C-reactive protein. In the event of a negative culture, the high clinical suspicion was used with ESR or C-reactive protein, relying on tests with a good negative predictive value. In a case of low clinical suspicion, they first tried to combine tests to increase their positive predictive values, looking for an alternative diagnosis with or without further investigations [108].

In another review, Parikh et al. [109] suggested an algorithm that relied on the full diagnostic workup, including serum and synovial assessments, in addition to cultures. When this was negative, if there was a suspicion of infection from other tests, surgery is recommended as a staged procedure with full tissue acquisition for more elaborate cultures and then relying on an interim aspirate to decide about the timing of the second stage. If there was no high suspicion of infection, then the aspirate is repeated every three to six months for a total of two years, with surgery suggested in the event of a positive culture or a recurrence of infection suspicion from the test results.

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In two other studies, Tzeng et al. and Wouthuyzen-Baker et al. dealt with negative cultures by using more advanced molecular-based techniques of diagnosis, namely, polymerase chain reaction, S16 RNA, and next-generation sequencing [110,111].

The remaining three suggested algorithms had some similarities and some differences. They all suggested a repeat aspirate with special suggestions for improving the yield, namely, stopping antibiotics, better techniques of culture and transportation, and extended cultures and special media. If still negative or a dry tap, one algorithm suggested by Perez-Prieto et al. [112] first excluded other causes before the repeat aspirate, and if still negative, then considered an arthroscopic or open biopsy. Palan et al. suggested the use of sonication or DTT together with special media for fungi and mycobacteria and then resorting to molecular-based diagnosis [107]. The third algorithm devised by Shohat et al. [113], based on the ICM criteria 2018, suggested repeating the aspiration, if negative, resorting to a nuclear medicine scan, a PET scan, followed by biopsy. This proposed algorithm resulted in an overall sensitivity of 96.9% and a specificity of 99.5%.

The major variations in the suggested algorithms, with no clear agreement on steps to follow, no validation, and variable factors included in the decision-making tree, confirm the need for the creation of a detailed algorithm suggesting the different steps clinicians should follow in the event of a CN result of aspiration. The different diagnostic steps to be taken can rely on the tools of investigations included in both the ICM (2018) and the EBJIS definitions (2021).

Based on the previously mentioned EBJIS definition (2021), McNally et al. [106] suggested, in a narrative form, an algorithm-like suggestion for a stepped approach to diagnosis. With a negative culture but likely diagnosis of infection, surgery is planned, and intraoperative sampling of $\geq$ five microbiological specimens and three to six histological specimens should be performed in all operated cases. Implants may be sent for sonication. If no surgery is planned, nuclear imaging may be considered as a rule-out test.

Conclusions

The most recent definitions of PJIs, namely ICM (2018) and EBJIS (2021), stressed the presence of an inconclusive group of patients wherein, in the event of a negative culture, one cannot identify with certainty whether this is a true aseptic failure or a false negative result. There is a plethora of different diagnostic tests, whether culture-based, with special emphasis on steps to be taken to improve the culture yield—namely, stopping antibiotics, taking more samples, extending the time of culture, using special media, and dislodging biofilm techniques such as sonication or DTT—or the more recent molecular-based diagnostic techniques such as polymerase chain reaction and next-generation sequencing. Creating a specialized diagnostic algorithm that incorporates these various diagnostic tools is essential for cases of CN-PJI to avoid missing an infection diagnosis with a high rate of early failure or exposing a case of aseptic failure to unwarranted investigations, surgical interventions, and/or prolonged administration of antibiotics. Among all reviewed algorithms, no one seemed to have been validated with a calculated sensitivity and specificity except for the study of Shohat et al. [113], which suggested a sensitivity of 96.9% and a specificity of 99.5%.

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The Journal of Arthroplasty 41 (2025) S285–S288

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Hip and Knee

2025 ICM: Immunocompromised Patients and Polymicrobial Agents

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Question 1: Do immunocompromised patients who have periprosthetic joint infection have a different microorganism profile?[1]

Response/Recommendation

Immunocompromised patients with periprosthetic joint infection (PJI) have similar microorganism profiles as non-immunocompromised patients with PJI.

Immunocompromised patients have a higher chance of developing opportunistic infections and atypical pathogens, and this should be taken into consideration when routine cultures remain negative.

Level of Evidence: Limited

Delegate Vote: Agree: 85.7%, Disagree: 10.1%, Abstain: 4.2% (Super Majority, Strong Consensus)

Rationale

Although we understand that immunocompromised patients face a higher risk for infection, the microorganism causing PJI in this patient population is not well studied. It is known that immunocompromised patients are at higher risk for developing infections with opportunistic and atypical pathogens, but due to the lack of adequate studies reporting the rate of infection with these atypical infections in nonimmunocompromised patients, the evidence behind such claims is weak.

In order to answer the question posed above, we performed a comprehensive systematic review using appropriate MeSH terms developed by librarians. The initial search yielded 396 papers, from which 127 studies were selected for analysis. Out of these, 61 studies met the inclusion criteria and were reviewed in full for data extraction. Most of the studies reviewed were case reports [2–46] some of which were associated with a literature review [47–56] providing insights into the number of cases involving atypical organisms in the literature.

Studies comparing the microorganism profile of PJI between immunocompromised patients and nonimmunocompromised patients are lacking. However, most observational studies describing the epidemiology of PJI comprise immunocompromised patients, and the reported causative microorganisms often do not include opportunistic pathogens. Therefore, the overall microorganism profiles in both groups are probably similar, although they can have a more severe course compared to the nonimmunocompromised host [57]. However, opportunistic infections and atypical or rare microorganisms can occur in immunocompromised patients who have PJI, as illustrated in many case reports [58]. Rare and/or opportunistic pathogens that have been described in immunocompromised hosts are Salmonella, mycobacteria, Listeria, Campylobacter, Mycoplasma, and Pasteurella [59,60].

It is important to determine the degree of immunodeficiency in a patient who has a PJI. Diaz-Ledezma et al. [61]emphasize the importance of the immune status as a key factor in the pathophysiological process of PJI. Systemic host grades (medical and immune status) are categorized as uncompromised (no compromising factors), compromised (one to two compromising factors), or significantly compromised (two compromising factors along with another factor such as an absolute neutrophil count less than 1,000, CD4 T cell count less than 100, intravenous drug abuse, chronic active infection at another site, dysplasia, or neoplasm of the immune system) [1]. The systemic host-compromising factors (medical and immune) include age greater than 80 years, alcoholism, chronic active dermatitis or cellulitis, chronic indwelling catheter, chronic malnutrition (albumin $\leq$ 3.0 g/dL), current nicotine use (inhalational or oral), diabetes (requiring oral agents and/or insulin), hepatic insufficiency (cirrhosis), immunosuppressive drugs (methotrexate, prednisone, cyclosporine), malignancy (history of or active), and pulmonary insufficiency (room air arterial blood gas oxygen).

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.109.

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https://doi.org/10.1016/j.arth.2025.10.109
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In addition, immunosuppression and systemic diseases have been reported as risk factors for invasive fungal infections [62,63]. In the review of Koutserimpas et al. [64], 40.4% of patients who have a fungal PJI were immunocompromised, mostly due to diabetes mellitus (53.8%).

In conclusion, although immunocompromised patients with PJI have similar microorganism profiles as nonimmunocompromised patients with PJI, good case-control studies are lacking. However, immunocompromised patients do have a higher chance of developing opportunistic pathogens. For this reason, rare causative pathogens should always be considered, particularly in culture-negative cases.

Question 2: In patients who have polymicrobial periprosthetic joint infection, is there a role for determining the dominant pathogen?[2]

Response/Recommendation

In polymicrobial infections, the interplay between different pathogens is complex and dynamic. However, there is no clinical data to support or refute the importance of determining the dominant pathogen in polymicrobial PJI.

Level of Evidence: Limited

Delegate Vote: Agree: 89.5%; Disagree: 7.9%; Abstain: 2.6% (Super Majority, Strong Consensus)

Rationale

To answer this question, the relevant literature was systematically reviewed across two search engines: PubMed and Embase. A total of 542 studies were imported for title and abstract screening after excluding 228 duplicates. Animal studies, case reports, narrative reviews of literature, studies on children, and reports on nonarthroplasty surgery were excluded. There were 17 included in the full-text review process; however, none were relevant according to the study question and exclusion criteria.

Periprosthetic joint infection appears to occur in 1.5 to 2.5% of primary arthroplasties [65] and is most frequently caused by bacteria, but also rarely involves fungi. Although most infections are caused by a single bacterial species based on culture results, 9 to 20% have been found to be polymicrobial, involving two or more species [66–68]. Recent advancements in molecular diagnostic methods have revealed that up to even 91% of culture-negative infections may be polymicrobial, which underlines the lack of sensitivity of the traditional culturing methods [69].

Polymicrobial PJIs are complex and more challenging to treat due to the interactions of multiple microbial species, causing more persistent and resistant infections [65]. The treatment of polymicrobial PJI is associated with higher costs, more complications, and worse clinical outcomes compared to monomicrobial PJI [66,67]. Polymicrobial PJIs develop earlier than monomicrobial infections [70–72], have higher revision failure rates (52 versus 36%), and frequently involve *E. faecalis*, *S. epidermidis, S. aureus,* and *Enterobacteriaceae,* especially *E. coli* and *P. aeruginosa* [65,67,68,71,73].

Bacterial interactions in polymicrobial PJIs complicate treatment markedly. These interactions can be synergistic, additive, or inhibitory. Mutualistic infections enhance biofilm resilience through mechanisms like horizontal gene transfer of antibiotic resistance, quorum sensing, metabolic cooperation, and byproduct influence [74]. Evidence regarding bacterial interactions in polymicrobial PJIs is insufficient; however, a few preclinical studies have been performed. For instance, *S. aureus* typically dominates biofilm growth under normal physiological conditions, but under stress, slow-growing *S. epidermidis* becomes dominant [75]. However, contradictory evidence suggests bacterial species in monomicrobial and polymicrobial PJIs may not significantly differ [70].

The notion of determining the dominant pathogen in polymicrobial infections remains unresolved, with no consensus on its clinical relevance or definition. Historically, limitations in diagnostic technology led to slow, unreliable results with false positives or negatives. Modern techniques like quantitative polymerase chain reaction with 16S ribosomal ribonucleic acid [76] and metagenomics next-generation sequencing [77] have importantly improved detection capabilities. Despite this progress, clinical evidence on the importance of identifying dominant pathogens remains limited.

The increasing prevalence and complexity of polymicrobial PJI underscore the need for a deeper understanding of their impact on clinical outcomes and treatment strategies, especially as the total number of arthroplasties increases with the aging population, suggesting that cases of PJI will become more common. Accurate diagnosis of polymicrobial PJIs is critical to improving treatment outcomes. Traditional culturing methods often yield false negatives due to overgrowth by fast-growing bacteria, highlighting the need for standardized genomic detection techniques. Future research should focus on evaluating the clinical impact of targeting dominant pathogens to optimize management strategies and enhance patient care.

In conclusion, determining the dominant pathogen in a polymicrobial PJI may be useful to help make treatment decisions; however, clinical studies are needed to provide input for evidence-based treatment recommendations.

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The Journal of Arthroplasty 41 (2025) S289–S296

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Hip and Knee

2025 ICM: Diagnostic Imaging for Periprosthetic Joint Infection

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Question 1: Do plain radiographs play a role in the diagnosis of periprosthetic joint infections?[1]

Response/Recommendation

Plain radiographs, on their own, play little role in diagnosing periprosthetic joint infections (PJIs). However, in some cases of chronic PJI, subtle signs of infection may be seen on plain radiographs.

Level of Evidence: Level 3

Delegate Vote: Agree: 80.5%, Disagree: 13.7%, Abstain: 5.8%

Rationale

It has been estimated that one million knee and hip arthroplasties are performed annually in the United States alone, and this number is expected to quadruple over the next one to two decades as the population ages [1]. Periprosthetic joint infection (PJI) is one of the serious complications that may occur after a joint arthroplasty procedure. The incidence of PJI is 1 to 2% of cases of knee and hip arthroplasties, resulting in high morbidity, resulting in a significant increase in health care expenses, and it is the principal cause of revision arthroplasty [2,3].

The diagnosis of PJI is challenging, as the clinical manifestations in the chronic phase are not always characteristic. There is no "gold standard" or a battery of tests that may be used to define and diagnose PJI [4–6]. The symptoms associated with PJI overlap tremendously with aseptic arthroplasty failure [7–10]. PJI can be classified as early, late, and late hematogenous based on the time of infection after the surgery [11]. If PJI is clinically suspected, plain radiographs are recommended as the first diagnostic imaging due to low cost and widespread availability; however, radiographs are nonspecific and may be normal, particularly in the early stages of infection. Moreover, plain radiographs are unable to differentiate between septic and aseptic loosening, as they can only identify implants that have been loosened, making them an ineffective tool for the diagnosis of PJI [12,13].

According to the consensus by the European Society of Radiology, the level of evidence to perform conventional radiography in patients suspected of PJI as the first line of diagnosis is low. Radiographs may be positive when a minimum of 30 to 50% destruction of bony trabeculae has occurred. Additionally, approximately 50% of the radiographs appear normal when performed on infected implants, with only 14% sensitivity and 70% specificity in the case of PJI [14]. A retrospective study on the diagnosis of early PJI showed unclear clinical relevance of the use of plain radiographs for evaluation. The study evaluated the radiographic evidence of soft tissue gas as an indicator of early PJI. The results identified soft-tissue gas in plain radiography in 54.2% of the cases (13 out of 24), three days after total knee arthroplasty (TKA). However, after two weeks of TKA, the presence of soft tissue gas on radiography had a sensitivity of 0.54 (95% confidence interval, 0.35 to 0.72) and a specificity of 0.99 (95% confidence interval, 0.97 to 1.00). This retrospective study, however, had its limitations, as no standard protocol was maintained regarding the timing of postoperative radiographic imaging or imaging intervals [15].

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to doi: 10.1016/j.arth.2025.10.083.

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https://doi.org/10.1016/j.arth.2025.10.083
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The radiographic changes in the case of PJI are time-dependent. The early PJI presents no radiographically important changes. The first clinically relevant changes on the radiographs appear three months after the presentation of initial symptoms. It has been observed that the validity of plain radiography as a means of diagnosis of low-grade PJI may be inconsistent within the first postoperative year [16]. Detection of periprosthetic osteolysis may also be dependent on the location, and radiographs may underestimate the extent and presence of the bone damage [17,18].

Conclusions

The clinical diagnosis of PJI remains challenging regardless of the availability of a number of clinical symptoms, histological tests, and imaging techniques. With the increasing percentage of the older population and the utility of joint arthroplasty, the number of infections may increase globally. Plain radiography is considered the first line of imaging modality in patients who have clinical manifestations of PJI. However, the radiographic manifestation of PJI is a function of time. There is a paucity of research on the clinical relevance of radiographs as a diagnostic tool in the early diagnosis of PJI. The low sensitivity of plain radiography in the diagnosis of PJI also makes it a less likely imaging technique for initial screening. It has also been observed that the radiographic findings associated with early PJI overlap markedly with aseptic prosthesis, making it a nonspecific diagnostic test. Based on available data, it is therefore suggested to explore advanced imaging techniques without solely relying on plain radiographs for the diagnosis of PJI.

Question 2: What imaging has the best ability to identify osteomyelitis in patients who have surgical site infection/PJI?[2]

Response/Recommendation

All the available imaging modalities, including conventional imaging such as plain radiography, computed tomography (CT), magnetic resonance imaging (MRI), and white blood cell (WBC) scintigraphy, have limited accuracy and should not be used as standalone tests to identify osteomyelitis.

Level of Evidence: Limited

Delegate Vote: Agree: 80.4%, Disagree: 13.8%, Abstain: 5.8% (Super Majority, Strong Consensus).

Rationale

Identifying osteomyelitis in the context of surgical site infection (SSI) or PJI (PJI) after hip or knee arthroplasty is critical, as proper debridement and complete removal of infected tissue are essential for effective treatment. Although the use of the different imaging modalities to diagnose osteomyelitis in osteoarticular infections is well-described [19], given the lack of robust studies directly comparing different imaging modalities, there is no clear consensus on the ideal imaging strategy for identifying osteomyelitis in PJIs [20,21]. The purpose of this systematic review was to determine the imaging examination with the best ability to identify osteomyelitis in hip or knee arthroplasty patients who have SSI or PJI, according to current literature.

We conducted a systematic literature search utilizing PubMed and Embase. Our search strategy included the use of Medical Subject Headings terms such as “hip arthroplasty,” “hip replacement,” “knee arthroplasty,” “knee replacement,” “osteomyelitis,” “prosthetic joint infection,” “SSI,” “diagnostic imaging,” “conventional radiography,” “CT,” “single-photon emission computed tomography (SPECT),” “MRI,” “positron emission tomography (PET),” “nuclear imaging,” “bone scintigraphy,” “leukocyte imaging,” “ultrasound” in each of the databases. We used the Boolean operators “AND” and “OR” to identify the intersection and union of terms. The database search yielded 2,193 articles, and after the initial screening of titles and abstracts, we identified 253 relevant articles. After full-text evaluation, 80 articles were selected for data extraction, including original studies, meta-analyses, reviews, and consensus articles.

Plain radiography, given its easy access and low cost, is usually the first diagnostic modality performed in PJI patients. However, plain radiographs have limited diagnostic value due to their low sensitivity and specificity [20]. In some instances, the presence of osteomyelitis may be speculated on radiographs, with periosteal reaction and signs of chronic infection; however, it is rather difficult to differentiate between other aseptic conditions. We did not find any articles suggesting plain radiography to identify the bony extension of infection in SSI/PJI; hence, we concluded that there is no evidence to support its use to assess osteomyelitis.

Ultrasonography (US) is also an easily accessible, inexpensive modality that can evaluate fluid collections and soft-tissue involvement in the presence of infection. It can be used to facilitate joint aspiration or soft-tissue biopsy [22,23]. However, the US cannot penetrate bone cortex or metallic components, limiting its use to the superficial soft tissues [24,25]. We did not find any articles suggesting the assessment of osteomyelitis in SSI/PJI using the US, which made us conclude that there is no evidence suggesting the use of this modality in this context.

Computed tomography is more sensitive compared to plain radiography in detecting osteolysis and bone destruction and identifying small osteolytic lesions [26]. Additionally, CT scans can assess soft-tissue abnormalities and recognize psoas abscesses that can mimic PJIs [27,28]. However, CT sensitivity is limited in detecting infectious bony involvement. Cyteval et al. [29] found that periprosthetic bone abnormalities cannot be distinguished by CT scan between aseptic and septic conditions, except for periostitis, which had 100% specificity, but only 16% sensitivity. Although CT may play a role in the diagnosis of PJIs [21], our literature review did not identify any studies suggesting the standalone use of CT for the identification of PJI-related osteomyelitis.

Magnetic resonance imaging can detect bone marrow changes, synovial lamellation, lymph node enlargement, and soft-tissue infection extension, but there is a lack of evidence to support its role in the assessment of PJIs. [30]. Metal-artifact-reduction software sequences show some promising results [31], but the ability of MRI to evaluate osteomyelitis is limited in the presence of metallic implants [32]. An MRI shows a high negative predictive value (NPV) for excluding PJI or osteomyelitis if the bone marrow appears normal on all sequences; however, the positive predictive value of this modality and its ability to differentiate osteomyelitis from other causes of marrow abnormalities is not as high. Reactive noninfectious marrow edema can occur adjacent to a site of an implant or soft-tissue infection, mimicking false-positive results for osteomyelitis [33]. Albano et al. reported that MRI features have limited accuracy in identifying infection in total hip arthroplasty (THA). They found that bone edema had 81.5% specificity, 76.3% sensitivity, 88% NPV, and 65.9% positive predictive value for infection [34]. Another study reported 92.5% specificity, but only 47.4% sensitivity for PJI when bone destruction was examined on MRIs of THA patients [35]. We did not find evidence suggesting the use of MRI alone to detect secondary osteomyelitis in SSI or PJI.

Nuclear medicine techniques can sometimes be used to facilitate the diagnosis of PJI; however, little is known, to date,

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about their ability to assess the extent of osteomyelitis around implants.

Bone scintigraphy is typically performed using technetium-99m–labeled diphosphonates, and it consists of three phases: assessing early perfusion, diffusion, and late bone uptake. It is a sensitive test (88 to 92%), but its specificity is low (50 to 70%) [36,37]. It may present misleading abnormal findings for more than 1 year after prosthesis implantation [38]. Despite the limited specificity, it has a high NPV, making it a useful screening test to rule out infection [36,39–41]. However, in the case of positive results, further assessment is warranted, as it cannot distinguish between osteomyelitis and normal postoperative changes, healing fractures, or aseptic loosening [42–44].

White blood cell scintigraphy is considered the most reliable imaging study in the diagnosis of PJIs. This modality targets the leukocytes (mostly neutrophils) that migrate to the sites of infection and inflammation. In the case of a positive bone scan, it has traditionally been considered the next step in the assessment algorithm. However, interpretation of images may be challenging due to the normal accumulation of WBCs in the bone marrow, where distribution varies not only between individuals but also within the same patient across different bone sites. Any condition that can change blood flow may alter the distribution of labeled WBCs [45]. Encouraging results have been reported in the identification of osteomyelitis in PJIs, although with wide variability [43,46–50]. Meta-analyses data showed pooled sensitivity and specificity of 84 and 77% for TKA and 92 and 88% for THA, respectively [51,52]. The variability of outcomes has limited its use, but it may be helpful in conjunction with other exams. The WBC scintigraphy with bone marrow imaging (typically with ^{99m}TC sulfur colloid, 48 to 72 hours after the WBC scan) can help to differentiate normal bone marrow from a site of infection, reducing the variability of radiotracer activity [53]. This test may be more accurate, with improved pooled sensitivity and specificity for PJI (80 and 93% in TKA; 69 and 96% in THA, respectively) [51,52]. However, bone marrow imaging makes the procedure more complex, increasing the time, the cost, and the radiation exposure of the examination, while this option is not widely available [42,54,55].

A fluoro-2-deoxyglucose PET (FDG-PET) represents an attractive alternative, as it requires only one scan. Compared with WBC scintigraphy, it offers advantages such as time efficiency and increased resolution [56]. It is specific for neoplastic conditions, but it also accumulates at high glycolytic activity, as in inflammation and infection. Modern PET scans are performed with low-dose CT for anatomic localization and attenuation correction [45]. The FDG-PET has been shown to be highly sensitive in the detection of chronic osteomyelitis [57]. However, controversial results have been reported regarding their diagnostic value in PJIs; hence, their utility is debated. This variability in outcomes may depend on the different imaging protocols and interpretation criteria used [54,56,58–60]. Nevertheless, most authors agree that its NPV is high, and it can be beneficial in cases of low probability of infection [61–63]. Meta-analyses data showed pooled sensitivity and specificity of FDG-PET in TKA PJIs to be 70 and 84% and in THA PJIs, 86 and 93%, respectively [51,52]. Similar findings have been reported by other studies [64,65]. This test has an evolving role in PJI assessment, but may not represent the preferred nuclear imaging modality due to its higher cost and the fact that it does not seem to be more effective than WBC scintigraphy [19,52].

An SPECT/CT also allows the correlation of scintigraphy results with anatomical images. It incorporates advanced algorithms that improve the quality of SPECT images using CT data (attenuation correction). This leads to a more accurate alignment of areas showing physiological variations or abnormal uptake with anatomical landmarks [66]. Some authors examined the usefulness of hybrid SPECT/CT in 99mTc–hexamethylpropylene amine oxime–labeled leukocyte scintigraphy for bone and joint infections. They found that SPECT/CT differentiated soft-tissue involvement from bone involvement both in patients who have osteomyelitis and those who have orthopaedic implants [67]. Another group analyzed the added value of the 99mTc-antigranulocyte SPECT/CT in comparison with SPECT alone on planar imaging in low-grade PJIs. They found that PECT/CT images further demonstrate the extent of infection in the bone or bone marrow [68]. In a comparative study, the diagnostic performance of dual-isotope WBC/bone marrow SPECT/CT for PJI showed 100% sensitivity, 97 and 98%; accuracy, while the corresponding results for FDG PET-CT were 100, 71, and 79%, respectively. The authors stated that FDG PET-CT has appropriate accuracy, but the utility of its use in the diagnostic algorithm needs further evidence [69]. In the same manner, SPECT/CT has demonstrated promising results, but limited high-quality data support its use [45]. More high-quality studies are needed to further explore the potential of these modalities.

Conclusion

Conventional imaging with CT and MRI offers high spatial resolution, visualizing the morphological alterations due to infection. They detect swelling, inflammation, and secondary effects of SSIs and PJIs, such as abscesses or soft-tissue alterations. However, their standalone use in the identification of osteomyelitis cannot be supported. Nuclear medicine modalities offer more reliable functional information related to the metabolic activity of infection, but may not be able to quantify the extent of bone involvement.

Question 3: Is there a role for the use of bone scans in the diagnosis of PJI?[3]

Response/Recommendation

In rare circumstances, when, despite performing serological and synovial tests, a diagnosis of PJI cannot be refuted or confirmed, a bone scan with the combined use of WBC tracers (with or without bone marrow scintigraphy) may be ordered.

Level of Evidence: Moderate

Delegate Vote: Agree: 75.0%, Disagree: 16.8%, Abstain: 8.2% (Strong Majority, Moderate Consensus)

Rationale

Accurately diagnosing PJI is crucial, as it directly influences treatment decisions and patient outcomes. Traditionally, a variety of imaging techniques, including radiography, US, CT, MRI, bone scintigraphy, leukocyte scintigraphy, and FDG-PET, have been employed to detect and evaluate PJI. Each modality offers unique insights, yet their comparative diagnostic efficacy remains a subject of ongoing debate among clinicians and researchers.

This systematic review aims to analyze and compare the diagnostic accuracy of bone scans against other nuclear imaging modalities in diagnosing PJI. A comprehensive literature search was conducted through PubMed, Embase, and Cochrane. A total of 2,953 articles were identified, with 169 selected for further review based on titles and abstracts. Of these, 69 articles underwent full-text evaluation and extraction using the Quality Assessment of

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Diagnostic Accuracy Studies, version 2 (QUADAS-2) tool for quality assessment.

A bone scan is a nuclear imaging technique that uses a small amount of radioactive material, typically technetium-99m, injected into the bloodstream to evaluate bone metabolism and activity [70]. The tracer accumulates in areas of high bone turnover, representing increased osteoblast activity, such as sites of infection, inflammation, or cancer, allowing for detailed imaging of skeletal anomalies and abnormalities, including PJI. There were two comprehensive systematic reviews with meta-analyses that were conducted by Verberne in 2016 [71] and 2017 [72] that analyzed the effectiveness of various nuclear imaging techniques for diagnosing PJI in hip and knee prostheses, covering studies published between 1988 and 2014. For hip prostheses, the reviews evaluated bone scintigraphy in eight studies encompassing 492 prostheses, demonstrating a pooled sensitivity of 80% and specificity of 69%. In comparison, for knee prostheses, bone scintigraphy was studied in six studies involving 216 prostheses, yielding a sensitivity of 93% but a lower specificity of 56%. There were five studies that were published subsequent to those included in the systematic review of Verberne et al. [73–77], which encompassed a total of 708 hip or knee arthroplasties, of which 151 were infected, corroborating the previously reported sensitivities and specificities. These recent studies report sensitivities ranging from 60 to 100% and specificities from 13 to 97.1%, depending on whether the imaging was analyzed during the bone phase, blood flow, or blood pool phase. This data reinforces the findings on the diagnostic performance of bone scans in PJI, aligning closely with earlier findings and highlighting the continued issue of varying low specificity in certain modalities.

Verberne et al. [71,72] found that combined modalities of bone and leukocyte scintigraphy were reviewed in three studies for hip prostheses (172 prostheses) and four studies for knee prostheses (114 prostheses), demonstrating specificities of 95 and 93%, respectively. Similarly, bone and gallium scintigraphy, analyzed in three studies for 121 hip prostheses, showed a notable specificity of 97% [71]. These findings underscore the heterogeneous diagnostic performance of various imaging techniques and suggest that combined imaging modalities may offer enhanced diagnostic accuracy, particularly in specificity, highlighting their effectiveness in ruling out PJI [72]. Similarly, three studies published after the systematic reviews of Verberne et al. [78–80], covering a total of 226 hip and knee arthroplasties, of which 45 were infected, reported sensitivities ranging from 70 to 100% and specificities between 93 and 100%.

Based on the vast literature published, the utility of bone scans in diagnosing PJI is constrained by a low specificity (as low as 50%). The reviews suggest that while bone scans can serve as an initial diagnostic tool, their effectiveness is markedly improved when used in conjunction with other modalities such as leukocyte or gallium scintigraphy, which enhance diagnostic specificity up to 93 to 100%. Therefore, bone scans are best utilized as part of a multimodal imaging strategy rather than in isolation. A 2020 European multidisciplinary consensus paper by Roman et al. [81] highlights the importance of bone scan timing postarthroplasty for PJI diagnosis due to variable uptake patterns. It advises cautious interpretation of positive scans for up to two years after hip surgeries and five years for knees, however, noting that a negative scan markedly lowers the risk of PJI even within these periods.

For most cases of PJI, diagnosis should primarily rely on serological and synovial fluid tests. When these tests are inconclusive, imaging techniques such as WBC scintigraphy (with SPECT/CT) with 99mTc–hexamethylpropylene amine oxime–labeled WBC are recommended, especially during the early postoperative period [82,83]. The WBC scintigraphy has demonstrated sensitivity and specificity ranging from 88 to 100% and 70 to 95%, respectively [71,72,82]. Alternatively, 99mTc-labeled monoclonal antibodies can also be used to assess PJI [71,72,84,85]. [18F]-FDG-PET/CT offers valuable diagnostic capabilities with sensitivity and specificity between 80 to 100% and 85 to 100%, although its application is constrained within the first three to six months postsurgery [71,72,86–90]. Current evidence does not show a definitive advantage of [18F]-FDG-PET over WBC scintigraphy, but it can be beneficial in cases with a low probability of infection. However, interpretation of data from individual studies should be approached with caution due to variability in labeling methods, imaging protocols, interpretation techniques, and patient selection presented in the studies. The majority of studies included fewer than 20 PJI cases, which may limit the robustness of their findings.

In conclusion, bone scintigraphy (with SPECT/CT) alone is not suitable for diagnosing PJI, lacking the necessary specificity, but a negative bone scan can rule out a PJI. WBC scintigraphy (with or without bone marrow scintigraphy) can be used to confirm a suspected PJI, but should not be regarded as a stand-alone test. Combining bone marrow and WBC scintigraphy may effectively rule out infection in cases with a low likelihood of infection.

Question 4: Is there a role for the use of MRI in the diagnosis of PJIs?[4]

Response/Recommendation

Although it has shown high specificity in some studies, variations in both sensitivity and specificity, and the lack of consensus on defining specific diagnostic features undermine its reliability and clinical applicability.

Level of Evidence: Moderate.

Delegate Vote: Agree: 79.0%, Disagree: 18.3%, Abstain: 2.7% (Strong Majority, Moderate Consensus).

Rationale

Recent advancements in MRI, particularly the development of sophisticated metal artifact reduction sequences, have enhanced MRI's utility in noninvasively evaluating conditions such as septic arthritis and persistent pain postarthroplasty. However, the diagnostic accuracy of MRI in detecting PJI in patients who have THA and TKA is still under debate. There is no consensus on the diagnostic criteria or the specific MRI features indicative of PJIs, necessitating a thorough evaluation.

This systematic review seeks to assess the role of MRI in identifying PJIs. A comprehensive literature search was conducted through PubMed and Embase, initially identifying 273 potentially relevant articles. Following a detailed screening of titles and abstracts by two independent reviewers, 15 articles, one guideline, and one consensus paper were selected for in-depth review and data extraction. Quality was assessed using the QUADAS-2 tool.

There were eight studies that focused on diagnosing PJI in THA [91–98], three on TKA [99–101], and two studies [102,103], along with one systematic review covering both THA and TKA [104]. An additional systematic review was exclusively dedicated to knee arthroplasties [105]. All studies adhered to well-defined criteria or clinical assessments and included intraoperative samples where feasible. Although some MRI features demonstrated high sensitivity and specificity, individual MRI indicators exhibited variability across the studies. Key MRI findings associated with PJIs are summarized below.

[4] These authors contributed to Question 4: Armita Armina Abedi, Atthakorn Jarusriwanna, Ruben A Limas, Jesus Moreta, Douglas E Padgett, Rafael J Sierra, Rosa Elena Silva, Chao Xie, Je-Hyun Yoo, Luigi Zagra

In patients who have hip or knee prostheses, synovitis is common, with varying patterns of synovial inflammation observed [101]. It appears that the finding of lamellated hyperintense synovitis (LHS) is consistently identified as the most suggestive sign of PJI in both THA and TKA. Studies have demonstrated that the sensitivity of LHS for diagnosing PJIs ranges from 26.3 to 86%, while specificity varies from 84 to 98.8% [91,98,99,101,102,106,107]. Additionally, the inter-rater reliability for assessing LHS was found to be reasonable, with kappa values between 0.44 and 0.89 [91,99,101,102,106], reflecting substantial yet variable agreement among clinicians in identifying this MRI feature [108].

The studies revealed that edema manifestations on MRI, such as bone or bone marrow edema [91,93,98,102], extracapsular edema [91,98,102,103], capsule edema [92,96,103], intramuscular edema [92,93,96], and adjacent soft tissue edema [94,96,98,100,103], were suggestive of PJI. The sensitivity of MRI-detected edema ranged from 68.4 to 100%, with specificity between 73.1 and 95% [91–94,96,98,100,102,103]. Additionally, the inter-rater reliability for these types of edemas is notably high, with kappa values ranging from 0.73 to 0.955 [91,92,100,103], demonstrating substantial to exceptional concordance among clinicians in identifying and interpreting edema on MRI scans.

Furthermore, MR findings of extracapsular fluid or fluid collections [91,92,96,98,102,103] and reactive lymphadenopathy were indicative of PJI [91,92,96,100,103]. For extracapsular fluid or fluid collections, the studies reported sensitivity and specificity ranging from 28 to 100% and 40 to 98%, respectively. Additionally, MRI findings of reactive lymphadenopathy demonstrated sensitivity and specificity of 33 to 93% and 47 to 100%, respectively. Specifically, Albano et al. [109] found that lymph node assessment of the affected compared to the unaffected hip identified infected implants with high accuracy, up to 93.1%.

Furthermore, Levack et al. [95] evaluated low-grade PJI of the hip with MRI with multiacquisition variable-resonance image combination and a metal artifact suppression technique. The study included 2,156 THAs, of which 53 had confirmed PJIs based on modified MusculoSkeletal Infection Society criteria. The study demonstrated a sensitivity of 56.6% and a specificity of 99.6%. The preliminary findings suggest that MRI may hold some promise in distinguishing PJI from noninfected pathologies. However, consensus and standardization regarding specific MRI features for diagnosing PJIs are currently lacking. Li et al. [101] investigated 108 consecutive patients who had TKAs and underwent MRI within 1 year before revision surgery. They found that diagnostic accuracy was higher in the cohort with initial TKAs than those with revision TKAs. This suggests a potential variation in the accuracy of MRI-based diagnosis of PJI, depending on whether it follows the primary or revision surgery.

With regard to quality assessment, the retrospective design of the studies increases susceptibility to selection bias. Furthermore, most studies did not clearly indicate whether assessments of the reference tests were blinded. Additionally, the majority of the included studies did not adequately provide necessary information concerning the index test, reference standard, and flow and timing.

The systematic reviews by Shufen et al. [104] and Schröder et al. [105] encompass most of the studies included in our analysis, which additionally integrates more research beyond those covered in earlier systematic reviews. Furthermore, the guidelines from the American Academy of Orthopaedic Surgeons (2019) [110] and an international consensus statement on the role of imaging in diagnosing PJI [111] were constrained by the publication dates of the studies they reviewed. Consequently, these guidelines did not find the available evidence sufficient to support or refute the use of MRI for PJI diagnosis.

In conclusion, the current literature suggests that current MRIs have a minimal role in the diagnosis of PJI, and the lack of standardization regarding specific MRI features for diagnosing PJIs currently limits their use. Proposed promising biomarkers, such as size and number of nodes, need to be further investigated on a larger scale and in different centers.

Question 5: Is there a role for the use of a CT scan for the diagnosis of PJI?[5]

Response/Recommendation: Based on available data, a CT scan alone has no role in the diagnosis of PJI.

Level of Evidence: Low

Delegate Vote: Agree: 92.6%, Disagree: 5.5% Abstain: 1.8% (Total consensus: Unanimity)

Rationale

Achieving an accurate preoperative diagnosis is crucial for surgical planning and managing patient expectations. Diagnosing PJIs and related implant infections poses significant challenges. Although the presence of clear signs such as draining sinuses or exposed implants may simplify diagnosis, differentiating between septic and aseptic implant failures can be highly complex. This difficulty often arises when patients present with nonspecific symptoms like variable pain levels and reduced function, or when laboratory tests yield inconsistent results. The utility of CT in the preoperative diagnosis of PJI remains a contentious issue. To explore this further, a comprehensive literature search was conducted using PubMed and Embase. Initially, 780 potentially relevant studies were identified. Following a detailed screening of titles and abstracts by two independent reviewers, five studies and two guidelines were selected for in-depth review and data extraction. Quality was assessed using the QUADAS-2 tool [112].

In a study of moderate quality conducted by Cyteval et al. [113], the diagnostic accuracy of CT for detecting infections at the site of hip prostheses was assessed among 65 patients. Patients underwent helical CT scans before their surgical revision, where the presence of infection was confirmed through the detection of the same bacterium in multiple deep-tissue biopsies. The CT scans were assessed for several diagnostic markers, including joint distention, fluid-filled bursae, and fluid collection in muscles and perimuscular fat. The results indicated varying diagnostic accuracy across different CT measures. The study found that CT may be useful for confirming infection, with specificities ranging from 89 to 100% for soft-tissue abnormalities and 30 to 100% for bone abnormalities or asymmetric position of the femoral head. There were six of the 10 CT measures that had specificities above 89%. These measures included joint distention, fluid-filled bursae, fluid collections in muscles and perimuscular fats, periostitis, iliopsoas involvement, and involvement around the greater trochanter. The four CT measures with specificities below 77% were focal low attenuation (77%), bone abnormalities (30%), nonfocal low attenuation (53%), and asymmetric position of the femoral head (72%). Although the study found that CT may be useful for confirming infection, eight of the 10 measures had sensitivities ranging from 8 to 42%, indicating that CT has a poor ability to rule out PJI when the test is negative. Only two measures demonstrated moderate to high sensitivity: bone abnormalities at 75% and joint distention at 86%. Despite the valuable insights provided by the study, it is essential to consider the inherent limitations of CT imaging, such as the potential for metallic artifacts that can degrade image quality. These artifacts can obscure critical details necessary for accurate diagnosis, which underscores the importance of using CT

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in conjunction with other diagnostic modalities. Furthermore, the small sample size of 65 patients may constrain the generalizability of the findings of the latter study. Additionally, the study does not specify whether the assessment of the CT scans was conducted in a blinded manner, which could impact the objectivity of the results.

Isern-Kebschull et al. [114] evaluated the diagnostic accuracy of CT-guided joint aspiration in 164 patients with suspected prosthetic hip infections referred for CT-guided aspiration. The results of cultures obtained from CT-guided aspirations performed in the radiology department were compared with intraoperative culture results. Specific CT measures varied in sensitivity and specificity: soft-tissue accumulation (sensitivity of 80%; specificity of 57.4%); acetabular malposition (sensitivity of 20%; specificity of 85.2%); periarticular calcification (sensitivity of 20%; specificity of 78.7%), and enlarged lymph nodes (sensitivity of 74.3%; specificity of 78.7%). Despite its rigorous methodology, which included blinded imaging assessments and a robust sample size, the study identified potential improvements in specificity for certain CT findings. It highlighted inherent limitations of CT imaging, such as the risk of overlooking small foci of osteolysis or isolated enlarged lymph nodes, often obscured by metallic artifacts. The study underscores the nuanced role of CT in the diagnostic process for PJIs, emphasizing its valuable application in CT-guided aspirations while also stressing the necessity of careful CT scan interpretations to prevent diagnostic errors.

Furthermore, the accuracy of CT-guided joint aspiration was 86.5%, revealing its effectiveness in preoperative diagnostics for suspected PJIs of the hip. This finding aligns with earlier research by Tomas et al. 2010 [115], reporting an accuracy of 84% for CT-guided aspirations relative to surgical findings in a cohort of 63 prospectively enrolled patients. Both studies illustrate the critical role and potential challenges of utilizing CT in diagnosing PJIs, highlighting the importance of optimizing CT protocols and techniques to enhance diagnostic outcomes.

Both the American Academy of Orthopaedic Surgeons Evidence-Based Clinical Practice Guidelines [116] and a multidisciplinary consensus statement [117] acknowledge that CT's role in diagnosing PJI is limited, primarily serving as a tool for joint aspiration. Recent advancements in CT technology, as demonstrated by Isern-Kebschull et al. [118] and Cheng et al. [119], highlight its evolving potential in diagnosing PJI. The former study confirms the efficacy of multidetector CT in differentiating septic from aseptic complications post-hip arthroplasty, while the latter introduces the use of dual-energy CT iodine maps to distinguish between these conditions. Although promising, these findings point to the need for further research to optimize the diagnostic potential of CT technologies in clinical practice.

In conclusion, while the role of CT in diagnosing PJI is insufficient as a standalone test, it may be a useful additional method when used alongside serological and synovial fluid analysis. To date, only two studies have specifically explored the diagnostic accuracy of CT, and both were limited to THA. Therefore, no definitive conclusions or recommendations can be extended to TKA. Based on the limited evidence available from these studies, CT may serve a supportive role in guiding joint aspirations, but not as a standalone test in the diagnostic workup for PJI.

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The Journal of Arthroplasty 41 (2025) S297–S325

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Hip and Knee

2025 ICM: Debridement, Antibiotics, and Implant Retention

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Question 1: What patients are candidates for debridement, implant retention, and antibiotic administration?[1]

Response/Recommendation

In general, all patients who have an acute onset of infection and who have a stable prosthesis are candidates for DAIR. However, the expected infection eradication rate greatly depends on several patient and infection characteristics. The following patients are considered good candidates for DAIR:

- Infection within six weeks of the index arthroplasty
- Infection with an onset of symptoms of less than seven days
- Well-fixed and stable implants
- Exceptions may apply

Level of Evidence: Strong

Delegate Vote: Agree 76.5%, disagree 11.7%, abstain 11.7% (strong majority, moderate consensus)

Rationale

Debridement, antibiotic administration, and implant retention (DAIR) have shown favorable outcomes in selected patient populations, and their efficacy is limited by several factors, including the timing of intervention, patient comorbidities, microbiological burden, and surgical complexity. Recent advances, such as predictive scoring systems and machine learning algorithms, have provided new tools to improve risk stratification and guide decision-making. Despite these developments, the criteria for selecting appropriate candidates for DAIR remain complex and require a nuanced understanding of the interplay between host-, procedural-, and pathogen-specific variables.

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to doi: 10.1016/j.arth.2025.10.076.

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https://doi.org/10.1016/j.arth.2025.10.076
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Timing Relative to Symptom Duration

A shorter symptom duration before intervention was associated with improved DAIR outcomes. Patients treated within two days of symptom onset achieved an infection control rate of 89%, whereas those treated between three and seven days had a success rate of 59.5% [1]. When the mean duration from symptom onset to debridement was less than seven days, the pooled success rate was 71.6%. Conversely, when this interval was extended beyond three weeks, the success rate dropped to 35%, a statistically significant decline ($P < 0.05$) [2]. This is echoed in multiple studies using different cutoff points; the duration of symptoms (>10 days) was identified as an independent risk factor for failure, with an 8.5-fold increase in the hazard of failure compared to patients treated earlier ($P = 0.016$) [3–6]. In addition, logistic regression revealed that each additional day of symptoms decreased the odds of success by 7.5% [7]. If symptoms persisted for greater than four weeks, patients were 2.35 times more likely to fail than those who had a symptom duration of less than one week [8-10].

Timing Relative to Index Arthroplasty

The interval between index surgery and DAIR also plays a major role in success rates. Infections managed within 14 days of surgery showed lower reinfection rates (24.3%) than those treated between 46 and 90 days (45.8%) [11]. While there was no significant difference in outcomes when DAIR was performed within 28 versus 42 days postoperatively (85 versus 88%), delays beyond 90 days led to a marked decline in success rates (60%) [12]. Failures peaked in week seven (23%), but remained significantly high from week one to six. However, delaying DAIR beyond six weeks from the index procedure increased the failure rates [13]. When comparing early and late infections, success rates were significantly higher for early interventions. DAIR conducted within four weeks of the primary surgery had an 8% revision rate compared with 13% for procedures performed between four and 12 weeks [14]. Chronic infections (> three months from surgery) were associated with poorer outcomes, with success rates dropping to 45% regardless of symptom duration [6,15,16]. When combined, the median time from the index surgery to DAIR was shorter in successful cases than in failures. However, the median interval from symptom onset to surgery remained similar between groups, emphasizing the importance of both parameters in determining outcomes [17,18].

Demographic Factors

Age was a significant factor in DAIR outcomes. Patients aged ≥ 85 years have a 391% increased risk of reinfection compared to those aged 65 to 69 years ($P < 0.001$) [11]. However, in some studies, age was not found to be a statistically significant factor for DAIR success [19,20]. Men have also been identified as a predictor of failure in several analyses [21–23]. The heterogeneity of the different comorbidity scoring indices used makes comparisons among these studies difficult. Patients who have higher Charlson comorbidity index scores (≥ 4) had similar failure rates (64%) to those who have scores of 1 to 3 (67%) [20]. Rheumatoid arthritis is a significant independent risk factor for failure, with hazard ratios (HRs) ranging from 2.20 to 45.1 in various studies [21,24–26]. Conditions such as ischemic heart disease, chronic obstructive pulmonary disease, and chronic kidney disease also predict poor outcomes [21,23,27–30]. Obesity, particularly morbid obesity, is an important predictor of treatment failure. Morbidly obese patients experienced significantly higher failure rates (57.9%) compared to nonobese patients (36.8%), with an HR of 2.77 ($P = 0.035$) [31]. Smoking is also associated with increased failure rates, particularly in early acute infections [32]. Psychiatric conditions, such as major depressive disorder and generalized anxiety disorder, have been identified as contributors to failure [22,32]. The use of immunosuppressive medications is a strong independent predictor of DAIR failure (odds ratio [OR], 0.13) [33,34]. Patients who underwent arthroplasty for nonosteoarthritis indications (e.g., inflammatory arthritis or hip fractures) had significantly higher failure rates [21,35,36].

Preoperative C-Reactive Protein

The C-reactive protein (CRP) is a well-established marker of inflammation and infection, and its levels are consistently correlated with DAIR outcomes. Patients who have failed DAIR had significantly higher CRP levels at presentation than those who had successful outcomes. In one study, the mean CRP was 162.5 mg/L in the failure group and 105.5 mg/L in the success group ($P < 0.001$) [37]. Another study identified a CRP cutoff of 65 mg/L, where 68.9% of patients who had CRP > 65 mg/L failed treatment compared with 43.6% with CRP ≤ 65 mg/L ($P < 0.0002$) [37]. Higher CRP thresholds further exacerbated the risk of failure. A preoperative CRP level > 100 mg/L was independently associated with failure ($P = 0.001$), and logistic regression showed that each unit increase in CRP level increased the odds of failure (OR 1.01, $P < 001$) [9,30,38,39]. However, some evidence suggests variability in the predictive value of CRP. In certain cases, preoperative CRP levels did not significantly correlate with DAIR success, suggesting that CRP alone may not always predict outcomes [17,40].

Erythrocyte sedimentation rate

The role of erythrocyte sedimentation rate (ESR) in predicting DAIR outcomes was less consistent than that of CRP level. In some studies, a higher preoperative ESR was associated with failure. Patients who have an ESR > 40 mm/hour were 4.7 times more likely to fail DAIR than those who have an ESR < 40 mm/hour [41]. Similarly, the mean ESR levels were significantly higher in the failure groups (103.5 mm/h) than in the success groups (69.1 mm/hour) [42]. However, in other analyses, ESR was not significantly associated with the DAIR outcomes [17]. The variability in findings may stem from differences in the study populations and ESR thresholds used for the analysis. Bacteremia at the time of DAIR was associated with a significantly lower success rate (31%) compared to those who did not have bacteremia (65%) [34,43]. Late acute and hematogenous infections were also associated with worse outcomes than early postoperative infections. Late acute periprosthetic joint infection (PJI) had an OR of 4.52 for failure, with bacteremia further worsening the success rates in these cases [24,34]. In patients who have acute hematogenous PJI, treatment success rates were significantly lower in those who had positive blood cultures (36.3%) than in those who had negative cultures (66.7%, $P = 0.047$) [44,45]. Bacteremia was particularly detrimental in late acute infections, where it was associated with worse outcomes compared to early acute infections (31% success versus 65%, OR 4.1) [5]. Furthermore, patients who have sepsis had lower treatment success rates (51%) than those who do not have sepsis (67%) [46].

Combined Consideration of Markers

Combining inflammatory markers with blood culture results provides a comprehensive assessment. Elevated CRP, ESR, and

bacteremia collectively increase the likelihood of DAIR failure. For instance, in one study, patients who had a CRP > 22 mg/dL and positive blood cultures exhibited significantly higher failure rates [47]. The use of CRP and ESR ratios has also been explored to differentiate between types of infections. For chronic postoperative reinfections, ESR demonstrated a sensitivity of 75% and a specificity of 84% at a cutoff of 1.31 [48]. The efficacy here is mild to moderate discrimination at best based on the AUC; these parameters are useful adjuncts, but no single variable is perfect in predicting the outcome.

Scoring Systems

The KLIC scoring system integrates factors such as CRP level, time from arthroplasty to debridement, and comorbidities to predict DAIR outcomes. A one-point increase in the KLIC score corresponds to a 1.32 to 1.45 times higher risk of failure [9,10]. Patients who have scores < 3.5 had high success probabilities, while scores > 6 were associated with significant failure rates (e.g., > 85% failure for scores >7) [10,30,49]. For example, a KLIC score of 3.5 had an AUC of 0.762, with a sensitivity of 77% and a specificity of 57% [49,50]. Patients who had scores of > 7 had a 100% failure rate [49]. Adjusting thresholds for clinical applicability revealed that scores < 4 had failure rates of 27.9%, while scores > 7 had failure rates exceeding 85% [30]. Similarly, the CRIME80 scoring system, which incorporates variables such as CRP, comorbidities, and infection chronicity, demonstrated a failure rate of 67.9% for scores $\geq$ 3 compared with 35.8% for scores < 3 ($P < 0.0001$) [50]. However, as with the KLIC score, its predictive accuracy diminishes in intermediate-risk categories, highlighting the need for further refinement of these models. Patients who have low scores (e.g., KLIC < 3.5 or CRIME80 < 3) are likely to achieve success with DAIR, allowing for more confident recommendations for conservative management. High-risk scores (e.g., KLIC > 6 or CRIME80 $\geq$ 3) highlight the need for alternative strategies, such as staged revisions, particularly when comorbidities or elevated inflammatory markers are present.

Machine Learning Predictive Algorithms for DAIR Outcomes

In a cohort of 556 patients, the algorithm predicted failure risk with varying degrees of success. Among patients categorized as low risk (< 30% failure probability), only 21.8% failed DAIR. For those in the intermediate-risk category (30 to 50% failure probability), 37.6% experienced failure. However, patients classified as high risk (> 50% failure probability) had a failure rate of 62.5%, underscoring the model's capacity to stratify patients effectively [21]. In a cohort of 64 patients, the overall success rate was 60.9%; most cases exhibited success probabilities between 40 and 80%, suggesting the moderate utility of the model in predicting outcomes [51]. The application of Shohat's scoring system to the same cohort yielded an AUC of 0.69, indicating moderate predictive ability. Using a 50% cutoff value, the score achieved a sensitivity of 82%, a specificity of 44%, and a negative predictive value of 0.611. This result supports Shohat's system as an adjunct for predicting DAIR success [51]. However, the limitations of these systems must be acknowledged. In some cohorts, AUCs for these models ranged from 0.6 to 0.8, reflecting moderate discrimination [49,52]. Furthermore, sensitivity and specificity are often suboptimal in intermediate categories, which reduces their clinical precision in such cases [10,49].

Revision Total Knee Arthroplasty

Recent advancements in machine learning have enhanced the ability to predict outcomes following revision total knee arthroplasty (TKA) for PJI. Neural network models demonstrated the highest predictive accuracy, with AUC values ranging from 0.81 to 0.84, indicating excellent discrimination [53]. Previous irrigation and debridement with or without modular component exchange and more than four open surgeries were the strongest predictors of failure [6,54]. Comorbidities, such as obesity, renal failure, diabetes, metastatic disease, and depression, significantly increase the risk of recurrent infection. The success of revision TKA in the context of PJI is influenced by the surgical approach chosen. For patients who have extensive instrumentation, success rates were similar between irrigation and debridement with chronic suppression (62.5%) and two-stage revision (67.7%) [55]. However, long-term infection-free survival favored two-stage revision, with a 5-year infection-free survival rate of 75% compared with 16% for DAIR or extended DAIR ($P = 0.006$) [56]. Megaprostheses pose additional challenges in the management of PJI. There was one study focusing on DAIR in nononcological femoral megaprostheses that reported a success rate of 64.3% with a minimum follow-up of five years [57]. However, these results must be interpreted cautiously, as the study did not account for other patient or procedural factors. Extended DAIR procedures in megaprostheses, which involve removing all components except the stems, have been explored as an alternative to complete revision. While these approaches preserve some structural integrity, their long-term efficacy remains limited, with Kaplan-Meier analysis showing a 5-year infection-free survival rate of 16% [56]. This highlights the critical need for improved strategies to manage infections in patients who have megaprostheses.

Debridement, antibiotics, and implant retention remain valuable limb- and implant-preserving options for managing PJI in appropriately selected patients. Critical factors influencing DAIR success include the timing of intervention relative to symptom onset and index surgery, patient demographics, comorbidities, inflammatory markers, bacteremia, and the use of predictive scoring systems. These factors should be considered when evaluating which patients are candidates for DAIR.

Question 2: Should debridement, antibiotics, and implant retention be offered to patients who have acute hematogenous periprosthetic joint infection?[2]

Response/Recommendation

A debridement, antibiotics, and implant retention is an acceptable option for patients who have acute hematogenous periprosthetic joint infection. However, the procedure, on average, has a nearly 40% failure rate in this patient population. Infection with *Staphylococcus aureus* and prolonged symptom duration are major risk factors associated with treatment failure.

Level of Evidence: Moderate

Delegate Vote: Agree 84%, disagree 11%, abstain 5% (super majority, strong consensus)

Rationale

A systematic review was conducted to evaluate the outcomes of debridement, antibiotics, and implant retention (DAIR) for the treatment of acute hematogenous periprosthetic joint infection (PJI). The search across PubMed, Scopus, Web of Science, and Embase yielded 906 records, of which 45 studies met the inclusion criteria following a two-step screening process by two independent reviewers [58–102]. The included studies comprised

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38 retrospective and seven prospective designs, with the majority (17 studies) conducted in the United States, followed by Spain (six studies) and Korea (four studies; Table 1). The treatment success rate in these patients was assessed using proportion analyses with the inverse variance method, conducted in R software (https://www.r-project.org/). Publication bias was evaluated using Egger's regression tests.

The 45 studies collectively included 1,989 patients who had reported mean ages ranging from 59 to 74 years across 30 studies. Among 20 studies reporting sex distribution, 49% of the patients

Table 1
Study Characteristics.

Study	County	Design	Hematogenous Infection Interval to Index Procedure	Joint	Population, *n*	Age (years)	Men, *n*	Follow-Up (y)
Soundarrajan et al., 2022	India	Retrospective	>4 wk	TKA	22	67 ± 9.85	10 (45%)	4.9 ± 2.4
Chen et al., 2021	USA	Prospective	>3 mo	78 TKA and 28 THA	106	67 ± 11.6	58 (55%)	4.9 (3.5 to 7)
Huotari et al., 2023	Finland	Retrospective	>3 mo	15 TKA and 11 THA	26	71 (38 to 86)	12 (46%)	4.5 (15 days to 9.3)
Rahardja et al., 2023	Australia and New Zealand	Prospective	>3 mo	TKA	129	70 (36 to 90)	75 (58%)	2
Karlsen et al., 2025	Norway	Prospective	>4 wk	4 TKA and 2 THA	6	63 ± 14	3 (50%)	4.2
Liukkonen et al., 2024	Finland	Retrospective	>3 mo	THA	25	NA	NA	1
Tarity et al., 2021	USA	Retrospective	>6 wk	84 TKA and 51 THA	135	66 ± 12.0	71 (53%)	0.3
Geurts et al., 2013	The Netherlands	Retrospective	>4 wk	3 TKA and 3 THA	6	NA	NA	2.8 (1 mo to 23)
Westberg et al., 2023	Norway	Retrospective	>4 wk	TKA and THA	25	75 (43 to 92)	26 (60%)	1
Segawa et al., 1999	USA	Retrospective	>4 wk	TKA	7	NA	NA	3.3 (0.3 to 5.5)
Bryan et al., 2017	USA	Retrospective	>4 wk	THA and HA	24	NA	NA	6 (2 to 15)
Chiu et al., 2007	China	Prospective	>4 wk	TKA	10	73	4 (40%)	6.6 (3 to 12)
Cook et al., 2007	Canada	Retrospective	NA	TKA	10	67	NA	10
Crockarell et al., 1998	USA	Retrospective	>4 wk	THA	4	59	2 (50%)	6.3 (0.14 to 22)
Tsukayama et al., 1996	USA	Retrospective	>4 wk	THA	6	NA	NA	2.6 (0.5 to 4.0)
Estes et al., 2010	USA	Retrospective	NA	TKA and THA	18	67 (28 to 91)	NA	3.5 (1.2 to 7.5)
Fink et al., 2016	Germany	Retrospective	NA	20 TKA and 8 THA	28	NA	NA	3.5 (2 to 11)
				8				
Flierl et al., 2016	USA	Retrospective	NA	TKA, THA	18	62 (32 to 88)	NA	1.1 (0.25 to 2.5)
Hernandez et al., 2019	USA	Retrospective	NA	UKA	4	NA	NA	At least 2 y
Uriarte et al., 2019	Spain	Retrospective	NA	THA	10	NA	NA	4 (1 to 12)
Engen et al., 2024	USA	Retrospective	>4 wk	TKA	34	NA	NA	2
Kim et al., 2011	Korea	Retrospective	>4 wk	TKA	7	65 ± 9.4	NA	At least 2 y
Koh et al., 2015	Korea	Retrospective	>4 wk	TKA	20	67 (44 to 80)	NA	At least 2 y
Konigsberg et al., 2014	USA	Retrospective	>6 mo	20 TKA and 20 THA	40	60 (25 to 86)	22 (55%)	At least 2 y
Koyonos et al., 2011	USA	Retrospective	>4 wk	34 TKA and 16 THA	50	63 (60.6 to 66.3)	28 (56%)	4.5 (1 to 9.6)
Son et al., 2017	Korea	Retrospective	>4 wk	TKA	15	70 (35 to 86)	NA	2.5 (2 to 2.9)
Kuo et al., 2019	USA	Retrospective	>3 mo	42 TKA and 7 THA	49	NA	26 (53%)	At least 1 y
Lora-Tamayo et al., 2013	Spain	Retrospective	NA	38 TKA and 13 THA	52	74 (65 to 79)	21 (40%)	2
Salmons et al., 2023	USA	Retrospective	>4 wk	11 TKA and 14 THA	25	71 (41 to 90)	NA	7 (2 to 15)
Renz et al., 2021	Germany	Retrospective	>4 wk	TKA and THA	50	74 (36 to 92)	NA	1.7 (0.2 mo to 7.5)
Lora-Tamayo et al., 2017	Spain	Retrospective	>3 mo	TKA and THA	242	72 (65 to 78)	111 (46%)	2.2 (1.4 to 3.7)
Shao et al., 2022	China	Retrospective	>3 mo	TKA and THA	24	62 (54 to 75)	NA	3.2 (2 to 7.6)
Chaiyakit et al., 2021	Thailand	Retrospective	>4 wk	TKA	12	65 (48.0 to 82.0)	3 (25%)	7.8 (4.7 to 11.1)
Iza et al., 2019	Spain	Retrospective	>3 mo	TKA	12	73 (57 to 83)	NA	3.4 (1 to 12)
Pérez-Prieto et al., 2023	Spain	Prospective	>3 and <12 mo	TKA	10	72	2 (20%)	8.5 ± 2.4
Chang et al., 2022	Korea	Retrospective	>3 mo	TKA	67	74 ± 9.2	12 (18%)	2
Toh et al., 2021	Singapore	Retrospective	>3 mo	TKA	73	64 ± 9.74	NA	1.9 (0.5 to 7.8)
Sendi et al., 2017	Switzerland	Retrospective	>3 mo	THA	14	73 (44.6 to 87.7)	NA	4.0 (1.4 to 10)
Shohat et al., 2019	USA	Retrospective	>3 mo	43 TKA and 9 THA	52	68 ± 11.6	27 (52%)	1
Swenson et al., 2017	USA	Retrospective	>4 wk	TKA and THA	19	NA	NA	2.89 (0.5 to 6.3)
Vilchez et al., 2011	Spain	Retrospective	>3 mo	10 TKA and 2 THA	12	74 (8.9)	6 (50%)	1.4 ± 1.2
Waldman et al., 2000	USA	Prospective	>6 mo	TKA	12	71	5 (42%)	4.2
Wouthuyzen-Bakker et al., 2019	International multicenter	Retrospective	>3 mo	247 TKA and 93 THA	340	NA	175 (51%)	2.8 (1.3 to 4.6)
Zhu et al., 2020	New Zealand	Retrospective	>4 wk >3 mo	TKA	102 123	NA	NA	6.9 ± 3.69
Nurmohamed et al., 2021	The Netherlands	Prospective	NA	10 TKA and 6 THA	16	NA	NA	At least 1 y

TKA, total knee arthroplasty; THA, total hip arthroplasty; HA, hemi-arthroplasty; UKA, unicompartmental knee arthroplasty; NA, not available.

were men (673 of 1,376). The mean follow-up duration ranged from 0.3 to 8.5 years. Of the included studies, 22 focused on acute hematogenous PJI after total knee and hip arthroplasty (TKA and THA), 16 exclusively on TKA, and five exclusively on THA (Table 1).

The definition of acute hematogenous PJI varied among the studies, but mostly was defined as infection occurring in the setting of hematogenous seeding to an arthroplasty, with or without documented bacteremia. There were 19 studies that defined it as an infection occurring after four weeks postindex procedure, 16 studies after three months, and three studies after six months. There were eight studies that did not specify a definition (Table 1). To consider an infection as acute, most studies considered the duration of symptoms to be less than 4 weeks.

Staphylococcus aureus was the most reported infective organism (pooled prevalence: 37.4%, 95% confidence interval [CI]: 31.5 to 43.6%], $I^2 = 54\%$), followed by Streptococcal species (pooled prevalence: 25.4% [95% CI: 17.9 to 34.6%], $I^2 = 68\%$). In studies reporting polymicrobial and culture-negative infections, polymicrobial cases accounted for 8.0% (95% CI: 5.1 to 12.3%, $I^2 = 63\%$), whereas culture-negative infections comprised 19.9% (95% CI: 11.2 to 32.9%, $I^2 = 70\%$; Table 2).

The mean interval from symptom onset to DAIR ranged from 3.3 to 15 days, whereas the mean time from the index procedure to DAIR (joint age) ranged from 1.3 to 6.5 years. Most studies used six weeks of intravenous antibiotics following DAIR, with considerable variability in the duration of oral antibiotics (Table 2). Definitions of treatment success were primarily based on the absence of clinical symptoms and laboratory markers of infection (e.g., erythrocyte sedimentation rate, C-reactive protein, synovial fluid analysis), whereas treatment failure was defined as infection recurrence, the need for further surgery, or PJI-related death (Table 3).

Across all included studies (comprising 1,986 cases), the treatment success rate for DAIR ranged from 20 to 100%, with an overall pooled estimate of 61.1% (95% CI: 55.5 to 66.5%, $I^2 = 74\%$; Figure 1). Egger's regression test indicated no publication bias ($P = 0.13$).

Subgroup Analyses

- TKA (knee joint): Success was reported in 385 of 677 cases (pooled prevalence: 60.3% [95% CI]: 51.7 to 68.3%, $I^2 = 74\%$).
- THA (hip joint): Success was reported in 76 of 116 cases (pooled prevalence: 63.8% [95% CI]: 46.9 to 77.8%, $I^2 = 56\%$).
- Definition of acute hematogenous PJI (three months): Among 16 studies ($n = 1{,}296$), success was achieved in 743 cases (pooled prevalence: 61.0% [95% CI]: 52.2 to 69.2%, $I^2 = 82\%$).
- Definition of acute hematogenous PJI (four weeks): Among 19 studies ($n = 447$), success was achieved in 255 cases (pooled prevalence: 61.2% [95% CI]: 52.3 to 69.4%, $I^2 = 61.5\%$).

Staphylococcus aureus infections were identified as a significant risk factor compared to other microorganisms in seven studies using multivariate regression analyses. There were five studies that reported that prolonged symptom duration increased the likelihood of failure. Previous reports have a related length of symptoms from two to eight days, although Uriarte et al. [77] identified 11 days as a critical cutoff point for success. The same study also highlighted that treatment by general orthopaedic surgeons was associated with a higher failure rate compared to hip specialists (85 versus 33%). Furthermore, the exchange of removable components was linked to improved success rates, as reported in three studies (Table 3). A multicenter study suggested that the CRIME80 score may be useful for selecting the appropriate candidates for DAIR in AHI PJI, although studies have failed to validate it in external cohorts [101]. Overall, the optimal candidate for DAIR in AHI PJI still needs to be defined but will probably include relevant factors, including the patient characteristics, coexistence with bacteremia or endocarditis, duration of symptoms, implant stability, or soft tissue viability.

In conclusion, DAIR for treating acute hematogenous PJI reveals a success rate of 61.1%. Although this is lower than the success rate for acute postoperative PJI, DAIR remains a viable option, particularly when considering the factors associated with treatment failure. *Staphylococcus aureus* infections and prolonged symptom duration are significant risk factors. The variability in definitions and treatment protocols across studies highlights the need for standardized guidelines to improve outcomes. Future research should focus on optimizing treatment strategies and identifying patient-specific factors that influence success rates.

Question 3: What is the optimal surgical protocol for performing debridement, antibiotics, and implant retention in patients who have an acute periprosthetic joint infection?[3]

Response/Recommendation

Debridement, antibiotics, and implant retention involve meticulous mechanical debridement and chemical debridement with the use of multiple antiseptic agents. Extended systemic antibiotics (for 12 weeks) are recommended.

Level of Evidence: Moderate

Delegate Vote: Agree 87.0%; disagree 10.9%; abstain 2.1%

Rationale

Debridement, antibiotics, and implant retention (DAIR) represent a viable surgical strategy for treating periprosthetic joint infections (PJIs). Addressing the infection while retaining the implants avoids the morbidity associated with revision arthroplasty and is characterized, when successful, by a markedly lower economic burden [103]. This surgical approach yields improved outcomes when the patient selection, timing of surgery, pathogen identification, and surgical techniques are optimized [104]. A DAIR encompasses a variety of surgical options, including radical debridement aimed at achieving a cure and DAIR-like nonradical treatments that focus on suppressing or controlling the infection. The true DAIR procedure involves radical surgical debridement, exchange of modular implant parts, and administration of appropriate antimicrobial therapy, aiming for a microbiological cure.

The reported success rate for DAIR has varied significantly, ranging from 33 to 100% [104,105].

Numerous factors influence the outcome of DAIR, with the correct indications for the procedure being perhaps the most important. However, the indications for DAIR are the subject of another inquiry, so we will not delve into this issue further. We conducted a comprehensive literature review across two databases (PubMed and the Cochrane Library) using MeSH terms developed by our librarians. After screening the potentially eligible studies, 332 were included for full review and data extraction; ultimately, 97 were selected.

The optimal surgical protocol for performing DAIR was previously discussed and published in the prior compendium of the International Consensus Meeting 2018 [106]. The latter emphasizes the importance of thorough and aggressive mechanical debridement of infected tissues, followed by chemical debridement using various antiseptic irrigation solutions [106].

Several authors have suggested creating distinct “clean” and “dirty” operating room setups.

[3] These authors contributed to Question 3: Pier Francesco Indelli, Ayman Ebied, Abtin Alvand, Felix Vilchez-Cavazos, Pedro Foguet, Nathan B. Kaplan, Satit Thiengwittayaporn, Rihard Trebše

Table 2
Microorganisms, Timing, Antibiotic Therapy, and Modular Component Exchange Rate.

Study	Infective Organisms Reported, *n* (%)	Time Intervals From Onset of Symptoms (d) to DAIR	Time Interval From Index Procedure and DAIR (Joint Age, years)	Exchange Modular Components, %	Duration of IV Antibiotic Therapy (weeks)	Duration of Oral Antibiotic Therapy (weeks)
Soundarrajan et al., 2022	NA	NA	1 to 6 months (4) 7 months to 1 year (4) 1 to 3 years (7) 3 to 5 years (5) More than 5 years (2)	NA	2	6
Chen et al., 2021	*S. aureus* 26 (24.5%) b-hemolytic *Streptococcus* 9 (8.5%) Coagulase NG *Staphylococcus* 7 (6.6%) Polymicrobial 9 (8.5%) Culture negative 24 (22.6%)	NA	NA	NA	6	NA
Huotari et al., 2023	*S. aureus* 26 (100%)	6.8 (3 to 18)	NA	100%	4.5 ± 1	10.9 (8 to 39.6)
Rahardja et al., 2023	*S. aureus* 63 (49%) Gram negative 17 (13%) Polymicrobial 22 (17%) Culture negative 12 (9%)	NA	NA	NA	NA	NA
Karlsen et al., 2025	*S. aureus* 3 (50%) *Streptococcus* spp 2 (33%) *Enterococcus faecalis* 1 (17%)	NA	NA	100%	2	4
Liukkonen et al., 2024	*S. aureus* 25 (100%)	NA	NA	100%	NA	NA
Geurts et al., 2013	NA	7.5 d	NA	0%	NA	NA
Westberg et al., 2023	*S.aureus* 16 (37%) *Streptococcus* spp 13 (30%) CoNS 3 (7%) Polymicrobial 0	7 (2 to 120)	6.5 (0.3 to 23)	72%	2	4
Segawa et al., 1999	NA	NA	NA	100%	6	NA
Bryan et al., 2017	NA	6 (1 to 21)	2.4 (36 weeks to 14)	70%	6	NA
Chiu et al., 2007	Coagulase NG *Staphylococcus* 4 (40%) *S. aureus* 4 (40%) Group B *strep* 1 (10%) *Candida* 1 (10%)	NA	NA	NA	At least 6	NA
Cook et al., 2007	*S. aureus* 3 (30%) Group B *strep* 1 (10%) *Pseudomonas* 2 (20%) *Streptococcus pneumoniae* 2 (20%) Coagulase NG *Staphylococcus* 1 (10%) Culture negative 1 (10%)	NA	2.8 (0.8 to 6)	90%	4.1 (2 d to 10.3)	10 (0.9 to 54%)
Tsukayama et al., 1996	Gram-positive *cocci*	2 to 7	NA	100%	6	NA
Estes et al., 2010	NA	NA	NA	100%	6	36
Fink et al., 2016	*S. aureus* 7 (25%) *MSSE* 4 (14.3%) *E. coli* 2 (7.1%) *Enterococcus faecalis* 2 (7.1%) *Streptococcus agalactiae* 2 (7.1%) *Staphylococcus lugdunensis* 2 (7.1%)	NA	NA	100%	2	4
Flierl et al., 2016	NA	NA	NA	100%	At least 6	Variable course
Hernandez et al., 2019	*S. aureus* 2 (50%) *Staphylococcus lugdunensis* 1 (25%) Culture negative 1 (25%)	NA	0.7	NA	6	NA
Uriarte et al., 2019	NA	NA	2 (1.2 months to 17)	NA	2.5 wk (0.5 to 8)	5.5 (1 to 8)
Engen et al. 2024	NA	NA	NA	100%	6	12-, 24-, or 48-wk
Kim et al., 2011	Coagulase-positive *staphylococci* 2 (28%) Coagulase-negative *staphylococci* 2 (28%) Culture negative 2 (28%) *Enterobacter* 1 (14%)	NA	NA	100%	6	NA
Koh et al. 2015	NA	8 (4 to 26)	1.4 (0.4 to 12)	94%	6	NA
Konigsberg et al., 2014	*S. aureus* 15 (38%) *Streptococcal species* 15 (38%) *E. coli* 2 (5%) Polymicrobial 2 (5%) Culture negative 2 (5%)	5.4 (1 to 28)	4.7 (0.5 to 15.5)	100%	6	42 (6 to 104)
Koyonos et al., 2011	*Staphylococcus* organism 20 (40%) *S. aureus* 17 (34%) Methicillin resistant 6 (12%)	NA	NA	NA	6	NA

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Table 2 (*continued*)

Study	Infective Organisms Reported, *n* (%)	Time Intervals From Onset of Symptoms (d) to DAIR	Time Interval From Index Procedure and DAIR (Joint Age, years)	Exchange Modular Components, %	Duration of IV Antibiotic Therapy (weeks)	Duration of Oral Antibiotic Therapy (weeks)
	Gram-negative organism 6 (12%) *Staphylococcus epidermis* 3 (6%) Culture negative 8 (16%)					
Son et al., 2017	NA	3.3 (1 to 5)	NA	100%	At least 4	2
Kuo et al., 2019	*Staphylococcal* species 26 (53%) *S. aureus* 24 (48%) *Streptococcus* 15 (30%) Gram negative 3 (6%) *Staphylococcus epidermidis* 2 (4%) Polymicrobial 5 (10%)	NA	NA	100%	6	NA
Lora-Tamayo et al., 2013	*S. aureus* 52 (100%) Polymicrobial 1 (2%)	NA	NA	63%	NA	NA
Salmons et al., 2023	NA	NA	1.3 (4.4 weeks to 12)	NA	5 (3 to 6)	NA
Lora-Tamayo et al., 2017	*Streptococci* 242 (100%) Polymicrobial 11 (5%)	5 (2 to 12)	NA	55%	3 ± 2.9	13 (8.3 to 24.4)
Shao et al., 2022	NA	NA	NA	Most cases	At least 2	At least 4
Chaiyakit et al. 2021	*S. aureus* 2 (17%) Group A *streptococcus* 2 (17%) Group B *streptococcus* 1 (8%) Culture negative 10 (83%)	4.5 (1 to 10)	2.5 (0.2 to 5.8)	100%	6	12
Iza et al., 2019	NA	15 (3 to 21)	2.2 (0.3 to 8)	100%	12 (4 to 53)	
Pérez-Prieto et al., 2023	*S. aureus* 3 (30%) *E. coli* 3 (30%) Coagulase-negative *staphylococci* 2 (20%) Culture negative 2 (20%)	2.75 ± 1.8	4.7 ± 3.6	100%	11.4 ± 1.9	
Chang et al., 2022	*S. aureus* 15 (22%) *Streptococcus* 15 (22%) Gram negative 9 (13%) Polymicrobial 3 (4%) Culture negative 14 (21%)	8.3 ± 8.2	1.3 (0.7 to 3.6)	100%	4 to 6	NA
Sendi et al. 2017	*S. aureus* 5 (36%) *Streptococcus* spp. 8 (57%)	NA	NA	59%	1 to 2	10 to 11
Shohat et al., 2019	*S. aureus* 26 (50%) *Streptococcus* 17 (33%) *VRE, MRSA,* or *MRSE* 7 (13%) Gram negative 5 (10%) Polymicrobial 7 (13%)	NA	NA	100%	6	NA
Swenson et al., 2017	NA	NA	NA	100%	At least 6	NA
Vilchez et al., 2011	*S. aureus* 12 (100%) Poly 0 (0%)	4.7 ± 3.7	4 ± 3.2	100%	1 ± 8.3	16.5 ± 7.9
Waldman et al., 2000	*S. aureus* 7 (58%) *S. epidermidis* 4 (33%) *b-hemolytic streptococcus* 1 (8%)	4.4 (1to 7)	3.3 (0.5 to 7.8)	NA	6	NA
Wouthuyzen-Bakker, et al. 2019	*S. aureus* 141 (41%) *Streptococcus* species 97 (29%) Gram negative 50 (15%) *Enterococcus* species 11 (3%)	NA	NA	NA	12	
Zhu et al., 2020	NA	NA	NA	81%	At least 6	NA
Nurmohamed et al., 2021	NA	12 (0 to 83)	NA	NA	12	

DAIR, debridement, antibiotics, and implant retention; NA, not available.

All drapes, surgical instruments, gowns, and gloves should be replaced with clean ones after the debridement and irrigation phases and before the reimplantation of the modular components [107]. Multiple authors have also advocated using disclosing agents to guide the debridement of biofilms; in particular, diluted methylene blue has been included in some DAIR protocols [108,109]. A radical synovectomy is strongly recommended, especially when the knee joint is involved. This surgical step should entail the removal of all infected tissue as well as the excision of all hypertrophic intra-articular synovium from the suprapatellar pouch, lateral gutters, and the posterior aspect of the knee [104,105,107,108,110].

After completing the mechanical debridement, it is recommended to use sterile saline irrigation along with various antiseptic solutions, if available. So far, no consensus has been reached regarding the use of low- or high-pressure lavage systems for delivering irrigation solutions during DAIR procedures [107].

Several antiseptic irrigation solutions have been recommended during DAIR, including povidone-iodine (PI), chlorhexidine gluconate (CHG), acetic acid, hydrogen peroxide, sodium hypochlorite, and many preformulated commercially available combination solutions [111]. It is recommended to use a liter of saline in between if multiple antiseptic solutions have been used in succession [104,109,111].

Different PI concentrations have been tested against various organisms to determine bactericidal activity in relation to host cells; however, the studies are too varied to conclude on an optimal antiseptic or formulation. A dilute (0.5%) PI sterile formulation is commercially available and was approved by the Food and Drug Administration in 2020 for clinical use. This

Table 3
Treatment Outcome and Risk Factors for Failure.

Study	Successful Patients, *n* (%)	Success Definition	Failed Patients, *n* (%)	Failure Definition	Surgical Option for Failed Patients	Failure Risk Factors
Soundarrajan et al., 2022	14/22 (64%)	Absence of laboratory signs (ESR, CRP, WBC, synovial fluid analysis)	8/22 (36%)	(1) Need any further surgery (2) Need antibiotic suppression therapy (3) Death related to PJI	Two-stage revision Redebridement Arthrodesis	Univariate analysis: symptom duration
Chen et al., 2021	81/106 (76%)	NA	25/106 (24%)	(1) Need any further surgery (2) Infection recurrence caused by the same organism strain (3) Death related to PJI	Single-stage revision (5) Two-stage revision (7) Arthrodesis (12) Amputation (1)	Multivariate analysis: diabetes mellitus and polymicrobial infections
Huotari et al., 2023	24/26 (92%)	(1) Retaining the original prosthesis (2) No death due to infection (3) No active signs of infection	2/26 (8%)	NA	Two-stage revision	NA
Rahardja et al., 2023	47/129 (36%)	(1) Retaining the original prosthesis (2) No death due to infection (3) No active signs of infection (4) No ongoing use of antibiotics	82/129 (64%)	NA	NA	Univariate analysis: time to PJI diagnosis
Karlsen et al., 2025	4/6 (67%)	Absence of laboratory (ESR, CRP, WBC) and clinical signs and no signs of implant loosening	2/6 (33%)	(1) Need any further surgery (2) Need antibiotic suppression therapy	NA	Univariate analysis: PJI following revision (versus primary)
Liukkonen et al., 2024	12/25 (48%)	NA	13/25 (52%)	Need any further surgery (due to any reason)	NA	Univariate analysis: DAIR (versus revision)
Tarity et al., 2021	102/135 (76%)	NA	33/135 (34%)	Need revision surgery	NA	Multivariate analysis: *Staphylococcus* infection
Geurts et al., 2013	5/6 (83%)	(1) Absence of laboratory (ESR, CRP, WBC), clinical, and radiological signs	1/6 (17%)	NA	Revision	NA
Westberg et al., 2023	10/25 (40%)	Absence of laboratory and clinical signs and no signs of implant loosening	15/25 (60%)	(1) Need any further surgery (2) Infection recurrence (3) Death related to PJI	Two-stage revision (6) Suppressive antibiotic (3) Amputation (2) DAIR and resection arthroplasty (2) New DAIR (1) Girdlestone procedure (1)	NA
Segawa et al., 1999	5/7 (71%)	Absence of clinical signs with a functional knee with a total joint prosthesis in place	2/7 (29%)	NA	Suppressive antibiotic (1) Arthrodesis (1)	NA
Bryan et al., 2017	19/24 (79%)	Absence of laboratory signs (ESR, CRP)	5/24 (21%)	(1) Need revision surgery (2) Infection recurrence (3) Death related to PJI	NA	NA
Chiu et al., 2007	5/10 (50%)	(1) Absence of clinical signs,. (2) preservation of prosthetic function, and (3) retaining the original prosthesis	5/10 (50%)	(1) Need revision surgery (2) Infection recurrence	Two-stage revision (3) Fusion (2)	NA
Cook et al., 2007	3/10 (30%)	NA	7/10 (70%)	NA	Resection arthroplasty and reimplantation (4) Resection arthroplasty and reimplantation plus I & D with liner exchange (3) Amputation (1)	NA
Crockarell et al., 1998	2/4 (50%)	NA	2/4 (50%)	(1) Need revision surgery	NA	NA
Tsukayama et al., 1996	3/6 (50%)	Absence of clinical signs	3/6 (50%)	NA	Revision (2) Resection (1)	NA
Estes et al., 2010	16/18 (89%)	Absence of laboratory (ESR, CRP) and clinical signs	2/18 (11%)	(1) Need revision surgery (2) Infection recurrence (3) Need long-term antibiotic therapy	Long-term oral antibiotics (2)	NA
Fink et al., 2016	16/28 (57%)	Absence of laboratory (CRP) and clinical signs	12/28 (43%)	Infection recurrence	NA	

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Table 3 (*continued*)

Study	Successful Patients, *n* (%)	Success Definition	Failed Patients, *n* (%)	Failure Definition	Surgical Option for Failed Patients	Failure Risk Factors
						Univariate analysis: time to PJI diagnosis Comorbidities score
Flierl et al., 2016	9/18 (50%)	NA	9/18 (50%)	NA	Two-stage revision Suppressive antibiotic	NA
Hernandez et al., 2019	3/4 (75%)	No need for reoperation	1/4 (25%)	Infection recurrence	Two-stage revision (1)	NA
Uriarte et al., 2019	2/10 (20%)	Absence of laboratory (ESR, CRP), clinical, and radiological signs and prosthesis retention	8/10 (80%)	(1) Need revision surgery (2) Need long-term antibiotic therapy (3) Death related to PJI	One-stage revision Two-stage revision Suppressive antibiotic	Univariate analysis: Male sex General orthopaedic surgeon (versus hip surgeon) Symptom duration (11 d was a significant cutoff point for success)
Engen et al., 2024	17/34 (50%)	Absence of laboratory signs (WBC, ESR, CRP)	17/34 (50%)	(1) Need any further surgery	NA	NA
Kim et al., 2011	2/7 (29%)	NA	5/7 (71%)	NA	Revision (4) Two times revision arthroplasty and arthrodesis (1)	NA
Koh et al., 2015	11/20 (55%)	Prosthesis retention and no ongoing use of antibiotics	9/20 (45%)	(1) Need antibiotic suppression therapy (2) Need revision surgery, arthrodesis, resection arthroplasty, or amputation	Two-stage revision (6) Suppressive antibiotic (1) Fusion or amputation (2)	Univariate analysis: Acute hematogenous (vs. early postsurgical) Symptom duration
Konigsberg et al. 2014	33/42 (79%)	NA	9/42 (21%)	(1) Need any further surgery (2) evidence of persistent infection (e.g. a sinus tract), or prosthetic loosening	Two-stage revision (8) Resection (1)	NA
Koyonos et al., 2011	22/50 (44%)	(1) Absence of laboratory signs (ESR, CRP)	28/50 (56%)	(1) Need any further surgery (2) Need long-term antibiotic therapy	Further surgery (22) Long-term oral antibiotics (2)	Multivariate analysis: *Staphylococcal* infection
Son et al., 2017	12/15 (80%)	Absence of laboratory and radiological signs	3/15 (20%)	(1) Need any further surgery (2) Need long-term antibiotic therapy (3) Death related to PJI	Two-stage revision (3)	NA
Kuo et al., 2019	26/49 (53%)	Absence of laboratory signs (ESR, CRP)	23/49 (47%)	(1) Need any further surgery (2) Infection recurrence (3) Death related to PJI	NA	Multivariate analysis: positive blood culture
Lora-Tamayo et al., 2013	20/52 (38%)	NA	32/52 (62%)	(1) Need revision surgery (2) Death related to PJI (3) Need for extradebridements (4) Need long-term antibiotic therapy	NA	Multivariate analysis: *Staphylococcal* infection Symptom duration
Salmons et al., 2023	20/25 (80%)	NA	5/25 (20%)	Need revision surgery	NA	NA
Renz et al., 2021	34/50 (68%)	NA	16/50 (32%)	(1) Death related to PJI (2) Infection recurrence	NA	Univariate analysis: DAIR (versus implant removal)
Lora-Tamayo et al., 2017	139/234 (59%)	NA	95/234 (41%)	(1) Need revision surgery (2) Death related to PJI (3) Need for extra debridements (4) Need long-term antibiotic therapy	NA	Multivariate analysis: Rheumatoid arthritis Bacteremia — Exchange of removable components was associated with a favorable outcome
Shao et al., 2022	18/24 (75%)	NA	6/24 (25%)	(1) Fistula, drainage, or pain, and infection recurrence caused by the same organism (2) Need any further surgery (3) Death related to PJI	NA	Multivariate analysis: symptom duration
Chaiyakit et al., 2021	13/15 (87%)	Absence of laboratory (ESR, CRP), clinical, and radiological signs; and synovial fluid analysis	2/15 (13%)	(1) Nonhealed wound with or without sinus tract, wound drainage, and persistent pain (2) Need any further surgery	Two-stage revision	NA

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Table 3 (*continued*)

Study	Successful Patients, *n* (%)	Success Definition	Failed Patients, *n* (%)	Failure Definition	Surgical Option for Failed Patients	Failure Risk Factors
				(3) Death related to PJI (4) Need long-term antibiotic therapy		
Iza et al., 2019	7/12 (58%)	(1) Absence of laboratory (ESR, CRP) and clinical signs (2) Prosthesis retention (3) No ongoing use of antibiotics	5/12 (42%)	(1) Need any further surgery (2) Infection recurrence (3) Death related to PJI	Two-stage revision Suppressive antibiotic	Multivariate analysis: *Staphylococcus* aureus
Pérez-Prieto et al., 2023	10/10 (100%)	NA	0/10 (0%)	(1) Need any further surgery (2) Infection recurrence (3) Death related to PJI (4) Suppressive antibiotic	NA	NA
Chang et al., 2022	48/67 (72%)	NA	19/67 (28%)	Repeated DAIR or two-stage revision	Repeated DAIR Two-stage revision	NA
Toh et al., 2021	51/73 (70%)	Chronic antibiotic suppression post-DAIR were considered a success	22/73 (30%)	Need revision surgery, arthrodesis, or amputation	Revision Arthrodesis Amputation	Multivariate analysis: *Staphylococcal* infection Higher preoperative ESR (above 107.5)
Sendi et al., 2017	12/14 (86%)	NA	2/14 (14%)	NA	Suppressive antibiotic (1) Single-stage revision	NA
Shohat et al., 2019	23/52 (44%)	NA	29/52 (56%)	(1) Need any further surgery (2) Infection recurrence caused by the same organism strain (3) Infection recurrence	NA	Multivariate analysis: Higher preoperative ESR Comorbidities score
Swenson et al., 2017	16/19 (84%)	NA	3/19 (16%)	NA	NA	NA
Vilchez et al., 2011	5/12 (42%)	Absence of clinical signs and prosthesis retention	7/12 (58%)	(1) Infection recurrence (2) aseptic loosening	NA	Multivariate analysis: Hematogenous infections (versus early postsurgical)
Waldman et al., 2000	4/12 (33%)	NA	8/12 (66%)	NA	Fusion Two-stage revision	NA
Wouthuyzen-Bakker et al., 2019	187/340 (55%)	NA	153/340 (45%)	(1) Need revision surgery (2) Death related to PJI (3) Need for suppressive antibiotic	Revision (55) Suppressive antibiotic (24)	Multivariate analysis: *Staphylococcus aureus* DAIR (versus implant removal) — Exchange of removable components was associated with a favorable outcome
Zhu et al., 2020	41/102 (40%) 53/123 (43%)	NA	61/102 (60%) 70/123 (57%)	(1) Need revision surgery (2) Death related to PJI (3) Need for suppressive antibiotic	NA	Multivariate analysis: Higher preoperative CRP (optimum threshold value of 65 mg/L) *Staphylococcus aureus* Gram-negative infections — Exchange of removable components and the lack of intraoperative purulence were associated with a favorable outcome
Nurmohamed et al., 2021	11/16 (69%)	Absence of laboratory and clinical signs and no ongoing use of antibiotics	5/16 (31%)	(1) Need any further surgery (2) Need for suppressive antibiotic (3) Infection recurrence	NA	NA

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; WBC, white blood cell count; PJI, periprosthetic joint infection; DAIR, debridement, antibiotics, and implant retention; NA, not available.

product has been tested against a range of organisms and has demonstrated a broad spectrum of activity against Gram-positive organisms, including methicillin-sensitive *S. aureus*, methicillin-resistant *S. aureus*, and coagulase-negative *Staphylococcus*, as well as Gram-negative bacteria, fungi, and mycobacteria [112].

In addition, at concentrations of 2 to 4%, CHG has demonstrated broad spectrum activity [111,113,114]. Due to potential cytotoxicity concerns with CHG, further studies are necessary to establish the optimal, nontoxic concentration of CHG. Andriollo et al. [115] suggested using a commercially available acetic acid solution to treat acute PJIs, as acetic acid has been shown to be effective against both Gram-positive and Gram-negative organisms [116]. Hydrogen peroxide at a 3% concentration has demonstrated effectiveness against viruses, bacteria, yeasts, and bacterial spores, exhibiting greater activity against Gram-positive bacteria [117]; however, most literature regarding its use pertains to *in vitro* studies.

Despite sodium hypochlorite being proposed as an antiseptic, there are limited *in vitro* and *in vivo* studies that focus on its effectiveness against biofilm and in managing PJI; this may be due to its short half-life and rapid degradation [118].

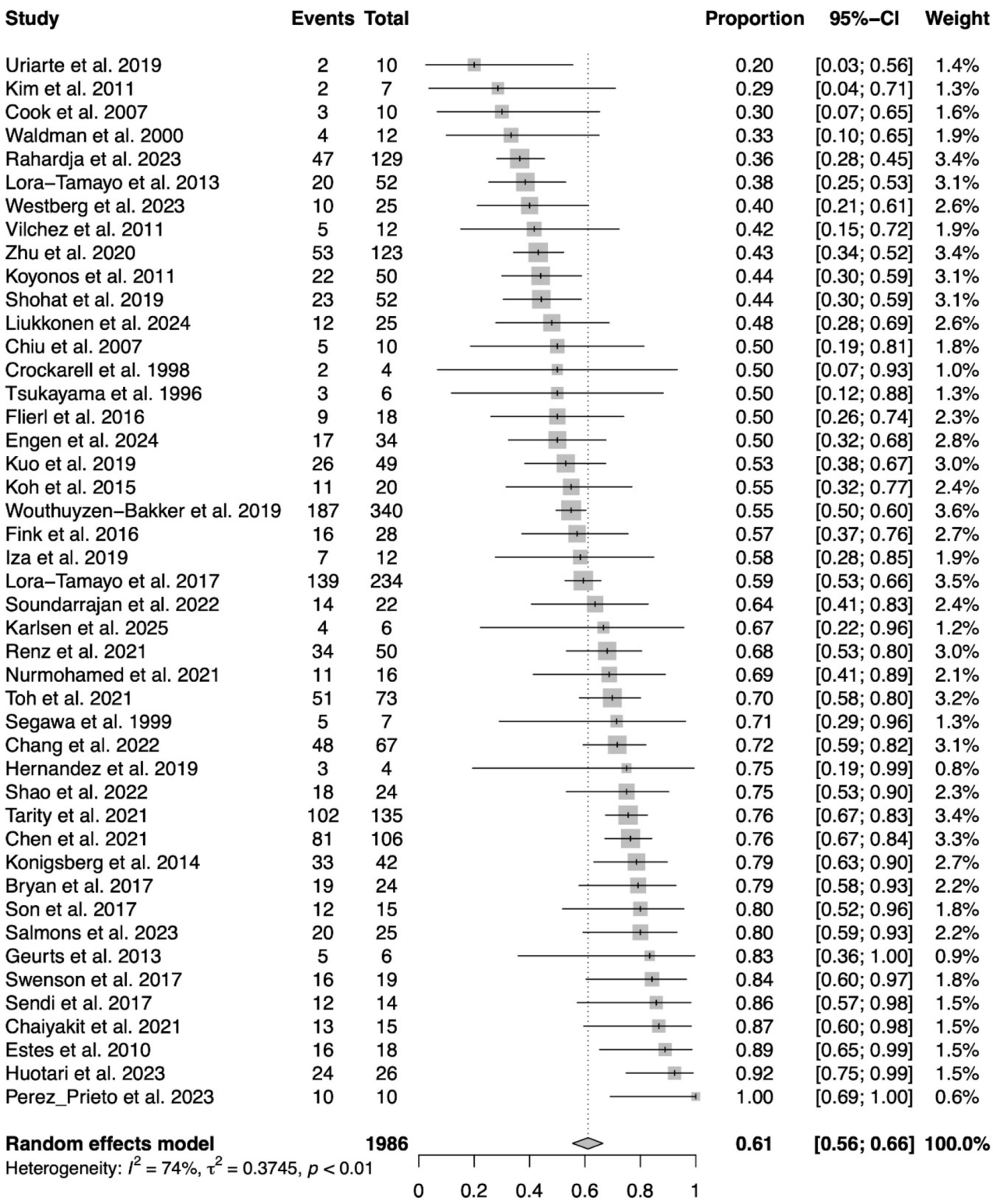


Figure 1. Forest plot showing the treatment success rate of debridement, antibiotics, and implant retention (DAIR) across included studies.

Commercially available combination solutions, such as propylbetaine and polyhexanide, have previously shown microbicidal activity in chronic wounds and burns. However, their use as intra-articular agents in the DAIR procedure has not yet been fully explored [119].

To effectively perform mechanical debridement, the exchange of modular components has been shown to be necessary [107,113]. The role of modular component exchange in DAIR has been addressed in another question and will not be discussed here.

Another important issue related to DAIR is the local delivery of antibiotics. A workgroup from the 2018 ICM concluded that there was no evidence to support the beneficial effects of local antimicrobial therapy at that time [120]. Recently, multiple authors [121] have provided evidence supporting the local delivery of antibiotics to enhance the efficacy of DAIR as an adjuvant to surgical treatment, particularly in cases where the pathogen has been identified [108,122]. Despite the lack of randomized trials to define the local antibiotics' type and delivery method in DAIR cases, emerging evidence supports its value. A notable improvement in the DAIR success rate was observed in patients who received both local and systemic antibiotics compared to those who received only systemic antibiotics [123,124]. However, there is no consensus on the efficacy of local antibiotics compared to standard therapy.

Another fundamental aspect of managing patients undergoing DAIR relates to postoperative antibiotic therapy. The critical element of antimicrobial treatment relates to isolating the infective organism(s), which may not be known at the time of DAIR, particularly when performed as an emergency procedure.

Systemic antimicrobials are crucial to treating patients undergoing DAIR [125]. For culture-negative patients, administration of broad-spectrum antibiotics has been recommended [126]. In general, particularly while awaiting culture results, administering broad antibiotic coverage, including vancomycin-based combinations, appears protective against future failures [127]. The optimal length of antibiotic therapy following DAIR is also a topic of discussion: 12 weeks have been recommended by several authors as part of the Duration of Antibiotic Treatment in Prosthetic Joint Infection trial [128]. The optimal length of antibiotic therapy following DAIR has been addressed in another question: 12 weeks is recommended by the majority of the ICM 2025 delegates.

Antibiotic administration should be parenteral at least during the initial periods (OVIVA trial) [129]. There is less data available on the efficacy of shorter durations of postoperative antibiotic therapy; a few authors recommend a minimum of six weeks of postoperative antibiotic therapy [130,131].

In conclusion, based on our review, the success rate of DAIR is substantially improved when meticulous mechanical and chemical debridement is used during surgery.

The administration of systemic antibiotics for 12 weeks and the local delivery of antibiotics through carriers, when possible, along with a multidisciplinary approach, are crucial aspects of managing patients undergoing DAIR.

Question 4: Should modular components be exchanged during debridement, antibiotics, and implant retention for acute periprosthetic joint infection?[4]

Recommendation

Based on current evidence, modular components should be exchanged at the time of total hip arthroplasty and total knee arthroplasty where feasible.

Level of Evidence: Moderate

Delegate Vote: Agree 91%, disagree 4%, abstain 4% (total consensus, unanimous)

Rationale

Periprosthetic joint infections (PJIs) are a devastating complication after arthroplasty associated with high clinical, psychological, and economic morbidity [132,133]. While implant preservation is desirable, treatment options for PJI are usually based on the type of infection, surgeon and patient preferences, and clinical factors [119]. Debridement, antibiotics, and implant retention (DAIR) in defined circumstances provide lower morbidity compared to two-stage revision procedures [134]. The rates of infection control with DAIR can vary significantly [135,136]. A factor that may affect the rate of infection control in DAIR may be modular component exchange (MCE) due to reduced bioburden and improved exposure to the effective joint space for more thorough debridement [135]. However, the effect of MCE on the failure rates of DAIR for the treatment of PJI remains unknown.

In multiple studies of large sample sizes, MCE showed no significant effect on the risk of failure after DAIR. However, these studies are at risk of bias from unmeasured confounding variables. Becker et al. assessed patients who had early PJI due to *Staphylococcus* sp. infection from four hospitals in France, finding no difference in failure with MCE (hazard ratio [HR] 1.19, 95% confidence interval [CI] 0.36 to 3.92, $P = 0.78$) compared to those without MCE [137]. Similarly, Rodriguez-Pardo et al. found no difference in failure with MCE (HR 0.73, 95% CI 0.35 to 1.51; $P = 0.40$) or without when performing DAIR to treat PJIs secondary to Gram-negative organisms [138]. In another study attempting to externally validate a preoperative risk score composed of chronic renal failure, liver cirrhosis, index surgery, cemented prosthesis, and C-reactive protein (KLIC) in a cohort of 386 patients in the Netherlands, Lowik et al. found no difference in failure with MCE within 60 days of initial debridement (MCE 58 versus no MCE 63%; $P = 0.46$) [139]. A multinational study conducted across Australia and New Zealand found no difference (OR 1.07, 95% CI 0.63 to 1.80; $P = 0.81$) with MCE in 352 patients [140]. However, this study defined the primary treatment modality with a hierarchical structure, wherein patients undergoing DAIR followed by one- or two-stage revision within 90 days of diagnosis were recorded as having undergone one- or two-stage revision. Hence, the rates of failure following DAIR were likely underreported in this study.

Multicenter studies show MCE was protective against failure after DAIR accounted for patient, surgical, and infection-related factors. A multinational study across the United States, Spain, Portugal, and the Netherlands found no difference in failure without MCE (odds ratio [OR] 1.70, 95% CI 0.96 to 3.00; $P = 0.07$) after adjusting for CRP, revision surgery, indication for index surgery, sex, and cemented implants [141]. While not statistically significant, this result may be a clinically important trend showing worse outcomes without MCE. Lora-Tamayo et al. found MCE was associated with lower rates of failure in PJIs secondary to *S. aureus* PJI (HR 0.65, 95% CI 0.44 to 0.95; $P = 0.03$) after adjusting for immunosuppressive therapy, bacteremia, polymicrobial infection, CRP, and the need for two or more debridements [142]. A large study across 27 centers in the United States and Europe found significantly higher rates of success with MCE (MCE 30% versus no MCE 39%; $P < 0.001$). A random forest analysis found that not performing MCE was the fourth most important factor associated with failure [143]. An international, multicenter study by Wouthuyzen-Bakker et al. including 340 patients found MCE was protective against failure of DAIR (OR: 0.35, 95% CI 0.18 to 0.67; $P = 0.002$) after adjusting for sex, age, hypertension, ischemic heart disease, heart failure, oral anticoagulant use, joint involvement, indication for index procedure, revision surgery, duration of symptoms, temperature > 38.5 C, physical signs of inflammation, CRP, leukocytosis, *S. aureus* infection, methicillin resistance, more than one DAIR, and use of local antibiotics [144]. In a multicenter study across three centers in New Zealand, Zhu et al. found MCE was associated with a lower chance of failure (OR 0.51, 95% CI 0.32 to 0.81; $P = 0.004$) after adjusting for CRP, intraoperative purulence, *S. aureus* infection, and Gram-negative infection [145].

[4] These authors contributed to Question 4: Siddharth Rele, Daniel Gould, Elise Naufal, Armin Arshi, Akram Hammad, Peter Gold, Javier Martinez Ros, Ola Rolfson, Goksel Dikmen, Peter F.M. Choong

Svensson et al. was the only study in this review that used an arthroplasty registry, finding MCE was protective for failure (HR: 0.51, 95% CI 0.38 to 0.68) after adjusting for primary diagnosis, sex, age, time from primary THA to symptoms, time from symptoms to DAIR, bacterial growth, and method of fixation [146]. Deng et al. found higher rates of success in patients who have a sinus tract (MCE 26% versus no MCE 56%; $P = 0.04$) but did not adjust for any confounding variables [147].

Some single-center studies also found mixed results but offered limited insight due to their small sample size. Bartsch et al. reviewed 31 primary TKAs with early postoperative or acute hematogenous infections, finding no difference in failure with or without MCE in open DAIR (40 versus 44%, $P = 0.69$) [148]. Similarly, no difference in failure was found with or without MCE in two studies published by Deirmengian et al. on the same cohort of 31 TKA patients [149,150] and by Ottensen et al. in a cohort of 52 primary TKAs (MCE 22 versus no MCE 13%; $P = 0.44$) [151]. There were two studies, including primary TKAs, that found MCE was associated with a significantly lower failure rate without adjustment for confounders (MCE 25 versus no MCE 100%; $P = 0.008$) [152] and after adjusting (MCE 47 versus no MCE 100%; $P < 0.001$) for age, sex, immunocompromise, diabetes mellitus, number of prior procedures, previous treatment for infection, revision surgery type of infection, isolated microorganism, and polymicrobial infection [153]. However, DAIR without MCE had a 100% failure rate in both studies. In another study, including 28 patients, open DAIR with MCE was compared with arthroscopic DAIR without MCE, finding that MCE was associated with lower odds of failures (OR 0.07, 95% CI 0.007 to 0.679; $P = 0.02$) after adjusting for age, sex, time from primary TKA to infection, time from symptom onset to DAIR, time from primary TKA to DAIR, previous ESR and CRP, type of microorganism, and Charlson Comorbidity Index [154]. Koh et al. included both primary and revision TKA performed in 52 patients, finding no difference with MCE ($P = 0.14$), though only three patients did not undergo MCE [155]. Sancho et al. assessed 64 patients who had acute PJI following THA and TKA from a prospectively maintained hospital database, finding no difference with MCE (MCE 74 versus no MCE 67%; $P = 0.15$) [156]. Chalmers et al. attempted to validate the KLIC and CRIME80 scores in a cohort of acute hematogenous PJIs in hip and knee arthroplasties, finding significantly lower rates of failure at 90 days with MCE ($P = 0.01$) [157]. Of note, this study also included arthroplasties performed for fractures (6%) and revision surgery (22.4%). In another study including primary and revision THAs and TKAs, MCE was protective for failure (HR 1.90, 95% CI 1.20 to 2.90), after adjusting for infection due to MRSA, number of surgical interventions, and duration of antibiotic treatment [158]. Walkay et al. found no difference with MCE in 60 patients diagnosed with PJI more than two years after arthroplasty (MCE 28 versus no MCE 32%; $P = 0.73$) [159].

We also performed a meta-analysis of 17 studies reporting on failure in 3,568 patients. Modular component exchange was associated with a lower risk of failure after DAIR compared to DAIR without MCE (relative risk [RR] 0.68, 95% CI 0.54 to 0.86; $P = 0.001$). Only one systematic review has been previously completed on this topic, using meta-regression to assess the effect of the rate of MCE on success at the study level [160]. This review included 65 studies, finding no clear benefit to MCE in DAIR for the treatment of PJI in modern PJI practice. Rather, MCE was associated with a 3.1 to 3.5% higher success rate per 10% increase in MCE rate only among studies published before 2004.

Conclusion

Modular component exchange at the time of DAIR was associated with lower rates of failure in 12 studies. These studies tended to account for relevant confounding factors. It is important to note that no studies have found that MCE at the time of DAIR was associated with higher rates of failure. Studies that found no association of MCE with failure were of small sample size and did not adjust for other relevant factors. Based on the current evidence, modular components should be exchanged at the time of THA and TKA where feasible.

Question 5: Is there a role for arthroscopy in performing debridement, antibiotics, and implant retention for patients who have acute periprosthetic joint infection?[5]

Response/Recommendation

Except in rare (palliative) cases, arthroscopy should not be used to perform debridement, antibiotics, and implant retention (DAIR).

Level of Evidence: Weak

Delegate Vote: Agree 87%, disagree 10%, abstain 3% (super majority, strong consensus)

Rationale

Debridement, antibiotics, and implant retention (DAIR) is a commonly used treatment strategy for acute periprosthetic joint infection (PJI), aiming to preserve the implant while controlling infection. While DAIR is traditionally performed as an open procedure, some studies have explored arthroscopy as a minimally invasive alternative for select cases. During the International Consensus Meeting on Infection in Orthopaedics 2013, it was voted that arthroscopy plays no role in DAIR [161,162]. This was confirmed by other authors [163].

However, arthroscopy offers a minimally invasive approach and potentially reduces postoperative pain and recovery time. With specialized instruments, arthroscopy enables targeted debridement and lavage, which could theoretically reduce the bacterial load in cases with early, localized infection. In addition, arthroscopy may allow the placement of antibiotic-laden materials in deep structures without fully exposing the joint capsule. Literature reports mixed outcomes for arthroscopic DAIR in acute PJI, with infection eradication rates lower than the typical rates reported for open DAIR. The successful DAIR procedure should not be considered a washout [164].

A case series of 16 patients showed a 38% survival rate for total knee arthroplasties (TKAs) treated with arthroscopic DAIR, with a mean follow-up of 64 months [165]. An earlier study showed in one case, treating knees had an inferior outcome for arthroscopic treatment [166]. A review concluded not to consider arthroscopy because it does not allow adequate debridement or exchange of the polyethylene insert [167]. Arthroscopic washout in acute infections is reported with much lower success rates when compared to open debridement [165,168–172]. All studies report retrospective data in terms of small series and case reports. However, in palliative situations, arthroscopy may be considered. For high-risk patients, arthroscopic debridement with continuous irrigation can be an alternative treatment to improve the quality of life during survival [173].

An early series on arthroscopic DAIR for late acute infections in total hip arthroplasty (THA) reported excellent success in eight consecutive patients, who had a mean follow-up of 70 months [174].

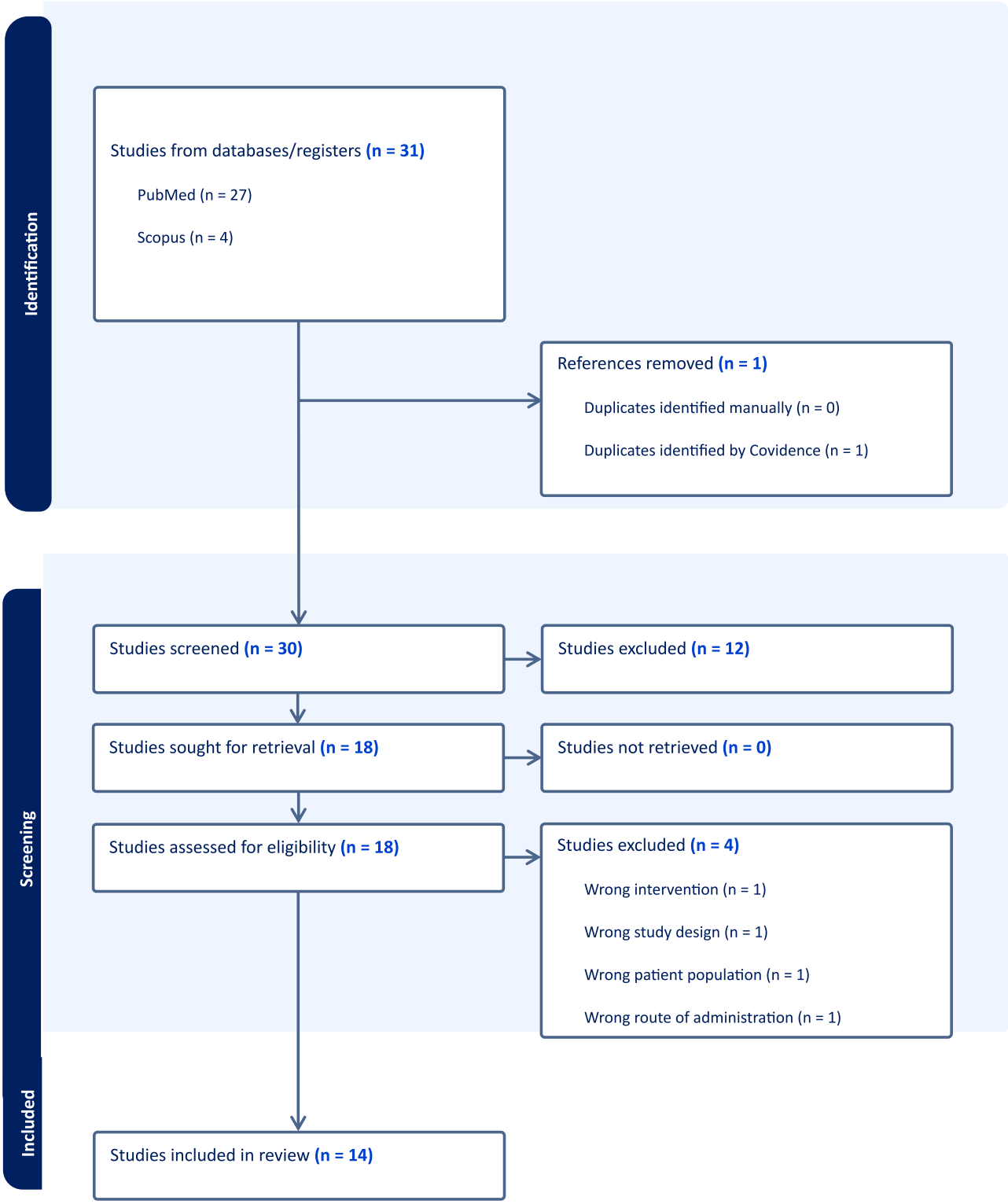
The success of arthroscopic DAIR appears to be highly dependent on careful patient selection and seems to be acceptable in THA. Suitable candidates are typically those who have had early, acute PJI, limited infection spread, and no systemic signs of sepsis.

[5] These authors contributed to Question 5: Carl Haasper, Felix C. Vilchez Cavazos, Haobo Wu, Francisco Arguelles Linares, Ignacio Sancho, Javier Martinez Ros, Jose Baeza-Oliete, Pawel Chodór, Robert McCulloch

Arthroscopic DAIR may be particularly advantageous for patients at substantial risk for complications associated with open surgery, such as those who have comorbidities that limit wound healing. However, success rates are lower, at least in TKA.

Comparative Efficacy and Outcomes

Although arthroscopy has certain advantages, current evidence does not consistently demonstrate sufficient infection control compared to open DAIR. In carefully selected cases, the benefits of



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a minimally invasive approach may outweigh the lower infection control rates.

Question 6: Is there a role for repeat debridement, implant retention, and antibiotic administration in patients who have acute periprosthetic joint infection of the hip or knee?[6]

Response/Recommendation

In patients who have an acute periprosthetic joint infection (PJI) of the hip or knee, repeat debridement, antibiotics, and implant retention (DAIR) appear to increase the overall success rate of infection eradication when performed after failure of initial DAIR or as a planned, two-stage procedure.

Level of Evidence: Moderate

Delegate Vote: Agree 78.2%, disagree 18.0%, abstain 3.8% (strong majority, moderate consensus)

Rationale

In the treatment of acute postoperative or late hematogenous PJI of the hip or knee, the DAIR procedure is considered the first option. However, high failure rates in controlling infection with DAIR have been presented in several studies [175–178]. Although a strong consensus (86%) against performing repeat DAIR after the failed first DAIR procedure was reported at the International Consensus Meeting in 2018, the role of repeat DAIR has evolved [179]. When reported as an individual procedure and not as part of the entire cohort, the literature demonstrates that a second DAIR has, at best, equivalent or typically lower success than an initial DAIR procedure. Hence, in 2018, Argenson et al. recommended the removal of the implants after the failure of the first DAIR procedure to avoid additional surgeries [179]. However, the latter study and other studies did not always evaluate the combined success rates of single and repeat DAIR procedures of the entire cohort for implant retention.

To answer the question posed earlier, we conducted a comprehensive systematic review and meta-analysis to determine if there are data regarding the efficacy of repeat DAIR procedures on the success rates of infection eradication. A search of PubMed/Medline, Scopus, and Embase databases was conducted from inception to September 2024 to identify potentially eligible studies investigating the success of repeat DAIR procedures. The initial literature search identified 544 articles, from which 291 duplicates were eliminated, leaving 252 records for screening by at least two independent reviewers. Ultimately, 12 studies, which were published between 1997 and 2022, that examined the success rates of single DAIR and repeat DAIR procedures in TKA and/or THA were included in this analysis, with the repeat DAIR procedures being performed on patients who had already undergone a failed DAIR procedure [175–178,180–187]. Therefore, the success of a single DAIR procedure was compared to the success of the combined results of single and repeat DAIR procedures for the entire cohort to evaluate its overall success for infection eradication and implant retention. Studies investigating outcomes of the planned multiple irrigation and debridement procedures were excluded because of differences in the surgical techniques. The total cohort included 1,396 joints. Among those, 1,046 joints (75%) underwent only a single DAIR procedure, and the remaining 350 joints (25%) underwent second or multiple DAIR procedures after the failure of the first DAIR (Figure 2). The analysis revealed that the success rate of single DAIR (57% [0.50; 0.64]) was slightly higher than that of repeat DAIR (53% [0.39; 0.66]), without a statistically significant difference. However, combined results of single and repeat DAIR procedures demonstrated a significantly increased success rate compared to the single DAIR technique (72% [0.61; 0.81]; $P < 0.01$). According to these results, we can assume that at least half of the patients undergoing resection arthroplasty for persistent acute infection would be treated with implant retention.

In a recent multicenter study involving 197 patients, Auñón et al. found that repeat DAIR had a lower success rate (54.5%) compared to one-stage (76.2%) or two-stage exchange (79.3%) [188]. The authors also identified key factors associated with failure, including nonspecialized surgical teams in the first DAIR, lack of mobile component exchange, polymicrobial infections, and antibiotic resistance. Crucially, the study also states that when patients who have these risk factors were excluded, the success rate of the second DAIR increased to 83.3%.

The optimal timing of repeat DAIR procedures is also a topic of debate. There is also no consensus on the optimal duration of antibiotic therapy following repeat DAIR procedures [175,184]. Wouthuyzen-Bakker et al. reported that repeat DAIR should be performed as soon as possible after the first DAIR fails [183]. Triantafyllopoulos et al. concluded that patients who had a longer duration between the first and second DAIR had a poorer outcome [184]. They used 20 days as a cutoff, suggesting that repeat DAIR may be more effective when performed sooner rather than later.

Planned repeat DAIR, also referred to as a two-stage debridement protocol, also referred to as double DAIR, involves an initial debridement with prosthesis retention and placement of antibiotic-impregnated cement beads, followed by a second debridement typically done five to six days after the first debridement to remove the beads and insert new modular parts [189]. This approach aims to provide a high local concentration of antibiotics while preserving the prosthesis and minimizing the need for more invasive procedures. Chung et al. reported an 86.7% success rate with this protocol in a cohort of 83 patients who had an acute PJI. This success rate is higher than that reported for single-stage debridement in other studies. The higher success rate may be attributed to the use of high-dose local antibiotics and the second debridement, which helps to further reduce the bacterial burden and remove any residual infected tissue.

The current analysis also has some limitations: the majority of the studies reviewed are limited by their retrospective nature, small sample sizes, and heterogeneity. Indications for repeat DAIR, patient selection, the time between index surgery and occurrence of symptoms, the interval between the two procedures, patient and organism characteristics, and lack of differentiation between acute postoperative PJI and late hematogenous PJI were not standard among all included studies.

In conclusion, the current analysis demonstrates an increased success rate of repeat DAIR when results of the entire cohort are reported (initial DAIR combined with repeat DAIR) in patients who have an acute PJI of the hip or knee. A shorter duration of time between the first and second DAIR and the exchange of modular parts is associated with increased success. Repeat DAIR procedures should be considered as a meaningful option over immediate one- or two-stage exchange arthroplasties. Shared decision-making between the surgeon and the patient is crucial, weighing the potential benefits and risks of repeat DAIR against alternative treatment strategies.

Question 7: How many debridement, antibiotics, and implant retention procedures are acceptable before consideration should be given to resection arthroplasty?

Response/Recommendation

Limited evidence suggests that after two failed debridement, antibiotics, and implant retention procedures, resection arthroplasty should be considered.

[6] These authors contributed to Question 6: Fatih Yıldız, Mustafa Alper Incesoy, Alvaro Auñon-Rubio, Osman Çiloglu, Massimo Franceschini, Akram A. Hammad, Huiwu Li, Felix Vilchez-Cavazos, Mark J. Spangehl

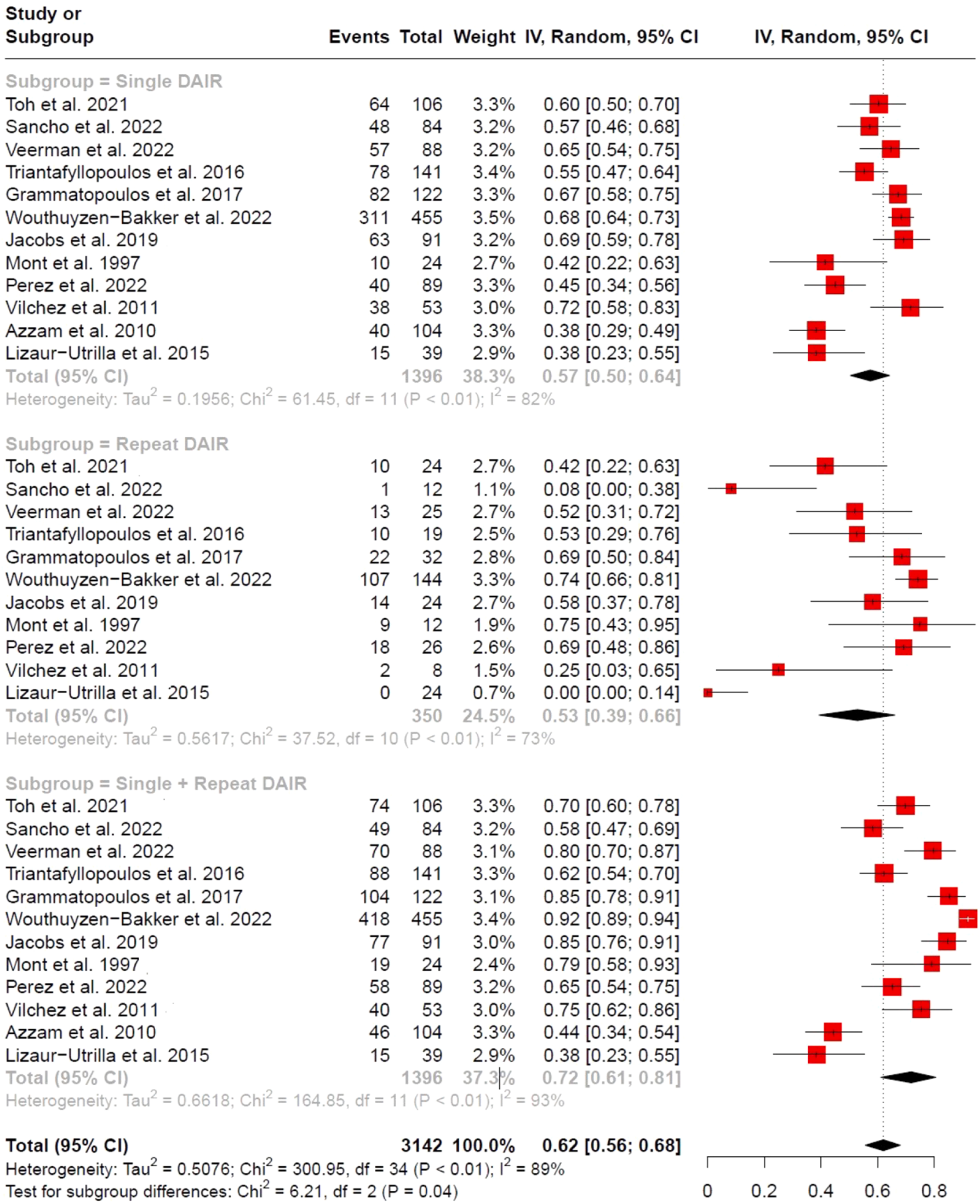

Figure 2. Forest plot illustrating the success rates of single and repeat debridement, antibiotics, and implant retention (DAIR) procedures in total knee and hip arthroplasty.

Level of Evidence: Limited

Delegate Vote: Agree 78.6%, disagree 18.0%, abstain 3.4% (strong majority, moderate consensus)

Rationale

Periprosthetic joint infections (PJIs) represent one of the most serious complications in total hip arthroplasty (THA) and total

knee arthroplasty (TKA). Prompt management of PJI is critical to preserve implant retention and improve outcomes. The debridement, antibiotics, and implant retention (DAIR) procedure is often used to manage early or acute infections. However, its efficacy diminishes with repeated attempts. Limited studies have investigated the rate of DAIR procedures and associated failure before considering resection arthroplasty in the context of total hip and knee arthroplasty.

Studies suggest that DAIR is most successful when performed as soon as feasible after symptom onset [190]. A 2019 study of 58 primary TKA patients treated with DAIR after acute PJI reported a success rate of 90% at two years if the DAIR procedure was performed within 90 days of the index TKA [191]. This level of success has not been consistently reported in the literature, with multiple studies reporting between 55 and 90% success rates in the primary setting [192]. A systematic review analyzed 14 studies involving 710 patients who underwent DAIR for early septic or late acute hematogenous PJI following hip or knee surgery. The average success rates for infection eradication were 45.9% after a single procedure and 52% after repeated procedures, with a mean follow-up of 53.3 months. Despite some methodological limitations and heterogeneity among the studies, the review concluded that DAIR has a relatively poor success rate with high rates of failure after multiple failed attempts [193]. Furthermore, in a study of 91 patients undergoing DAIR for suspected early PJI following primary TKA or THA, multivariable analysis revealed that higher failure rates were multifactorial, including multiple DAIR procedures ($\geq$ two) [194]. These results have also been reported in the setting of DAIR for revision arthroplasty. The study by Veerman et al., carried out in the setting of revision arthroplasty, showed that DAIRs performed with an interval of > 30 days after the index revision procedure (odds ratio [OR] 0.24, 95% confidence interval [CI] 0.08 to 0.72; $P = 0.008$) and a repeated DAIR within 90 days (OR 0.37, 95% CI 0.14 to 0.97; $P = 0.040$) were associated with a significantly reduced success rate of 68% at two years [195].

Patient health status, including the presence of comorbidities such as diabetes, immunosuppression, or obesity, can influence the success of DAIR [196]. Immunocompromised patients or those who have multiple comorbidities may have poorer outcomes with repeated DAIR attempts [197]. For these patients, resection arthroplasty should be considered earlier, even after a single failed attempt [198]. In cases where the implant has been compromised by the infection (e.g., loosening or mechanical failure), resection arthroplasty should be considered after even a single failed DAIR attempt, as continuing with DAIR may not resolve the infection or restore function [199].

The investigation of a planned second DAIR procedure was reported in a study that evaluated the failure rate of a second DAIR procedure in patients who have an acute PJI of the hip or knee, with the authors finding 25.7% failure in 144 cases. Independent predictors of failure included positive cultures during the second DAIR and chronic renal insufficiency. Despite the high proportion of failures, the study suggests that a second DAIR can still be a viable option for infection control and implant retention in acute PJIs, particularly when the soft tissue remains intact [200]. In addition, unplanned second DAIR procedures and subsequent failure have been investigated by Lin et al. In a 2024 study, a total of 138 patients, comprising 112 with initial DAIR and 26 with an unplanned second DAIR, were investigated. The overall success proportion for two-stage exchange arthroplasty was 87%, with factors such as reinfection with the same pathogen, high pre-DAIR C-reactive protein (CRP) levels, and a history of PJI within two years linked to higher failure after a single or unplanned second DAIR procedure. Implant failure rates remained consistent across all exchange arthroplasty cases, regardless of whether the DAIR procedure was initial or unplanned [201].

The largest systematic review and meta-analysis on multiple DAIR procedures was conducted by Salman et al. in 2024 [202]. This review examined nine observational studies composed of 1,104 participants, focusing on the effectiveness of single, double, and triple DAIR procedures in treating acute periprosthetic joint infections (PJI) following TKA and THA. The cohort had a mean age of 58 years (range, 25.8 to 91.0) and an average body mass index of 31.43 (range, 28.9 to 35.0). The studies had a mean follow-up period of 58.4 months (95% CI: 25.8 to 91.0), with a low overall risk of bias as indicated by an average methodological index for nonrandomized studies (MINORS) score of 17.6 ± 3.46. The review found no significant difference in success between single and double DAIR procedures. The proportion of successful single DAIR procedures was 67% (95% CI: 64 to 71%), whereas double DAIR had a slightly higher success rate of 70% (95% CI: 48 to 86%), with no statistically significant difference ($P = 0.740$). For triple DAIR, success ranged from 50 to 60%, suggesting diminishing returns with increasing numbers of procedures.

The study concludes that double DAIR is a valid treatment option for acute PJI following TKA and THA, showing a success rate comparable to single DAIR. However, the effectiveness of triple DAIR appears to be lower, with a success rate ranging between 50 and 60%. Interpretation of these data is difficult due to heterogeneity across the included studies, particularly in terms of patient comorbidities, DAIR protocols, and antibiotic regimens. The number of DAIR procedures performed is a crucial factor. Success rates for DAIR drop markedly after one failure, and after two failed DAIR procedures, the likelihood of retaining the prosthesis diminishes.

Conclusion

In conclusion, the threshold for considering resection arthroplasty in total hip and knee arthroplasty following multiple DAIR procedures in acute cases is typically set at two failed DAIR attempts; however, there are limited data without robust randomized controlled trials for comparison. Factors such as infection timing, microbial resistance, and patient health status all play a role in this decision. After two failed DAIR procedures, particularly in cases with chronic infection or resistant organisms, resection arthroplasty should be strongly considered as the next step in management. Early intervention is key to optimizing outcomes and preventing further complications.

Question 8: Should a previously nonresurfaced patella be resurfaced in patients who have acute periprosthetic joint infection of the knee undergoing debridement, antibiotics, and implant retention?[8]

Response/Recommendation

Resurfacing the patella in previously nonresurfaced patients undergoing DAIR for acute PJI can be performed at the surgeon's discretion if adequate patellar bone stock is available.

Level of Evidence: Weak

[8] These authors contributed to Question 8: Juan D. Lizcano, Robert Mcullogh, Vasily Artyukh, Christian Hipfl, Saad Tarabichi, George C Babis, Je-Hyun Yoo, Julio C Palacios, Jorge Manrique-Succar

Delegate Vote: Agree 81.7%, disagree 13.2%, abstain 5.2% (super majority, strong consensus)

Rationale

Patellar resurfacing in primary total knee arthroplasty (TKA) remains controversial, being mostly used in the United States compared to European countries, according to registry data [203]. While the impact of patellar resurfacing has been thoroughly investigated in primary TKA, its use in the setting of septic revision TKA has not been well delineated [204–206]. Patellar resurfacing may potentially enhance the area of antibiotic-loaded bone cement elution, affect patello-femoral biomechanics, and influence patient-reported outcomes [207,208]. However, the evidence supporting its use in septic revision cases remains limited.

The bulk of the literature focuses on patellar resurfacing at the time of reimplantation in staged exchange arthroplasty procedures. Buller et al. described a cohort of 103 consecutive 2-stage septic revisions without previous patellar resurfacing, in which the patella was resurfaced based on available bone stock. They found comparable PJI (four of 43, 9.3% versus two of 60, 3.3%) and aseptic (four of 43, 9.3% versus four of 60, 6.7%) revision among the resurfaced and unresurfaced cohorts ($P \geq 0.232$) [209]. Similarly, Joo et al. examined a smaller cohort of two-stage exchange procedures and found that more patients in the patellar resurfacing group developed PJI (three of 23, 13%, versus zero of 21, 0%). Of note, the authors did not perform any statistical comparison between groups for reinfection [210]. Although no differences have been reported in terms of reinfection, in a study by Glynn et al., patellar resurfacing at the time of reimplantation led to better functional outcomes, defined as a Knee Society Score ≥ 60, as opposed to patelloplasty (25 of 54, 46.3% versus two of 11, $P = 0.080$) [211].

However, the findings of the aforementioned studies cannot be extrapolated to patients undergoing debridement, antibiotics, and implant retention (DAIR) for acute infection, as many variables, such as infection chronicity and femoral and tibial implant exchange, could impact postoperative outcomes. Previously described risk factors for failure after DAIR include chronic infection, *Staphylococcus aureus* and Gram-negative infections, increased preoperative erythrocyte sedimentation rate, and repeat DAIR [212,213].

To explore the impact of patellar resurfacing in DAIR procedures for acute infection, we screened 474 articles and found that none of them examined postoperative outcomes in this patient population. A sizable number of the articles focused on the role of tibial polyethylene exchange in reinfection rates [214]. Only two articles quoted a "retention of the patellar component when present" [215,216]. However, none of the articles stratified the patients based on the type of patella at the time of the DAIR. The lack of literature surrounding this topic could be explained by the high rates of patellar resurfacings during primary arthroplasty procedures, primarily in North America, in addition to the relatively low incidence of PJI and the need to control for additional variables leading to complex study designs.

Taking into account the rising incidence of PJI and DAIR procedures for treating infections in the acute postoperative period, we encourage investigators to provide a detailed description of the patellar component as part of the methodology and potential variables influencing the risk of PJI and extensor mechanism-related outcomes [217,218].

Conclusion

Resurfacing the patella in previously nonresurfaced patients undergoing DAIR for acute PJI can be performed at the surgeon's discretion if adequate patellar bone stock is available [219].

Question 9: Does a prior debridement, antibiotics, and implant retention procedure influence the outcome of subsequent exchange arthroplasty in patients who have a periprosthetic joint infection?[9]

Response/Recommendation

Prior DAIR may be associated with an increase in the likelihood of failures in two-stage reimplantation. This may be due to selection bias; those patients failing DAIR may be sicker or have organism-related or surgery-related factors predisposing them to worse outcomes.

Level of Evidence: Limited

Delegate Vote: Agree 70.7%, disagree 17.1%, abstain 12.2% (strong majority: moderate consensus)

Rationale

Among the treatments for periprosthetic joint infection (PJI), debridement, antibiotics, implant retention (DAIR), and two-stage revision are widely used. A DAIR is less invasive, less morbid, and less costly but has failure rates ranging from 10 to 44.5% (mean: 29%) [220]. This raises the question of whether a failed DAIR procedure affects the outcome of the subsequent two-stage revision. The previous International Consensus Meeting had an inconclusive response to the above-posed question due to limited evidence. With new evidence, we tried to draw further conclusions.

A comprehensive database search, including PubMed, Scopus, Web of Science, and Embase, found 772 papers. Studies were identified, and after two-step screening, seven were selected for a meta-analysis. All studies were retrospective cohorts [221–227]. Outcomes measured in the collected studies are (1) success of the procedure, (2) functional knee scores, and range of motion (Table 4).

The overall success rate of direct two-stage revision is 85%, whereas it is 79% for failed DAIR. There was a high heterogeneity between studies ($I^2 = 64\%$). Though in general, pooled study data favored two-stage revision over failed DAIR, the result was not significant (odds ratio [OR] = 0.655, confidence interval [CI] = 0.393 to 1.092; $P = 0.105$; Figure 3). Sensitivity analyses showed that excluding certain studies made the results significant, favoring two-stage revision over failed DAIR (Figure 4). The retrospective observational study of Brimmo et al. [221] has inherent limitations, including the lack of detailed clinical information, variability in treatment protocols, and restrictions on publishing small cell sizes. The follow-up period was limited to four years, potentially missing late failures. The authors also decided to exclude anyone who had a DAIR greater than two years before their two-stage procedure. Additionally, this study has some statistical flaws. The study lacks a discussion on statistical power, particularly due to the small sample size in the DAIR group ($n = 57$), which might limit the ability to detect significant differences. Kaplan-Meier curves are suitable, but small group differences and lack of significance suggest low statistical power.

Excluding Brimmo et al. [221] resulted in a change in the overall pooled OR from 0.655 (CI: 0.393 to 1.092) to 0.554 (CI: 0.354 to 0.874), making the results significant ($P = 0.011$) and favoring direct two-stage revision over one carried out after a prior failed DAIR (Figure 4). This change not only resulted in statistically significant findings but also reduced the heterogeneity from $I^2 = 64\%$ to $I^2 = 49\%$, indicating improved consistency among the included

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Table 4
Summary of Studies[a]

Study	Location	Joint Studied	Groups	Sample Size	Mean Age (years)	Men (%)	ASA Classification 3&4	ASA Score	CCI	Success Rate (%)	Definition of Success	Follow-Up Time	HR for Failed DAIR	Outcomes
Brimmo 2016	USA	Knee	Failed DAIR	57	68 ± 10.4	58	-	-	-	91.3	No subsequent surgery due to infection within 4 years	2 to 4 y	0.49 (0.2 to 1.2)	Prior DAIR has no effect ($P = 0.1$)
			No DAIR	693	66 ± 11.1	47	-	-	-	82.5				
Nodzo 2017	USA	Knee	Failed DAIR	45	66 ± 11.4	53.3	-	2.4 (0.5)	3.1 ± 1.9	82.2 93.3	(1) The lack of clinical signs and symptoms at final postreimplantation follow-up without the need for any further surgical intervention for infection (2) The lack of clinical signs and symptoms of infection at final postreimplantation follow-up with retention of components.	4.53 (2.45 to 6.61) years	-	Prior DAIR has no effect ($P = 0.957$)
			No DAIR	132	65 ± 9.8	62.9	-	2.4 (0.5)	3.5 ± 2	82.5 96.2				
Rajgopal 2018	India	Knee	Failed DAIR	88	69	48.9	23	2.23	-	79.54	(1) Successful eradication of the infection after the 2-stage procedure;. (2) No recurrence of infection, with negative culture reports;. (3) No need for chronic antibiotic suppression for more than 6 mo; and (4) No requirement for further surgical procedures due to successful eradication of the infection.	5.3 (2.5 to 9.8) y	1.94 (1.01 to 3.714)	Prior DAIR has a negative effect[a] ($P = 0.047$)
			No DAIR	96	68	36.5	36	2.32	-	85.41				
Kim 2019	New Zealand	Knee	Failed DAIR	75	64 ± 9.6	61.3	-	2.4 (0.7)	3 ± 1.9	72.0 80.0	(1) Retention of components without antibiotics at follow-up	6.18 (2.48 to 9.88) years	0.57 (0.27 to 1.1)	Prior DAIR has no effect ($P = 0.222$)
			No DAIR	63	67 ± 10.3	58.7	-	2.7 (0.8)	3.3 ± 1.9	81.0 84.1	(2) Retention of components with or without antibiotics at follow-up			
Lizaur-Utrilla 2019	Spain	Knee	Failed DAIR	43	73 ± 6.2	34.9	14	-	2.7 ± 1.6	62.7	Complete resolution of the infection following the initial surgical procedure, without the need for additional surgery, prolonged antibiotic treatment, or recurrence of the infection.	4.1 (3 to 7) years	-	Prior DAIR has a negative effect ($P = 0.046$)
			No DAIR	49	72 ± 7.5	22.4	12	-	2.2 ± 1.2	81.6				
Kavolus 2020	USA	Hip	Failed DAIR	49	57 ± 13.8	46.9	-	-	-	51.1	No additional surgery required due to infection after reimplantation.	2 years minimum	-	Prior DAIR has a negative effect ($P < 0.001$)
			No DAIR	65	63 ± 13.2	53.8	-	-	-	87.7				
Huffaker 2022	USA	Knee	Failed DAIR	150	-	-	-	-	-	88.6	No reoperation performed after the DAIR or 2-stage revision where an implant was exchanged for infectious reasons	10 years	1.11 (0.58 to 2.12)	Prior DAIR has no effect ($P = 0.647$)
			No DAIR	410	68 ± 8.9	49.3	224	-	-	90				

CCI, Charlson comorbidity index.
[a] Based on HAZARD RATIO.

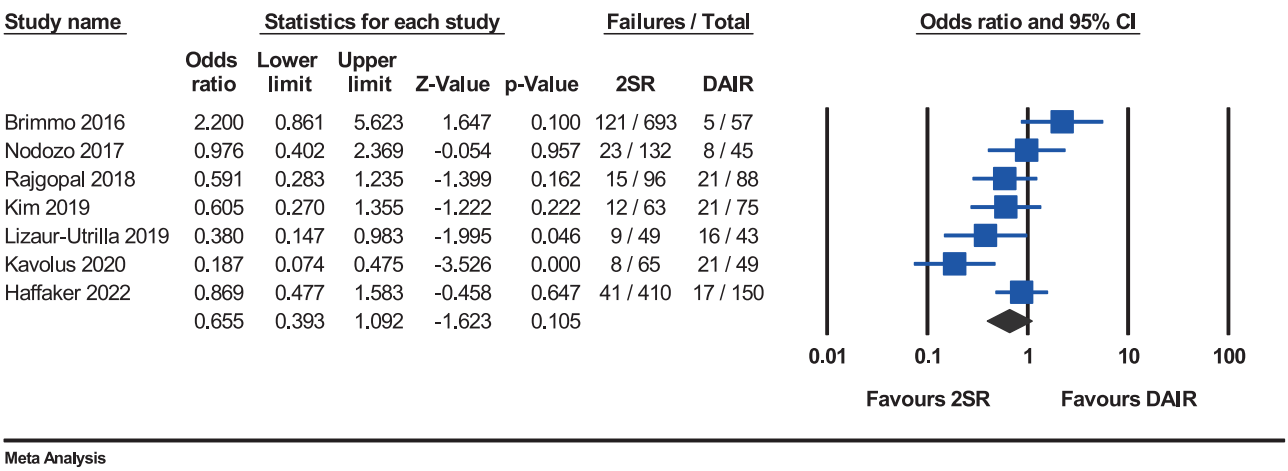

Figure 3. Forest plot for 2SR failure rates. 2SR, 2-stage revision; CI, confidence interval.

studies. However, heterogeneity among studies remained moderate.

The negative effect of prior DAIR on subsequent two-stage revision might be due to an inherent selection bias. Patients who were optimal hosts, had an infection with a sensitive organism, and received an adequate DAIR in a timely manner were excluded based on the successful eradication of infection. This might have resulted in only those who failed their DAIR being left as a group of poor hosts with more virulent organisms and who experienced delayed or inadequate debridement.

There were two studies [223,224] that compared the functional outcomes of two-stage revision after prior DAIR and direct two-stage revision. They found that the range of motion was significantly lower in the DAIR group. Both studies reported lower clinical and functional Knee Society Scores in the DAIR group, although only one study showed a statistically significant difference.

This meta-analysis has several important potential limitations. Most of the included studies are retrospective and observational. There is a risk of selection bias, where more compromised patients may have been preferentially treated with DAIR initially to avoid the morbidity of a resection. However, most studies included adjusted analyses to account for host quality in an attempt to address this limitation. Also, there is a moderate heterogeneity between the included studies.

In conclusion, the findings of this meta-analysis suggest that a prior DAIR procedure may negatively impact the outcomes of subsequent two-stage reimplantation in patients who have a PJI. The overall success rate of direct two-stage reimplantation is higher compared to one carried out in patients who have a failed DAIR, and functional outcomes such as range of motion and Knee Society Scores are generally lower in the DAIR group. However, the results also highlight the inherent potential limitations and variability among the included studies, such as selection bias and

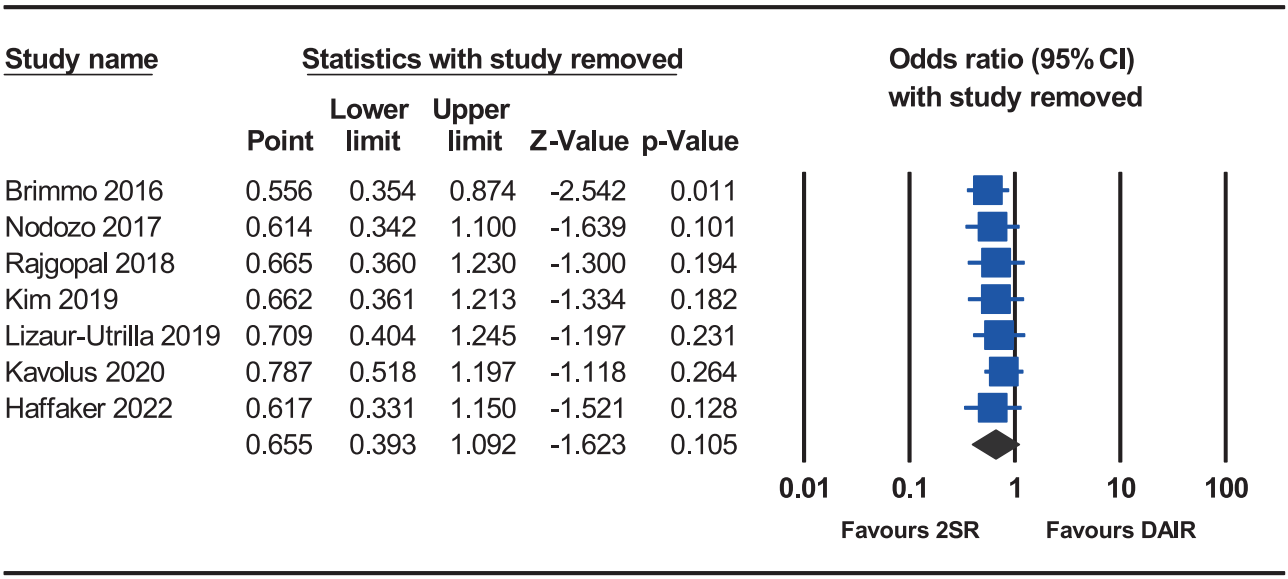

Figure 4. Sensvity analyses of outcomes.

differences in treatment protocols. Despite these limitations, the evidence indicates that careful consideration should be given when opting for DAIR, as it may compromise the success of future revision surgeries. Further research with more robust study designs is needed to confirm these findings and provide clearer guidance for clinical practice.

Question 10: Does the type of infective organism influence the success rate of debridement, antibiotics, and implant retention?[10]

Response/Recommendation

Yes. Based on retrospective studies, the type of infective organism appears to influence the success rate of DAIR.

Level of Evidence: Moderate

Delegate Vote: Agree: 80.1%, Disagree: 12.3%, Abstain: 7.6%

Rationale

There are a number of factors that influence the outcome of DAIR in patients who have acute periprosthetic joint infections (PJIs; REF). To answer the question posed above, we conducted a comprehensive review of the literature. Using MeSH terms developed by librarians, we searched for the designated Patient/Problem, Intervention, Comparison, and Outcome terms in two databases (PubMed and Embase). There were 453 studies that were initially identified as appropriate. After screening, 112 studies met the inclusion criteria for full review and data extraction. All the studies reviewed were retrospective in nature and attempted to investigate the influence of organism type on the success of DAIR.

Several studies have demonstrated that infections caused by *Staphylococcus aureus* are associated with a significantly increased risk of treatment failure [228–233]. Reported odds ratios (ORs) for failure vary between 3.27 ($P = 0.02$) [234] and 7.1 ($P = 0.0012$) [235]. When comparing methicillin-resistant *S. aureus* (MRSA) with methicillin-sensitive *S. aureus* (MSSA), Lora et al. [236] analyzed a series of 345 patients. Although they found no overall prognostic differences between MRSA- and MSSA-related PJIs, there was a higher incidence of treatment failure in MRSA-PJI during therapy (hazard ratio [HR] 2.34).

Scheper et al. [237] conducted a systematic review and meta-analysis of 4,380 patients and reported that the overall success rate of *S. aureus* treatment after debridement, antibiotics, and implant retention (DAIR) was 62% (based on 2,922 patients across 54 studies). When comparing MRSA and MSSA outcomes, no significant difference was found (MRSA: 58%, MSSA: 60%; $P = 0.459$). This trend remained consistent when outcomes were analyzed by joint type.

For late acute infections, *S. aureus* was identified as a significant independent variable for treatment failure [238] with an odds ratio (OR) of 1.8 ($P = 0.03$) [239]. Treatment success rates for late acute PJIs were significantly lower (34%) compared to 75% for other PJIs ($P < 0.001$) [240]. In another study by Nandi et al. [241] on 115 patients, infections with *S. aureus* were associated with a much higher risk of reoperation due to recurrence in total knee arthroplasty (TKA) infections (OR 24.9; $P = 0.0004$). Conversely, Huotari et al. [242] studied 85 acute *S. aureus* PJIs treated with DAIR, reporting that the original implant was retained in 80% of patients (89.3% in late acute PJIs and 75.4% in early acute PJIs). Suppressive antibiotic therapy, which was not considered a failure in their study, was administered to 26.5% of patients and was more commonly used in late acute PJIs (46.2 versus 17.5% for early acute PJIs; $P = 0.006$).

After *S. aureus*, enterococcal PJIs are also associated with poor outcomes [228,243]). The largest study on enterococcal PJIs, conducted by Tornero et al. [244], analyzed 94 patients treated with debridement, antibiotics, and implant retention (DAIR). Their findings were that *Enterococcus* infections were challenging to treat as they frequently occurred in the context of polymicrobial infections in hosts that had comorbidities.

Gram-negative infections have also been identified as predictors of failure after DAIR. Zhu et al. [230] reported an increased risk of failure for patients who have Gram-negative PJI (OR 1.85, $P = 0.027$). Similarly, Rodríguez-Pardo et al. [245] documented a DAIR success rate of only 41% in Gram-negative, ciprofloxacin-resistant PJIs. Papadopoulos et al. [246] further highlighted that DAIR is associated with significantly higher failure rates in multidrug-resistant (MDR) and extensively drug-resistant (XDR) Gram-negative bacterial (GNB) PJIs compared to implant removal (OR 3.57, $P < 0.001$).

In a systematic review, González et al. [247] observed 1-year and 2-year free-of-treatment failure rates after DAIR for acute infections: 65 and 67% for hip PJIs and 67 and 72% for knee PJIs. Among these cases, *Proteus spp.* infections were identified as significant risk factors for treatment failure in acute PJIs.

Streptococcal infections appear to be associated with a poorer prognosis. Also, Lora et al. [248], in a study of 462 patients, reported a failure rate of 42.1%. While no specific Streptococcal species was significantly linked to higher overall failure rates, a nonsignificant trend suggested a better prognosis for *S. pneumoniae*. These findings are consistent with those of Mahieu et al. [249], who observed a poor prognosis for patients treated with DAIR: 50% experienced relapse, whereas all patients treated with prosthesis exchange did well with no (adjusted $P < 0.001$). In addition, *S. agalactiae* was identified as an independent factor for treatment failure. Supporting this, Fiaux et al. reported that DAIR was associated with a higher risk of failure, particularly in patients who have an infected total knee arthroplasty [250]. In contrast, Lam et al. [251] reported a notably high success rate of 91% for patients treated with the DAIR strategy as the final surgical procedure.

Polymicrobial infections appear to be associated with a worse prognosis, as evidenced by data from Bernaus et al. [252] ($P = 0.024$) and Chen et al. [253] ($P < 0.01$), both of which highlight significantly higher failure rates in these cases compared to monomicrobial infections.

Also, fungal infections have been associated with poor outcomes. In a recent study, Dinh et al. [254] identified the use of DAIR (OR, 1.946, $P = 0.012$) and infections caused by *C. parapsilosis* as significant risk factors for treatment failure. Similarly, González et al. [255], in a systematic review of fungal PJIs, concluded that two-stage revision is more effective than DAIR in preventing recurrence. Specifically, two-stage revision showed a protective effect against recurrence in hip and knee PJIs (OR 0.20, $P = 0.016$) and knee PJIs alone (OR 0.18, $P = 0.04$).

The 2018 International Consensus Meeting on fungal infections recommended that DAIR should be offered selectively to immunocompromised patients because of its relatively high failure rates. DAIR is best reserved for truly acute PJIs after the initial arthroplasty, especially in otherwise healthy patients (type A).

In conclusion, and based on our research, it appears that a number of factors influence the outcome of DAIR in patients with acute PJI. One of those factors appears to be the type of infective organism. The presence of resistance, such as methicillin resistance, and infection with fungal organisms and polymicrobial infections are among the challenging infections to treat and carry a relatively high failure rate after DAIR.

[10] These authors contributed to Question 10: Álvaro Auñón, Rene Mihalič, Claudia Arias, Ignacio Sancho, Jay D. Shah, Ibrahim Tuncay, Enrique Gómez-Barrena, Sumon Nandi

Question 11: What is the optimal duration of antimicrobial treatment for patients undergoing debridement, antibiotics, and implant retention (DAIR) for acute periprosthetic joint infection (PJI)?[11]

Response/Recommendation

A minimum of 12 weeks of antibiotic therapy is recommended for patients undergoing DAIR for acute PJI.

Strength of Recommendation: Strong

Delegate Vote: Agree: 70.5%, disagree: 23%, abstain: 6.5%

Rationale

The Duration of Antibiotic Treatment in Prosthetic Joint Infection trial was a high-quality, randomized, open-label, noninferiority study that investigated the optimal duration of antimicrobial therapy for PJIs treated with different surgical interventions, including DAIR [256]. The trial, conducted across 28 French centers, compared the outcomes of six versus 12 weeks of antibiotic therapy.

A total of 410 adult patients who had microbiologically confirmed hip or knee PJI were randomized into two groups receiving either six or 12 weeks of antibiotics. The primary outcome was the rate of persistent infection, defined as the recurrence of the original pathogen within two years after treatment completion. The primary analysis revealed a higher rate of persistent infection in the 6-week group (18.1%) compared to the 12-week group (9.4%), with a risk difference of 8.7 percentage points (95% CI, 1.8 to 15.6); thus, noninferiority of the 6-week regimen was not established. Per-protocol and sensitivity analyses were consistent with these findings. Notably, the difference was larger among the patients managed with DAIR, emphasizing the need for a longer antibiotic course in this subgroup (16.2 risk difference; 95% CI, 2.9 to 29.5).

The findings demonstrated that a 12-week antibiotic regimen provided superior treatment outcomes compared to 6 weeks, particularly in cases managed with DAIR. This extended duration likely ensures better eradication of infection within retained implants, where biofilms pose a challenge to eradication.

Another randomized, multicenter clinical trial focused exclusively on acute postoperative or hematogenous staphylococcal PJIs managed with DAIR [257]. The trial was performed in 17 Spanish hospitals and compared the outcomes of eight weeks of treatment (short schedule) versus a long schedule (three or six months for hip or knee PJI, respectively). The primary outcome was the rate of cure, defined as retention of the prosthesis and resolution of infection based on examination. A total of 63 patients were included, and the median follow-up period was 540 days. The intention-to-treat analysis revealed cure rates of 58 and 73% in patients receiving the long and short schedules, respectively (risk difference −15.7%, 95% CI −39.2 to 7.8%). The findings of this clinical trial suggested that an 8-week regimen may be sufficient. However, it is important to note that the trial exclusively analyzed patients who have early or acute hematogenous staphylococcal PJI treated with levofloxacin and rifampin, and therefore, the results cannot be generalized to patients who have other microbial etiologies or are managed with other antibiotic therapies. Furthermore, this study was terminated early and did not achieve its target sample size of 195, markedly limiting the power of the study.

Some observational studies have attempted to investigate the effectiveness of longer durations of therapy, including suppressive antimicrobial therapy (SAT), in this setting. A systematic review included seven studies, predominantly retrospective, with low-level evidence, comprising 772 cases of PJI. The findings revealed that the mean infection-free survival rate following DAIR combined with SAT was 75% ($n = 424$) [258]. Importantly, the studies varied markedly in the duration of SAT, which ranged from 1.5 years to over five years. The review also underscored the heterogeneity in study designs, definitions of success, and patient populations, which limits the ability to draw definitive conclusions.

A multicenter study found significantly higher infection-free survival (68.5 versus 39.4%) in patients receiving extended oral antibiotics beyond six weeks compared to those receiving only initial therapy (adjusted hazard ratio [HR] 0.4, 95% CI 0.21 to 0.86; $P = 0.2$) [259]. They observed diminishing returns after 12 months of therapy, concluding that there is a benefit to continuing antibiotics up to a year.

Another study investigated the outcomes of 115 patients who had acute hip or knee PJI who underwent DAIR between 2015 and 2020 [260]. The study found that reoperation-free survival at a mean follow-up of 2.8 years was 83.3% for TKA patients and 65.1% for THA patients. It concluded that longer SAT durations were linked to a reduced risk of reoperation, with the optimal duration identified as approximately two years (TKA: OR 0.89; 95% CI 0.8 to 1.0; $P = 0.04$; THA: OR 0.88; 95% CI 0.78 to 1.0; $P = 0.04$).

Observational studies are markedly limited in investigating this question. Immortal time bias is a potential issue in these studies, particularly regarding the assessment of SAT duration and its impact on outcomes. In these studies, patients who survived longer were more likely to receive prolonged SAT, which could create a bias favoring longer durations. For example, if a patient dies or undergoes early reoperation, they cannot contribute to the longer SAT group, potentially making this group appear to have better outcomes.

A multicenter retrospective study examined the impact of SAT on the outcomes across centers in Europe and the United States [261]. The analysis used a Cox model landmarked at 12 weeks, with SAT treated as a time-varying covariate to address immortal time bias. A total of 510 patients were included, with 66 treatment failures and a median follow-up of 801 days. The study did not find a statistically significant association between SAT and treatment failure (HR 1.37; 95% CI, 0.79 to 2.39; $P = 0.27$), and subgroup analyses for joint, country cohort, and type of infection (early or late acute) also did not reveal a benefit from routine SAT. The study found that the majority of patients remained infection-free after 12 weeks, even without SAT, supporting findings from other studies in countries without routine SAT use.

A notable potential limitation was selection bias. The study could not exclude patients in the US cohort who were prescribed SAT due to concerns about persistent infection, which likely skewed the results against the use of SAT in the analysis. Furthermore, differences between the US and European cohorts, such as longer symptom duration, higher body mass index, and more comorbidities (e.g., rheumatoid arthritis, chronic obstructive pulmonary disease), may have contributed to poorer outcomes in the US cohort that uses routine SAT.

Conclusion

Based on available evidence, the optimal duration of antimicrobial treatment for patients who have acute bacterial PJI managed with DAIR is at least 12 weeks. More studies are needed to assess the impact of highly active antibiofilm agents and various microbial etiologies on the duration of therapy. Robust, adequately powered randomized controlled trials are needed to determine the utility of therapy beyond 12 weeks. Also, future studies should

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investigate the risk factors for failure of DAIR after completion of antibiotic therapy to identify the candidates best suited for SAT.

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The Journal of Arthroplasty 41 (2025) S326–S340

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Hip and Knee

2025 ICM: One-Stage Exchange

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Question 1: What is the optimal treatment for acute postoperative periprosthetic joint infection for patients who have received uncemented implants?[1]

Response/Recommendation

Inconclusive. Based on the available data, there is no optimal treatment for acute postoperative periprosthetic joint infection (PJI) in patients with cementless implants. At a minimum, a debridement, antibiotics, and implant retention (DAIR) with modular component exchange should be performed, and in the absence of osseointegration, a one-stage exchange could be considered.

Level of Evidence: Limited

Delegate Vote: Strong consensus: Agree 86.1%, Disagree 5.6%, Abstain 8.3%

Rationale

The recommended surgical treatment of acute postoperative periprosthetic joint infection (PJI) has traditionally been a debridement, antibiotics, and implant retention (DAIR) with or without modular component exchange. The success of this approach has been quoted in the literature to be approximately 70%. Failure can be potentially attributed to the existence of biofilm, and therefore, other treatment options have been considered and explored, including multiple DAIR and one-stage exchange revision. The scenario of an acute postoperative PJI involving cementless implants poses a conundrum since sufficient time may not have passed to allow for solid osseointegration within the first four to six weeks after implantation. Therefore, some surgeons rationalize explanting all components and performing a one-stage revision to allow more aggressive debridement of the bony interfaces and remove all potential biofilm-covered implants without incurring the morbidity of removing well-fixed implants at a later stage if DAIR fails.

Historically, since most primary total hip arthroplasties (THAs) implanted are cementless and most primary total knee arthroplasties (TKAs) are cemented, the majority of the data focuses on acute postoperative PJI of primary THA. However, cementless TKA and revision cementless THA will also be reviewed.

There are many limitations in the current literature on the optimal treatment of acute postoperative PJI in cementless implants:

- Historic definitions of an early or acute PJI utilized a 3-month postoperative threshold. However, the majority of the recent literature on acute, postoperative PJI now utilizes a cutoff limit of two to six weeks. This will unquestionably have a pivotal role in interpreting the existing literature, which has been published over a long period of time, with an evolving understanding of the necessity of thorough surgical debridement to remove biofilm. This review has utilized a pragmatic approach, and the definition of acute PJI of less than six weeks has been adopted by the individual authors unless otherwise specified.

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.099.

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https://doi.org/10.1016/j.arth.2025.10.099
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- Furthermore, the acuity has serious clinical implications for the likelihood of osseointegration of cementless implants and progression of biofilm formation.
- Many studies combined acute postoperative and acute hematogenous PJIs in the treatment of the 'acute PJI,' and therefore, the results are often merged without stratification. The delegates performed sub-analyses of cohorts when the details were available. There is tremendous heterogeneity in terms of protocols and treatment strategies, including, but not limited to, modular component exchange, use of antiseptic solutions, local antibiotics, and postoperative antibiotic courses. This confounds the overall success rates of each treatment strategy.

DAIR

Historically, the recommended surgical treatment of acute postoperative PJI following total joint arthroplasty has been DAIR, and as a result, the vast majority of the literature on this topic has focused on this strategy. There is wide variability in the reported success of DAIR for acute postoperative PJI, ranging from 55.5 to 90% across many studies, with an average of 71% [1]. Multiple prognostic factors have been identified that may impact the success of this procedure, including joint affected [2], exchange of modular components [3], acuity of infection [4,5], preoperative infectious laboratory values [2,6], patient comorbidities [2], gender [7], organism type and resistance profile [8,9], dual surgical setup [10], local antibiotic use [11–13], and postoperative antibiotic courses [14–16].

Modular component exchange provides greater access to irrigate and debride the whole joint and implant surfaces that may harbor biofilm. In a systematic review on the topic, Gerritsen et al. reported the success rate for hip DAIRs increased by 2.6% for each 10% increase in component exchange, but there was no significant difference in reinfection rates when restricted to more modern studies after 2004 [17].

Most studies report that earlier DAIR after index arthroplasty provides improved outcomes, though that threshold is not well defined in the literature: one week or less [5,18], less than 45 days [3], less than six weeks [19], and less than three months [20].

Significantly elevated preoperative inflammatory laboratories, likely reflecting a more virulent organism and aggressive infection, have been associated with a higher failure rate after DAIR for acute postoperative PJI: ESR greater than 60 [6], C-reactive protein greater than 200 [9], synovial WBC greater than 5,168/mL, and PMN% greater than 88.5 [2].

Host factors also play a major role in a patient's ability to clear an infection, especially as it relates to systemic inflammation and immunosuppression leading to failure of DAIR: elevated body mass index (BMI) (> 35, [9]), rheumatoid arthritis [6], increased CCI (odds ratio (OR) 1.57) [2], and ASA (American Society of Anesthesiologists) classification greater than 2 [9].

There is one systematic review that has evaluated the impact of sex on outcomes of PJI after DAIR and found that the odds of treatment failure were 29% lower in women after adjusting for duration of symptoms > seven days and *S. aureus* infection, though the authors note that none of the 64 studies included in the paper conducted sex-specific analyses [7].

Local antibiotic adjuncts have demonstrated promising results in the setting of PJI treatment: antibiotic-loaded hydrogel (DAC: Defensive Antibacterial Coating) [21] [22], antibiotic-impregnated cement and cancellous allograft bone [23,24], intra-articular infusion [12], and intraosseous antibiotics [25].

Most studies support a minimum of a 6-week course of parenteral antibiotics following DAIR procedures. There has been a trend toward shortened courses without affecting the results [14]. The addition of rifampin may be considered for *Staphylococcus* infections because of its unique mechanism of action against biofilm [26]. Oral suppressive antibiotics of varying durations are often initiated following completion of the intravenous (IV) course, though the length of treatment differs. There was one multicenter study suggested that the optimal duration is two years and does not induce resistance [15]. However, these suppressive antimicrobials are not benign, with at least one systematic review demonstrating a mean adverse effect of 15 and a 4% rate of adverse events leading to discontinuation [16].

Multiple DAIR

The planned "double DAIR" for acute postoperative PJI is a protocol in which an initial DAIR (without component exchange) is followed by a second DAIR (with modular component exchange) and has reported infection control rates of 94 to 100% in primary THA and 72% in revision THA [27,28]. A systematic review and meta-analysis comparing the outcomes of single versus multiple DAIR for early PJI included nine observational studies with 1,104 patients and included both hips and knees, finding that the success rate of the two approaches was similar (67 and 70%, $P = 0.7$) [29]. It was not possible to separately analyze the hip results compared to the knee results in this study, which may have blunted the true benefit of multiple DAIR procedures for the acutely infected THA because of the often inferior results of infected knees.

Unplanned second DAIR operations may also have some utility as an alternative to component exchange. A multicenter cohort study demonstrated a high success rate of a second DAIR in patients who had clinical failure of the first DAIR, and the implant could be retained in 84% of cases [20]. The study included acute postoperative PJI in 129 of 144 repeat DAIR and a majority of hips (105 of 129).

One-stage exchange

The one-stage exchange arthroplasty, initially described by Buchholz et al. [30] for chronic infections, relied on preoperative identification of the infecting bacteria and the use of microbe-directed antibiotic-cemented revision components. Since that time, the technique has undergone iterative improvements and expanded indications over the past decades. In an acute postoperative infection of cementless implants that have not achieved osseointegration, the one-stage exchange arthroplasty allows for the removal of all biofilm-covered components with minimal additional surgical morbidity. Component removal facilitates a more thorough debridement of all bony interfaces and the potential for improved infection-free survivorship. Riemer et al. published a series of 18 patients who had acute postoperative (< six weeks) PJI after primary THA using this CORIHA (Cementless One Stage Revision of Infected Hip Arthroplasty) technique, with all patients retaining their implants at a minimum of 3-year follow-up and only two further surgeries for superficial irrigation and debridement [31]. A separate multicenter study including 27 similar patients reported that 19 (70%) were able to retain their implants at a mean of 50-month follow-up, with four patients requiring further operative debridement with modular component retention [32].

Cementless TKA

In recent years, there has been a rapid adoption of cementless total knees [33,34]. Similar to a primary total hip, an acutely infected cementless total knee before bony fixation could be treated with DAIR or a one-stage exchange arthroplasty. However, there have been no publications to date on this particular topic. If extrapolating data from acute hip PJI, a DAIR may also be reasonable if the cementless TKA has not achieved osseous ingrowth at

the time of surgery. A one-stage exchange arthroplasty with antibiotic-loaded bone cement could be considered if able to be performed with minimal iatrogenic bone loss during explant, with the added benefit of local antibiotic delivery.

Revision arthroplasty

Revision hip arthroplasty carries a much higher risk of infection than primary THA, and most revision constructs are cementless because of the documented improved survivorship compared to their cemented counterparts. However, very little is written about the treatment of the acutely infected revision total hip. [27,35]. One study provided the outcome of DAIR for 88 early postoperative (less than 90 days) infected arthroplasties, of which 53 were revision THA. They found that 72% of their infected revision total hips were successfully treated at a minimum of two years of follow-up [35]. Utilizing a double DAIR technique, Chung et al. reported a similar success rate in 13 of 18 patients in their revision hip cohort. It is noteworthy that more than half of these patients were on suppressive antibiotics at the last follow-up [27].

Conclusions

The acute postoperative PJI in a patient who has cementless implants presents a conundrum for the treating surgeon. A one-stage exchange arthroplasty represents an attractive option to facilitate removal of biofilm-covered implants and allow for a more aggressive surgical debridement. Thorough debridement of all necrotic and infected tissues is a critical component of surgical procedures for these patients. It is technically easier and less morbid to remove cementless components before osseointegration, thereby removing potential biofilm-coated implants and surfaces. The current literature on this topic is very heterogeneous, reporting varying infection control rates with various intraoperative adjuncts (e.g., antiseptics, local antibiotics, etc.) combined with different postoperative antibiotic treatment courses. Successful and nearly equivocal results have been demonstrated with DAIR and double DAIR for both primary and revision cementless total hip implants. Currently, there is no data on the scenario of an acutely infected cementless TKA, but with the recent rise in popularity of cementless TKA, future studies on this topic are needed. In summary, there are many factors that more accurately predict the successful treatment of an acute postoperative infection in a patient who has cementless implants. Customized, patient-specific decisions to choose DAIR versus one-stage exchange revision should be made considering the acuity of infection, host and microbial factors, implant modularity, available sensitive antibiotics, and degree of osseointegration of cementless components. Future studies are required to clarify the optimal treatment in this challenging cohort of patients.

Question 2: Are there any absolute contraindications to performing one-stage exchange arthroplasty for patients who have chronic periprosthetic joint infection (PJI)?[2]

Response/Recommendation

No. We do not feel that there are any absolute contraindications to one-stage exchange arthroplasty. However, relative contraindications may include signs of systemic sepsis, severely immunocompromized status, and extensive soft-tissue defects that compromise primary wound closure.

Level of Evidence: Moderate

Delegate Vote: Agree 90.1%, Disagree 7.6%, Abstain 2.4% (total consensus, unanimity)

Rationale

The reasonable indications and contraindications for one-stage exchange arthroplasty have long been at the center of debate, particularly as recent evidence increasingly supports its comparable infection control rates to two-stage revision, along with the benefits of reduced patient morbidity, improved functional outcomes, and lower costs [36–38]. Since Professor Buchholz first introduced the concept of one-stage exchange arthroplasty in 1981 [39], strict patient selection has consistently been regarded as a critical prerequisite for achieving excellent outcomes [40]. According to the 2018 International Consensus Meeting on orthopaedic infections, "in patients with signs of systemic sepsis, extensive comorbidities, infection with resistant organisms, culture-negative (CN) infections, and poor soft-tissue coverage, one-stage exchange arthroplasty may not be a good option." This recommendation received a 93% agreement rate, reflecting a high level of consensus [41]. Following a thorough search of articles published after 2018 that explicitly outlined contraindications for one-stage revision, we identified that systemic sepsis and poor soft-tissue coverage, though not directly supported by clinical studies, have been widely acknowledged across regions based on the inherent "2-in-1" characteristics of one-stage exchange arthroplasty (Table 1). In contrast, the other three factors—extensive comorbidities, CN infections, and infection with resistant organisms—have been subjected to validation or questioned by various studies over the past few years.

Conducting randomized controlled trials to evaluate contraindications for one-stage exchange arthroplasty is inherently challenging due to practical and ethical constraints. Therefore, most studies are retrospective with 2- to 5-year follow-up. Despite their limitations, they provide valuable insights, and our conclusions are derived from a combination of these studies and systematic reviews that synthesize the available evidence.

The overall health status of the host is a crucial factor in determining the success of treating PJI. Ji et al. [50] reported a small series of 17 immunocompromized patients who underwent one-stage revision, achieving infection eradication in only eight cases (47%) over a mean follow-up of 68 months. Both patients who have recurrent infections exhibited severe immunosuppression with extensive comorbidities. Similarly, Wolf et al. [51] found poor infection eradication rates for one-stage revision in compromised patients (McPherson type B plus C), with eradication rates of 33% compared to 95% for two-stage revision. Comparable outcomes were observed in patients who had major local soft-tissue and bone compromise (McPherson Grade 3), with eradication rates of 0% for one-stage versus 95% for two-stage revision. Although the ENDO-Klinik team recently reported that the MSIS stage of host status and limb status were not significantly associated with reinfection after repeated one-stage revisions [52,53], it is important to interpret these findings cautiously. The MSIS classification may perform more reliably for first-time revisions for infection, whereas in cases where the infection has not been controlled, there is an inherent selection bias toward sicker patients. These "fragile" patients often have a limited life expectancy and lower functional demands for their limbs. Therefore, the goals of PJI treatment in such patients may prioritize their preferences and focus more on disease control rather than complete eradication.

Identifying the pathogen preoperatively is critical for the success of one-stage exchange arthroplasty. However, in some highly specialized hospitals where a tried, effective PJI management protocol has been established with comprehensive antibiotic options, the traditional contraindication of "CN PJI" appears to be less

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Table 1
Contraindications for One-Stage Revision Published After 2018.

Institutes	The Time of Publish	Contraindications
Endo-Klinik Hamburg, Germany [42]	2024	- Unknown pathogen - Severe soft-tissue defects - concurrent sepsis
First Affiliated Hospital of Xinjiang Medical University, China [43]	2022	- Active systemic infection - Infection involving neurovascular bundles and peripheral vascular disease - Severe immunocompromised host - Severe soft-tissue defects
Universitätsmedizin Berlin, Germany [44]	2023	- Severe soft-tissue defects - Severe bone defects - Multiple prior revisions for PJI - Concurrent sepsis
University College of London Hospital, United Kingdom [45]	2018	- Unknown pathogen - Concurrent sepsis - Severe immunocompromised host
Hospital of Buenos Aires, Argentina, Buenos Aires, Argentina [46]	2021	- ≥1 prior revision for PJI - Antibiotic-resistant organism - Sinus tract - Unknown pathogen
2018 ICM [41]	2019	- Systemic sepsis - Extensive comorbidities - Infection with resistant organisms - Unknown pathogen - Severe soft-tissue defects
RCT in United States [47]	2023	- Unknown pathogen - Severe soft-tissue defects - Immunosuppressed patients
Rothman Orthopedic Institute, United State [48]	2024	- Severe soft-tissue defects - Had PJI history - Extensive bone loss requiring endoprosthesis
RCT in Denmark [49]	2021	- Severe soft-tissue defects - Major bone loss - Concurrent sepsis - Malignant disease with less than 2 years of life expectancy - Re-infection after previous two-stage procedure - Bilateral knee infection

RCT, randomized controlled trial; NA, not available.

absolute. Van den Kieboom et al. [54] compared the outcomes of 105 patients who had chronic CN PJI and found no significant differences in treatment failure rates for reinfection between one-stage and two-stage revision (16.7 versus 20%) (Table 2). Ji et al. [55] reported a 90.2% infection control rate in 51 CN PJI patients after one-stage revision, with a mean follow-up of 4.4 years, showing no significant difference from culture-positive (CP) patients. Similarly, Greenfield et al. [56] found no significant difference in reinfection rates between patients who had identified pathogens (3.6%) and those who did not have (9.1%) after one-stage hip revision. Another study from Charite Hospital has confirmed these findings, noting no significant differences in demographics between CN and CP PJI patients, who have only one CP reinfection after a 2-year follow-up [44]. The ENDO-Klinik team, pioneers of one-stage revision, reported a 90.9% infection control rate in 22 CN patients after one-stage revision with a 3.6-year follow-up, concluding that “the absence of preoperative pathogen detection may not be a contraindication to one-stage revision in selected patients.” [57].

Antibiotic-resistant organisms represent another critical consideration for one-stage revision. Interestingly, only the 2018 International Consensus Meeting included resistant organisms as a

Table 2
The Results From Studies Published in the Past 5 Years Regarding One-Stage Revision for Culture-Negative PJI.

Publish year	Comparative Group	Number of Patients	Follow up Time (Years)	Infection Control Rate
2020 [55]	Culture negative versus Culture positive	51	4.4	Culture negative: 90.2% versus Culture positive: 94.3%
2021 [54]	One-stage versus two-stage for culture negative PJI	105	4.2	One-stage: 83.3% versus two-stage:80.0%
2021 [56]	Culture negative versus Culture positive	77	6	Culture negative: 90.29% versus Culture positive: 96.4%
2022 [57]	Culture negative versus Culture positive	30	2	Culture negative:100% versus Culture positive: 96.7%
2023 [58]	None	22	3.6	90.90%

contraindication, while major one-stage revision centers worldwide do not consider it a contraindication (Table 1). A meta-analysis of 1,856 PJI cases from 44 cohorts found methicillin-resistant *Staphylococcus aureus* in 20% of one-stage patients versus 10% in two-stage patients. Reinfection rates per 1,000 person-years were lower for one-stage (16.8) than two-stage (32.3) [58]. The longest follow-up study on one-stage revision reported that 49.5% of patients had antibiotic-resistant pathogens. With a minimum follow-up of 10 years, the infection-free survival rate was 94% [59]. Similarly, Ji et al. [60] evaluated 126 patients undergoing one-stage revision with broad inclusion criteria, including 17% infected with methicillin-resistant *Staphylococcus aureus* or MRSE, achieving an average 5-year infection control rate of 89.2%.

Taken together, it is important to recognize that not all situations of poor outcomes following a one-stage revision should be regarded as contraindications. Certain conditions, such as fungal or *Enterococcus faecium* infections, or patients who have infected megaprostheses, yield suboptimal results regardless of whether a one-stage or two-stage revision is performed. The decision to perform a one-stage revision should be based on a comprehensive assessment of the surgeon's experience, hospital resources, and patient-specific factors. While contraindications for one-stage revision do exist, there are no "absolute" contraindications, as the concept of "absolute" cannot be definitively proven in many unique clinical scenarios.

Question 3: During single-stage exchange arthroplasty, should we use two separate instrument setups and redrape after resection?[3]

Response/Recommendation

Yes. The use of two separate instrument setups and the use of new drapes after resection in the setting of debridement and implant retention procedures (DAIR), two-stage exchange, and single-stage exchange arthroplasty may decrease the risk of contamination and the possibility of infection recurrence. Further studies specific to single-stage exchange are needed.

Level of Evidence: Limited

Delegate Vote: Agree 81.3% Disagree 16.3% Abstain 2.5%

Rationale

Recurrence of PJI remains a major challenge in revision arthroplasty. A single-stage exchange arthroplasty is increasingly utilized as an alternative to a two-stage exchange; however, the utility and optimal intraoperative protocol to minimize contamination and reduce reinfection rates remain debated. Protocols have existed with descriptions of two separate setups, and, in some instances, two separate rooms have been described [61–64]. While some surgeons favor a single sterile field for the entire procedure, concerns regarding bacterial and intraoperative contamination have driven the exploration of using two separate instrument setups with redraping, or the use of a new drape, after the resection arthroplasty is completed [61]. This review evaluates whether employing two separate instrument setups and redraping after resection reduces the risk of infection recurrence in single-stage procedures and discusses potential barriers to the widespread adoption of this practice.

A comprehensive literature search was conducted using PubMed and Embase, initially identifying 19 potentially relevant studies. These articles were screened by two independent reviewers, from which seven were selected for an in-depth review.

It is well known that bacterial contamination increases with the time surgical trays are opened and the duration of the surgical procedure [65,66]. Although Russell et al. failed to demonstrate the time-dependent nature of contamination, this limited cohort did not evaluate the setting of PJI treatment [67]. Beldame et al. found that contamination and glove perforation increased during certain aspects of THA [68]. While the organisms were felt to be cutaneous and originating from the surgeon, other studies have found bacterial contamination to be from the infected patient. In a prospective collection of swab samples from multiple surgical surfaces (gloves, gown, patient, scalpel, and light handle) during revision arthroplasty, it was found that the surfaces were significantly more contaminated (77%) compared to aseptic revisions (13%). Often, the contaminating organism was the same organism found in cultures from the septic revision [69]. Given that the surgical site gets contaminated, it is relevant to question whether interventions to decrease the bacterial burden are sufficient. Morrison et al. conducted a randomized, controlled trial comparing single versus repeat surgical preparation. They found that repeated skin antiseptic preparation before closure resulted in a reduction in surgical site infections. Although there was no exchange of drapes, this randomized, controlled study demonstrated a significant decrease in the risk of superficial surgical site infection (6.5 versus 1.8%, $P = 0.02$) with the simple step of reprepping the surgical site [70].

Maale et al. reported an 88% success rate in single-stage procedures using a dual setup [71]. Similar reports adopting the European models for single-stage arthroplasty have led to increased utilization. El-Husseiny et al. included a redraping step in complex reconstructions and reported an infection control rate of 83% [72]. The question of whether a separate instrument setup and re-preparation are worthwhile from a time and cost standpoint remains a critical discussion point. A single-stage procedure inherently aims to avoid the costs of a second admission and second-stage surgery, albeit with the trade-off of a prolonged primary surgery. For such a protracted and expensive procedure, the additional costs of reprepping, redraping , and setting up extra instruments are relatively negligible.

Katakam et al. evaluated a dual surgical setup in debridement and implant retention procedures (DAIR) and demonstrated a significant reduction in infection recurrences when a new sterile field was established. This group found that when the entire retrospective cohort of 263 patients was stratified by setup type (single versus dual), the infection control rate was lower, 48% for the single setup compared to 75% for the dual setup ($P = 0.043$). Multivariate regression analysis revealed that a single setup was a predictive variable for DAIR failure [OR 0.3, 0.08 to 0.93, $P = 0.048$] [73]. Mittal et al. reviewed dual surgical setups for two-stage arthroplasty and found a significant reduction in complications when a sterile field was re-established before final implantation. Overall, a 29.9% recurrence of PJI was observed in the 134 patients reviewed. In the single setup group, 36.1% experienced a PJI recurrence, whereas only 6.9% in the dual setup group had a recurrence ($P < 0.01$) [74]. The steps proposed by Katakam et al. and Mittal et al. involved a double-drape setup with the outer drapes removed at the interval period, and the dirty instruments, tables, gowns, and gloves were changed before the clean procedure. The barriers to widespread adoption include challenges related to increased time and workflow, cost considerations, and the need for surgical team training to establish procedural standardization.

Conclusions

The reviewed literature demonstrated increased contamination in the setting of septic revisions and increased duration during

[3] These authors contributed to Question 3: Matthew J. Dietz, Thomas L. Hilton, Johannes Goosen, Jakub Ratkowski, Jesse W.P. Kuiper, Jesse E Otero, Plamen S Kinov, Hamed Vahedi, Peter Gold

revision arthroplasty cases. This review also suggests that separate instrument setup and redraping may lead to a lower risk of bacterial contamination and possibly a decreased recurrence of infections in the settings of DAIR, two-stage exchange, and possibly single-stage exchange. Additional research is needed to conclusively determine if redraping and new instrument setups are beneficial in single-stage arthroplasty in terms of recurrence rates. This practice can help standardize procedures across teams and reduce variability in outcomes. The cost-effectiveness, ease of introduction, and satisfaction of both the surgical team and patients should also be evaluated to further determine its success.

Question 4: Can one-stage exchange be performed in patients who have culture-negative periprosthetic joint infection (PJI)?[4]

Response/Recommendation

Yes. A one-stage exchange can be considered a viable option for patients who have CN periprosthetic joint infections (CN PJIs).

Level of Evidence: Limited

Delegate Votes: Agree (76.5%), Disagree (17.7%), Abstain (5.9%)

Rationale

Periprosthetic joint infection remains a major challenge in orthopedic surgery, with two-stage exchange arthroplasty being considered the “gold standard” for treatment in North America [75,76]. However, one-stage revision has emerged as a viable alternative [77], particularly in CP cases [78,79]. The role of one-stage revision in CN PJI, however, remains unclear due to the limited available literature. This review aimed to evaluate the outcomes of one-stage revision in CN PJI cases compared to CP cases and to explore its potential as an effective treatment option.

A comprehensive search of Web of Science (WoS) and PubMed databases identified 240 studies for screening. After removing 79 duplicates, 161 studies were screened for eligibility. Of these, 111 studies were excluded as irrelevant, and 50 full-text articles were assessed. Ultimately, six studies met the inclusion criteria, and five studies were included in the final analysis (Tables 3 and 4). Data were extracted to compare between reinfection and aseptic revision rates in CN versus CP one-stage revisions.

There were five studies comparing one-stage revision in CN versus CP PJI cases, with follow-up periods ranging from 2.1 to seven years, with a reported pooled OR of 0.733 for reinfection (95% confidence interval 0.324 to 1.659, $P = 0.456$, $I^2 = 0\%$) (Figure 1). A random-effects model analyzing aseptic failure rates across three studies yielded an OR of 1.96 (95% confidence interval: 0.391 to 9.815, $P = 0.414$, $I^2 = 0\%$) (Figure 2). These findings indicate no statistically significant differences in reinfection or aseptic failure rates between the two groups, suggesting comparable outcomes.

The available data suggest that one-stage revision in CN PJI cases yields outcomes comparable to CP cases, challenging the notion that culture negativity should be a contraindication for one-stage revision [80]. The available evidence highlights the potential benefits of one-stage revision, including reduced morbidity, shorter treatment duration, lower health care costs, and improved patient convenience compared to the traditional two-stage approach [81]. However, the limited number of studies and small sample sizes underscore the need for further high-quality research to establish definitive guidelines and determine the optimal treatment strategy for CN PJI.

In conclusion, our review of available studies demonstrated no statistically significant differences in reinfection or aseptic failure rates between CN and culture-positive cases undergoing one-stage revision.

Question 5: Can one-stage exchange be done in patients who have a fungal periprosthetic joint infection?[5]

Response/Recommendation

Yes. A one-stage exchange arthroplasty is a viable option for selected patients who have fungal PJI.

Level of Evidence: Low

Delegate Vote: Agree 68.1%, Disagree 23.9%, Abstain 8.0%

Rationale

Fungal prosthetic joint infections (PJI) represent a challenging condition requiring a multidisciplinary approach to optimize patient outcomes. Key components of management include patient optimization, thorough surgical debridement, administration of both systemic and local antifungal therapies, and extended postoperative care. Both single- and two-stage exchange arthroplasties have demonstrated high success rates, with the choice of surgical strategy influenced by patient-specific factors, the identified pathogen, and the presence of comorbidities. A tailored approach is essential for achieving the best possible outcomes in patients who have PJI, particularly those caused by fungi.

In a multicenter study, Dinh et al. [88] evaluated the outcomes of PJI caused by *Candida* species. The study found significant differences in outcomes when comparing DAIR versus single-stage exchange ($P = 0.008$) and DAIR versus two-stage exchange ($P = 0.003$). However, there was no significant difference in outcomes between single- and two-stage exchange arthroplasties. Factors influencing treatment failure included age and the absence of prosthesis removal. Notably, infections caused by *C. parapsilosis* had better prognoses compared to other species. Similarly, Fusini et al. [89,90] conducted systematic reviews on fungal PJI treatment after THA and TKA. Both reviews highlighted the low level of evidence in the literature. Despite this, the results indicated no significant difference in relapse or eradication rates between single- and two-stage exchange arthroplasties. While two-stage exchange was the most frequently used approach, single-stage exchange yielded comparable outcomes. *C. albicans* and other *Candida* species showed similar relapse and eradication rates. Grzelecki et al. [91] analyzed treatment outcomes for fungal PJI and found that two-stage exchange protocols were more effective for *C. parapsilosis* infections compared to *C. albicans*. Their literature review concluded that single- and two-stage exchange strategies generally yielded similar success rates across all *Candida* species.

In a systematic review of surgical treatments for fungal PJI after THA, Guan et al. [92] reported pooled success rates of 50.0% for surgical debridement, 42.9% for spacer implantation, 55.0% for resection arthroplasty, 86.7% for one-stage revision, and 88.5% for two-stage revision, with significant differences between these approaches ($P = 0.009$). While one-stage exchange arthroplasty showed success rates comparable to two-stage revisions in selected cases, the latter was typically reserved for more complex situations. There is emerging evidence for utilizing the single-stage approach. George et al. [93] reported that single-stage revisions with fluconazole monotherapy were effective for selected TKA cases, particularly in nonimmunocompromised patients who have good soft-tissue conditions. Prolonged postoperative

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[5] These authors contributed to Question 5: Akos Zahar, Chikodi Angad, Jose Baeza-Oliete, Nicholas A. Bedard, Timothy S. Brown, László Bucsi, Ayman Ebied, Bálint L. Horváth, Shivaprasad Kolur, Róbert Szódy

Table 3
Characteristics of Studies Included in the Meta-Analysis.

Author (year)	Country	PJI Definition Criteria	Patients in Each Group	Age (Mean; Total)	Sex (Total)	BMI (Mean; Total)	Affected Joint	Follow-Up Time (Mean; Total)	Failure Definition	Comorbidities	Other Complications
Ji et al. [82] 2023	China	Musculoskeletal Infection Society Criteria	105 (CP), 27 (CN)	68.6 years	34 m, 98 f	26.3 kg/m^2	TKA	51.6 months	Recurrence of infection in the same knee and mechanical failure unrelated to PJI or sepsis as endpoints.	HTN (57 total), DM (30 total), others (14 total)	Four aseptic osteolysis cases, three flexion instability cases, two arthrofibrosis cases, two hematomas, six venous thrombosis cases, and three femoral stem tip pain (all total population).
Razii et al. [83] 2021	UK	ICM 2013	68 (CP), 16 (CN)	68 years	53 m, 31 f	NR	TKA	7 years	Recurrence of infection as confirmed by clinical findings, culture results, and reoperation.	NR	NR
Karczewski et al. [84] 2023	Germany	EBJIS 2021	20 (CP), 10 (CN)	70 years	13 m, 17 f	NR	THA	2.1 years	Reinfection based on Delphi Consensus criteria: infection signs, surgical intervention, or death due to PJI.	NR	One quadriceps paralysis, one femoral nerve palsy, and one dislocation requiring reoperation.
Zanna et al. [85] 2023	Germany	ICM 2018	22 (only CN)	73.2 ± 9.8 years	16 m, 6 f	29.5 ± 4.9 kg/m^2	TKA and THA	3.6 ± 2.6 years	Recurrence of infection or mechanical failure requiring surgical intervention; aseptic loosening defined separately.	ASA >3 reported	NR
Ji et al. [86] 2020	China	MSIS 2011	192 (CP), 51 (CN)	59.3 years (CN), 63.6 years (CP)	20 m, 31 f (CN); 85 m, 107 f (CP)	24.5 ± 5.8 kg/m^2 (CN), 25.3 ± 4.4 kg/m^2 (CP)	TKA and THA	53.2 months (CN); 59.3 months (CP)	Recurrence of infection or mechanical failure requiring surgical intervention; aseptic loosening defined separately.	HTN, DM	Two cases of renal impairment (CN), three cases of hip dislocation (CP).
Xu et al. [87] 2022	China	MSIS	One-stage: 7 (CP), 6 (CN)	63.6	37 m, 40 f	23.8 kg/m^2	TKA and THA	29.2 months	Recurrence of infection or need for additional surgical intervention for failure	HTN: 14; DM: 4	Myelosuppression: 5; Renal damage: 4; Liver damage: 1

PJI, prosthetic joint infection; CN, culture-negative; CP, culture-positive; MSIS, Musculoskeletal Infection Society; ICM, International Consensus Meeting; EBJIS, European Bone and Joint Infection Society; THA, total hip arthroplasty; TKA, total knee arthroplasty; ASA, American Society of Anesthesiologists; HTN, hypertension; DM, diabetes mellitus; FU, follow-up; NR, not reported; DAIR, debridement, antibiotics, and implant retention.

Table 4
Included Studies and Number of Included Patients.

Author (year)	One-Stage CN	One-Stage CP
Ji et al. [82] 2023	Twenty-five success, two reinfection, and zero mechanical failure.	95 success, seven reinfection, and three mechanical failures.
Razii et al. [83] 2021	Sixteen success, zero reinfections, and zero mechanical failure.	53 success, eight reinfections (9.5%), and seven mechanical failures.
Karczewski et al. [84] 2023	Nine success, zero reinfection, and one mechanical failure	17 success, one reinfection, and two mechanical failures.
Zanna et al. [85] 2023	Twenty-two total, two reinfections, and one mechanical failure.	NA
Ji et al. [86] 2020	Forty-six success, five reinfections.	181 success, 11 reinfections.
Xu et al. [87] 2022	Four success, two reinfections.	Seven success, zero reinfection.

CN, culture-negative; CP, culture-positive.

antifungal therapy guided by C-reactive protein levels was essential. Klatte et al. [94] presented a single-stage protocol with only one reinfection observed in 10 cases over seven years. Success relied on comprehensive preoperative, intra-operative, and post-operative management. Ji et al. [95] advocated for single-stage revisions with uncemented implants for chronic PJI after THA, including fungal infections. However, fungal cases were rare in their dataset, and long-term outcomes require further investigation. Rowan et al. [96] highlighted evidence supporting single-stage revisions even for atypical PJIs, including those caused by fungal species. Prerequisites included preoperative identification of the causative microorganism and thorough mechanical debridement. Jenny et al. [97] report two successful cases of one-stage exchange for *C. albicans* PJI, where the pathogen was identified solely through intraoperative samples. Both patients remained infection-free two years postoperatively, despite the typically poor prognosis associated with the absence of preoperative identification.

In the majority of the reviewed literature, two-stage revision seems to be a reliable approach for most patients, and it is considered the preferred procedure. Gonzalez et al. [98] analyzed 225 fungal PJI cases, reporting highly variable recurrence rates ranging from 0 to 50%. Despite the absence of standardized treatment guidelines, two-stage exchange arthroplasty emerged as the predominant approach due to its reliability. Koutserimpas et al. [99–101] conducted several reviews highlighting the success rates of various surgical strategies. For fungal PJI after TKA, two-stage revision demonstrated a success rate of 92%, compared to 75% for one-stage revision, 80% for resection arthroplasty, and 67% for both arthrodesis and DAIR. In a 2019 systematic review of PJI caused by non-*Candida albicans* species, two-stage revision had significantly higher success rates compared to one-stage revision (96 versus 73%; $P = 0.023$). These findings underscore the superior outcomes of two-stage approaches, particularly in complex fungal infections. Kuiper et al. [102] reviewed 164 cases and similarly recommended two-stage revision as the standard for all fungal PJI cases. Their analysis found no compelling evidence supporting alternatives such as one-stage revision, DAIR, or antifungal therapy alone. Kuo et al. [103] highlighted poor long-term outcomes with irrigation, debridement, and single-stage revisions, emphasizing the importance of optimizing patients' systemic health before two-stage surgery. Nace et al. [104] explicitly recommended against one-stage revision and DAIR for fungal PJI due to the robust biofilm associated with fungal pathogens, which diminishes the efficacy of these interventions. Starnes et al. [105] recommended aggressive surgical management, including two-stage exchange combined with prolonged antifungal therapy ($\geq$ three months), as the current best practice. Debridement and Girdlestone procedures were shown to be less effective compared to staged revisions. Theil et al. [106] provided further evidence supporting two-stage revision, particularly when fungal organisms are identified preoperatively. In a retrospective analysis, Brown et al. identified 31 fungal PJI cases (13 THA and 18 TKA) in 31 patients treated during a period of 18 years, representing 0.9% of the 3,525 PJIs treated at the Mayo Clinic [107]. *Candida* species accounted for 81% of infections. At a mean follow-up of 4 years, survivorship free from revision or implant removal at two years was 45% in THA and 70% in TKA. Survivorship free from reinfection at two years was 38% in THA and 76% in TKA.

In conclusion, the management of fungal PJI is a complex process requiring a multidisciplinary approach tailored to patient-specific factors, the causative microorganisms, and the presence of comorbidities. While one-stage revision is a viable option for carefully selected patients, particularly for those who have favorable conditions and preoperative pathogen identification, two-stage exchange arthroplasty still remains the most commonly employed approach, especially in complex cases. Prolonged antifungal therapy and rigorous perioperative management are crucial to optimizing the outcome of PJI, particularly those caused by fungal species.

Question 6: Can one-stage exchange be done in patients who have an active sinus tract?[6]

Response/Recommendation

Yes. A one-stage exchange can be done in patients who have a sinus tract as long as soft-tissue coverage can be obtained at the conclusion of surgery.

Level of Evidence: Moderate

Delegate Vote: Agree: 70.7%, Disagree: 24.7%, Abstain: 4.7% (strong majority, moderate consensus)

Rationale

Some patients who have PJI develop a sinus tract, which is an abnormal communication between the joint and the skin. Patients who have an active sinus tract present major challenges in surgical management due to concerns about persistent infection, impaired soft-tissue conditions, and increased risks of complications. Specific factors for the development of a sinus tract remain unknown, but it seems that a number of factors associated with poor soft-tissue healing, such as smoking, hypothyroidism, hypoalbuminemia, and polymicrobial infections, may predispose these patients to the development of a sinus tract [108,109].

Note that PJIs presenting with sinus tracts are associated with worse treatment outcomes regardless of whether these patients undergo a one- or two-stage revision [108,110–112].

[6] These authors contributed to Question 6: Wenbo Mu, Ayman Ebied, Jonathan T Evans, Markus Rupp, Mathias Glehr, Ricardo Sousa, Rosalba Tortia, Xiaogang Zhang

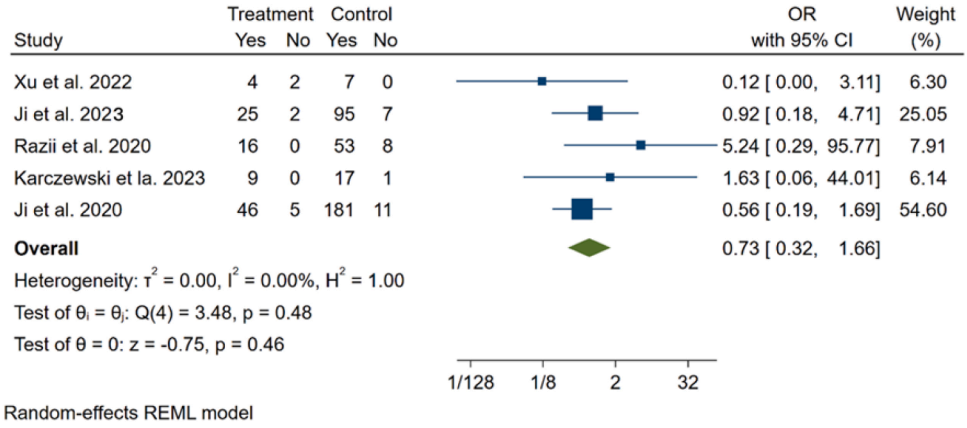

Figure 1. Reinfection.

As such, a sinus tract is traditionally thought of as a contraindication for a one-stage exchange [113]. Ilchmann et al. excluded patients who had sinus tracts from their study of one-stage hip exchanges, achieving a 100% infection control rate, which underscores the importance of intact soft-tissue conditions [114]. Others have shown similar success both for hips [115] and knees [116] by implementing strict selection criteria with no soft-tissue compromise (including no sinus tract).

In fact, sinus tracts have been shown to be associated with higher rates of treatment failure and rerevision after one-stage exchange. Abdelaziz et al. identified sinus tracts as a major risk factor for rerevision, with a 9.16 times higher likelihood compared to cases without sinus tracts. These patients often required aggressive debridement and proximal femoral resection, particularly when chronic osteomyelitis was present [117]. Furthermore, Lausmann et al. demonstrated that sinus tracts significantly increased the risk of reoperation, even though reinfection control was achieved in 78.3% of cases [118].

Gehrke et al. noted that uncomplicated sinus tracts without bone involvement may facilitate natural decompression of infection without severe soft-tissue destruction. When appropriately excised, these cases can achieve high cure rates following a one-stage exchange [119]. In another study, Citak et al. [120] performed a case-control comparison evaluating risk factors for failure after a one-stage exchange for TKA. Comparing 91 infection relapses with controls matched by age, sex, and date of the surgical procedure, they were not able to show the sinus tract to be a significant risk factor.

Several other studies suggest that one-stage exchange can be successful in carefully selected patients who have sinus tracts. Raut et al. further demonstrated that discharging sinuses was not a contraindication for one-stage exchange, achieving high infection control rates through meticulous debridement and complete removal of infected tissues [121]. Zeller et al. included patients who had sinus tracts in their cohort of one-stage revisions for PJI around hip arthroplasties, and this made up 20% of included patients (31 of 157). After a minimum of two years, they reported only two cases of reinfection with rigorous preoperative planning, although it is not clear whether these patients had sinuses or not [122]. A few years later, the same group reported on 66 hip PJIs, all of them with sinus tracts, treated with a one-stage protocol, and achieved a 95% infection control rate after a minimum 2-year follow-up [123]. The treatment protocol included thorough surgical debridement (including a separate approach to excise a distinct fistula pathway in 20% of cases), preoperative microbiological confirmation, and tailored antibiotic therapy [123]. Additionally, a different study utilizing antibiotic-impregnated cancellous allograft bone reported a 90% survival for reinfection and 80% survival for implant failure for any reason at two years, despite 30% of patients presenting with sinus tracts, highlighting the feasibility of this approach even in high-risk scenarios [124]. Cao et al. extensively evaluated the outcomes of one-stage exchange in managing PJIs with sinus tracts [125]. They reported infection control rates of 80.5% in sinus tract cases versus 94.6% in nonsinus tract cases, focusing on patients undergoing one-stage exchange after multiple failed PJI surgeries [126]. For polymicrobial, Gram-negative, and CN PJIs, infection control rates were 89.4, 90.6, and 90.2%, respectively, with sinus tracts present in approximately one-third of cases. These findings underscore sinus tracts as a significant risk factor for polymicrobial infections but also highlight the feasibility of one-stage exchange with intra-articular antibiotic infusion [127–129].

Active sinus tracts in PJI present major challenges. Although it is not clear whether they are a risk factor on their own or a proxy for other risk factors such as polymicrobial infections, poor soft tissues, or poor host nutritional status, they are traditionally associated with poorer outcomes both for one- and two-stage revision surgeries.

Further research is needed to standardize protocols and refine patient selection, but current evidence supports challenging traditional contraindications. Successful one-stage exchange in patients who have a sinus tract seems feasible as long as meticulous planning and execution are undertaken in experienced centers. Key factors for success include thorough debridement, local antibiotic delivery, and effective soft-tissue reconstruction.

Question 7: Should collateral ligaments be removed during one-stage exchange arthroplasty for periprosthetic joint infection (PJI) of the knee?[7]

Response/Recommendation

Collateral ligaments should generally be preserved during one-stage exchange arthroplasty for PJI. Evidence indicates that single-stage revisions using hinged implants versus unhinged implants achieve comparable success rates in infection control and functional outcomes. Removal of the collateral ligaments should be considered when ligaments are irreparably damaged or extensively involved in infection.

Level of Evidence: Limited

Delegate Vote: Agree: 73.2%, Disagree: 19.3%, Abstain: 7.5%

[7] These authors contributed to Question 7: Alisina Shahi, Ricardo Sousa, Julian Costantini, Artyukh Vasily, Abhay Elhence, Fabiano Kupczik

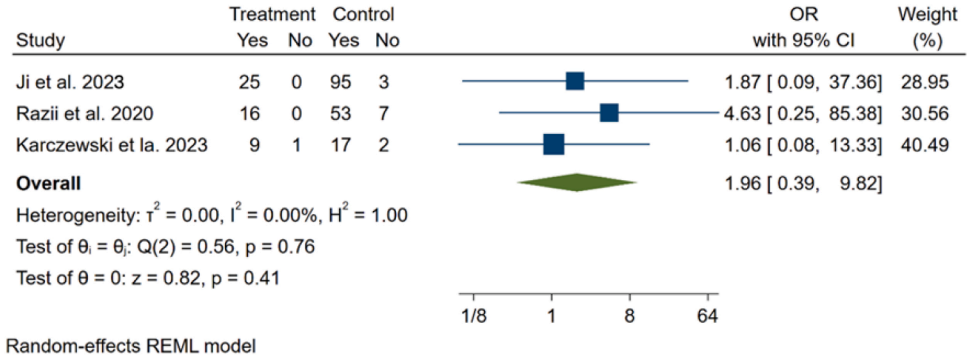

Figure 2. Aseptic failure.

Rationale

Periprosthetic joint infection (PJI) following TKA is a challenging complication with major morbidity. One- and two-stage exchange arthroplasty are the two most commonly accepted management protocols for PJI, with one-stage exchange gaining momentum due to comparable infection control rates and improved functional outcomes [130]. Unfortunately, regardless of the treatment protocol, the failure rate for revision due to PJI remains high [130–132]. Sacrificing the collateral ligaments to perform a complete and radical soft-tissue resection is advocated by some in a single-stage exchange. However, this approach carries potential disadvantages and must be carefully weighed against its risks.

In a study by Ohlmeier et al. [133], the authors investigated the outcomes of various implant designs used in single-stage revision for PJI. The study analyzed 161 patients divided into groups based on the type of implant revision: bicondylar TKA to rotating-hinge implant, rotating-hinge to rotating-hinge implant, rotating-hinge to full-hinge implant, and full-hinge to full-hinge implant. At a mean follow-up of six years, the overall revision rate was 23%, with 9% of patients experiencing a recurrent PJI. While group-specific revision rates ranged from 16 to 29%, the authors found no statistically significant differences in survival rates or functional outcomes among the groups ($P = 0.902$). Despite the relatively small sample sizes in each group, the study concluded that constrained and nonconstrained implants had comparable survivorship and infection control outcomes, supporting the flexibility of implant choice based on patient-specific factors.

Collateral ligaments are essential for maintaining the mechanical stability and natural biomechanics of the knee. Sacrificing these ligaments to perform a complete and radical soft-tissue resection is a measure that should only be reserved for cases where the ligaments are markedly affected or impaired by infection or structural damage. Hinged-constrained implants, often required when collateral ligaments are sacrificed, are less bone-preserving, which can make potential future revisions more challenging for surgeons and more morbid for patients. The increased bone loss and technical complexity associated with such implants underscore the importance of preserving collateral ligaments whenever possible. Furthermore, highly constrained implants, while providing stability in the absence of ligaments, can introduce increased stress at the bone-implant interface. This stress tremendously raises the risk of aseptic loosening and implant failure, compromising the long-term success of the revision procedure. By maintaining the collateral ligaments, surgeons can achieve more natural knee kinematics, enhance patient satisfaction, and reduce the risk of long-term complications [134,135].

In cases where collateral ligaments are directly involved in infection or are severely damaged, their removal may be unavoidable to ensure adequate infection control and joint stabilization. Such scenarios necessitate careful planning for implant selection and reconstruction to restore functionality and stability. Studies have shown that the use of constrained implants, such as rotating-hinge or full-hinge designs, is often required in these cases [134,136,137].

Preserving tissue while performing thorough debridement is a delicate matter and can be a double-edged sword. While retaining native structures like collateral ligaments is crucial, inadequate debridement risks incomplete infection control, jeopardizing the success of the revision. Striking the right balance is critical for achieving optimal outcomes in one-stage revisions for periprosthetic joint infections (PJI). Systematic and meticulous debridement protocols emphasize the importance of preserving native tissue, including ligaments, whenever feasible, as this approach improves functional recovery and stability. Ligament retention reduces dependence on constrained implants, which are associated with increased stress on the bone-implant interface and are less bone-preserving [138–140]. However, ligament preservation should not compromise infection control, as thorough debridement remains paramount to long-term success [134,138,141]. The evidence collectively supports the conclusion that preserving collateral ligaments during one-stage revisions can optimize functional outcomes and long-term implant performance, providing that infection control is not compromised [134,135,142,143].

In conclusion, collateral ligament preservation during one-stage exchange arthroplasty for knee PJI is recommended whenever possible. Retaining these ligaments helps maintain the natural biomechanics of the knee, reduces the reliance on constrained implants, and preserves bone stock, which is critical for the long-term success of the reconstruction. Exceptions to this recommendation should be limited to cases where the collateral ligaments are irreparably damaged or directly involved in the infection, necessitating their removal to achieve adequate infection control. In such cases, careful preoperative planning and intraoperative decision-making are essential to ensure stability and functionality through alternative reconstruction techniques. By prioritizing ligament preservation, this approach effectively balances the goals of eradicating infection, restoring function, and minimizing both surgical morbidity and the complexity of potential future revisions.

Question 8: What is the optimal duration of antimicrobial treatment for patients undergoing single-stage exchange for implant-associated infections?[8]

Response/Recommendation

Based on the limited available evidence, after single-stage exchange, an antibiotic course for a total duration of at least six weeks is recommended.

Level of Evidence: Moderate

Delegate Vote: Agree: 82%, Disagree: 11%, Abstain: 7% (strong consensus)

Rationale

Antibacterial therapy is a mandatory part of the treatment algorithm following one-stage exchange revision arthroplasty in patients with PJI. After a structured search in PubMed, Embase, and MEDLINE resources, 30 studies were found, comprising five prospective studies, 16 retrospective studies, nine reviews, and one systematic review [144–173]. Also, three studies were added manually [174–176].

The vast majority of studies evaluated the effectiveness of one-stage exchange in hip [150,152,155,156,158,159,163,164,170–175] or knee [144,148,149,153,154,161,162,166–168] PJI, while four studies compared one- and two-stage surgical treatment algorithms [157,160,169,174]. In these studies, authors discussed the duration of antimicrobial therapy, referring to other studies, sometimes with a similar design. It is also noteworthy that in 12 studies, the analysis was performed on small cohorts consisting of fewer than 40 patients [144,146,147,150,152,159,160,163,164,169,170,175].

Regarding the optimal duration of IV antibiotic therapy, in most studies, antibiotics were administered intravenously for seven to 14 days [145–149,151,152,158,161–163,165–167,170–172,174,175], even though some studies prolonged this phase up to 42 days [147,150,169,173]. However, the randomized clinical trial showed no significant differences in failure after one-stage exchange ($n = 76$) in the subgroups of oral and IV antibiotics for six weeks (OR 2.16 (95% CI 0.58 to 8.00)) [176]. In the majority of studies, the course of oral antibiotics varied from five to 10 weeks, with an average infection eradication efficacy of 90.2% in these studies [144,145,152,154,156,157,159–163,166,168–170,173–175]. Prolonged duration of oral antibiotics does not increase treatment effectiveness, according to a number of studies with infection eradication from 70 to 100% [150,164,165]. According to several studies, the decision to discontinue antibacterial therapy could be based on laboratory findings, focusing on the erythrocyte sedimentation rate, C-reactive protein, or albumin levels [146,149,157,163,169].

The mean total duration of antimicrobial treatment among the studies that presented full data ranged from 6 to 14 weeks, with an average level of infection eradication from 70 to 93.8% [144–147,150–152,154–158,160–164,166–170,173–175]. Additional prolonged (16 days) intra-articular infusion of antibiotics combined with IV therapy led to a comparable outcome [157].

The efficacy of single-stage exchange in the setting of a standardized course of antimicrobial treatment was evaluated in three of 33 identified publications [145–147]. In the study by Dubée et al., the total course of antimicrobial therapy after one-stage arthroplasty in patients who have chronic PJI caused by methicillin-resistant *Staphylococcus aureus* (MRSA) was 12 weeks. In the first six weeks, patients received combined therapy with continuous infusion of vancomycin followed by six weeks of oral antibiotics. Only two relapses occurred in 32 PJIs treated with one-stage exchange at 18 months of follow-up; however, 32% experienced nephrotoxicity during therapy [147]. Another study, which only included four cases of single-stage exchange arthroplasty, had patients receive 12 to 20 days of IV administration with a further six to 26 weeks of oral antibiotics, which resulted in 100% effectiveness at the 2-year follow-up. It is impossible to draw any major conclusions from the obtained data due to the small cohort size and wide range of antimicrobial therapy duration [146]. A recent retrospective cohort study investigated the outcomes of one-stage revision of hip and knee PJI followed by 6-week antimicrobial therapy in 50 patients. Antibiotics were administered intravenously for an average of 11 days, after which 92% of patients were transferred to oral therapy. The cohort consisted of patients infected with several different pathogens, including polymicrobial infections. Culture-negative infections were excluded. Infection was eradicated in 90% of patients who had an average follow-up period of 32 months, lending support to the concept of a short (6 weeks) course of antimicrobial therapy after one-stage exchange for PJI [145].

Antibiotic therapy for six weeks was not shown to be non-inferior to antibiotic therapy for 12 weeks (all surgical strategies) in the randomized controlled trial; the subgroup analysis showed no significant risk difference (1.2 (95% confidence interval 4.8 to 7.1)) for the primary outcome (persistent infection) between six and 12 weeks for the 146 patients undergoing one-stage exchange [174]. However, the authors conclude that this observation should be confirmed in a specific randomized controlled trial.

A systematic review made by Sandiford et al. included 21 publications and assessed the impact of IV treatment duration on the outcome of single-stage exchange in 643 patients who had hip PJI. The treatment efficacy in short (less than four weeks) and long (four to six weeks) courses of IV antibiotics was found to be comparable; the PJI eradication rate was 92.6 and 89.3%, respectively ($P = 0.7434$) [165].

In conclusion, currently, there is no high-level evidence supporting a significant advantage of one or another antimicrobial treatment duration for patients undergoing single-stage exchange for PJIs. Most studies report successful outcomes in > 90% regardless of postoperative treatment duration. There were two recent studies [145,174] that lend further support to a strategy consisting of a short course of IV antibiotics for 10 to 14 days followed by a course of oral antibiotics for a total duration of six weeks after a one-stage exchange in PJI. Randomized prospective studies are needed to determine the optimal duration of the overall course of antimicrobial therapy. Furthermore, the role of local administration of antibiotics following one-stage exchange needs to be further investigated.

[8] These authors contributed to Question 8: Bozhkova Svetlana, Preobrazhenky Peter, Lastinger Allison, Tevell Staffan, Davis Joshua S, Kramer Carolyn, Wang Weijun, Taupin Daniel H, Malhotra Rajesh

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The Journal of Arthroplasty 41 (2025) S341–S361

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Hip and Knee

2025 ICM: Spacers

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Question 1: How long do antibiotics elute from cement spacers?[1]

Response/Recommendation

Although many confounding factors influence antibiotic elution levels over time, making it difficult to compare studies regarding antibiotic delivery via polymethylmethacrylate (PMMA) spacers, the available data indicate sufficient release occurs to maintain levels above the minimum inhibitory concentration (MIC) of most bacteria for at least six to 12 weeks.

Level of Evidence: Low

Delegate Vote: Agree: 90.4%, Disagree: 5.3%, Abstain: 4.3% (Total consensus, Unanimity)

Rationale

Many factors influence the antibiotic elution characteristics of PMMA spacers, including the type, concentration, and combinations of antibiotics (with synergistic effects of two or more antibiotics), as well as the type and porosity of the cement itself [1,2], the geometry of the spacer, and the cement mixing technique [3–5] (Table 1). Because there are great differences in these specific details, it is difficult to directly compare studies, and different outcomes may result from different preparation methods. For this review, reports were selected that gave results for elution characteristics where antibiotics were used in powdered form, at a cumulative antibiotic proportion of not more than 10%, using one or more antibiotics added to PMMA without any other additives (such as glycine, calcium phosphate, or carbonate).

Antibiotic elution from PMMA spacers has been extensively evaluated *in vitro*, typically involving measurements of antibiotic levels in fluid using fluorescence polarization immunoassays or by examining zones of inhibition on culture plates. Most studies investigate devices other than spacers, such as PMMA disks as surrogates [6–9]. Since the release of antibiotics from bone cement is a surface-dependent phenomenon [10], it is valid to question the relevance of these *in vitro* observations for hip and knee spacers that have a different surface area and geometry. Moreover, the amount and frequency of fluid exchange around bone cement *in vitro* vary between studies, and although most study protocols changed the eluate daily, some only changed it weekly [11]. Greater amounts of fluid and more frequent exchange will influence elution by disturbing the concentration gradient [1].

Table 1
Common Factors Influencing the Elution of Antibiotics From PMMA Cement Spacers.

Influencing Factor	Effect on Elution Out of Spacer
Type of antibiotics	Tobramycin > vancomycin (for example)
Concentration of antibiotics	Larger dose of additional antibiotics, increased elution
Number of antibiotics	Dual antibiotics > single antibiotic (synergistic effect)
Type of cement	Palacos > Simplex (for example)
Porosity of cement	Greater porosity, increased elution
Geometry of cement body	Increasing surface area, increased elution
Cement mixing technique	Without vacuum > with vacuum
Type of spacer	Articulating spacer > hemi-spacer

PMMA, polymethylmethacrylate.

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.106.

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https://doi.org/10.1016/j.arth.2025.10.106
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The concentration gradient between the spacer surface and culture medium does not necessarily recreate *in vivo* conditions that faithfully model antibiotic diffusion to tissue. In addition, antibiotic and physiological differences, such as local blood flow and pH, may have an influence on the pharmacokinetic behavior of spacers, resulting in different antibiotic elution profiles. Moreover, the spacers are tested *in vitro* under ideal bacterial growth circumstances. Tryptic soy broth is an ideal growth medium, and often a new aliquot of the microorganism was added daily, whereas the antibiotic amount has not been changed [12]. Therefore, the results of *in vitro* studies cannot be directly translated into clinical practice under *in vivo* conditions.

Nearly all *in vitro* studies demonstrate very high peaks of antibiotic concentration and elution after 24 hours, followed by a continuous decline [2,12–29] (Table 2). An important limitation of several *in vitro* studies designed to answer the question posed by

Table 2
In Vitro Studies.

Author	Reference	Antibiotic	Dosages	Cement	Method	Test Duration	Duration of Sufficient Antibiotic Release
Kummer	9	Vancomycin, daptomycin, fosfomycin	2 g vancomycin, 1.5 g daptomycin, 1.5 g fosfomycin per 40 g cement	Palacos R + G (0.5 g Gentamicin)	LCMS	6 week	6 weeks for vancomycin, gentamicin, daptomycin
Anagnostakos	11	Gentamicin (G), vancomycin (V) teicoplanin	Different (0.5 g G + 1 g V in 40 g cement)	Palacos R + G (0.5 g Gentamicin)	FPIA + photometric (bacterial growth)	20 day	20 days gentamicin + vancomycin, 4 days teicoplanin
Gálvez-López	12	11 different	10 and 20% (4 and 8 g per 40 g cement); results for 10%	Medium viscosity cement from DePuy	Beads: HPLC + DAA	30 day	30 days vancomycin, gentamicin, moxifloxacin, daptomycin, ertapenem, meropenem, cefotaxime
Anagnostakos	13	Linezolid		Palacos R + G (0.5 g gentamicin)	HPLC, FPIA + photometric (bacterial growth)	8 day	8 days
Humez	14	Daptomycin	1.5 g in 40 g cement	Palacos R + G (0.5 g gentamicin)	HPLC	2 day	2 days
Allen	15	Gentamicin	0.5 g in 40 g cement	Palacos R + G (0.5 g gentamicin)	DDA	12 day	12 days sufficient
Haseeb	16	Ceftaroline, vancomycin	Ceftaroline 3 wt% (1.2 g), vancomycin 2.5 wt% (1g) liquid	SmartSet	HPLC + ZI	8 week	6 weeks ceftaroline, 3 weeks vancomycin
Ikeda	17	Vancomycin	5 wt%	Cemex RX	HPLC	84 day (12 week)	56 days (8 weeks)
Slane	18	Vancomycin, tobramycin	Different	Palacos R	HPLC	28 day	28 days
Goltzer	19	Gentamicin	Different	Different prefabricated spacers + hand mixed Palacos	NA	7 day	7 days
Oungeun	20	Hydrophilic vancomycin, erythromycin	55 mg vancomycin/ 55 mg erythromycin	Palacos R	UV-S	6 week	6 weeks for vancomycin and erythromycin
Bitsch	21	Ofloxacin, vancomycin, clindamycin, gentamicin	2, 4, and 6 g in 40 g cement	Copal spacem (no antibiotics)	Area of clearance	50 day	2, 4, and 6 g for 50 days, vancomycin: 2 g 20 days, 4 g 43 days
Andollina	22	Vancomycin, meropenem	Different	Cemex XL	CA + microbiological investigation	5 week	5 weeks for 1 g vancomycin +1 g meropenem
Boelch	23	Vancomycin		Copal spacem (no antibiotics) and Palacos R + G (0.5 gentamicin)	HEIA	28 day	28 days gentamicin, vancomycin
Greene	24	Tobramycin, vancomycin	Each 4 g on 40 g Simplex or Palacos R	Simplex or Palacos R	ZI	100 day	100 days tobramycin, 32 vancomycin in Palacos
Shiramizu	25	Cefazolin	2 g cefazolin in 40 g cement	Simplex and CMW 3	HPLC	7 day	7 days
Stevens	26	Vancomycin, tobramycin	Different (suff: 3.6 g tobramycin and 3.0 g vancomycin = 14.2 wt%)	Simplex and Palacos	DAA with ZI	80 day	14.2 wt%: 80 days MIC; 25 days tobramycin, 4 days vancomycin in Palacos
Moore	27	Vancomycin, tobramycin	2.0 g in 40 g cement	Simplex	LCMS	2 day	2 days
Liawrun-rueang	28	Gentamicin	2.0 g in 40 g cement	Palacos R + G (0.5 g gentamicin)	EMIA; FPIA	6 week	6 weeks
Salih	29	Gentamicin	0.5 g; 1.5 g; 23 g in 40 g cement	Palacos and copal G + C	LCMS	9 week	9 weeks

HPLC, high performance liquid chromatography; LCMS, liquid chromatography mass spectrometry; EMIA, enzyme multiplied immunoassay; FPIA, fluorescence polarization immunoassay; ZI, zone of inhibition (bacterial growth); HEIA, high enzyme immunoassay; DDA, disc diffusion assay; NA, ninhydrin assay; CA, chromatographic assay; UV-S, ultraviolet visible spectrometry; g, gram; wt%, weight percent.

this review is the duration of the analysis period. Most studies analyzed the elution for a period of several days up to one week [14,16,20,23] (Table 2). For these short periods, sufficient release of antibiotics over the MIC was observed [14,16,20,23]. Boelch et al. [24] reported sufficient release of vancomycin and gentamicin for the whole test period of 28 days, Slane et al. [19] the same for tobramycin and vancomycin, and Galvez-Lopez et al. [13] for seven of 11 different antibiotics across the test duration of 30 days. Oungeun et al. [21] observed sufficient elution for a test period of six weeks for vancomycin and erythromycin, Kummer et al. [11] for vancomycin, gentamicin, and daptomycin, and Liawrunrueang et al. [28] for gentamicin (Table 2). There were three independent studies that reported substantially shorter elution periods for vancomycin compared to other antibiotics [17,22,25].

In an *in vitro* model, Stevens et al. [2] simultaneously demonstrated the three important considerations of PMMA type, antibiotic synergy, and antibiotic dosage. In their study, a Palacos articulating knee spacer containing both vancomycin and tobramycin (three grams vancomycin and 3.6 grams tobramycin per 40 grams PMMA) eluted in excess of the MIC for most common orthopedic pathogens for greater than 80 days. However, PMMA spacers may certainly exhibit different activity *in vivo*. The anatomical location, the vascular supply and perfusion of the infected area, and the protein-binding capacity of each antibiotic used are some of the parameters that may actively influence spacer performance *in vivo*.

Due to the limitations of the *in vitro* studies, the more important investigations to address the issue of a sufficient elution period for PMMA spacers are *in vivo* studies. Here, methodologically, the different studies can be separated into animal *in vivo* studies and human *in vivo* studies. The latter can be further distinguished between studies where antibiotic concentrations were measured in joint fluid drainage a few days after surgery and those where the spacers removed during the second surgery of the two-stage protocol were analyzed for continued antibiotic elution.

Numerous factors also influence the release kinetics and elution period from PMMA in vivo. Besides the factors mentioned above, the surface roughness and total surface area of the spacer, the duration of spacer implantation, spacer geometry, spacer articulation, and the environmental circumstances are recognized as factors influencing antibiotic release from bone cement in vivo [30–32]. Moreover, articulating spacers generally exhibit abrasion from cement particles [33], potentially leading to new surfaces on the spacer from which antibiotics can elute, which may be associated with increased and prolonged antibiotic release [22,34]. In addition, an increase in the distance between the cement and the surrounding tissues results in decreased concentration of the antibiotic in the tissue [35]. The type of tissues around the spacer also affects antibiotic elution from the spacer and antibiotic diffusion into the inflamed tissues. Cancellous bone absorbs more antibiotic than cortical bone, and any hematoma (dead space) that potentially lies between the spacer and the bone or soft tissues absorbs more antibiotic than cancellous bone [35,36].

Several *in vivo* studies on animals, especially those evaluating selected shapes of PMMA spacers, merit discussion here. In dogs, Adams et al. [37] noted detectable concentrations of tobramycin and vancomycin from PMMA beads over a period of 28 days. Chapman and Hadley [38] observed a peak of antibiotic release on the first day but no elution after 37 days in serum and soft tissue from antibiotic-loaded cement pellets implanted in the intramedullary canal of rabbit femora and quadriceps muscle. Alternatively, Bunetel et al. [39] reported sufficient release of gentamicin up to 18 months after femoral implantation of gentamicin (0.6 and 1.2 grams per 40 g PMMA) in sheep, and Chohfi et al. [40] observed adequate elution for three months using high-dose vancomycin (three grams in 40 grams PMMA) impregnated cement in sheep femora. Gatin et al. [41] noted sufficient release of colistin in PMMA for implantation of a silicone elastomer implant in the knee of rabbits for the whole test duration of only 21 days. The differences reported may simply be the result of various methodological differences and inherent weaknesses in the study designs.

The studies of greatest relevance are clinical investigations in humans who have spacers. However, *in vivo* analysis of the drainage fluid concentration is limited by the time for which the drainage tubes can be left *in situ*, usually a period of only a few days. Anagnostakos et al. [42] confirmed sufficient antibiotic elution in the drainage fluid for seven days when adding vancomycin to Palacos R plus G cement. As with the in vitro studies and animal in vivo studies, the analysis of the antibiotic concentration in the joint fluid drainage demonstrated a peak after 24 hours, well above the MIC of the microorganism for all tested antibiotics, followed by a much lower concentration for several days [40,42–46], typically still greater than the MIC at the end of the test period (Table 3). However, the antibiotic concentrations collected from drains are not necessarily representative of the full pharmacokinetic properties of the spacers but instead reflect only their intra-articular surfaces. Particularly for hip spacers, this only accounts for the pharmacokinetic properties of either the spacer's head alone or the spacer head in combination with a spacer cup. The antibiotic release from the spacer stem in the femoral medullary cavity cannot be determined from the joint fluid, and the measured concentrations represent only a portion of the true antibiotic elution *in vivo* [5]. Fink et al. [34] measured the antibiotic concentration in the membrane around hip spacers six weeks after implantation and noted antibiotic levels above the MIC for gentamicin, clindamycin, and vancomycin. Bertazzoni Minelli et al. [47] analyzed the antibiotic concentration in the periprosthetic tissue in two cases after explantation of hip spacers and reported concentrations greater than those determined in other elution studies, with values obtained locally exceeding the MICs of most of the common pathogens involved in periprosthetic joint infections.

Generally, because elution for longer periods *in vivo* could not be measured from drainage fluid, the analysis of spacers after removal during the second stage of two-stage revision arthroplasty seems to be more appropriate to address the question posed by this review. Joint aspiration at the time of spacer removal and analysis of the antibiotic concentration in the joint fluid revealed a sufficient concentration above the MIC for three months or more in most studies [48–50] (Table 3).

One additional feature of hip spacers—hemispacers versus articulating two-part spacers—may influence the antibiotic release in clinical use. Hsieh et al. [43] reported sufficient antibiotic concentrations above the MIC in the joint fluid of 46 hip spacers with vancomycin and aztreonam after a mean period of 107 days. These spacers were articulating two-part spacers with a cemented stem head articulating on a cement cup. These observations are in concordance with the findings of Fink et al. [34], who noted sufficient concentrations of gentamicin, clindamycin, and vancomycin in the tissue around the spacer after six weeks. These spacers were also two-part articulating spacers with a metal head articulating on cement cups. These articulations create wear, as confirmed by histological analyses, X-ray fluorescence spectroscopy, and plasma-mass spectrometry [33]. This wear exposes new surfaces from which additional antibiotic elution can then occur. However, Masri et al. [48] reported sufficient antibiotic concentrations four months postoperatively when using Prostalac spacers containing tobramycin. Therefore, two-part articulating spacers in the hip (as well as articulating knee spacers) may have additional

Table 3
In vivo Studies on Humans.

Author	Reference	Antibiotic	Dosages	Cement	Spacer	Method	Test Duration	Duration of Sufficient Release
Chohfi	40	Vancomycin	3 g in 40 g PMMA (Cerafix)	Cerafix (low viscosity)	THA	Drainage 2 mo 5 d, IEA	5 days max	4 days
Anagnostakos	42	Gentamicin + vancomycin	0.5 gento +2 g vancomycin in 40 g (80 g spacers in 17 patients)	Refobacin/ Palacos	Two-part hip	Drainage, FPIA	7 days max	7 days (study period)
Hsieh	43	Vancomycin + aztreonam	Je 4g auf 40 g PMMA	Simplex	Two-part hip	Drainage for 7 d, in joint fluid at spacer removal, HPLC	32 to 156 days, Ø107 days	32 to 156 days, Ø107 days
Regis	44	Gentamicin + vancomycin	2.5% gentamicin, 2.5% (1g) cancomycin manually added	Cemex	Hemi-spacer hip (Spacer-G, Tecres)	Drainage, FPIA	1 day (24 h)	1 day (24 h)
Isiklar	45	Vancomycin	2 g cancomycin in 40 g cement	n. a.	Hemi-spacer hip	Drainage	2 days	2 days
Balato	46	Gentamicin und clindamycin	1 g gentamicin +1 g clindamycin in 40 g cement	Refobacin revision biomet	Two-part knee hemi-spacer hip	FPIA	2 days	Hip: 48 h gentamicin, knee: 12 h in 75%, 36 h in 50%
Masri	47	Tobramycin + vancomycin	3.6 g tobramycin +1 g vancomycin in 40 g Palacos	Simplex P	Two-part hip two-part knee Prostalac	Aspirate joint fluid at spacer removal, FPIA	42 to 340 days, Ø 118 days	4 months tobramycin
Mutimer	48	Gentamicin	0.76 g gentamicin in 40 g cement	Spacer K, Cemex (Tecres)	Two-part knee	Aspirate joint fluid at spacer removal	99 (63 to 274)	99 days median (64 to 274 days) = 3 months minimum
Kelm	49	Gentamicin + vancomycin	0.5 gentamicin +2 g vancomycin in 40 g cement (80 g spacers in 10 hip spacers)	Refobacin/ Palacos	Hemi-spacer hip	Drainage + bacterial growth (photometric) at spacer removed	3 to 14 weeks	Vancomycin 17 days, gentamicin 14 days
Hsieh	50	Liquid gentamicin, vancomycin	480 mg/20 mL cement monomer; 3 g vancomycin in 40 g cement	Simplex	Two-part hip	Aspirate joint fluid at spacer removal, FPIA	Ø 87 days (27 to 128 days)	87 days (27 to 128 days)
Bertazzoni Minelli	51	Gentamicin + vancomycin in holes	0.76 g gentamicin in 40 g cemex, 1 g. vanomycin in 40 g cement	Cemex RX	Hemi-spacer hip Spacer-G (Tecres)	Spacer removed in phosphate buffer, FPIA	3 to 6 months	3 to 6 months gentamicin
Fink	34	Gentamicin + clindamycin, vancomycin	2 g vancomycin in 40 g copal-cement	Copal G + C	Two-part hip	Spacer membrane: (LC-MS/MS)	6 weeks	6 weeks

PMMA, polymethylmethacrylate; HPLC, high performance liquid chromatography; LC-MS/MS, high-pressure liquid chromatography coupled to tandem mass spectroscopy; FPIA, fluorescence polarization immunoassay; HEIA, high enzyme immunoassay; IEA, immunoenzymatic assay; THA, total hip arthroplasty (no spacer); Ø, average; h, hours; g, grams.

advantages regarding antibiotic elution and may also prevent acetabular bone resorption and spacer migration (as sometimes observed with hemi-spacers) [3].

The potential value of long-term antibiotic elution from spacers has been verified by studies evaluating the residual antimicrobial and pharmacokinetic properties following their explantation. Minelli et al. [47] and Kelm et al. [51] both demonstrated sufficient elution kinetics and bacterial growth inhibition for all tested spacers, independent of their particular implantation period. Also, Griffin et al. [52] analyzed six spacers with different dosages of vancomycin and tobramycin after removal between 37 and 175 days (average 85 days) and noted no adhering biofilm using scanning electron microscopy, perhaps an indirect sign of sufficient release of antibiotics for these periods.

Question 2: Can a previous implant be "cleaned" and used as a spacer in patients undergoing resection arthroplasty and insertion of a spacer?[2]

Response/Recommendation

Unknown. Available limited evidence shows a similar reinfection rate when using autoclaved components compared to other spacers. Further studies are required.

Level of Evidence: Limited

Delegate Vote: Agree: 85.5%, Disagree: 5.6%, Abstain: 8.9% (Super Majority, Strong Consensus)

Rationale

A two-stage revision strategy has been employed as the preferred surgical management of patients who have chronic periprosthetic joint infection (PJI) [53–55]. This procedure involves the removal of infected implants and the insertion of a spacer that is retained until the second-stage surgery, namely, reimplantation. Various types of antibiotic-loaded spacers are available, including static spacers made from cement blocks reinforced with wireform endoskeletons, as well as articulating spacers, which encompass molded designs, prefabricated spacers, and either new or autoclaved total knee arthroplasty (TKA) components [56–59].

In 1995, Hofmann et al. [60] introduced a method for managing infected TKA by utilizing an articulating spacer. This approach involved sterilizing the original femoral component through autoclaving and reimplanting it alongside a new tibial polyethylene liner. The components were fixed in place using bone cement with antibiotics. While numerous studies have since evaluated the outcomes of this type of spacer [57,59,61–78], no randomized controlled trials have been conducted to date.

A systematic review was conducted in PubMed, Scopus, and Web of Science using appropriate MeSH terms developed by librarians. The search yielded 83 references from relevant studies. After screening and removal of duplicates, 20 studies met the inclusion criteria for full-text review and data extraction. No

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randomized controlled trials or meta-analyses were identified on this topic.

This strategy offers the potential to preserve the range of motion and reduce material waste by leveraging the anatomical compatibility and structural strength of the original implants. However, it also raises critical concerns regarding infection control, sterilization efficacy, and long-term safety.

In a recent systematic review [57], the analysis encompassed a total of 567 patients, with 394 patients receiving autoclaved components and 173 patients treated using spacers constructed from new components. The overall reinfection rate was similar with reused autoclaved components and new components (13.7 and 13.3%, respectively). In a prospective nonrandomized study [78] involving 33 patients who had knee PJI undergoing two-stage revision, the use of autoclaved femoral components and polyethylene tibial inserts resulted in a reported infection rate of 9% after an average follow-up period of 28 months.

When looking at retrospective comparative studies, Nodzo et al. [77], including 140 patients who have knee PJI, divided them into three groups: a reinfection rate of 20.6% in the autoclaved group, 17.3% in the prefabricated spacer group, and 11.6% in the handmade mold spacer group was observed at the final follow-up. Chen et al. [62] found that patients treated with autoclaved femoral components and tibial inserts had a 20% reinfection rate at a mean follow-up of 32 months, compared with a 15% reinfection rate at a mean follow-up of 40.8 months in patients treated with sterile static spacers. Kalore et al. [71] reported patients treated with autoclaved femoral components had a reinfection rate of 13.3% at an average follow-up of 73 months, while patients treated with new femoral components had a reinfection rate of 6.2% at an average follow-up of 19 months, and patients treated with silicone mold component spacers had a reinfection rate of 9.1% at an average follow-up of 32 months. Emerson et al. reported a reinfection rate of 7.7% in the autoclaved components group at 3.8 years mean follow-up and a reinfection rate of 9% at 7.5 years mean follow-up in patients receiving sterile spacers. Reinfection rates between autoclaved and other techniques were not statistically significant in any of these studies.

A major concern regarding autoclaved implants is the potential for residual viable organisms. This issue with the sterility of autoclaved femoral components has limited the widespread use of articulated antibiotic spacers [79]. The Centers for Disease Control, the Association of Operating Room Nurses, health care institutions, implant manufacturers, and medical consult teams have expressed hesitancy toward the temporary reuse of implants due to medical, legal, and financial considerations. Current Centers for Disease Control guidelines do not address protocols for temporary reuse in infection settings [80,81]. Park et al. [82] reported no microbial growth from retrieved autoclaved femoral components before sterilization; however, sonication revealed growth in 10.5% of cases. Despite this, Lyons et al. [79] demonstrated that autoclaving significantly reduced the biofilm burden on cobalt–chrome fragments, confirming sterility of the femoral component following a standard gravity-displacement cycle (132 °C, 27 PSIG, 10 minutes).

In 2020, Woon et al. [59] analyzed 140 unilateral TKA cases, categorizing them into three groups: cement-based spacers, new components, and autoclaved components. The overall survival rate of the reimplanted prosthesis was reported to be 82%. Survival rates across groups within a minimum follow-up period of two years were 81, 96, and 73%, respectively. A significant difference was observed in the median interval to reimplantation among the groups (cement-based spacers: 72 days; new: 111 days; autoclaved: 84 days; $P = 0.003$). When adjusted for the time to reimplantation, new spacers showed superior reimplanted prosthesis survival compared to autoclaved spacers ($P = 0.044$) and demonstrated a trend toward better survival compared to cement-based spacers ($P = 0.086$). Even after excluding early failures (less than 90 days), new spacers maintained a higher survival rate than autoclaved spacers ($P = 0.046$). The authors reasoned that despite negative pre-reimplantation joint aspiration, incomplete elimination of viable organisms from autoclaved implants may have contributed to persistent subclinical infection.

Autoclaved spacers are cheaper than other spacers [57,59,71,79]. Kalore et al. [71] reported that prefabricated cement spacers cost $3,589, and the cement mold technique costs $3,945. However, both methods were considerably more expensive than using autoclaved components, which had the lowest cost at $932. Therefore, autoclaving components is a cost-efficient method compared to other methods [57].

Articulating autoclaved spacers offer major advantages over static spacers in the management of PJI, particularly in preserving and improving the range of motion during the interim period before reimplantation [62,65]. Kalore et al. [71] found no significant difference in range of motion comparing the autoclaving component, the new femoral component, and the silicone mold component.

The reuse of previously autoclaved implants in PJI presents several challenges that must be addressed to optimize this technique. Standardized sterilization protocols are essential to ensure the safety and efficacy of reused implants. Currently, there are no established guidelines for selecting appropriate cases or implants for reuse. Developing such guidelines is crucial to identifying suitable candidates and minimizing risks. Furthermore, the existing evidence base is limited by small sample sizes and short follow-up durations. To validate current findings and expand the applicability of this approach, multicenter studies with larger cohorts and long-term follow-up periods should be conducted. These efforts will provide a stronger foundation for integrating implant reuse into clinical practice.

Conclusions

The reuse of previous implants as spacers in resection arthroplasty is a sustainable and cost-effective alternative to traditional methods. While current evidence supports its feasibility and safety, rigorous sterilization protocols remain critical. Ongoing research and innovation will be essential to optimize this technique and expand its applicability.

Question 3: Is there a difference in the success rate of two-stage exchange arthroplasty when static spacers versus articulating spacers are utilized?[3]

Response/Recommendation

Although in hip and knee two-stage exchange arthroplasty both articulating and static spacers yield similar results in infection eradication, articulating spacers offer better functional and clinical outcomes without significantly increasing the treatment costs.

Level of Evidence: Moderate

Delegate Votes: Agree: 92.7%, Disagree: 5.4%, Abstain: 2% (Total consensus: Unanimity)

Rationale

The periprosthetic joint infection (PJI) is a serious complication in arthroplasty [83–86] and occurs in approximately 1 to 3% of primary total hip arthroplasty (THA) and total knee arthroplasty

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[84,86–89]. A two-stage revision arthroplasty remains the preferred method for treating chronic PJI in North America (8-15), which involves prosthesis removal, antibiotic-loaded spacer placement, and then reimplantation [83,86,90–92].

Spacers used in two-stage exchange arthroplasty of the knee and hip are typically classified into two types: static spacers that immobilize the joint and articulating spacers that allow for some range of motion (ROM) [83,85,92–95]. Some authors suggest that a static spacer facilitates infection control through immobilization [93,96–102] and is more cost-effective than articulating spacers [85,103–105], but may lead to adverse effects such as joint stiffness with poor ROM after reimplantation [96,100,106,107]. Articulating spacers were introduced to address the latter issues associated with static spacers [85,102,108–110]. The goal of this systematic review was to assess the clinical success rates and outcomes of two-stage exchange arthroplasty for PJI of the knee and hip when articulating versus static spacers were used.A comprehensive literature search was conducted in MEDLINE, Embase, and the Cochrane databases to identify relevant studies using the carefully developed MeSH terms in collaboration with librarians. After initial identification of the relevant studies and screening by multiple delegates, 79 studies met the final inclusion criteria.

Infection eradication

Most studies, including meta-analyses and randomized controlled trials, show that in two-stage exchange arthroplasty of the hip and knee, antibiotic-loaded static and articulating spacers achieve similar infection eradication rates [86,91,94,96,99,101,103,106,107,109,111–143], although articulating spacers seem to provide better results in some reports [90,95,100,120,144–147]. The proponents of static spacers claim that limiting soft tissue mobilization provides better antibiotic delivery [95,98,99,103,110,119,120,148], which is an important principle in the treatment of infections [144,146,149], but many studies have shown that both the static and the articulating spacers have similar potential in infection eradication with resistant germs [90,92,93,96,99,101,126,129,150,151].

Functional outcomes and mobility

Articulating spacers provide significantly greater ROM postreimplantation and preserve mobility during interim periods in knee two-stage arthroplasty [86,90,93,94,96–99,101,105–107,110–120,122–124,126,127,129,131,136–138,141,145,147,149,152,153].

There is no true static spacer that fully prevents hip movement [104,105,114,154–157], and few studies have directly compared the use of static and articulating spacers in treating PJI following THA [91,105,114,153,156,158]. However, studies indicate that the use of an articulating spacer in the hip provides a better ROM and significantly enhances patient mobility postreimplantation [91,94,101,104,105,112,113,116,142,147,149,151,156,159–161].

Most studies have shown superior functional outcomes [94–97,100,101,103,105,110,113,115,116,122,124,129,131,133,141,142,144–147,149,153,162], improved quality of life [85,101,113,120,123,124,126,129,135,145,163,164], and enhanced level of activities [107–110,144,147,164,165] using AS in hip and knee two-stage arthroplasty, which may directly result from better ROM [91,93,97,107,119].

Although some authors suggest similar functional outcomes between articulating and static spacers [91,95,107,109,110,114,123,137,144,164,165], it is essential to note that confounding factors such as health conditions, pain levels, follow-up duration, and nature of the measurement tools may have influenced the functional outcome [166].

Complications

The literature highlights heterogeneous definitions of complications with varying outcomes. Soft tissue contractures, joint dysfunction, and especially bone loss are among the most critical and common complications (9, 30, 39), often resulting in poor outcomes. Using a static spacer for treatment of PJI in the hip and the knee frequently causes severe bone loss, joint stiffness, soft tissue shortening [85,90,91,93–97,99,101,103,106,107,110–114,116–120,124,126,128,133,137,140–143,147,151,159,160,167,168], muscle weakness [85,95,98,103,104,108,117,118,121,123,127,141,144,153,160,169–171], and leg-length discrepancy in revision total hip arthroplasty [94,101,113,140,147,160,162,172,173].

Dislocation and fracture of the spacers are other common complications. It is reported more commonly with articulating spacers [90,94,96,102,104,105,109,111,113–119,131,136,137,140,155,160,174], due to higher mobility, but the difference in incidence appears to be insignificant [91,97,107,118,121,133,142,151]. Spacer dislocation occurs mainly in 2-stage hip revision arthroplasty [109,151,155] and increases significantly when using an articulating spacer without acetabular augmentation [104,113,114,119,142,155,156,165,169,171,175–182].

The patient's conditions, surgeon's skills, bone and soft tissue deficiencies, construction technique, time interval until reimplantation, bias in selecting patients, and other factors may have a more severe impact on causing mechanical complications than spacer type [90,94,95,102,107,111–113,115,116,118,124,131,133,141,142,145,147,151,155,160,164–166,169,171,172,174,176,179,183–185].

Costs

The cost of spacers is a minor part of the total cost of managing PJI, which is more related to hospitalization and antibiotic treatment [186–188]. Articulating spacers are more expensive due to their complex design and materials used [85,91,93,95,96,103,117,119,138,185], but through reducing the hospital length of stay [86,91,93,95,96,105,110,114,126,147,160,162,173], minimizing the need for extensive surgery [90,93,95,96,99,100,103,110,112,114,116–121,123,126,127,134,135,141], faster recovery of function [86,91,93,96,101,109,117,124,129,131,138,143,147,173,189], and fewer complications [95,114,119,124,143], articulating spacers may reduce the overall cost of PJI management [91–93,95,113,121,126,133,134,137,138,162,170,172].

Conclusions

Articulating spacers provide comparable results to static spacers in infection eradication, while offering superior mobility, quality of life, fewer complications, and lower overall treatment costs, making them a preferred option for PJI management.

Question 4: Does the type of spacer (hand-made versus manufactured versus primary implant) influence the outcome of two-stage exchange arthroplasty?[4]

Answer

Yes. The infection eradication rate is comparable for different types of spacers, but the risk of complications seems to be lower with the use of functional articulating spacers for both the hip and the knee. Patient function in the interval period may be better with a functional articulating spacer.

Strength of Recommendation: Limited

[4] These authors contributed to Question 4: Ewout S Veltman, Marijn H. Stelwagen, Giorgio Cacciola, Henrique B. Cabrita, Ismail Ghadi, Dipak Dave, Gabriel Baron Girgulsky

Delegate Vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Total consensus, Unanimity)*

Rationale

Spacers can be broadly categorized into three types: static spacers, prefabricated/molded spacers, and functional (implant) spacers. Static spacers are blocks or beads of antibiotic-loaded cement. Prefabricated/molded spacers come in various sizes and can be either commercially available off-the-shelf implants or made intraoperatively using a mold. Functional spacers consist of regularly used (primary or revision) hip or knee implants, which are covered in antibiotic-loaded cement that contains tailored antibiotics according to the causative pathogen. The use of all three types of spacers has been described in the literature for both the hip and the knee. Studies are prone to selection bias, as patient-specific factors (bone loss, tissue compromise) may partly determine eligibility for some types of spacers. For clarity, we will evaluate the hip and the knee spacers separately.

The hip

Studies report no difference in infection eradication rates between different types of antibiotic-loaded spacers for the management of prosthetic joint infection of the hip [190–196].

Studies generally do not report significant differences in functional outcomes among various types of hip spacers [190,192,194,196–200]. A study by Cabrita et al. [201] showed improved results in the spacer group versus the Girdlestone. There were two retrospective studies by Wang et al. and Zhang et al. [191,193] that reported better hip function during the interim period during resection arthroplasty and before reimplantation when comparing functional spacers with handmade ones, though this difference was no longer evident at the final follow-up.

There seems to be a distinct disadvantage associated with static and prefabricated/molded spacers, as they are associated with an increased risk of complications, especially spacer fracture and dislocation, longer hospital stays, and more frequent discharge to an extended care facility when compared to functional articulating spacer types [191–193,198–200,202,203]. However, studies comparing functional spacers with prefabricated/molded spacers are scarce, and differences in complication rates are not always found [194,197]. Kugelman et al. [204] observed less leg-length discrepancy when utilizing functional spacers. In addition, patients were more likely to be discharged home [204]. Tseng et al. [198] reported fewer reoperations after reimplantation when using a functional spacer. A retrospective study by Jones et al. [205] showed that dislocation was associated with reduced femoral offset, while periprosthetic fractures were linked to increased femoral offset. Restoration of offset was best in the functional spacer group compared to hand-made and prefabricated hip spacers [205].

For all spacers where cement articulates with bone, there is a risk of acetabular bone loss. Much less acetabular bone loss is reported in spacers with an acetabular component compared to those without [206]. Increased acetabular bone loss subsequently results in a greater requirement for complex revision hardware [207].

The knee

Similar to the hip, antibiotic-loaded knee spacers, nearly all studies report no difference in infection eradication rates between the different types of spacers [190,196,208–221]. A systematic review by Guild et al. demonstrated a significantly lower reinfection rate in dynamic knee spacers (both prefabricated/molded and functional), whereas four other systematic reviews did not observe this difference [213–217].

Extensive comparative research has been conducted on static and dynamic knee spacers. There were four systematic reviews that reported improved range of motion (ROM) after reimplantation when utilizing dynamic spacers [213,215–217]. However, only the review by Ding et al. [215] also identifies a difference in functional scores. A randomized controlled trial reported better ROM and Knee Society Score with dynamic spacers after 3.5 years of follow-up [218].

A systematic review by Spivey et al. [214] differentiates between various types of dynamic spacers: handmade, molded/prefabricated, and functional spacers. Functional spacers demonstrated the best ROM during the interim period, while prefabricated spacers had the poorest ROM after reimplantation. Beyond this, no significant differences in functional outcomes were observed between the groups [214]. More recent retrospective studies present mixed results; Rossi et al. [219] found no functional difference between functional and prefabricated/molded spacers. Schneider et al. and Wu et al. [209,210] reported better interim ROM with functional spacers, but this advantage was not present at follow-up. Roof et al. and Fei et al. [211,212] demonstrated improved ROM at final follow-up with functional spacers.

When static spacers are compared with all types of dynamic spacers, no significant difference in overall complication risk is typically found, aside from greater bone loss during the interim period with static knee spacers [213,215,216]. This lack of difference may be attributed to the high incidence of spacer subluxation/dislocation, spacer fractures, and instability commonly observed with prefabricated/molded spacers [213,216]. These issues are less frequent—or, in the case of spacer fractures, absent—with functional spacers, as shown in the systematic review by Spivey et al. [214]. In addition, more frequent use of complex revision hardware during reimplantation, longer hospital stays, and higher rates of discharge to extended care facilities have been reported with prefabricated/molded spacers compared to functional ones [211,212].

Conclusions

Although there is a lack of high-level data and considerable heterogeneity between studies and included groups of patients, the use of functional spacers (implants) seems to lead to a lower complication risk compared to other spacer types, while achieving a comparable infection eradication rate for both the hip and the knee.

Question 5: What, if any, are the indications for the exchange of cement spacers?[5]

Response/Recommendation

In cases of persistent infection during the interstage, spacer exchange may be performed; however, both the surgeon and the patient should be aware of the lower eradication rate associated with this procedure. For mechanical complications, the decision to exchange the spacer or proceed directly with an earlier reimplantation should be carefully weighed against the higher failure risk linked to spacer exchange.

Level of Evidence: Limited

Delegate Vote: Agree: 80%, Disagree: 7.6%, Abstain: 12.4% (Super Majority, Strong Consensus)

Rationale

Periprosthetic joint infection (PJI) remains one of the most challenging complications in orthopedic surgery, often

[5] These authors contributed to Question 5: Daniele De Meo, Paolo Adravanti, Ireneusz Babiak, Giorgio Cacciola, Dipak Dave, Antonio Russo, T. David Tarity, Hua Tian

necessitating a staged revision approach. The exchange of a cement spacer during a two-stage exchange (TSE) procedure is a debated topic, with varying indications and outcomes reported in the literature. Spacer exchange rates span around 14 to 17% in literature [220,221].

A systematic review was conducted to identify the indications for spacer exchange and its associated outcomes. A comprehensive search of the Scopus and PubMed databases identified 566 studies for screening. After removing 211 duplicates, 355 studies were assessed. Inclusion criteria included the presence of a patient cohort undergoing interim spacer exchange, with clearly defined indications for the exchange and reported patient outcomes. After full-text assessment of 56 articles, 20 studies were included in the final analysis. All studies were classified as levels III or IV evidence, with 18 retrospective cohort studies and only two prospective case series [221-240].

Indications for an additional spacer exchange include persistent infection, wound-related complications, draining sinus, or mechanical issues such as spacer dislocation or fracture. However, the definition of persistent infection varies among studies because of heterogeneous criteria. Some authors rely solely on local clinical signs and inflammatory markers (e.g., C-reactive protein) [224,227–230,232,235,237–239], while others perform joint aspiration during an antibiotic holiday to guide their decision based on culture results [223,225,226,231,234,240]. In addition, some studies use scores made up of cell count and polymorphonuclear percentage for reinfection risk or preoperative open biopsy [236,241].

In two studies, spacer exchange was performed as an intended strategy. Baeker et al. [222] described a three-stage exchange protocol for patients who have "difficult-to-treat pathogens," defined as pathogens lacking susceptibility to biofilm-active antibiotics (e.g., rifampicin-resistant *staphylococci*, ciprofloxacin-resistant gram-negative bacteria, and fungal infections), reporting an infection eradication rate of 88%. Perry et al. analyzed outcomes of a multi-stage exchange strategy in knee PJI patients who were referred with a preexisting spacer, regardless of signs of active infection. In their series of 54 cases, 45 patients achieved infection eradication (83%) [233].

Among the included studies, 13 compared infection eradication rates between the spacer exchange group and a standard TSE group [Table 4]. Patients undergoing spacer exchange had lower infection eradication rates compared to those in a standard TSE approach (66.4 versus 78.4%). In addition, increasing the number of spacer exchanges (one, two, or three) was significantly associated with a higher reinfection rate (10.5, 40.0, and 100%, respectively) ($P = 0.001$) [239]. Patients who have spacer exchange fail to reach reimplantation more frequently. In their series, Gomez et al. [242] reported that only 66% of patients who underwent spacer exchange ultimately reached reimplantation, and spacer exchange was identified as an independent risk factor for treatment failure. Klemt et al. [231] performed a propensity score–matched analysis comparing patients who underwent spacer exchange with those undergoing a standard TSE, demonstrating a significantly increased reinfection risk in the exchange group (24 versus 15%, $P = 0.03$). Their protocol involved an antibiotic holiday, and the decision to exchange the spacer was based on preoperative aspirations and serologic tests. Similar findings were reported in other unmatched cohort studies [221,238]. However, a separate propensity score–matched study by Frank et al. [227] reached different conclusions, finding no significant differences in re-revision rates ($P = 1.00$) or reinfection rates ($P = 0.32$). In their study, the decision to reimplant or exchange the spacer was at the surgeon's discretion and based on evaluation of inflammatory markers, clinical symptoms, and intraoperative findings, without an antibiotic holiday between stages.

The overall lower success rate observed in patients undergoing spacer exchange could be attributed to the underlying reasons necessitating the exchange itself [223]. Since these patients already exhibited signs of persistent infection despite spacer implantation, certain host-related or microbial factors may have rendered their infection less responsive to the standard protocol of debridement and antibiotic-loaded spacers. Therefore, additional studies are needed to enhance our understanding of why infections persist in spacers despite high-dose local and systemic antibiotic therapy.

Several comorbidities and pathogen characteristics have been identified as independent risk factors for interim failure and subsequent spacer exchange. A higher Charlson Comorbidity Index (odds ratio (OR), 1.56; $P = 0.01$) and the presence of *Enterococcus* species (OR, 1.43; $P = 0.03$) were significant risk factors [231]. Furthermore, Tan et al. [221] reported that patients requiring spacer exchange had a significantly higher body mass index ($P < 0.001$), a higher prevalence of rheumatoid arthritis ($P = 0.018$), and were more likely to have PJI caused by polymicrobial organisms ($P = 0.007$) or antibiotic-resistant strains ($P = 0.048$). Jaubert et al. also identified resistance (OR = 8.8; $P < 0.0008$) as a critical risk factor, along with the presence of gram-negative bacilli in hip aspiration (OR = 3.7; $P < 0.026$) and methicillin-resistant *Staphylococcus aureus* in surgical samples from the first-stage procedure (OR 17.294; $P < 0.012$). Additional risk factors included a high American Society of Anesthesiologists score ($P < 0.012$), chronic liver disease (OR 2.6; $P < 0.001$), and a time to reimplantation exceeding eight months (OR 20.88; $P < 0.0001$) [243]; younger age (adjusted OR = 0.95; $P < 0.001$), the use of an articulating spacer (OR = 0.42; $P = 0.003$), and commercial spacers (OR = 0.25; $P = 0.029$) were protective factors for spacer exchange [244].

Regarding mechanical spacer complications, some authors advocate for shortening the interim period instead of performing a spacer exchange whenever possible [232,245]. In fact, spacer exchange has been shown to have a deleterious impact on functional outcomes. Klemt et al. [231] reported significantly lower postoperative scores for the hip disability and osteoarthritis outcome score physical function (46.0 versus 54.9, $P = 0.01$); knee disability and osteoarthritis outcome score physical function (43.1 versus 51.7, $P < 0.01$); and patient-reported outcomes measurement information system physical function short-form (41.6 versus 47.0, $P = 0.03$).

In conclusion, the heterogeneity in study designs and reporting standards limits the ability to draw definitive conclusions. While certain indications, such as persistent infection, may justify spacer exchange, further high-quality research is needed to establish standardized criteria and assess success rates compared to an earlier definitive reimplantation. In conclusion, the decision to exchange a cement spacer should be carefully weighed against its potential risks, considering patient-specific factors and available clinical evidence.

Question 6: Is there a limit to the number of exchange arthroplasties or surgical procedures in patients who continue to fail treatment for periprosthetic joint infection (PJI)?[6]

Response/Recommendation

[6] These authors contributed to Question 6: Ashley Castan, Tomislav Madjarevic, Jesse Wolfstadt, Jeffrey B. Stambough, Andrea Sambri, Nicholas A. Bedard, Joseph Benevenia

Table 4
Studies Reporting the Comparison of Infection Eradication Rates Between the Spacer Exchange Group and a Standard TSE Group.

Author, Y	Primary Country	Total N	Mean Age	Women N (%)	Joint (s)	Custom, Molded, Cumars	Local Antibiotic	Static/ Articulated	Antibiotic Holiday During Interstage	Indication for Spacer Exchange	Spacer Exchange	Comparison	Comparison	Infection Eradication Total # (%)	Infection Eradication Spacer Exchange # (%)	Infection Eradication Control Group # (%)
Boelch, 2021	Germany	60	67.8	39 (65)	Knee	Custom-made	Gentamicin, vancomycin	Articulating	N	Infection persistence	8	TSE	52	48 (80)	3 (37)	7 (86)
Caglar, 2020	Turkey	42	61	26 (62)	Hip	Custom-made	Vancomycin	Articulating	Y	Infection persistence	5	TSE	37	39 (93)	4 (80)	35 (95)
Frank, 2023	Austria	104	71	20 (38)	25 hips; 27 knees	Molded or custom-made	N/a	Articulating and static	N	Infection persistence or mechanical complication	52	PSM TSE	52	84 (81)	40 (77)	44 (85)
George, 2018	USA	347	65.8	180 (48)	117 hips; 230 knees	N/a	N/a	Articulating and static	Y	Infection persistence	59	TSE	288	236 (74)	39 (66)	227 (79)
Hipfl, 2019	Germany	97	70	56 (58)	Knee	Custom-made	Gentamicin, vancomycin	Static	N	Infection persistence	9	TSE	88	82 (84)	6 (67)	76 (86)
Klemt, 2021	USA	245	66	82 (33)	Hips and knees	Molded or custom-made	N/a	Articulating and static	Y	Infection persistence	49	PSM TSE	196	204 (83)	37 (76)	167 (86)
Pignatti, 2010	Italy	41	59	25 (61)	Hip	Preformed or molded	Gentamicin, vancomycin, meropenem	Articulating	Y	Infection persistence	9	TSE	32	41 (100)	8 (100)	32 (100)
Springorum, 2024	Germany	66	65	25 (38)	Knee	Custom-made	Gentamicin, vancomycin	Articulating	Y	Spacer exchange during pre-reimplantation open biopsy per protocol	30	TSE	36	58 (88)	27 (90)	31 (86)
Staats, 2018	Austria	44	66	17 (39)	15 hips; 29 knees	N/a	Gentamicin, vancomycin	N/a	N	Infection persistence	22	TSE	16	23 (52)	10 (45)	12 (75)
Tan, 2019	USA	533	66	46 (51)	203 hips; 330 knees	Molded or custom-made	Vancomycin, tobramycin	Articulating and static	N/a	Infection persistence or mechanical complication	90	TSE	443	319/425 (75)	37 (59)	282 (80)
Tsai, 2024	Taiwan	361	62.6	179 (50)	187 hips; 174 knees	Preformed or custom-made	Vancomycin, piperacillin, ceftazidime	N/a	Y	Infection persistence	61	TSE	300	334 (92)	53 (87)	281 (94)
Vielgut, 2021	Austria	77	64.9	42 (54)	Knee	Custom-made	Vancomycin	Static	Y	Infection persistence	17	TSE	57	60 (81)	8 (53)	51 (12)
Wichern, 2020	USA	46	65.3	20 (43)	Hip	Preformed, molded or custom-made	Vancomycin, tobramycin	Articulating or static	Y	Infection persistence or mechanical complication	6	TSE	40	44 (96)	5 (83)	39 (97)

TSE, two-stage exchange; PSM, propensity score matched.

While many studies have analyzed the efficacy and outcomes of various treatment algorithms and approaches for recurrent PJI management, no single study has explicitly demonstrated that a finite number of procedures exist in the treatment of chronic PJI of the knee or hip. There is limited and heterogeneous evidence on the number of repeated surgeries. Based on this review, a definitive procedure (above-knee amputation [AKA], knee arthrodesis [KA], or RA) should be seriously considered after a failed second two-stage procedure.

Level of Evidence: Unanimity

Delegate Vote: Agree: 92.2%, Disagree: 3.4%, Abstain: 4.4%

Rationale:

Chronic periprosthetic joint infection (PJI) of the knee and/or hip is a complex problem faced by orthopedic surgeons that lacks a clear course of treatment. Many surgeons rely on their judgment, patient anatomy, and past experience to guide surgical decision-making. Our recommendation aims to serve as a guide for surgeons in preoperative discussions with patients as to the extent of repeated surgeries to treat PJI. To answer this question, we focused on literature demonstrating the outcome of staged procedures—in this case, specifically, repeating the two-stage exchange. The current literature specifies five to six procedures before definitive treatment.

We conducted a literature review based on International Consensus Meeting instructional guidelines (see Appendix).

Based on our literature review, the success of a second two-stage procedure at the knee ranged from 36.4 to 78.9% [246–248]. The success of a second two-stage procedure at the hip ranged from 36 to 74% [246,247,249–251]. Factors that influence the success of recurrent infection treatment include polymicrobial infections, invasive infections (osteomyelitis), soft-tissue status of the limb, and medical comorbidities such as anemia, diabetes, and immunosuppression. Since it is not possible to quantify the influence of these patient factors, the following suggestions are recommendations for best-case scenarios. The final, definitive procedure following a failed repeat two-stage for the knee was defined as an AKA or a KA. The final, definitive procedure for the hip was a resection arthroplasty or hip disarticulation. Patients placed on chronic suppression were not included.

We excluded third-stage procedures due to their extremely low success rate [252]. Khanna et al. [253] closely analyzed the course of seven patients who all ultimately underwent an AKA after an average of seven procedures. Multiple studies have shown that a majority of patients report that, knowing what they know now, they would have undergone the AKA sooner [253,254]. The choice of definitive procedure may affect patients' overall outcomes, as illustrated in a study by Son et al [255]., demonstrating that patients who underwent AKA had a higher mortality rate, but those who underwent KA did not experience any change in mortality. Schnetz et al. [256] found that the 2-year mortality rate was significantly lower in patients who underwent arthrodesis compared to those who underwent AKA. Robinson et al. [257] observed an average of three procedures for patients who had PJI before undergoing a KA.

Less data are available on the number of procedures for hip patients requiring salvage procedures like resection arthroplasty or hip disarticulation. Khan et al. [258] evaluated the outcomes of repeat two-stage exchanges and found that further hip surgery was required to provide definitive treatment to patients but did not specify the type of procedure. Kheir et al. [246] reviewed both the knee and hip patients who had failed prior two-stage exchanges and described patients undergoing amputations and arthrodesis but did not specify outcomes by hip and knee. For hips and knees, 17.2% of patients did not tolerate spacer retention and required an additional procedure [259].

While mortality is lower in arthrodesis patients than in AKA patients, persistent infection and subsequent operations are lower in AKA patients. Patient satisfaction is lower with arthrodesis [248,254,260,261]. Patients who have KA have a better functional status than those who have AKA. On the contrary, less than 50% of patients who have AKA are ambulatory [262–264]. The mortality rate of patients who have PJI—specifically those who undergo a repeat two-stage procedure—is confounded by any final procedure the patient undergoes and by the overall health of the patient. Khan et al. [258] found a 33% mortality rate at two years in patients who underwent a repeat second-stage procedure. In a study by Hungerer et al. [265] comparing arthrodesis to AKA, those who underwent arthrodesis experienced a mortality rate of 4%, while those who underwent AKA experienced a mortality rate of 13%. A bias exists in the difference in mortality between these procedures since AKA may be more likely to be indicated in patients who have higher medical risks.

While many studies have analyzed the efficacy and outcomes of various treatment algorithms and approaches for recurrent PJI management, no single study has explicitly demonstrated that a finite number of procedures exist in the treatment of chronic PJI of the knee or hip. There is limited and heterogeneous evidence on the number of repeated surgeries. Based on this review, a salvage procedure should be seriously considered after a failed second two-stage procedure (Figure 1).

Methodology

Following the International Consensus Meeting instructional guidelines, a literature review was conducted via PubMed and Scopus with the following terms: "prosthetic joint infection," "hip," "knee", "total knee arthroplasty," "total hip arthroplasty," "complications," "hip disarticulation," "knee arthrodesis," "revision knee," "revision knee," "resection arthroplasty," and "above knee amputation." Covidence was used to conduct an initial abstract review of articles (N = 1,504). Of the 1,504, 84 were distributed among the delegates for manuscript review. Ultimately, 32 articles were deemed helpful in this analysis.

Note: Articles pertinent to consensus discussion, but not referenced [266–280].

Question 7: What factors should be considered when deciding on the dose and type of antimicrobials to be added to polymethylmethacrylate (PMMA) spacers?[7]

Response/Recommendations

The primary factor surgeons should consider when selecting antimicrobials to add to bone cement (PMMA) spacers is the infecting organism identified in cultures and its susceptibility profile. While vancomycin combined with an aminoglycoside is historically the most common drug loading regimen for periprosthetic joint infections (PJI) treatment, there is currently no clinical evidence to support specific quantities of these drugs per pack of PMMA or whether this drug-loading regimen is superior to other drug loading regimens. Acute kidney injury (AKI) as a result of spacer antibiotic systemic absorption is more common than previously appreciated. In patients with pre-existing renal compromise, loading PMMA spacers with low doses of nephrotoxic antibiotics or using non-nephrotoxic antibiotics is advised.

Strength of Recommendation: Limited

Delegate Vote: 89.5% Agree, 7.0% Disagree, 3.5% Abstain

[7] These authors contributed to Question 7: Matthew Squire, Roger Rojas Sayol, Minna Hassaballa, David Rodriguez

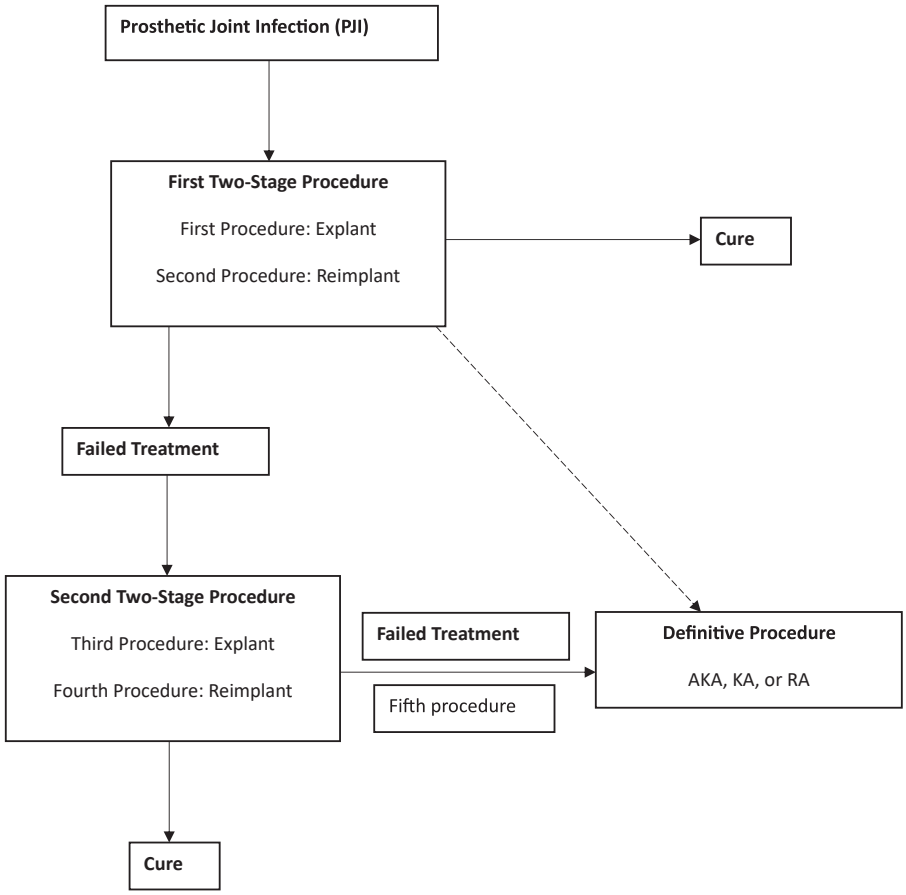

Figure 1. An algorithm representing the process in which a patient who has failed a second two-stage procedure would ultimately have undergone five procedures for definitive treatment. It is possible for a patient to undergo definitive treatment after the first two-stage procedure. Patients may also be cured at any step. AKA, above-knee amputation; KA, knee arthrodesis.

Rationale

Management of chronic PJIs following hip and knee arthroplasty commonly consists of a 2-stage revision arthroplasty with an antibiotic-loaded PMMA spacer and organism-specific intravenous or oral antibiotics [281]. Periprosthetic joint infection microbial profile and drug susceptibilities are the major factors guiding antimicrobial selection and dosing for PMMA spacers. After implant removal, placement of a PMMA spacer containing antibiotics has been shown to effectively eradicate infection 80 to 95% of the time [282–285]. Host factors must also be considered when deciding on PMMA spacer antibiotic type and dosing. In particular, surgeons must be aware of reasons for prior failed PJI treatment, immunocompromised hosts, the presence of sinus tracts, patient allergies, and pre-existing medical conditions such as renal failure. Tailoring PMMA spacer antimicrobial drugs and dosages to these different patient issues is imperative to optimize PJI treatment success and avoid major adverse medical events [286].

We performed a systematic review of English-language literature according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, which revealed 1,261 publication titles between 1994 and the present, including mentions of PJI treatment and antibiotic spacers. Exclusion criteria for this systematic review were shoulder, ankle, and elbow investigations; nonhuman studies; patient cohorts of less than 10; investigations of spacers that were not later revised to hip or knee prostheses; technique articles; review articles; and opinion articles. Inclusion criteria for this systematic review were investigations detailing 2-stage PJI treatment utilizing an antibiotic-loaded spacer, a patient cohort that received spacers loaded with consistent drug(s) and dosage(s), spacer drug dosages clearly stated and quantified as grams of antibiotics per 40 g pack of bone cement, PJI treatment success rate present in text, and average patient cohort follow-up of one year or greater. After exclusions, 273 publications were identified for full-text review. After review, further exclusions were done given data parameters, and a final number of 58 studies (containing 60 distinct patient cohorts) were included for analysis of spacer drugs and dosages as well as PJI treatment success rates.

The 58 studies spanned 1994 to 2024, and the average PJI treatment success rate for all investigations was 85% (range, 56 to 100%). The average duration of follow-up was 45.8 months (range, 12 to 120). The publications identified by this review contained 21 studies dealing with only total hip arthroplasty spacers, 28 dealing with only total knee arthroplasty spacers, and 19 in which a combination of total hip arthroplasty and total knee arthroplasty spacers was studied. A total of 4,379 patients were identified who were treated with a 2-stage exchange that utilized an antibiotic-loaded PMMA spacer.

Each of these studies detailed the antibiotic(s) contained in the spacer and quantified the amount of each antibiotic put in a 40 grams pack of cement, which allowed the calculation of the total antibiotic per pack (TAPP). The amount of antibiotic placed in the PMMA spacers varied widely among the different investigations, with TAPP values ranging from 1.0 to 8.8 grams (mean 4.5, STDEV 2.1). The spacers were constructed with two antibiotics in 41 investigations (43 distinct patient cohorts) with an average

TAPP value of 5.13 grams (range, 2.0 to 8.8), one antibiotic with an average TAPP value of 2.2 grams (range, 1.0 to 4.8) in 13 investigations, and three different antibiotics with an average TAPP value of 4.1 grams (range, 3.0 to 7.5) in the remaining four studies. The drugs included in the different PMMA spacers, listed from most frequent to least frequent, were vancomycin (50 studies), tobramycin (36 studies), gentamycin (13 studies), erythromycin–colistin (three studies), piperacillin/tazobactam (three studies), ceftazidime (two studies), as well as meropenem, clindamycin, and cefotaxime (one study, each). Within the selected investigations, 69% of spacers contained the dual antibiotic combinations of either vancomycin and tobramycin (30 studies) or vancomycin and gentamicin (10 studies), which is consistent with historic data demonstrating synergistic antibacterial activity and enhanced antibiotic elution as a result of these antibiotic combinations [287,288].

To facilitate statistical analysis, the TAPP values of all spacers were divided into three separate groups: TAPP $\leq$ two grams (10 studies with 495 patients), two grams < TAPP $\leq$ four grams (12 studies with 543 patients), and TAPP > four grams (36 studies with 3,341 patients). Kruskal–Wallis analysis of variance was then used to determine if there were differences in the PJI treatment success rates between these three groups. In addition, the cohorts were divided into two groups, with one group whose spacers included both an aminoglycoside and vancomycin (40 studies with 3,342 patients) and one group whose spacers did not contain the combination of an aminoglycoside and vancomycin (18 studies with 1,037 patients). A two-tailed Student *t*-test was used to compare these groups. Also, the cohorts were divided such that one group had spacers containing only one drug (13 studies with 612 patients) and another group had spacers containing two or more drugs (45 studies with 3,767 patients). A two-tailed Student *t*-test was used to compare these two groups.

Kruskal–Wallis analysis of variance assessing the different TAPP groups revealed no statistically significant difference between the success rates of the TAPP $\leq$ two grams, two grams < TAPP $\leq$ four grams, and TAPP > four grams groups ($P = 0.92$). Student *t*-test revealed no significant difference between the success rates of the spacer group containing both vancomycin and an aminoglycoside versus the spacer group containing different drugs ($P = 0.12$). Also, Student *t*-test revealed that the success rate of spacers containing only one drug did not statistically differ from that of the success rate of spacers containing more than one drug ($P = 0.09$).

While not specifically addressed by this systematic review, many of the assessed investigations documented the challenges posed by culture-negative PJI and the variable treatment outcomes of this entity [289]. Currently, there are no concrete recommendations regarding the best antimicrobial drugs and their doses to be included in spacers for the treatment of culture-negative PJI; however, broad-spectrum antibiotic coverage with activity against resistant, fastidious, gram-positive, gram-negative, and potentially fungal organisms is recommended [290]. For these situations, loading of spacers with vancomycin (typically effective against methicillin-resistant *Staphylococcus aureus*) combined with aminoglycosides (activity against gram-negative organisms, including *Pseudomonas aeruginosa*) or a 3rd-/4th-generation cephalosporin (effective against gentamicin-resistant bacteria) and, in select cases, amphotericin or voriconazole should be considered [291].

Acute kidney injury following antibiotic-loaded spacer placement has been increasingly recognized as an avoidable medical complication caused by systemic absorption of nephrotoxic antibiotics that are released by spacers. The incidence of nephrotoxicity following spacer placement varies significantly, with reported rates ranging from 0 to 45% depending on the patient population and antibiotic regimen used [292]. Springer et al. [293], highlighting the risks associated with the choice and concentration of antibiotics used in spacers, reported that spacers containing more than 3.6 grams of nephrotoxic drugs per 40 grams bag of cement can precipitate AKI. Dagneaux et al. [294] found that AKI following spacer placement occurred in 14% of patients who had normal renal function but increased to 45% in patients who had pre-existing chronic kidney disease. In particular, the use of high doses of aminoglycosides has been noted to increase the odds of AKI by approximately six times, especially when utilizing > 4.8 grams per cement batch [294,295].

To mitigate these risks, some institutions have recommended using broad-spectrum and less nephrotoxic antibiotics such as daptomycin, cefotaxime, meropenem, or piperacillin–tazobactam, instead of aminoglycosides in spacers [296,297]. Park et al. [298] demonstrated infection control in 32 of 36 patients (89%) treated with a combination of 4.5 grams piperacillin/tazobactam and two grams vancomycin per 40 grams bone cement pack. In addition, the substitution of vancomycin with daptomycin in high-risk chronic kidney disease patients has also been suggested to reduce renal complications, as daptomycin is less likely to cause creatinine elevation postoperatively [296]. Therefore, to minimize the risk of AKI associated with spacer placement, it is recommended that antibiotic loading of the spacer should be adjusted on a patient-by-patient basis according to pre-existing renal function and that regular renal monitoring should be performed following spacer placement.

Also, case reports of drug allergies and severe reactions as a result of systemic absorption of antibiotics released by antibiotic spacers have been documented. Vancomycin, the most common drug in this systematic review to be included in spacers, can lead to allergic reactions such as severe rash and more serious skin and systemic manifestations. Harper and Incavo [299] documented severe drug reaction with eosinophilia and systemic symptoms syndrome following the use of spacers for PJI treatment. Williams et al. [300] reported on a patient who experienced a diffuse desquamating rash following exposure to vancomycin-impregnated bone cement. Occasionally, systemic or cutaneous reactions to antibiotics released by spacers may be so severe that spacer removal is required. Thus, clinicians must be vigilant in monitoring for signs of allergic reactions or systemic toxicity, especially in patients receiving spacers with higher doses of antibiotics or who have experienced prior reactions to antibiotics contained within the spacer [293–295].

Conclusions

The main factor affecting spacer antibiotic selection should be the susceptibility profile of the infecting organism(s) causing PJI. While this systematic review can find no statistically significant differences in success rates based on antibiotic type or dosages placed within PMMA spacers, host factors such as renal function and allergy history must be accounted for when selecting antibiotics and their doses to be included in spacers. The risk of nephrotoxicity, particularly with high-dose aminoglycosides within a spacer, has raised concerns, prompting some institutions to explore alternative antibiotics with reduced renal risks. Ultimately, personalized antibiotic selection, renal-based dosing adjustments, and close monitoring of patient renal function are

essential for maximizing PJI treatment success and minimizing associated medical complications.

Question 8: What antibiotics should be added to a cement spacer in patients undergoing resection arthroplasty for culture-negative periprosthetic joint infection (CN PJI)?[8]

Response/Recommendations

The addition of vancomycin combined with either an aminoglycoside, meropenem, or piperacillin/tazobactam to a cement spacer is a reasonable approach for the treatment of patients who have CN PJI.

Level of Evidence: Limited

Delegate Vote: Agree: 73%, Disagree: 22.7%, Abstain: 43% (Strong Consensus)

Rationale

Periprosthetic joint infections continue to be the leading cause of revision hip and knee arthroplasties in the United States and Europe [301]. Around 1% of patients undergoing total hip or knee arthroplasty develop a PJI, with annual treatment expected to cost health care around $2 billion by the year 2030 [302,303]. With the number of revision hip and knee arthroplasties on the rise, the even higher incidence of PJI in revision arthroplasty requires arthroplasty surgeons to focus on both prevention and appropriate infection eradication practices [303].

Even though there are recent data documenting acceptable success with debridement and antibiotics with implant retention and one-stage exchange for acute and chronic PJI, two-stage revision has been considered the gold standard for treating PJI [304–307].

Spacer antibiotic selection during two-stage revision arthroplasty is guided by preoperative cultures and sensitivities. Between 5 and 42% of PJIs are CN infections, which pose major challenges in terms of antibiotic selection for both cement spacer construction and parenteral antibiotic treatment [308,309]. Documented risk factors for CN cases include prior use of antibiotics before aspiration/procedure, inappropriate culture tools, insufficient culture period, persistent wound drainage or draining sinus, and infection with fastidious organisms or fungi [310].

Studies show that fastidious organisms such as fungi, mycobacteria, *Listeria monocytogens*, *Propionibacterium acnes*, *Brucella spp*., and *Coxiella burnetii* are present in up to 50% of CN PJI cases [308,311,312]. The use of advanced microbial identification techniques, such as culture of specimens in blood culture vials, extended incubation times, and, more recently, next-generation DNA sequencing, may allow for more accurate detection of fastidious bacteria and fungi [313]. In addition to guiding optimal antimicrobial selection during PJI treatment, successful organism identification also enhances antimicrobial stewardship by eliminating the need for excessively broad-spectrum empiric antimicrobial use.

Reported success rates for the two-stage treatment of CN PJI vary, with numerous studies showing comparable and sometimes higher success rates in CN cohorts as compared to culture-positive cohorts [314,315]. Currently, no consensus exists with respect to the type or dose of antimicrobials that should be added to the spacer in the first stage of treatment. [316,317]. To improve our understanding of the optimal drug(s) and dose(s) to be placed in spacers for CN PJI, a systematic review was performed assessing PJI treatment success as a function of the antimicrobial drug(s) placed in spacers used in the two-stage treatment of CN PJI.

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we conducted a systematic search of the online bibliographic databases MEDLINE and PubMed from inception through November 2024 to identify studies evaluating success rates on CN PJIs undergoing two-stage revision hip or knee arthroplasty. Exclusion criteria were as follows: articles not written in the English language, investigations not including specific doses and types of antimicrobials added to the spacer, shoulder, elbow, and ankle arthroplasty PJI studies, editorials, commentaries, case reports, reviews, and technique articles without patient success and/or follow-up data. There were two of the authors who independently screened the titles and abstracts of an initial number of 654 articles to apply the selection criteria. Disagreements were solved by consensus after reading the full text. We reviewed the full text of 68 articles and finally included 21 articles for analysis. For comparative analysis of the outcomes of each study, a data sheet containing the author's name, year of publication, study design, number of CN cases, spacer contents, two-stage exchange arthroplasty success rate, and average follow-up was designed. The review results of the 21 included studies are summarized in table 1 [311–313,315,318–334].

In the 21 studies identified for data analysis, a total of six (1702) patients were identified, of which 41% (266 (698) patients) had CN PJI. There were no studies that reported results according to the Musculoskeletal Infection Society 2019 Outcome Reporting Tool for PJI, which confounded direct comparisons among them. To facilitate meaningful data analysis, our study group decided to divide and analyze five subgroups depending on the antibiotic combination and dosage within the spacer. The cohorts were as follows.

a. Cohort 1 (High-dose vancomycin/tobramycin): Patients who received vancomycin three to four grams/tobramycin two to six grams (n = 386).
b. Cohort 2: Patients who received vancomycin one to two grams/piperacillin/tazobactam one grams (n = 27).
c. Cohort 3: Patients who received vancomycin one to two grams/meropenem/imipenem two grams (n = 80).
d. Cohort 4: Patients who received vancomycin one to two grams only (n = 40).
e. Cohort 5 (Low-dose vancomycin/tobramycin): Patients who received vancomycin one to two grams/tobramycin 80 mg to 1.2 grams (n = 165).

Of the 80 patients treated with the vancomycin/carbapenem combination, there were no PJI treatment failures noted. The low-dose (n = 165) and high-dose (n = 386) vancomycin/aminoglycoside cohorts demonstrated 96.6 and 89.2% PJI treatment success rates, respectively. A *Chi*-square test to compare the success rate among these cohorts did not reveal any statistically significant differences between them (P = 0.003). Our group understands the potential for selection bias of this noted significance, given the different numbers in the high-dose and low-dose groups. In the very limited spacer cohort containing vancomycin and piperacillin/tazobactam (n = 27), there were no failures noted. The vancomycin-only cohort (n = 40) demonstrated the lowest success rate, with only a 75% success rate. With the potential of CN infections being caused by multiple organisms, it is possible to suggest that utilizing antibiotic-loaded bone cement with a single antibiotic might increase the risk of treatment failure.

Studies suggest that CN infections are not a negative prognostic factor for the eradication of infection [335,318]. Our data support the combined use of vancomycin with either an aminoglycoside, meropenem, or piperacillin/tazobactam in spacers for CN PJI. While our data present support for the use of spacers containing

[8] These authors contributed to Question 8: David Rodriguez, Conor George, Jonathan Sauer, Temiloluwa Olufemi, Matthew Squire

either a low- or high-dose combination of vancomycin and an aminoglycoside, prior investigations have shown that spacers containing lower doses of both vancomycin and aminoglycosides may increase the risk of PJI treatment failure as compared to spacers containing high doses of both vancomycin and aminoglycosides [319]. With the limited data available for this systematic review, the use of spacers containing a single antibiotic in low doses is not recommended for CN PJI. In a cohort of 114 CN PJI cases, Yang et al. utilized two different spacer antimicrobial combinations. The spacer antimicrobial combination of vancomycin, meropenem, and amphotericin (VMA protocol) had a 100% success rate in 45 patients, illustrating the importance of covering for fungal and other fastidious organisms in CN PJI [320].

Conclusions

Our systematic review reveals that even though CN PJIs pose a major challenge, a negative culture might not be an adverse predictor of success during two-stage revision arthroplasties. The overall results of this review indicate that dual antibiotic cement spacer regimens (vancomycin–aminoglycoside, vancomycin–piperacillin/tazobactam, vancomycin–meropenem) provide comparable and high success rates for the treatment of CN PJI, and the use of these antibiotic combinations in polymethylmethacrylate (PMMA) spacers can be recommended for the treatment of CN PJI. In contrast, this systematic review suggests spacers containing only vancomycin may have inferior treatment success rates; therefore, the use of PMMA spacers containing only vancomycin is not recommended for the treatment of CN PJI. In cases where CN PJI occurs in immunocompromised hosts, is present after a failed 2-stage exchange for PJI, or is associated with the presence of a sinus tract, fastidious organisms, including fungi, must be suspected. It is recommended that PMMA spacers used to treat these challenging clinical scenarios contain a combination of antimicrobial drugs that provides broad-spectrum coverage against all suspected pathogens.

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The Journal of Arthroplasty 41 (2025) S362–S375

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Hip and Knee

2025 ICM: Antibiotic Prophylaxis in Primary Joint Arthroplasty

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Question 1: Should antimicrobial prophylaxis be given to patients who have a joint arthroplasty in place and who are undergoing invasive procedures (e.g., dental, colonoscopy, cystoscopy, etc.)?[1]

Response/Recommendation

Based on the evidence in the literature, we do not advocate for the use of antimicrobial prophylaxis for patients who have a joint arthroplasty and undergo dental, urologic, or gastrointestinal procedures.

Level of Evidence: Limited

Delegate Vote: Yes 82.5%, Disagree 14.5%, Abstain 3.5% (Super Majority, Strong Consensus)

Rationale

Although our understanding of periprosthetic joint infection (PJI) has evolved, how host factors and the degree of bacterial exposure combine to drive dysbiosis and subsequent PJI remains unclear [1–3]. Procedures of the gastrointestinal (GI) tract, genitourinary (GU) tract, and oral cavity produce transient bacteremia and, therefore, in theory, could cause hematogenous PJI [4–6]. Multiple subspecialty societies in the United States have guidelines for antibiotic prophylaxis prior to dental, GU, or GI procedures for patients who have a history of arthroplasty, but these are inconsistently followed by clinicians and continue to be debated [7–9].

Dental procedures

Various definitions of invasive (e.g., gingival work, surgical tooth extraction, and dental implants) versus non-invasive (e.g., periodontal work) dental procedures determined by dentists exist in the literature [10,11] As pointed out by Legout et al., studies have shown mastication and oral hygiene may contribute more than dental procedures to a patient's cumulative exposure to transient bacteremia episodes - making concerns about the invasiveness of a dental procedure trivial. Their review and the systematic review by Salgado-Peralvo et al. determined there were no data to support prophylaxis among arthroplasty patients undergoing invasive dental implant surgery [12]. This conclusion contradicts suggestions from a 2020 Milic et al. review in the oral and maxillofacial surgery literature, which recommended prophylaxis for invasive extractions of third molars, comminuted mandibular fractures, temporomandibular joint arthroplasties, clean-contaminated tumor removal, and complex implants [13]. The applicability of these findings is limited as studies were of low quality and their review was focused on patients undergoing oral and maxillofacial surgery procedures.

Prospective data from Berbari et al. found that antibiotic prophylaxis in high-risk or low-risk dental procedures did not decrease the risk of subsequent total hip or knee infection (adjusted odds ratio [OR], 0.9 [95% confidence interval [CI], 0.5 to

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.08.061.

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https://doi.org/10.1016/j.arth.2025.08.061
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1.6] and 1.2 [95% CI, 0.7 to 2.2], respectively) [14]. Kao et al. found no difference in 1-year cumulative incidences of PJI for patients who have (0.6%) or do not have (0.6%) dental procedures [(95% CI, 0.6 to 0.7%) and 0.6% (95% CI, 0.5 to 0.6%) respectively ($P = 0.3$)], and in multivariate analyses found both that dental procedures were not associated with PJI risk and that periprocedural prophylactic antibiotics did not modify PJI risk [15]. These studies and seven others were included in a systematic review by Slullitel et al., which also found no association between antibiotic prophylaxis and the incidence or prevention of PJI [16]. In another systematic review, Moreira et al. found no evidence supporting the use of prophylaxis among patients who have known periodontal disease [10,11,13–18]

Later studies by Sax et al. and Park et al. reported no significant difference in PJI rates by prophylaxis status [10,18]. Masuda et al. found no association between dental procedures or prophylaxis and PJI risk [10]. Simon et al. reported no association between oral prophylaxis and PJI, and all four of their PJI cases had dental procedures and prophylactic antibiotics [19]. Also, reviewing more than 9,000 patients who have a total joint arthroplasty (TJA) in England (where periprocedural antibiotic prophylaxis is not recommended), Thornhill et al. found no temporal association between invasive dental procedures and subsequent PJI [20]. These findings reinforce clinical practice guidelines and prior systematic reviews that advise against the use of oral antibiotic prophylaxis. A recent study found that 81% of surveyed surgeons prescribed antibiotics for their arthroplasty patients before dental procedures, despite American Dental Association and American Academy of Orthopaedic Surgeons guidelines advising against the practice, suggesting the need for new strategies and implementation science promoting evidence-based practice [8].

Gastrointestinal procedures

With endoscopic procedures known to cause bacteremia, studies evaluating their risk for PJI and whether prophylaxis is warranted are needed [1,2,6,21]. The American Society for Gastrointestinal Endoscopy recommends against antibiotic prophylaxis before any endoscopic procedure, and our literature search found no evidence disputing this guidance [22]. Coelho-Prabhu et al. performed a prospective study among arthroplasty patients who underwent endoscopic procedures such as esophagogastroduodenoscopy, colonoscopy, sigmoidoscopy, and esophageal dilation and found the risk of PJI associated with esophagogastroduodenoscopy with biopsy (OR 2.8 [95% CI 1.1 to 7.1], $P = 0.03$), but not for other endoscopic procedures.[23] However, they did not find significant differences in the proportion of GI-tract-associated organisms among their cohorts with or without biopsy, and inadequate sample size made it difficult to determine whether antibiotic prophylaxis mitigated this risk [23].

Albana et al. found that prophylaxis before colonoscopy with biopsy did not reduce the risk of PJI in total knee arthroplasty (TKA) patients [24]. Bains et al. found no difference in PJI rates for those who did or did not undergo screening colonoscopy, even when stratified by prophylaxis status [25]. A retrospective database study by Chiu et al. with over 1.6 million patients showed diagnostic colonoscopy was not associated with increased all-cause or septic revision surgery for any arthroplasty and unexpectedly was associated with decreased risk of septic revision for TKA and total hip arthroplasty (THA) recipients [26]. The only study suggesting prophylaxis might have value was that of Shin et al., in which a cumulative incidence rate of PJIs was 0.038% in non-recipients of colonoscopy within one year postoperative and 0.070% in those who underwent colonoscopy ($P = 0.005$); however, the impact of antibiotic prophylaxis on PJI after colonoscopy was not assessed [27].

Urologic procedures

The American Urological Association's best practice guidelines recommend antibiotic prophylaxis for all patients before many invasive surgeries/procedures and therefore are not relevant to this consensus statement [28]. For patients who have a history of arthroplasty within the past two years, the American Urological Association's guidelines recommend antibiotic prophylaxis before procedures with a high risk of bacteremia, specifically transrectal prostate biopsy or treatment of infected stones. However, the guidelines comment that there is no evidence that these procedures increase the risk of PJI, and the recommendation is based on orthopedic surgeon preferences rather than data. Punjani et al. found an association between transurethral prostatectomy and risk of subsequent PJI (hazard ratio (HR) 3.42, 95% CI 1.29 to 9.10), $P = 0.01$), but no such association with cystoscopy (HR 1.05, 95% CI 0.85 to 1.30, $P = 0.66$) [29]. The authors of this study noted overall risk was low for transurethral prostatectomy patients and may be present regardless of perioperative prophylaxis. Though not pulled in our formal query, findings from a second observational study by Gupta et al. are worth noting: their prospective study found no increased risk of PJI following urological procedures, either with or without antibiotic prophylaxis. A recent study on arthroplasty patients undergoing GU procedures highlighted inconsistencies in prophylaxis practices, underscoring the need for high-level data examining the relationships between urologic procedures (regardless of invasiveness), prophylaxis, and PJI [30].

Conclusion

Based on the data presented, we do not advocate for the use of routine prophylactic antibiotics prior to invasive dental, GI, or GU procedures in patients who have joint arthroplasty (Tables 1 and 2). Special consideration may be warranted for a minority of patients at elevated risk for PJI; however, current literature has yet to identify any subpopulations that demonstrably benefit from prophylaxis. More robust studies focusing on populations clinicians perceive to be at elevated PJI risk are needed.

Question 2: What is the optimal prophylactic antibiotic for patients undergoing primary arthroplasty?[2]

Response/Recommendation

Cephalosporins, particularly cefazolin, are strongly recommended as first-line prophylaxis in primary arthroplasty based on consistent quality evidence, significant infection risk reduction, and minimal adverse effects.

Strength of Recommendation: Strong

Delegate Vote: Agree 98.3%, Disagree 0%, Abstain 1.7% (Super Majority, Strong Consensus)

Rationale

Periprosthetic joint infections (PJI) represent a major complication in TJA, contributing to increased patient morbidities, prolonged hospital stays, heightened healthcare costs, and frequent needs for complex revision surgeries. Effective antibiotic prophylaxis is a cornerstone in minimizing these risks, with cephalosporins, particularly cefazolin, emerging as the gold standard due to their efficacy, safety, and cost-effectiveness. Over the last decade, an extensive body of evidence has supported the use of cephalosporins, addressing their benefits in routine arthroplasty

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Table 1
Search Terms.

Database	Search Terms
Pubmed	((("arthroplasty" [MeSH] OR joint arthroplasty OR joint replacement OR Hip arthroplasty OR Knee arthroplasty OR Shoulder arthroplasty OR Hip replacement OR Knee replacement OR Shoulder replacement) AND (Invasive procedure OR Colonoscopy OR Cystoscopy OR dental procedures OR endoscopy OR "Minimally Invasive Surgical Procedures" [Mesh] OR "Oral Surgical Procedures" [Mesh] OR "Dental Care" [Mesh])) AND ("anti-infective agents" [Pharmacological Action] OR "anti-infective agents" [MeSH Terms] OR "Antibiotic Prophylaxis" [Mesh] OR ("Anti-Infective Agents" [Mesh] AND "prevention and control" [Subheading]) OR Antimicrobial prophylaxis OR Antibiotic Prophylaxis)) AND ((((1990:3000/12/12 [pdat]) AND (english[LA])) OR (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab])) NOT (animals [mh] NOT humans [mh]))
Embase	((('arthroplasty'/exp OR 'joint arthroplasty' OR 'joint replacement' OR 'hip arthroplasty' OR 'knee arthroplasty' OR 'shoulder arthroplasty' OR 'hip replacement' OR 'knee replacement' OR 'shoulder replacement') AND ('invasive procedure' OR 'colonoscopy' OR 'cystoscopy' OR 'dental procedures' OR 'endoscopy' OR 'minimally invasive surgery'/exp OR 'oral surgery'/exp OR 'dental procedure'/exp)) AND ('anti-infective agents' OR 'antiinfective agent'/exp OR 'antibiotic prophylaxis'/exp OR ('antiinfective agent'/exp AND 'prevention and control') OR 'antimicrobial prophylaxis' OR 'antibiotic prophylaxis')) AND ((((['1990 to 3000-12-12]/pd) AND ('english':la)) OR ('randomized controlled trial':it OR 'controlled clinical trial':it OR 'randomized':ti,ab,kw OR 'placebo':ti,ab,kw OR 'drug therapy' OR 'randomly':ti,ab,kw OR 'trial':ti,ab,kw OR 'groups':ti,ab,kw)) NOT ('animal'/exp NOT 'human'/exp))

cases, high-risk populations, penicillin-allergic patients, and their role in combination with adjunctive strategies.

To address the posed question above, we conducted a comprehensive systematic review. Initially, using the search in PubMed and Embase, we identified 924 studies. After eliminating duplicates and case series, 167 studies were selected for full-text analysis. Following a review conducted by two reviewers, we finalized 41 articles for data extraction. For the final analysis of the strength of recommendation, 22 articles were used due to their consistency in the necessary data. Analysis of these most relevant studies spanning from 2015 to 2024 has demonstrated consistent reductions in infection rates, culminating in a strong recommendation (Grade A) for cephalosporins in primary arthroplasty, as assessed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [31].

The systematic review by Voigt et al. in 2015 remains foundational in supporting cephalosporin use. This study synthesized data from randomized controlled trials involving over 12,000 patients and demonstrated that cephalosporins reduced surgical site infection (SSI) rates by 40% compared to non-cephalosporin antibiotics (Level I evidence) [32]. Concurrently, Hickson et al. analyzed 4,500 arthroplasty cases and identified cefazolin and cefuroxime as highly effective agents when administered correctly, achieving consistent infection rates of approximately 2.5% [33].

Robertsson et al. analyzed the Swedish Knee Arthroplasty Register, encompassing 55,350 patients who underwent primary knee arthroplasty during the period from 2009 to 2015, and highlighted that clindamycin, often used in penicillin-allergic patients, was associated with a 50% higher risk of infection revision compared to cephalosporins (relative risk = 1.5, P = 0.001) [34]. In the same year, Parvizi et al. published guidelines emphasizing the importance of timely preoperative antibiotic administration, nasal decolonization with mupirocin, and dual-agent skin preparation to mitigate infection risks in arthroplasty [35] In 2019, Wyles et al. evaluated 29,695 arthroplasties from 2004 through 2017 at the Mayo Clinic and demonstrated that allergy testing significantly improved cefazolin use in patients with reported penicillin allergies. This retrospective cohort study showed that delabeling penicillin allergies increased cefazolin use from 70 to 95%, resulting in a reduction in infection rates from 1.49 to 1.15% (odds ratio [OR] = 0.78, $P < 0.05$). This study found a lower rate of PJI when cefazolin is used for prophylaxis in primary THA and TKA compared with vancomycin or clindamycin [36].

Further evidence emerged in 2020, when Babu et al. conducted a multicenter study comparing five antibiotic regimens across 4,500 arthroplasties [37]. This analysis found no significant differences in infection rates among regimens involving cefuroxime, teicoplanin, and gentamicin [38]. Rivera et al. added further laboratory evidence demonstrating cefazolin's superior efficacy in preventing intraoperative bacterial contamination compared to alternative agents, underscoring its critical role in infection prevention during arthroplasty [39]).

Table 2
Study Inclusion and Exclusion Criteria.

Category	Include	Exclude
Population	Humans	Animals
	Age >18 year old	Age <18 year old
	Total hip arthroplasty	Total shoulder arthroplasty
	Total knee arthroplasty	Total elbow arthroplasty
	Gastrointestinal procedure	
	Dental procedure	
	Genitourinary procedure	
Publication date	1990-present	Studies before 1990 (unless a randomized control trial)
Language	English	Non-English
Intervention/Exposure	No antibiotic prophylaxis	
Comparator/Outcome	Antibiotic prophylaxis	
Outcome	Periprosthetic joint infection	
Study Characteristics	Randomized controlled trial	Case report
	Observational clinical study (retrospective or prospective)	Narrative review
	Systematic review	
	Meta-analysis	

The 2021 American Association of Hip and Knee Surgeons (AAHKS) Annual Symposium further emphasized weight-based cefazolin dosing and the necessity of preoperative administration within 30 minutes of incision to optimize tissue concentrations. Recommendations included one gram for patients < 60 kg, two grams for patients 60 to 120 kg, and three grams for patients > 120 kg. In Addition, cefazolin monotherapy was strongly recommended over vancomycin for routine-risk patients, while dual antibiotic regimens were selectively advocated for high-risk cases [40]. In a separate study presented by Mabrouk et al., guideline adherence across 109 institutions in the United Kingdom highlighted variability in practices related to the drug used, weight-based dosing, and methicillin-resistant *Staphylococcus aureus* (MRSA) screening protocols, underscoring the need for standardization [41].

In 2022, Badge et al. conducted a large retrospective study involving 1,838 high-risk patients. They found that weight-based cefazolin dosing reduced infection rates from 5.2 to 2.9%, emphasizing the necessity of adjusting doses based on patient weight to enhance effectiveness [42]. Similarly, Indelli et al. (2022) surveyed international arthroplasty experts, recommending routine preoperative decolonization, MRSA screening, and weight-based cefazolin dosing [43].

By 2023, studies increasingly focused on adjunctive therapies and addressing penicillin-allergic patients Ashkenazi et al. evaluated gentamicin's addition to cefazolin in 1,590 TKA cases, observing a 34% reduction in infections (from 1.3 to 0.86%), although findings were not statistically significant ($P = 0.43$) [44]. Bukowski et al. demonstrated cefazolin's safety in penicillin-allergic patients, showing a 0.1% rate of mild allergic reactions in 5,508 patients with no increased infection risks [45]. Another study by Jones et al. reported that stewardship interventions increased cefazolin use in penicillin-allergic patients from 54 to 91%, reducing superficial infections from 4.5 to 2.8%.

This study also emphasized that cephalosporins are safer and more effective than alternatives such as vancomycin or clindamycin for penicillin-allergic patients, reinforcing the importance of stewardship programs [46].

Bains et al. evaluated whether adding vancomycin to cefazolin for preoperative antibiotic prophylaxis reduces infection rates in TJAs. It analyzed 2,907 patients (1,437 receiving vancomycin plus cefazolin and 1,470 receiving cefazolin only) over seven years. Results showed no significant difference in rates of SSI or periprosthetic joint infections (PJIs) between the two groups at 90 days and one year. Vancomycin was associated with reduced MRSA colonization in pre-screened patients, but did not lower overall infection rates. The study concluded that vancomycin is unnecessary for most patients and should be limited to MRSA-positive cases [47].

Peel et al. conducted a multicenter, double-blind, placebo-controlled randomized clinical trial involving 4,239 patients undergoing primary arthroplasty (hip, knee, and shoulder) without MRSA colonization. The study compared cefazolin monotherapy with cefazolin plus vancomycin and found no significant difference in SSI rates (4.5 versus 3.5%, $P = 0.11$). Subgroup analysis showed higher infection rates with dual therapy in knee arthroplasty (5.7 versus 3.7%, $P < 0.05$), but no difference in hip arthroplasty. Although vancomycin reduced the risk of acute kidney injury (2.1 versus 3.6%, $P < 0.01$), it was associated with increased hypersensitivity reactions (1.2 versus 0.5%, $P < 0.05$). The study concluded that cefazolin monotherapy suffices for infection prophylaxis in non-MRSA colonized patients, reserving vancomycin for high-risk populations [48].

Sequeira et al. highlighted the effectiveness of novel antimicrobial lavage solutions, reducing bacterial loads by 92% and preventing biofilm formation [49] whenin 2024, Hassanzadeh et al. reviewed national prescribing practices, identifying cefazolin as the most commonly recommended antibiotic in arthroplasty. Standardizing evidence-based protocols was emphasized to reduce variability and improve outcomes and the emergence of antibiotic resistance [50].

In the same year, Egerci et al. conducted a comprehensive review on strategies to prevent PJI in THA and TKA, emphasizing the importance of a multidisciplinary approach and patient-specific strategies to reduce PJI risk and improve surgical outcomes [51].

In conclusion, there is strong evidence that supports the use of cefazolin as the first-line prophylaxis in patients undergoing primary arthroplasty.

Question 3: What is the recommended duration of prophylactic antibiotics for patients undergoing outpatient arthroplasty?[3]

Response/Recommendation

Our systematic review found no clear consensus on the optimal duration or method of prophylactic antibiotic use in outpatient arthroplasty. From the studies reviewed, one dose of perioperative intravenous antibiotic may be sufficient for patients undergoing outpatient arthroplasty.

Level of Evidence: Limited

Delegate Vote: Agree 92.6%, Disagree 3.9%, Abstain 3.5%

Rationale

Prophylactic antibiotics are critical in arthroplasty to reduce the risk of SSIs [52], but the optimal duration of prophylactic antibiotics in the outpatient setting remains uncertain. This review analyzed current evidence on antibiotic use, identifying variations in practice across healthcare settings and administration methods. Out of 81 initially identified studies, 27 were selected after title and abstract screening, with six included in the final analysis following full-text review.

Our systematic review yielded the following key findings (Table 3).

- A retrospective study of 20,682 primary TJAs performed between 2006 and 2017 compared the effectiveness of single-dose (n = 4,523) versus multiple-dose (n = 16,159) prophylactic antibiotics in preventing PJI. The PJI rates were 0.60% for the single-dose group and 0.88% for the multiple-dose group. Statistical analyses showed no significant difference between the two approaches in univariate (OR = 0.674, $P = 0.064$), multivariate (OR = 0.755, $P = 0.205$), or propensity score-matched analyses (OR = 0.746, $P = 0.277$). Even in high-risk patients, multiple-dose regimens provided no additional benefit ($P = 0.136$) [53].
- Antibiotic timing and type: In the largest study population, only 16.5% of 73,015 THA andTKA patients received perioperative prophylactic antibiotics. Among these patients, 51.6% filled their prescriptions on the day of surgery, 29.7% filled them one to five days before surgery, and 20.8% filled them one to three days after surgery. The most commonly prescribed antibiotic was cephalexin 500 mg (median 2-days supply). Among non-cephalosporin options, clindamycin 300 mg was prescribed in 6.8% of cases, typically provided as a 3-day supply [54].
- Comparison of 24-hour and single dose of intravenous antibiotics: In unicompartmental knee arthroplasty and total

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Table 3
Included Studies.

Author, year	Study Question Addressed in This Review	Findings
Tan et al. 2019	Is single dose as effective as multiple doses	The PJI rate was 0.60% (27/4,523) with a single antibiotic dose and 0.88% (142/16,159) with multiple doses. There was no significant difference between groups in univariate (OR = 0.674, $P = 0.064$), multivariate (OR = 0.755, $P = 0.205$), or propensity score matched analyses (OR = 0.746, $P = 0.277$). Multiple doses also provided no added benefit for high-risk patients ($P = 0.136$).
Yendluri et al. 2024	Describing current practices on oral perioperative antibiotic prophylaxis for outpatient total hip and knee arthroplasty	Only 16.5% of 73,015 outpatient THA and TKA patients received perioperative antibiotics. Of these, 51.6% filled prescriptions on the day of surgery, 29.7% 1 to 5 days before, and 20.8% 1 to 3 days postoperatively. Cephalexin 500 mg was most commonly prescribed with a median 2-day supply, while clindamycin 300 mg was used in 6.8% of cases, typically given for 3 days.
Wyles et al. 2019	24-hours versus single IV antibiotics in UKA?	Failure/Total: Inpatient (24-h): (2/256), Outpatient (single dose): (0/40) |P -value = 1.00
Fryburger et al. 2021	Single versus 24-hours IV antibiotics in TSA?	Failure/Total: Inpatient (24-h): (13/896), Outpatient (single dose): (2/126) | P-value = 0.71
Keulen et al. 2024	Trends in 24-hours perioperative antibiotic therapy in TKA and THA	1 Dose / 2 Doses / 3 Doses TKA Outpatient (/Total): 1/16 / 7/16 / 8/16 Inpatient (/Total): 16/86 / 10/86 / 58/86 P -Value: 0.014 THA Outpatient (/Total): 2/17 / 9/17 / 6/17 Inpatient (/Total): 11/66 / 2/66 / 52/66 P -Value: <0.001

PJI, periprosthetic joint infection; TKA, total knee arthroplasty; THA, total hip arthroplasty; UKA, unicompartmental knee arthroplasty; OR, odds ratio; TSA, total shoulder arthroplasty.

shoulder arthroplasty, intravenous antibiotics administered for 24 h perioperatively showed no significant difference in infection outcomes compared to a single preoperative dose of intravenous antibiotics [55,56].
- Variation in total number of antibiotic doses between inpatient and outpatient surgery: As expected, outpatient THA and TKA patients received fewer antibiotic doses within the 24-hour perioperative period compared to inpatient cases [57].

The findings of our systematic review highlight considerable variability in the modality, timing, dosage, and duration of prophylactic antibiotic use in outpatient arthroplasty (Table 3). Although prophylactic antibiotics are effective in reducing SSIs, robust evidence to establish optimal guidelines for outpatient settings is lacking [58]. Studies on perioperative antibiotic use for hip and knee arthroplasty specific to the outpatient setting are limited. A previous meta-analysis examined all orthopaedic procedures involving implants and found no significant difference in infection risk between single and multiple perioperative antibiotic doses. The authors, however, noted that the quality of evidence was low [59]. In one series, a national antibiotic shortage prompted a change in protocol from 24 hours of perioperative antibiotics to a single preoperative dose. A comparative analysis found no significant differences in acute PJI rates, 90-days reoperations, or 90-days complications between the two groups. The authors, however, acknowledged the potential for selection bias in outpatient arthroplasty cases and therefore excluded these patients from the study [60]. Current trends further suggest that oral antibiotics may be sufficient for many patients, given the lack of significant differences in outcomes between oral and intravenous administration. This approach could simplify care, reduce costs, and improve accessibility for outpatient arthroplasty patients [61]. Further high-quality research is needed to determine the ideal duration and administration of perioperative antibiotics for outpatient hip and knee arthroplasty.

Question 4: Is there a role for extended oral antibiotic prophylaxis (EOAP) for patients at high risk of infection after primary total joint arthroplasty (TJA)?[4]

Response/Recommendation

There is insufficient evidence to recommend the routine use of EOAP in high-risk patients following primary TJA.

Strength of Recommendation: Limited

Delegate Vote: Agree: 94.8%, Disagree: 2.8%, Abstain: 2.4% (Total Consensus/Unanimity)

Rationale

Periprosthetic joint infection (PJI) continues to be the leading cause of revision total joint arthroplasty (TJA) despite advances in prevention and surgical techniques [62,63]. It is associated with patient morbidity, socioeconomic burden, diagnostic challenges, the need for multiple surgical interventions, and extensive resource utilization [64]. Recent literature has explored the potential benefits of extended oral antibiotic prophylaxis (EOAP) in high-risk patients beyond the traditionally accepted protocols of a single preoperative dose or 24-hour antibiotic coverage. This approach aims to extend the “golden period,” a phase where the bacterial burden is stabilized by a balance between antibiotic-mediated bacterial elimination and bacterial replication [65,66]. High-risk patients have been variably defined as those who have comorbidities including obesity (body mass index [BMI] $\geq$ 35), diabetes mellitus, active smoking, chronic kidney disease, autoimmune disorders, or nasal colonization with methicillin-resistant and/or sensitive *Staphylococcus* aureus (MRSA/MSSA) [66]. Notably, Potter et al. found that 72.9% of primary TJA patients across three institutions met high-risk criteria, highlighting the need for PJI-specific risk stratification to mitigate the adverse effects of additional antibiotic use and the growing concern for

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Table 4
Studies That Have Shown a Benefit in EOAP Protocols.

Author, year	Minimum Follow-Up	PJI Diagnosis Criteria	Definition of High-Risk/EOAP Indication	Power	# Of EOAP	# Of Controls	Complication Assessed	EOAP Rate (%)	Control Rate (%)	*P*-Value
Inabathula, 2018	90 day	2011 MSIS	High risk: BMI >35, DM, active smoker, CKD, autoimmune disease, MRSA nasal colonization	No power analysis performed	450 276	468 282	90-day TKA PJI rate 90-day THA PJI rate	0.4 1.1	2.1 4.3	0.009[a] 0.02[a]
Kheir, 2021	One year	MSIS criteria	High risk: BMI >35, DM, active smoker, CKD, autoimmune disease, MRSA nasal colonization	No power analysis performed	1,903 1,196 707	870 561 309	1-year TJA PJI rate 1-year TKA PJI rate 1-year THA PJI rate	0.89 0.59 1.41	2.64 1.78 4.21	0.001[a] 0.022[a] 0.022[a]
Bundschuh, 2024	90 day	2018 ICM criteria	All patients received EOAP after certain timepoint High risk: BMI >35, DM, active smoker, CKD, autoimmune disease	Underpowered post-hoc	1,323 726	1,354 696	90-day TJA PJI rate in all patients 90-day TJA PJI rate in high-risk only patients	0.23 0.14	0.74 0.86	0.04[a] 0.06
Dasari, 2024	Not mentioned/ limited by meta-analysis design	Not mentioned/ limited by meta-analysis design	Variable	Not mentioned/limited by meta-analysis design	5,700 3,075 2,625	7,012 4,210 2,802	Pooled, weighted TJA PJI rate Pooled, weighted THA PJI rate Pooled, weighted TKA PJI rate	0.86 1.07 0.6	1.7 2.2 0.96	0.008[a] 0.02[a] 0.17

BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; EOAP, extended oral antibiotic prophylaxis; ICM, international consensus meeting; PJI, prosthetic joint infection; MRSA, methicillin resistant *Staphylococcus* aureus; MSIS, musculoskeletal infection society; THA, total hip arthroplasty; TJA, total joint arthroplasty; TKA, total knee arthroplasty.
[a] Statistically significant.

antibiotic resistance [67]. At the same time, Zhao et al. reported that the use of EOAP following primary total hip arthroplasty (THA) has increased by 366% from 2010 to 2022 [68].

Currently, there is conflicting evidence regarding the effectiveness of EOAP at mitigating PJI in high-risk patients. Inabathula et al. demonstrated an 81 and 74% reduction in PJI rates for high-risk TJA patients receiving EOAP (seven days of cefadroxil 500 mg [mg] twice daily or sulfamethoxazole and trimethoprim [SMZ-TMP] twice daily for those that were MRSA-positive) compared to controls TKA: 2.1 versus 0.4%, $P = 0.009$; THA: 4.3 versus 1.1%, $P = 0.02$) [66]. Kheir et al. expanded the sample to 4,278 TJAs and reported significantly lower 1-year PJI rates with EOAP (0.9 versus 2.6%; $P < 0.001$) compared to high-risk controls [69]. Importantly, neither of these studies included a power analysis. They also reported a consecutive series of patients who had other potential confounding variables across the study period. Bundschuh et al. compared 2,677 TJAs and found a lower 3-months PJI rate with EOAP (0.23 versus 0.74%; $P = 0.04$), and that EOAP patients were 3.85 times less likely to develop a PJI at three months ($P = 0.04$). However, when looking at only the high-risk primary TJA patients (as defined by Inabathula et al. [66]), there was no difference in 90-days PJI rates between the EOAP and control groups (0.14 versus 0.86%; $P = 0.06$) [70]. A meta-analysis by Dasari et al. of 10 studies (5,700 EOAP versus 7,012 standard of care [SoC]) found EOAP significantly reduced PJI risk in TJA (RR = 0.61; 95% CI 0.42 to 0.88; $P = 0.008$) and in THA (RR = 0.60; 95% CI 0.39 to 0.93; $P = 0.02$), but not in TKA (RR = 0.62; 95% CI 0.31 to 1.23; $P = 0.17$) [71]. Limitations included protocol and indications variability as well as retrospective study design (Table 4).

Recent retrospective studies have failed to demonstrate a consistent reduction in PJI with EOAP. Carender et al. evaluated 650 TJAs, comparing 177 EOAP patients (BMI $\geq$ 40, seven to 14 days of antibiotics) to 473 controls, finding no difference in 90-days wound complications (9.6 versus 7.4%; $P = 0.36$) or PJI (1.7 versus 0.6%; $P = 0.35$) despite adequate power to detect a difference in PJI among morbidly obese primary TJA patients [72]. Flynn et al. confirmed these observations in an analysis of 4,576 TJAs, with 1,769 EOAP patients (10 days of cefadroxil) and 2,807 controls, reporting no difference in 90-days (1 versus 0.8%; $P = 0.6$) and 1-year PJI rates (1 versus 1%; $P = 0.9$). [73]. Patients were stratified into the EOAP group at the discretion of the surgeon, an important limitation of the study. Kubsad et al. used a national database of 2,738 THA patients prescribed EOAP, matched with 2,738 controls based on age, sex, obesity, Charlson Comorbidity Index , and history of nicotine dependence. They found a significantly higher 90-days PJI rate in the EOAP group (1.73 versus 0.95%; $P = 0.012$). The lack of granular data on specific EOAP protocols and the lack of information on other PJI risk factors outside of the CCI are considerable limitations of the study (Table 5) [74].

With growing interest in EOAP and a rise in its use, concerns have arisen regarding antibiotic resistance. Carender et al. retrospectively reviewed 119 confirmed PJI cases, of which 37% received EOAP, and examined the antimicrobial resistance profiles of the causative organisms. The authors reported no difference in the rate of antimicrobial resistance among the groups ($P > 0.05$) except for two instances: there was an increase in resistance to SMZ-TMP (44 versus 0%; $P = 0.02$) and to erythromycin (89 versus 17%; $P < 0.01$) in coagulase-negative *Staphylococci* in the EOAP cohort compared to controls. Additionally, there was a significantly higher frequency of gram-negative infections in the EOAP group compared to controls (22 versus 8%; $P = 0.03$). Notably, there was a higher number of aseptic revision TJAs in the EOAP group at the time of review; EOAP protocols were up to the discretion of the surgeon with no standardization, and the sample size was underpowered [75].

Table 5
Studies That Have Shown No Difference With EOAP Protocol.

Author, year	Minimum Follow-Up	PJI Diagnosis Criteria	Definition of High-Risk/EOAP Indication	Power	# Of EOAP	# Of Controls	Complication Assessed	EOAP Rate (%)	Control Rate (%)	*P*-Value
Carender, 2021	90 day	2018 ICM criteria	EOA prescribed to those with BMI >40 and at the discretion of operating surgeon	Adequately powered	177	473	90-day TJA PJI rate	1.7	0.6	0.35
							90-day TJA wound complication rate	9.6	7.4	0.36
Flynn, 2024	One year	2018 ICM criteria	EOA prescribed at discretion of surgeon	No power analysis performed	1,769	2,807	90-day TJA PJI rate	1	0.8	0.6
							One-year TJA PJI rate	1	1	0.9
Kubsad, 2024	90 day	Not mentioned/limited by database study design	Not mentioned/limited by database study design	Not mentioned/limited by database study design	2,738	2,738	90-day THA PJI rate	1.73	0.95	0.012[a]

BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; EOAP, extended oral antibiotic prophylaxis; ICM, international consensus meeting; PJI, prosthetic joint infection; MRSA, methicillin resistant *Staphylococcus* aureus; MSIS, musculoskeletal infection society; THA, total hip arthroplasty; TJA, total joint arthroplasty; TKA, total knee arthroplasty.
[a] Statistically significant.

Also, Lipson et al. conducted the sole study evaluating the cost-effectiveness of EOAP protocols in reducing PJI rates in high-risk patients. The authors employed a break-even economic model to assess cost-effectiveness and concluded that a 7-days course of cefadroxil, costing approximately $52.08, was cost-effective with an absolute risk reduction of 0.187% for TKA and 0.151% for THA. Their analysis used a PJI rate of 2.1% and a PJI treatment cost of $27,870 for TKA, as well as a PJI rate of 4.3% and a PJI treatment cost of $34,445 for THA [76].

Conclusion

There is insufficient evidence to recommend the routine use of EOAP in high-risk patients following primary TJA. The high variability in indications and protocols also limited our ability to conduct a meta-analysis. Given the conflicting findings in the literature, the insufficient follow-up to diagnose PJI (as most studies had a minimum follow-up of only 90 days), the lack of high-quality studies, and the absence of clear standardized indications and protocols, the potential benefit of reducing PJI may not outweigh the potential risk of increased antibiotic resistance.

Question 5: Is there a role for intraosseous administration of prophylactic antibiotics?[5]

Response/Recommendation

Low-dose (500 mg) intraosseous (IO) administered vancomycin distal to an inflated tourniquet results in tissue concentrations six to 10 times greater than intravenously administered vancomycin. The use of IO administration of vancomycin, when combined with a first-line intravenously administered prophylactic antibiotic (e.g., cefazolin), results in a lower postoperative infection rate compared to systemic administration alone.

Level of Evidence: Moderate

Delegate Vote: Agree 55%, Disagree 30%, Abstain 15% (No Consensus)

Rationale

Certain antibiotics, such as vancomycin, when used as a perioperative prophylactic antibiotic, can be difficult to administer before skin incision and can lead to adverse effects such as 'Red Man Syndrome.' Underdosing or incomplete infusion before incision results in suboptimal tissue concentrations and leads to an increased risk of PJI. [77–79].

Intraosseous (IO) administration of prophylactic antibiotics is easy and rapid to administer and provides high tissue concentrations. The technique involves a needle inserted into the proximal medial tibia between the tibial tubercle and joint line, distal to an inflated tourniquet, through which antibiotics can be administered [80–82]. The IO administration provides consistently higher tissue concentrations compared to intravenously administered antibiotics. Young et al. reported on comparing the IO administration of cefazolin (one gram) to intravenous administration (also one gram) in patients undergoing primary total knee arthroplasty [83]. The IO-administered group had tissue concentrations over 10 times greater than the intravenous group. Subsequently, multiple studies comparing tissue concentration of low-dose vancomycin (500 mg) have shown six to 10 times higher concentrations with IO infusion compared to ideally timed and fixed or weight-based vancomycin intravenous infusion [84–87]. This high tissue concentration of vancomycin is maintained even with shortened

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tourniquet duration (10 minutes) [85], in high BMI patients [84], and in revision TKA [87].

When infused without tourniquet restriction, IO administration results in antibiotic tissue levels similar to intravenous infusion [88,89]. However, IO administration avoids the difficulties of incomplete systemic administration before skin incision and results in lower systemic levels, potentially reducing systemic side effects.

The majority of earlier studies using IO vancomycin are underpowered to detect differences in PJI and were undertaken to measure tissue concentrations of IO versus intravenous administration in various clinical scenarios. However, there is growing evidence of the clinical benefit for PJI reduction when IO vancomycin is used prophylactically in conjunction with a first-line intravenously administered antibiotic in aseptic primary and revision arthroplasty surgery, as well as for the treatment of acute PJI.

In a multicenter retrospective study on patients undergoing primary TKA, Parkinson et al., noted a reduced rate of postoperative PJI at one year in patients receiving IO prophylaxis (0.1% IO group versus 1.4% IV group, $P = 0.03$) [90]. It should be noted that the IO group was a mix of either cefazolin or vancomycin. Similar results were reported by Park et al. in a single-institution retrospective study of 488 patients receiving IO-administered low-dose (500 mg) vancomycin compared to 572 patients receiving IV weight-based (15 mg/kg) vancomycin, both combined with IV cefazolin [91]. The incidence of PJI at 90 days was 0.22% in the IO group and 1.4% in the IV group ($P = 0.047$). There were no increased adverse events noted in the IO group. Also, Klasen et al. (2021) reported on the safety of IO administration in 631 primary TKAs and found the PJI rate at 90 days and one year was 0 and 0.2% respectively [92].

Although there are no prospective studies comparing dual intravenous antibiotics to IO administration of vancomycin combined with intravenous first-line antibiotics, with the outcome of PJI rates in aseptic arthroplasty surgery or for the treatment of PJI, there are studies comparing IO to retrospective IV cohorts.

In a retrospective cohort study of 117 aseptic revision knee arthroplasties, the use of prophylactic IO vancomycin, when combined with a first-line (e.g., cefazolin) intravenously-administered antibiotic (dual antibiotic prophylaxis), resulted in substantially lower PJI rates when compared to historical controls: 0% at three months and remaining at 0% for the 113 patients followed to one year [93]. A similar study by McNamara et al. compared 386 cases of intravenously administered vancomycin to 333 IO administered vancomycin. Both groups received weight-based cefazolin perioperatively. At 30-days (0.3 versus 2.1%, $P = 0.03$), 90-days (0.9 versus 3.1%, $P = 0.04$), and 1-year follow-up (1.6 versus 4.9%, $P = 0.04$), the IO-administered group had a significantly lower rate of PJI than the intravenous cohort, respectively [94].

There is limited data on the use of IO administration for the management of PJI. Kildow et al. (2021) reported on a retrospective series of 26 acute and nine chronic PJI patients treated with debridement, irrigation, and implant retention in conjunction with IO administration of vancomycin and noted infection control in 92.3% of the acute PJI cases, but only 44.4% of the chronic PJI cases [95].

In addition, the safety of IO vancomycin administration has been specially studied by Klasen et al., who reported on 631 primary TKA cases with no cases of Redman syndrome or neutropenia, nor increased risk of acute kidney injury [92]. Similarly, Harper et al. (2020) reported on a mixed group of primary and revision total knee arthroplasties and noted no differences in complications between the groups and no specific complications related to IO administration [96]. Parkinson et al. also noted no adverse reaction in a group of 725 IO injections [90].

In summary, IO administration of antibiotics results in tissue concentration, on average, a magnitude greater than levels achieved with intravenous administration. The IO vancomycin combined with a first-line intravenous prophylactic antibiotic (e.g., first-generation cephalosporin - cefazolin) results in lower PJI rates compared to intravenous administration alone in primary and revision knee arthroplasty. There is some evidence for treatment benefit using IO vancomycin in acute PJI treated with debridement, irrigation, and implant retention. There was no increase in adverse events reported with the use of IO administration.

Question 6: Should antibiotic prophylaxis be altered for patients undergoing primary joint arthroplasty secondary to prior septic arthritis?[6]

Response/Recommendation

Given the relatively high risk (10 to 15%) of periprosthetic joint infection (PJI) in patients with prior septic arthritis, patients should receive prophylaxis directed toward the previous causative pathogen or standard perioperative prophylaxis if the previous pathogen is unknown. Consideration should be given to extending the course of antibiotic prophylaxis in this patient population.

Level of Evidence: Limited

Delegate Vote: Agree (89.6%) Disagree (3.9%) Abstain (6.5%) (Super majority, Strong consensus)

Rationale

Periprosthetic joint infection is one of the most devastating causes of morbidity after total joint arthroplasty surgeries. Antibiotic prophylaxis is one of the most significant non-patient-related factors that can prevent PJI. Preoperative antibiotic prophylaxis before total joint arthroplasty is now recommended by most guidelines [97,98]. Septic arthritis is one of the common causes of cartilage damage and secondary arthritis that is eventually treated with total joint arthroplasty. A prior history of septic arthritis increases the risk of PJI after total joint arthroplasty in up to 15% of patients, putting these patients at higher risk of infection-related complications and morbidity [99,100].

In order to address the question posed, we performed a comprehensive systematic review on the subject. A search of PubMed and Scopus databases using the MeSH terms developed by librarians was conducted. The initial search yielded 2,272 potential studies. We excluded 2,256 articles by title and abstract screening. There were 16 articles that were eligible for full-text screening. Finally, nine articles were included in our review. All included studies had limited data with few details about the antibiotic regimens used.

In one study by Bettencourt et al., the risk of PJI between two cohorts was compared, with the first cohort undergoing total knee or hip arthroplasty after native joint septic arthritis and the second cohort undergoing TJA, but after osteoarthritis (OA). The septic arthritis cohort had an 8% higher risk of PJI and superficial wound infection (9% risk compared to 1% in the OA cohort). They reported an increased rate of reoperation and aseptic revisions in the septic arthritis cohort. They also found no relation between the time from the diagnosis of septic arthritis to TJA and the risk of PJI. They used organism-specific antibiotic prophylaxis in most patients

[6] These authors contributed to Question 6: Ibrahim Elganzoury, Lucas A Anderson, Sofiene Kallel, André Dias Carvalho, Julie E Reznicek, Dolors Rodriguez-Pardo, Barry Brause, Ahmed Saeed Younis

[101,102]. Similarly, Sultan et al. studied 62 patients who underwent TKA and THA after native joint septic arthritis. The mean interval from treatment of the native septic joint to their total joint arthroplasty was 3.7 years. The most commonly used antibiotic prophylaxis agents were first-generation cephalosporins and vancomycin, administered intravenously for at least four weeks. The study reported a higher risk of PJI in their cohort, reaching 8% [102]. Chen et al. studied 22 patients who underwent TKA after native joint septic arthritis. They used double antibiotic treatment for a longer duration for prophylaxis against PJI [103]. Both studies reported that factors such as smoking, multiple debridement surgeries to eradicate the native infection, polymicrobial infection, or high-virulence pathogens causing the native infection required more aggressive treatment, sometimes even a two-stage arthroplasty, and reported that those factors are strongly associated with a high risk of PJI and poor function of the joint arthroplasty [103,104].

Portier et al. reported the results of 49 patients undergoing TJA after prior septic arthritis. They used intraoperative antibiotics directed toward the causative organism of the native septic arthritis and continued until the results of the intraoperative cultures were obtained. If the cultures remained negative, the antibiotics were stopped after seven to 14 days. However, if the cultures were positive, the regimen was extended for a prolonged period. Most patients received an intravenous first-generation cephalosporin (e.g., cefazolin), amoxicillin, or vancomycin [105]. The risk of PJI was about 10% in their cohort, and only one patient had a PJI with the same organism as the native septic arthritis (*Staphylococcus aureus*), which was considered a new infection, given the long duration between the native joint septic arthritis and PJI. [105]. There was no consensus on the time period between the cure of native septic arthritis and total joint arthroplasty. Some authors recommend at least two years to ensure a complete cure for infection. Others recommended a shorter period of three to six months [103,105]. Huang et al. reported the results of 14 patients who had septic hip arthritis treated in a two-stage procedure with a 100% success rate during the period of follow-up. All patients received intravenous antibiotics against the organism causing the native septic arthritis, but if no organism was identified, the patients received a combination of a first-generation cephalosporin and gentamicin [106]. Jerry et al. used systemic antibiotic prophylaxis (semisynthetic penicillin or cephalosporin) for 48 to 72 hours in 65 patients undergoing primary TKA after a native knee septic arthritis. Recurrence of infection occurred in five patients (five of 65) who had Staphylococcal species [107]. Ohlmeier et al. reported the results of treatment of 68 patients with prior septic arthritis of the knee receiving TKA with the use of empirical flucloxacillin (32%), cefazolin (22%), vancomycin (21%), ampicillin/sulbactam (12%), and others: fosfomycin, imipenem, meropenem (13%). There were two patients (2.9%) who had septic revisions during the period of follow-up [108]. Kim et al. reported the use of a 2-days regimen of intravenous antibiotic prophylaxis with cephalosporins in 44 hips with native septic arthritis [109]. Mainard et al. reported the treatment of 92 cases of hip and knee arthroplasty after a native septic arthritis and used prophylactic antibiotics according to intraoperative samples [110].

Conclusion

Because of the higher risk of PJI in patients who have prior septic arthritis, reaching up to 10 to 15%. Based on the reviewed evidence, two primary approaches may be suggested.

1. Extended prophylaxis: Administer intravenous antibiotics for two to 14 days postoperatively. Common regimens include first-generation cephalosporins (e.g., cefazolin) or vancomycin, depending on patient-specific factors such as prior colonization or allergies.
2. Pathogen-specific prophylaxis: Utilize intravenous antibiotics targeting the organism responsible for native septic arthritis. If the causative pathogen is unknown, consider broad-spectrum combinations of a first-generation cephalosporin with quinolones, vancomycin, or ampicillin/sulbactam. Antibiotics can be discontinued once intraoperative cultures are confirmed negative. If cultures are positive, therapy should be extended and guided by culture and sensitivity results.

Table 6
Included Studies.

Study	N	N MPJI	Same Organism	Risk Factors/Comments
Jafari et al. [114]	55	9	2	Chronic PJI
Bedair et al. [111][a]	90	10	NA	Women; SA organism
Haverstock et al. [120]	206	12	6	5 were SA
Abblitt et al. [105]	76	6	3	Bacteremia
Chalmers et al. [113][a]	102 primary TKA	7	2	6 were on chronic AB
Chalmers et al. [112][a]	50 primary THA	1	NA	-
Komnos et al. [116]	197	26	8	Women; RA; MRSA; Bacteremia
Wouthuyzen-Bakker et al. [117]	108 hematogenous	4	2	-
Lee et al. [118]	96	19	12	MRSA
Agarwal et al. [119][a]	447 primary TSA	NA	NA	Higher revision in 2 y
Akkaya et al. [121]	106 ipsilateral	20	NA	Distance of less 7 cm between ipsilateral prosthesis
Braig et al. [122][a]	12 primary TEA	0	-	Higher revision in 2 y
Lee et al. [122]	337	18	NA	Tobacco users; Bacteremia
Sangaletti et al. [124]	661	73	34	Women; Diabetes; Multi-organism PJI
Karczewski et al. [125]	205 ipsilateral	3	2	-
Wetzel et al. [126]	47	8	NA	-

PJI, periprosthetic joint infection; MRSA, methicillin-resistant *Staphylococcus aureus*; SA, suppressive antibiotics.
[a] These studies evaluated the rate of infection after primary arthroplasty.

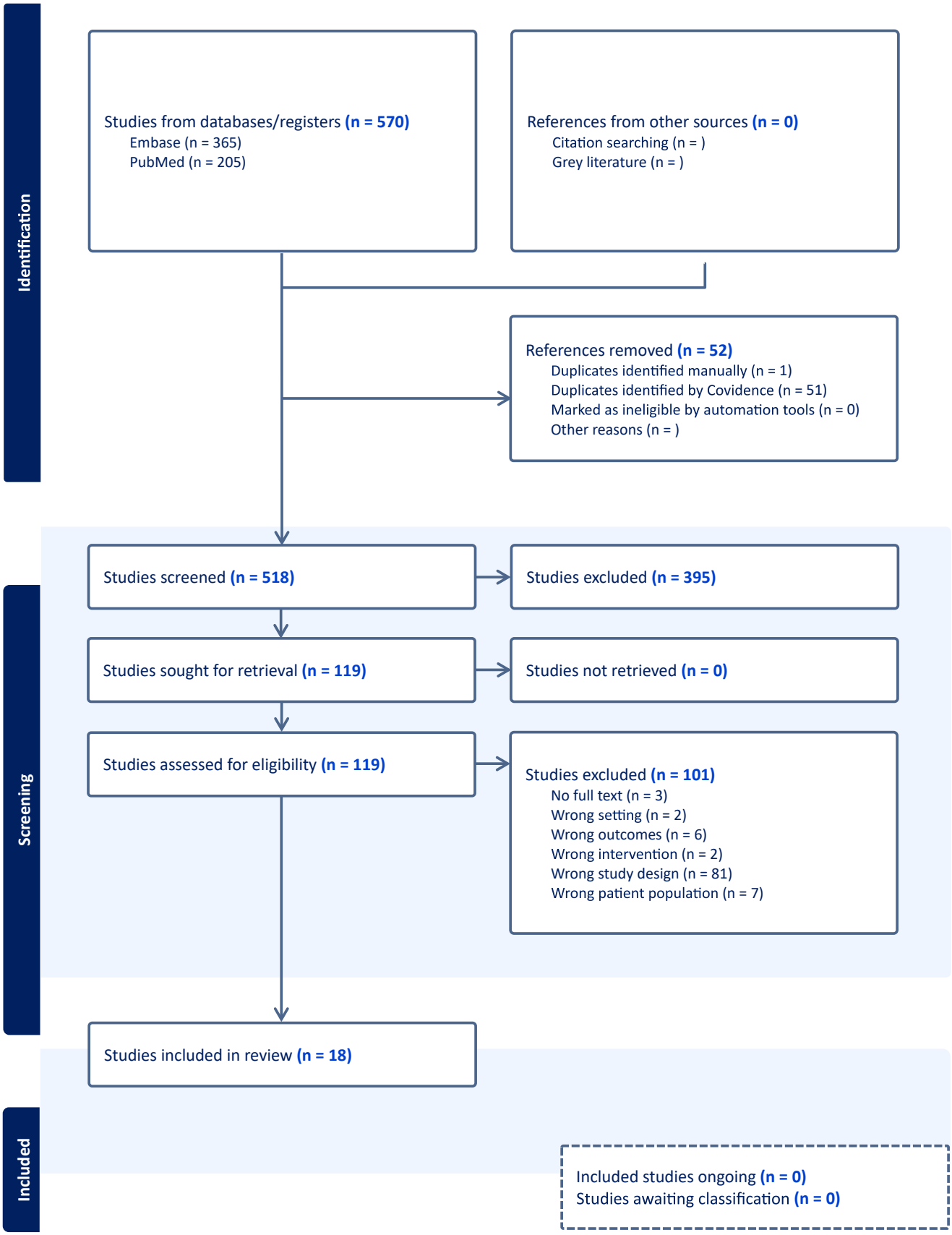

Figure 1. Flow diagram of search results.

Question 7: Should prophylactic antibiotics be altered for patients undergoing primary arthroplasty who have a history of prior periprosthetic joint infection in another joint?[7]

Response/Recommendation

Although patients who have a history of PJI are at a higher risk of developing another PJI, no studies address this question specifically. The benefits of altering/extending prophylactic antibiotics in this patient population need to be weighed against the potential risks.

Level of Evidence: Limited

Delegate Vote: Agree 92%, Disagree 5%, Abstain 3% (Total Consensus, Unanimity)

Rationale

Patients who have a history of prior PJI in one joint appear to be at increased risk for developing PJI in subsequent total joint arthroplasty (TJAs) [111–113]. This elevated risk raises the question of whether standard prophylactic antibiotic protocols are sufficient for these high-risk individuals or if tailored antibiotic strategies are necessary. To address this question, we conducted a systematic review of the existing literature to determine if there is evidence to support altering prophylactic antibiotic regimens in this patient population. A comprehensive literature search was performed using databases such as PubMed, Embase, Web of Science, and Scopus to identify studies evaluating prophylactic antibiotic strategies in patients who have a history of PJI undergoing primary arthroplasty (Figure 1). Inclusion criteria encompassed studies that reported on infection rates and outcomes in this specific patient group. Our systematic review revealed a lack of studies directly addressing the modification of prophylactic antibiotic regimens for patients who have prior PJIs. Although several studies indicated that a history of PJI is a risk factor for subsequent infections, none provided specific guidance or evidence on altering antibiotic prophylaxis based on previous infection history or the organisms involved in prior PJIs [110–125]. We included studies that reported these data on metachronous PJI [114–118,120,121,123–126] (Table 6).

There are multiple studies that reported the use of extended oral antibiotics in high-risk TJA patients. The use of extended antibiotics reduced the risk of infection in those populations [127–131]. The high-risk patients in those studies were defined as having high HbA1C, low albumin, nasal colonization of MRSA, immunocompromised patients [127,131], diabetes, obesity, smokers [128], chronic kidney disease [129], and a previous DAIR procedure after PJI [130]. Although none were exclusively conducted on patients who had a previous PJI undergoing TJA, it could be inferred that these populations may benefit from extended antibiotic treatment. The potential risks of extended oral antibiotic therapy should also be considered, which could include the development of antimicrobial resistance, selection of gram-negative organisms, or *Clostridioides difficile* infection [127,132].

Some recurrent infections involved the same organisms responsible for the initial PJI, while others were caused by new pathogens [113–118,120,124,125]. This indicates that tailoring antibiotic therapy exclusively to the causative organism of the initial PJI may not adequately address the risk of subsequent infections, but this has not been adequately investigated or reported in the literature.

There is currently insufficient evidence to support altering prophylactic antibiotic protocols for patients undergoing primary arthroplasty who have a history of prior PJI in another joint. Extended oral antibiotic prophylaxis regimens may be beneficial, but further research is necessary to provide clarity on whether tailored antibiotic strategies could benefit this high-risk population [130,133–136]. Future studies should focus on the relationship between the causative organisms of previous PJIs and the efficacy of different prophylactic antibiotic approaches in preventing reinfection.

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The Journal of Arthroplasty 41 (2025) S376–S380

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The Journal of Arthroplasty

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Hip and Knee

2025 ICM: Antibiotic Prophylaxis in Revision Arthroplasty

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Question 1: Does extended antibiotic prophylaxis reduce periprosthetic joint infection (PJI) rate in patients undergoing aseptic hip or knee revision arthroplasty?[1]

Response/Recommendation

No. There is no concrete evidence that administration of extended antibiotic prophylaxis reduces the rate of PJI in patients undergoing aseptic revision knee or hip arthroplasty.

Level of Evidence: Limited

Delegate Vote: Agree 90%, Disagree 7%, Abstain 3% (Super Majority, Strong Consensus)

Rationale

Failures after aseptic knee or hip arthroplasty are often because of periprosthetic joint infections (PJIs) [1,10,14,15,19]. Prophylactic administration of antibiotics is used to prevent PJIs or even superficial surgical site infections. However, there is conflicting evidence for using extended antibiotic prophylaxis following total joint arthroplasty for both primary and aseptic revision arthroplasties [6–9,21,24].

To answer the posed question, we conducted a comprehensive literature search using PubMed and EMBASE databases, using the MeSH terms developed by librarians. We searched for studies, in English, starting from 2010, including aseptic revision of knee or hip arthroplasty. Only studies comparing the use of short-term antibiotics (24 hours or less) with extended antibiotic use (more than 24 hours) and mentioning the outcome of PJI following the aseptic procedure were included. Our search revealed 349 potential studies. After title and abstract screening, 78 studies remained for full-text review. There were 70 studies that were excluded based on our predefined study criteria, leaving eight studies for analyses [2–5,11–13,23]. GRADE (Grading of Recommendations Assessment, Development and Evaluation) [18] was used to evaluate the certainty of evidence. The remaining studies were performed in the United States, Taiwan, and Spain. Three studies had the same first author, but different collaborators and patient populations (revision total knee arthroplasty (rTKA) and revision total hip arthroplasty [rTHA]), and two studies were performed by the same study group, but included different patient populations. All of the included studies were performed in 2015 [5] or later [2–4,11–13,23].

From the studies assessing both primary arthroplasty and revision arthroplasty, the patients who underwent primary total joint arthroplasty were excluded. Patients who had unsuspected PJI based on culture samples taken during revision arthroplasty were also excluded. We used a random effects and inverse variance model, reporting an odds ratio with a 95% confidence interval for our final outcome. We considered $P < 0.05$ significant. Data extraction was done using the online platform Covidence [22], and data were transferred to the online platform RevMan [20] of Cochrane to create a forest plot based on the total number of PJIs in each group (short versus extended use of antibiotics).

All studies were retrospective. A total of 4,480 aseptic revision surgeries were assessed with follow-up periods from 90 days to 10 years. There was no clear distinction between patients according to risk factors for infection. All studies defined aseptic revision arthroplasty as a surgical intervention with replacement of at least one component, including isolated insert replacement, and no evidence of infection based on the Musculoskeletal Infection Society (MSIS) criteria [16,17] or a description thereof.

There were no included studies that showed a statistical difference in preventing a PJI in patients undergoing aseptic revision knee or hip arthroplasty with extended use of antibiotics compared to antibiotic usage of 24 hours or less. However, our final analysis and forest plot show a combined odds ratio of 0.61 with a 95% confidence interval of 0.42 to 0.87, slightly favoring the use of extended postoperative antibiotics (Figure 1).

Conflict of Interest: One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.079.

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https://doi.org/10.1016/j.arth.2025.10.079
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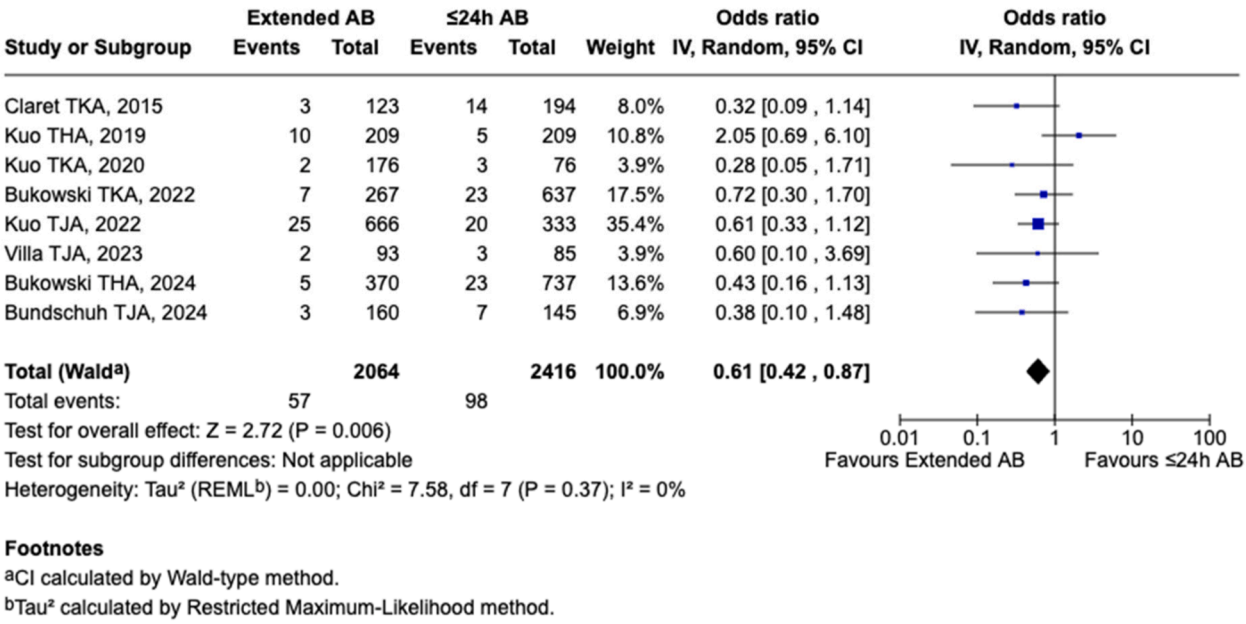

Figure 1. Meta-analysis for periprosthetic joint infection after aseptic revision hip or knee arthroplasty comparing >24 hours versus ≤24 hours antibiotic prophylaxis.

There are several potential limitations to this study and its results. The certainty of evidence was very low because of several factors. All studies were of retrospective design, with many of them coming from a single institution, lowering the overall quality of evidence. Follow-up periods differed significantly; different antibiotic regimens were used postoperatively. Only two studies had a fixed number of days of postoperative extended antibiotics consisting of five days intravenously [5] or seven days orally [4]; all others had either completely oral or a combination of intravenous and oral extended antibiotic prophylaxis. In addition, these decisions were also based on the surgeon's choice, and the duration of antibiotics varied substantially from two to 180 days [2,3,11–13,23]. There was some variation in the type of antibiotics given, although most used either cephalosporin, vancomycin (in case of allergies), or clindamycin orally. There were no studies that focused on a difference in host risk factors for developing an infection, so no distinction could be made between these factors. Furthermore, different definitions for PJI were used. Also, we included only studies starting from 2010 and later. Doing so, we might have missed some earlier studies. However, surgical protocols concerning preoperative screening and nasal decolonization, surgical site preparation, and cleaning before closing have evolved and improved over time, and we wanted to include the most recent studies to have a more homogenous comparison.

There were two authors from this review (KV and JG) who are part of a research group that has just completed a randomized controlled trial comparing the use of a single dose of intravenous antibiotics preoperatively to adding five days of extended oral antibiotics in patients undergoing aseptic knee or hip revision surgery [25]. They found 11 out of 379 (2.9%) PJIs in the single-dose group and eight out of 371 (2.2%) PJIs in the extended group ($P = 0.64$) while observing significantly more antibiotic-related side effects in the extended group, though these data are currently submitted for publication.

Conclusions

Although based on prior, retrospective studies, a very weak signal exists that the rate of PJI may be slightly lower in patients receiving extended antibiotics after revision joint arthroplasty, a recent randomized controlled trial (pending publication) did not detect any benefit for extended antibiotics in this patient population.

Question 2: What is the optimal intravenous prophylactic antibiotic for patients undergoing assumed aseptic revision arthroplasty?[2]

Response/Recommendation

Given the absence of comparative studies, the optimal prophylactic antibiotic for patients undergoing assumed aseptic revision arthroplasty should follow the current evidence for patients undergoing primary total joint arthroplasty, which remains a weight-based intravenous dose of a first- or second-generation cephalosporin. Targeted use of additional vancomycin may be considered, but the evidence is limited to a single retrospective review.

Level of Evidence: Weak

Delegate Vote: Agree: 75.6%, Disagree: 20.4%, Abstain: 4.0% (Strong Majority, Moderate Consensus)

Rationale

According to the American Joint Replacement Registry 2024 annual report, PJI remains the leading cause of revision hip and knee arthroplasty in the United States over the last decade [26]. Approximately 1 to 2% of all patients undergoing total hip or knee arthroplasty suffer from PJI and estimate project that the annual costs to treat PJI related to the hip and knee will be $1.85 billion by 2030 [27–30]. However, in revision hip and knee arthroplasty, the

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risk of PJI is even higher, with estimates around 5 to 9% [31–33]. A comprehensive review of the literature was conducted to identify studies related to the optimal prophylactic antibiotic for patients undergoing assumed aseptic revision arthroplasty.

There were no identifiable studies regarding an optimal prophylactic antibiotic that is superior in reducing infection rates for those undergoing aseptic revision arthroplasty [34]. In 2019, the American Academy of Orthopaedic Surgeons released its clinical practice guidelines and recommended the use of a first- or second-generation cephalosporin or the use of a glycopeptide antibiotic for surgical prophylaxis to prevent PJI [35]. However, there was "limited" evidence to support the use of any particular preoperative antibiotic in reducing the risk of PJI. Additionally, there is literature to support the particular use of cefazolin, as other antibiotics have demonstrated an increased risk of PJI. Wyles et al. retrospectively reviewed all patients who underwent total hip or knee arthroplasty at a single academic institution from 2004 to 2017. A total of 28,174 arthroplasties (94.9%) received cefazolin, while 1,521 (5.1%) received noncefazolin antibiotics. The overall risk of PJI was 32% lower among patients who received cefazolin after adjusting for comorbidities [36]. Blumenthal et al. also conducted a retrospective cohort study at a single hospital of patients who have and do not have a reported penicillin allergy. Of the 8,385 patients who underwent 9,004 procedures, 922 patients reported an allergy to penicillin, and 241 suffered an SSI. Patients who have a reported penicillin allergy were significantly less likely to receive cefazolin and had a significantly increased odds ratio of 1.51 for surgical site infection [37].

Kheir et al. published a retrospective study of 1,828 patients undergoing primary hip or knee arthroplasties who received vancomycin prophylaxis between 2008 and 2014. They also evaluated 5,810 patients who underwent primary total joint arthroplasty and received cefazolin for surgical prophylaxis during that same time period. The authors reported that patients who received vancomycin had a significantly higher rate of PJI when compared to those who received cefazolin prophylaxis. Additionally, the authors also noted that the majority of patients who were given vancomycin were underdosed according to the weight-based dosage recommendations [38]. However, underdosing is not unique to vancomycin, and patients receiving cefazolin prophylaxis may also be susceptible to underdosing, especially in the obese population [39].

Liu et al. retrospectively evaluated whether the addition of vancomycin to cefazolin as surgical prophylaxis was associated with reduced rates of PJI in rTKA. The authors noted that their institution had an unacceptably high rate of methicillin-resistant *Staphylococcus* PJIs, and in an effort to combat this, vancomycin was added to cefazolin prophylaxis for all presumed aseptic revision knee arthroplasties. The overall rate of PJI in the year preceding the implementation of vancomycin to cefazolin was 7.89%. After the addition of vancomycin to cefazolin prophylaxis, the institutional rTKA PJI rate dropped to 3.13% ($P = 0.046$). The authors recommended identification of high-risk subgroups who may benefit from the addition of vancomycin if the concern for methicillin-resistant organisms is high enough [40].

Given the absence of comparative studies in the aseptic revision setting, we recommend that patients receive a prophylactic antibiotic based on the existing literature within primary hip and knee arthroplasties, which remains a weight-based intravenous dose of a first- or second-generation cephalosporin. Targeted use of additional vancomycin may be considered, but the evidence is limited to a single retrospective review. However, the application of current evidence from primary arthroplasty to aseptic revision arthroplasty requires caution due to the more extensive tissue trauma and longer operative times, which carry a higher risk of infection.

Question 3: Should prophylactic antibiotics be withheld during revision arthroplasty for aseptic failure until culture samples are taken?[3]

Response/Recommendation

No. Prophylactic antibiotics should not be withheld to obtain culture samples during revision arthroplasty for aseptic failure.

Level of Evidence: Strong

Delegate Vote: Agree: 94.9%, Disagree: 5.1%, Abstain: 0% (Unanimous, Total Consensus)

Rationale

Periprosthetic joint infection (PJI) remains the leading cause of revision in total hip and knee arthroplasties [41]. Revision arthroplasty carries a higher risk of PJI compared to primary hip and knee arthroplasties [42–44]. Historically, prophylactic antibiotics were thought to interfere with culture yield, and this led to hesitation regarding their use. However, recent data have challenged this notion. Additionally, some advocate for antibiotic administration before incision to allow systemic distribution of antibiotics and potentially decrease the risk of PJI and surgical site infections.

A thorough review of the literature was performed to assess whether prophylactic antibiotics should be withheld during revision arthroplasty for aseptic failure until culture samples are taken. There were nine studies identified—two randomized controlled trials, two prospective cohort studies, and five retrospective reviews—and all concluded that there was no significant difference in the rate of culture positivity with respect to antibiotic prophylaxis pretissue or post-tissue sampling. The majority of the literature evaluated patients who had known PJI and were undergoing revision arthroplasty, but one retrospective review specifically evaluated patients who underwent aseptic revision total hip arthroplasty [45].

Perez et al. performed a randomized controlled trial evaluating whether preoperative antibiotic prophylaxis increased the rate of culture negativity in patients who were treated for PJI. There were 14 patients in each group, and four patients in each group had culture-negative PJIs ($P > 0.05$). The authors concluded that antibiotic prophylaxis did not affect intraoperative cultures in suspected or confirmed PJI [46]. Tetreault et al. also conducted a randomized controlled trial, randomizing 65 patients who had known PJIs to either administration or holding of prophylactic antibiotics before obtaining intraoperative samples. A total of 82% of patients who received prophylactic antibiotics had identical intraoperative and preoperative culture results, and 81% of patients who did not receive prophylactic antibiotics had identical intraoperative and preoperative culture results. The authors concluded that prophylactic antibiotics did not affect the culture results [43].

Bedencic et al. prospectively evaluated 40 patients who had suspected PJI undergoing revision arthroplasty. There were three tissue samples obtained for culture after arthrotomy was made, and then two grams of cefazolin were administered. Later in the procedure, but before irrigation and debridement, a second set of tissue samples was obtained for culture. There were no differences in colony-forming units between specimens before and after antibiotic prophylaxis. There was also no difference in the likelihood that an infection would be diagnosed between the cultures obtained before or after antibiotic administration. The authors concluded that prophylactic antibiotic administration does not likely compromise the diagnostic sensitivity of tissue cultures [47].

[3] These authors contributed to Question 3: Joshua P. Rainey, Carlos A. Higuera-Rueda, Elido A. Perez-Gonzalez, Julian Guerra Perez, Paulo Alencar, Amir Khoshbin, Anders Odgaard, Lucas A. Anderson

Burnett et al. also prospectively evaluated 26 infected TKAs with a known preoperative organism. The authors then re-aspirated these knees, and antibiotic prophylaxis was administered; then culture swabs and tissue were obtained after arthrotomy. In all 26 knees, the cultured organisms from preoperative aspiration and the organisms obtained intraoperatively were the same organism, despite the infusion of antibiotics. The authors noted that preoperative prophylactic antibiotics did not impact the results of intraoperative cultures [48].

In their retrospective review, Groot et al. evaluated 490 patients undergoing presumed aseptic revision total hip arthroplasty. Of these patients, 61 received prophylactic antibiotics before incision, while 429 patients received prophylactic antibiotics after tissue samples were collected for culture. Prophylactic antibiotics were noted not to yield fewer culture results compared to patients who received antibiotics after tissue samples, and there was a nonsignificant increase in subsequent PJI rate in patients who received antibiotics after tissue biopsy (3.0 versus 1.6%, $P = 0.54$) [45]. In the retrospective review by Stoll et al., 124 patients underwent revision shoulder arthroplasty for septic and aseptic etiologies. There were 48 patients who received prophylactic antibiotics before incision and 76 patients who received antibiotics after cultures were obtained. The authors noted no significant difference in culture positivity between the preculture and postculture antibiotic groups (16 versus 15%, $P = 0.82$) [49].

Ghanem et al. published their retrospective review of 171 patients undergoing revision arthroplasty for PJI of the knee. A total of 72 patients received preoperative antibiotics before incision, whereas 99 patients received antibiotics after samples for culture were obtained. The rate of culture-negative infection was not significantly different between groups ($P = 0.34$), with 12.5% culture negative in the preoperative antibiotic group and 8% in the group who received antibiotics after tissue sampling [50].

Wouthuyzen-Bakker et al. performed a retrospective review of 284 patients undergoing aseptic knee revision, of whom 141 received antibiotic prophylaxis before incision. The percentage of cases with greater than or equal to one positive culture was not significantly different between those who received preoperative antibiotic prophylaxis versus those who received antibiotics after tissue sampling (26 versus 27%, $P = 0.70$) [51]. Anagnostopoulos et al. also published a retrospective review of 110 patients undergoing orthopedic joint surgery. The authors assessed whether antibiotic prophylaxis before incision influenced the rate of positive *C. acnes* cultures. There was no association between the proportion of positive samples and administration of prophylactic antibiotics (71.6 versus 65.9%, $P = 0.39$) [52].

In summary, the literature appears to support the administration of prophylactic antibiotics in revision arthroplasty, even in cases of suspected PJI. Given the low pretest probability of PJI in presumed aseptic revision arthroplasty, we recommend that prophylactic antibiotics can be administered before incision.

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The Journal of Arthroplasty 41 (2025) S381–S384

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The Journal of Arthroplasty

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Hip and Knee

2025 ICM: Abbreviated Two- and 1.5-Stage

James Cashman, Guilherme Falotico, Vasily Artyukh, Vaibhav Bagaria, Giovanni Balato, Gabriel Baron, David Deckey, Thomas Hilton, Christian Hipfl, Christopher Jones, Scott Matthews, James Nace, Bryan Springer, Tobias Winkler, Piers Yates

Question 1: Is there a role for abbreviated two-stage exchange arthroplasty?[1]

Response/Recommendation

A number of studies demonstrate that early reimplantation provides similar outcomes to the traditional two-stage exchange with a reimplantation window of four to 12 weeks. The role of high-dose local antibiotics in improving clinical outcomes and the criteria for selecting suitable candidates have yet to be defined.

Level of Evidence: Limited

Delegate Vote: Agree 86%, Disagree 9.4%, Abstain 4.7% (Super Majority, Strong Consensus)

Rationale

The growing popularity of single-stage exchange arthroplasty raises some questions regarding two-stage exchange arthroplasty and the protocols associated with the latter surgical procedure. An issue related to two-stage exchange arthroplasty relates to the optimal timing of reimplantation [1]. No definite timing window for reimplantation has been identified in the literature to date. With most studies quoting between four and 12 weeks as the optimal window [2], a common classification by Trampuz and Zimmerli defines intervals of two to four weeks (a short interval) and six to eight weeks (a long interval) until reimplantation [3]. Some studies suggest an interval period of four to six weeks [4] or nine weeks between the stages [5]. Clinical studies range from a few days to several hundred days or even years; however, an interval of around 60 to 100 days is mostly reported [6–13]. This heterogeneity in clinical practice indicates that the optimal duration of the interval between the stages has yet to be defined [2].

There is a paucity of evidence to support earlier than standard long-interval reimplantation at the 2nd stage. Even in literature, where this early reimplantation has been investigated, there is variable timing to the 2nd stage with no consistency across the board. In a cohort of 32 periprosthetic hip infections, Lieberman et al. report no difference between reimplantation at six weeks versus one year [14]. Haddad et al. showed no compromise of success with early reimplantation at three weeks in 32 total hip arthroplasties (THAs) [15]. Burnett et al. also report similar success with a shortened interval of three to four weeks compared to four to six weeks [16].

Winkler et al. prospectively compared reimplantation at less than four weeks (mean 19.3 days, range, seven to 27) versus longer than four weeks (mean 63 days, range, 28 to 204) for 38 patients undergoing second-stage periprosthetic joint infection (PJI). Their group used non–biofilm-active antibiotics between stages and highly active biofilm-antibiotic treatment following reimplantation. About half the patients were included in the short interval group with no reinfections at a mean follow-up of 40 months. A reinfection occurred in the longer interval group [8].

However, some studies contradict the above and suggest that early reimplantation may compromise the outcome. Vielgut et al. retrospectively analyzed 72 hip PJI and four native hip infection patients operated between 2005 and 2010. All cases were infected, but four were native joint infections. They found that 90% of a cohort of 40 patients undergoing reimplantation between four and 11 weeks remained infection-free. The reinfection rate was higher in patients undergoing early reimplantation (less than four weeks) or later than 11 weeks. The five patients who were in the less than four weeks group got reinfected and 23 were in the greater than 11 weeks group, with a 47.8% reinfection rate. Since the study was retrospective, no clear inclusion and exclusion criteria could be applied, making the results difficult to interpret [17].

In recent years, the role of abbreviated two-stage exchange arthroplasty has been investigated in a number of prospective studies. A study has evaluated the implantation of an antibiotic drug-eluting device instead of a spacer following resection arthroplasty [18]. In these cases, intra-articular antibiotics, as well as systemic antibiotics, were administered. After one week, the device was then removed, and reimplantation was carried out. The outcome of this protocol has been very encouraging. Numerous

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.075.

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https://doi.org/10.1016/j.arth.2025.10.075
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presentations and pending publications demonstrate that the local delivery of antibiotics allows for early reimplantation without compromising the outcome of the two-stage exchange.

Based on the currently available literature, the optimal timing for reimplantation remains unknown. One of the until-now-used standard protocols of administering six weeks of antibiotics, followed by a 2-week drug holiday, and subsequent reimplantation needs to be examined since shorter intervals might have an advantage. The 2-week drug holiday is based on little evidence and has also been shown in some studies to be outdated [19,20]. Accurate and cost-effective tests for optimal reimplantation timing are still needed. Beyond that, however, there is a need to work on selection criteria for choosing patients, in which an abbreviated two-stage protocol yields similar or improved clinical outcomes compared to traditional long-interval reimplantation.

Question 2: Is there a role for 1.5-stage exchange arthroplasty in periprosthetic joint infection?[2]

Response/Recommendation

The 1.5-stage revision does not show inferior results compared to the two-stage technique, with the advantage of reducing the number of additional surgical procedures.

Strength of Recommendation: Limited

Delegate Vote: Agree (72.6%); Disagree (12.8%); Abstain (14.7%) – Strong Majority/Moderate consensus

Rationale

Periprosthetic joint infection (PJI) is one of the most serious and difficult complications following joint arthroplasty [21]. Several procedures are available for the management of PJI, including DAIR (debridement, antibiotics, implant retention), single-stage revision, and two-stage revision [22]. In chronic infections, two-stage revision has been considered the most effective treatment in most series, with the main drawback being the morbidity and cost associated with two separate surgical procedures [23,24]. The single-stage revision is an excellent alternative, particularly for patients who have a competent immune system, a known pathogen, suitable antibiotic therapy options, and good soft tissue quality for wound closure; however, in cases of infection recurrence after a single-stage revision, the prognosis becomes compromised [25].

Description of the procedure

A 1.5-stage revision arthroplasty has evolved as a relatively novel surgical approach that is being increasingly employed to manage chronic PJI of the hip and knee. This technique combines elements of both single-stage and two-stage revisions. Typically, a 1.5-stage revision involves the removal of the infected prosthesis and thorough debridement of the infected tissues. High-dose antibiotic-loaded bone cement is employed as fixation for the implants. In the knee, this typically involves a new femoral component and an all-polyethylene tibia. In the hip, this may consist of both cemented femoral and acetabular components. The intent of this technique is that the implant remains *in situ* for an indefinite period, prolonging and perhaps obviating the need for a second-stage revision unless reinfection, deterioration of functional status, or construct failure occurs. In many cases, this 1.5-stage revision implant becomes the definitive or "destination" prosthesis. This method seeks to balance the benefits of prosthetic arthroplasty, as seen in single-stage revisions, with some of the possible infection control advantages of the two-stage procedure [26,27].

Indications and contraindications

Current indications for this technique vary across institutions, with some hospitals utilizing a 1.5-stage technique for the vast majority of PJI revisions. Other centers have focused 1.5-stage revisions on patients who are not deemed to be candidates for two major surgical interventions in a short period of time, patients who have short survivorship in whom 1.5 stages are believed to suffice, hospitals that have limited resources for two major surgeries, or patients who need time to recover before being subjected to another major reimplantation surgery. The contraindications for 1.5-stage revisions are more well defined; in the knee, 1.5-stage revisions are contraindicated in patients who have extensor mechanism deficiency, gross instability with collateral ligament deficiency, massive bone loss, and soft-tissue defects requiring flaps; in the hip, 1.5-stage revisions are contraindicated in cases of massive femoral bone loss and/or recurrent instability.

Current data

Festa et al. [28] (2024) developed a systematic review to investigate if a 1.5-stage revision can be an effective alternative for chronic periprosthetic hip and knee infections. A meta-analysis was performed to evaluate the infection eradication rate using either the 1.5-stage revision or the two-stage technique. A total of 494 patients (111 hips and 385 knees) underwent 1.5-stage procedures, had a mean age of 69 years (range, 61 to 82), and were identified in the 10 included studies. The most common cause of reoperation was the conversion to the definitive prosthesis, followed by aseptic loosening. Infection control was reached in 84.6% of the 1.5-stage and 76.1% of the two-stage cohorts. The infection recurrence rate was higher in the two-stage cohort than in the 1.5-stage group (21.8 versus 14.3%). The authors concluded that the 1.5-stage technique represents a valid treatment option in selected patients who have chronic PJI and cannot undergo further surgeries, combining the benefits of the 1.5- and two-stage procedures.

Outcomes of the 1.5 stage in TKA

In 2020, Siddappa and Meftah [29] described the outcomes of an articulated spacer in the treatment of chronic PJIs. There were 32 patients who had methicillin-resistant *Staphylococcus aureus* infection who were analyzed. There was one patient who progressed to a transfemoral amputation due to intractable wound dehiscence. Of the 31 patients who remained with the spacer, infection control was achieved in 30 patients (97%), with follow-up ranging from nine months to three years. Also in 2020, Hernandez et al. [30] evaluated 31 patients who had an articulated spacer in the treatment of PJI. The average follow-up was 2.7 years, and 25 patients (81%) retained a functioning prosthetic joint. In 2021, Hooper et al. [31] studied the comparative outcomes of the 1.5-stage versus two-stage technique in the treatment of degenerative knee osteoarthritis secondary to septic arthritis. In the group that received one-stage functional prosthetic spacers, the survivorship free of any revision was 83% (confidence interval (CI): 82 to 89%) at both one and three years, and the survivorship free of any revision was 100% (CI: 100 to 100%) for the nine patients who proceeded to second-stage surgery at both one and three years of follow-up.

In 2022, Siddiqi et al. [32] describe indications, contraindications, clinical outcomes, and pearls and pitfalls of 1.5-stage

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revision total knee arthroplasty (TKA) utilizing a primary TKA femoral component, all-polyethylene tibial component, and handcrafted antibiotic cement for the management of chronic PJI. This surgical technique paper found the 1.5-stage revisions to have equivocal outcomes with infection and patient-reported outcomes, decreased health care costs, and decreased morbidity when compared to the two-stage revision. In the same year, Nabet et al. [33] examined all patients who underwent a 1.5-stage exchange TKA at a single institution compared to historical two-stage controls. The authors analyzed all patients undergoing 1.5-stage (n = 114) and two-stage TKA exchange (n = 48) with a mean 2.6-year follow-up. The infecting organism profile was similar between the two groups (coagulase-negative *Staphylococcus*), 14.9 versus 16.7%, respectively; methicillin-sensitive *Staphylococcus aureus* (MSSA), 13 versus 12.5%, respectively; methicillin-resistant *Staphylococcus aureus*, 11.4 versus 10.4%, respectively; culture-negative, 36 versus 44%, respectively. The 1.5-stage exchange TKA resulted in a 10.1% difference in infection-free survival (85.1 versus 75.0%, $P = 0.158$) compared to the two-stage exchange. Postoperative complications were lower among 1.5-stage exchanges (8.8 versus 31.3%, $P < 0.001$), while the Knee Injury and Osteoarthritis Outcome Score, Joint Replacement (KOOS, JR) scores improved more from baseline in the 1.5-stage group (24.7-point difference versus 16.6-point difference, $P < 0.001$) than those in the two-stage cohort.

Also, in 2023, Belay et al., [34] reporting on 116 patients, compared the clinical outcomes and costs associated with articulating spacers (1.5-stage) and a matched two-stage cohort. There was no significant difference between groups with respect to the rate of reoperation (1.5-stage: 24.1% versus two-stage: 25.9%, $P = 0.83$) or the rate of infection clearance (1.5-stage: 79.3% versus two-stage: 79.3%, $P = 1.0$) after 2 years. There were no differences in the initial spacer surgery and 90-day cost; nevertheless, they found a significantly higher overall cost for the two-stage exchange through the first two years after the index surgery. Song et al. [35] investigated the aseptic survival of 1.5-stage exchange arthroplasty for PJI after TKA. There were 88 cases of 1.5-stage exchange arthroplasty for PJI without reinfection that were retrospectively analyzed. The autoclaved femoral component and new polyethylene insert (PE) were implanted using antibiotic-mixed cement. The survival rates were 90.9, 86.4, and 80.6% at one, two, and five years postoperatively, respectively.

In conclusion, the infection control rate with the 1.5-stage knee revision technique ranged from 79.3 to 100% with a minimum average follow-up of one year and was not inferior to the two-stage revision. The mechanical complications of the 1.5-stage components were acceptable, with 80.6% survival at five years of follow-up [35].

Outcomes of 1.5 stage in THA

In 2022, Charalambous et al. [36] studied the cost drivers in two-stage treatment of hip PJI with an antibiotic-coated cement hip spacer and no significant difference in costs at one or two years for patients who received a “destination” or “1.5-stage” exchange arthroplasty. In 2023, Nace et al. [37] reviewed a consecutive series of 1.5-stage or planned two-stage THAs. A total of 123 hips were included (1.5-stage: n = 54; two-stage: n = 69) with a mean clinical follow-up of 2.5 years (up to eight years). The 1.5-stage exchange had 11% greater infection-free survivorship at final follow-up compared to two stages (94 versus 83%, $P = 0.048$). Morbid obesity was the only independent risk factor demonstrating increased reinfection among both cohorts. No differences in surgical/medical outcomes were observed between groups ($P = 0.730$). A total of 82% of 1.5-stage patients did not demonstrate progressive femoral or acetabular radiolucencies, while 94% of two-stage recipients did not have femoral radiolucencies and 90% did not have acetabular ones.

In 2024, Wang et al. [38] compared the clinical efficacy and complications associated with handmade spacers (group A) utilized during two-stage treatment and 1.5-stage functional articulating hip spacers (group B). They included 41 patients who had PJIs. All patients were followed up for at least 24 months after the last surgical procedure. No significant differences were noted in the infection eradication rate between the two groups (100 versus 96.30%, $P = 1.0$). The incidence of mechanical complications, especially spacer fracture, was significantly lower in group B than in group A ($P = 0.044$). Hip function and quality of life were significantly better in group B during the interim period. Group B patients had a longer interval time (median 7.4 versus 4.3 months, $P = 0.004$) and a lower reimplantation rate than group A patients (42.3 versus 82.6%, $P = 0.004$). The authors concluded that the 1.5-stage surgical technique is feasible for the treatment of hip infection, with a lower mechanical complication rate, better hip function, and better quality of life during the interim period compared to that of handmade spacers.

In conclusion, the infection control rate with the 1.5-stage hip revision ranged from 90 to 96.3% with a minimum average follow-up of two years and was not inferior to the two-stage revision [15–17]. The mechanical complications of the 1.5-stage components were acceptable, with 82% of patients not demonstrating progressive femoral or acetabular radiolucencies [17].

Cost-effectiveness

There are limited data regarding the cost-effectiveness of 1.5-stage revision arthroplasty. In one study, Okafor et al. (2023) evaluated the cost-effectiveness of one-stage versus two-stage revision surgeries for chronic PJI in TKA [39]. This study demonstrated that the incremental cost-effectiveness ratio (ICER) for two-stage revisions compared to one-stage was $231,000 per quality-adjusted life year (QALY), significantly exceeding the commonly accepted willingness-to-pay threshold of $50,000 per QALY. The probabilistic sensitivity analysis demonstrated that approximately 98.5% of simulations indicated that two-stage revisions are not cost-effective when compared to one-stage revisions [18].

Challenges and future research

The importance of arthroplasty joint registries in establishing gold standards for implant survivorship and, in some cases, patient-reported outcome measures (PROMs) is well established. Arthroplasty national registries are databases that track joint arthroplasty surgeries, such as hip and knee arthroplasties, to improve outcomes and monitor implant performance. Examples include the National Joint Registry (NJR) in the UK, the American Joint Replacement Registry (AJRR), the Australian Orthopedic Association National Joint Replacement Registry (AOANJRR), and the Swedish Hip Arthroplasty Register. These registries collect data on patient demographics, surgical techniques, implant types, and complications like infections or revisions. At the time of writing, no national joint arthroplasty registry has been able to accurately quantify and analyze the utilization of the 1.5-stage revision prostheses in their cohorts. This remains a significant challenge internationally.

Likewise, there are limited data comparing 1.5 stage revision to single-stage revision, “two-in-one” stage revision, and/or formal 2-stage revision. A well-designed, large, international, multicenter, randomized controlled trial comparing 1.5- versus two-stage

revision TKA and THA for PJI is an obvious direction for future research.

Conclusions

The 1.5-stage revision is a treatment with equivalent outcomes, lower overall morbidity, and potentially reduced cost compared to the two-stage exchange arthroplasty. Current considerations for this technique should include patients who are not deemed to be candidates for two major surgical interventions within a short period of time, patients who have a short life expectancy in whom a 1.5-stage procedure is believed to suffice, and patients who have limited resources or need time to recover before being subjected to another major reimplantation surgery. Multicenter prospective trials should be encouraged to further elucidate the role of 1.5-stage revision for PJI and validate the present findings.

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The Journal of Arthroplasty 41 (2025) S385–S398

Contents lists available at ScienceDirect

The Journal of Arthroplasty

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Hip and Knee

2025 ICM: Two-Stage

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Question 1: What metrics can we use to determine the optimal timing of reimplantation in patients undergoing two-stage exchange for periprosthetic joint infection (PJI)?[1]

Response/Recommendation

The available serological and synovial tests cannot be relied on solely to determine the optimal timing of reimplantation. A combination of clinical signs indicating infection resolution, together with declining serological and synovial markers, may be used to guide the timing of reimplantation. A recent scoring system integrating serum D-dimer levels, synovial fluid (SF) white blood cell (WBC) count, and polymorphonuclear percentage in the backdrop of clinical healing, declining erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) provides promising new insight regarding the risk of reinfection following reimplantation.

Level of Evidence: Level III

Delegate Vote: Agree: 90.0%; Disagree: 8.0%; Abstain: 2.0%

Rationale

The incidence of periprosthetic joint infection (PJI) following hip and knee arthroplasty approaches 1 to 2% [1,2]. A two-stage exchange arthroplasty is a popular treatment of choice for the management of chronic PJI. Despite treatment advancements, the reported reinfection rate can be relatively high [3]. A major issue related to two-stage exchange arthroplasty is the challenge of determining the optimal timing of reimplantation. Although serological and synovial markers are critical for the diagnosis of PJI, their role in determining the persistence of infection and the timing of reimplantation has been disappointing [4].

This systematic review summarizes key findings, focusing on diagnostic accuracy, sensitivity, specificity, and the clinical utility of biomarkers such as leukocyte esterase (LE), alpha-defensin-1 (AD), fibrinogen, D-dimer, CRP, ESR, SF analysis, and advanced diagnostic techniques like rotational thromboelastometry (ROTEM), thromboelastography (TEG), interleukin-6 (IL-6), next-generation sequencing (NGS), and frozen section (FS) analysis.

Leukocyte esterase

Logoluso et al. [5] investigated the LE strip test as a potential diagnostic marker for persistent infection, comparing it with CRP and ESR. The results indicated that the LE test had a sensitivity of 82%, a specificity of 99%, and an area under the curve (AUC) of 0.9044, outperforming CRP (AUC 0.8416) and ESR (AUC 0.7493). They therefore concluded that the LE test, owing to its ease of use and cost-effectiveness, is a valuable tool for guiding reimplantation decisions. In contrast, Kheir et al. [6] found that the LE test had a lower sensitivity (26.3%) and high specificity (100%). While a positive result strongly correlates with persistent infection, its low sensitivity limits its standalone utility. Patients who have positive LE tests had a higher failure rate (25.3%) postreimplantation; LE serves an adjunctive role, and its utility as a standalone test remains uncertain.

Synovial fluid Alpha-Defensin-1

Carender et al. [7] retrospectively evaluated the efficacy of AD in 52 antibiotic spacers during two-stage PJI. Although AD testing

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.095.

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https://doi.org/10.1016/j.arth.2025.10.095
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demonstrated high specificity (96%), its sensitivity was alarmingly low at 0%, thereby failing to identify persistent infection, though it exhibited a negative predictive value of 85%. They concluded that AD testing offered no significant advantage over commonly used diagnostic tests like SF analysis or serum markers to determine reimplantation timing. Similarly, Bielefeld et al. [8], in a prospective study with 20 patients, observed that AD testing could not significantly differentiate no infection from reinfection at 1-year follow-up. This undermines its diagnostic value.

Fibrinogen and D-Dimer

Ackmann et al. [9] observed that CRP and IL-6 levels significantly decreased, and D-dimer levels showed inconsistent change, with 50% of patients demonstrating increased levels between the first and second stages. This highlights the challenges of using D-dimer alone to predict persistent infection during the two-stage exchange.

Ascione et al. (2021, 2024) [4,10] reported that D-dimer levels greater than 1,110 ng/mL had moderate diagnostic accuracy for predicting recurrent PJI after reimplantation. Although the sensitivity (74%) and specificity (61%) were moderate, the combination of D-dimer with SF markers like SF-WBC count and SF polymorphonuclear neutrophil percent (PMN%) improved diagnostic accuracy. They proposed a scoring system by integrating D-dimer (greater than 1,110 ng/mL, given a score of 1.5), SF-WBC count (greater than 934 cells/mL, given score of 2), and SF-PMN% (greater than 52%, given score of 2), which was applied to patients who have declining clinical signs of active infection and CRP and ESR either within the normal range or in a downward trend. They found higher (58%) reinfection rates in those who had a preoperative total score greater than 2 than in those who had a total score ≤ 2.

Other studies have questioned the utility of D-dimer in diagnosing PJI and assessing infection resolution. Wu et al. [11] reported that D-dimer had a fair diagnostic performance (AUC 0.728), but it was less effective than fibrinogen, CRP, and ESR. Similarly, Xu et al. (2021) [12] reported poor performance (AUC 0.669) compared to CRP, ESR, and fibrinogen. Tarabichi et al. [13] stated that D-dimer was superior to CRP and ESR in diagnosing persistent infection, with a cutoff value of 1,604 ng/mL predicting treatment failure after reimplantation. Although its specificity was high (92.6%), the sensitivity remained unsatisfactory (51.5%). Pannu et al. (2021) [14] reported that D-dimer has poor diagnostic accuracy for two-stage exchange PJI, questioning its standalone diagnostic role. However, in combination with ESR and CRP, this can help to confirm the diagnosis. Pannu et al. in 2022 [15] reported a paradoxical increase in D-dimer levels before reimplantation, complicating its interpretation, as other markers (ESR and CRP) decreased.

Sahin et al. [16] found that serum D-dimer levels were significantly higher in two-stage septic revisions compared to primary or aseptic revisions. While D-dimer can aid in diagnosing PJI, it is not useful for determining the timing of reimplantation.

Shahi et al. [17] reported elevated D-dimer levels in PJI and proposed an optimal cutoff value of 850 ng/mL for diagnosing PJI. A better sensitivity and specificity were reported using this threshold for D-dimer in diagnosing PJI, and it was suggested that D-dimer is useful in predicting persistent infection. Shao et al. [18] evaluated the diagnostic efficacy of CRP, ESR, D-dimer, and fibrinogen levels during two-stage reimplantation for PJI, identifying optimal cutoff values of 1,740 ng/mL for D-dimer and 365.6 mg/dL for fibrinogen. All tests had a diagnostic sensitivity of 72.7%, except for ESR (63.6%); CRP and fibrinogen showed reliability in predicting infection. Xu et al. [19] found that fibrinogen (AUC 0.773) outperformed D-dimer (AUC 0.565), with a threshold of 3.61 g/L, had high sensitivity (87.5%), and negative predictive value (98.3%). Findings suggest fibrinogen as a promising biomarker; however, further validation is needed.

Synovial fluid analysis

Synovial fluid analysis, including WBC count and PMN%, is crucial in diagnosing PJI during two-stage revision. Zmistowski et al. [20] reported that elevated PMN% (greater than 62%) and WBC count (greater than 640 cells/mL) were significantly associated with persistent infection. However, the sensitivities of these markers were modest (63% for PMN% and 54.5% for WBC count), limiting their diagnostic accuracy.

Li et al. [21] compared synovial CRP (syCRP) and serum CRP (seCRP) in 186 patients, finding syCRP (AUC 0.93) offered better predictive value for infection recurrence than seCRP (AUC 0.80). With a cutoff of 8.89 mg/L, syCRP demonstrated high sensitivity (77.8%) and specificity (89.2%), indicating superior diagnostic accuracy for PJI.

Seetharam et al. [22] evaluated 249 patients and found synovial absolute neutrophil count and WBC counts had the highest diagnostic accuracy for total knee arthroplasty, while seCRP and synovial PMN% were more effective for total hip arthroplasty, highlighting synovial markers' superior accuracy for reimplantation timing.

Rotational thromboelastometry and thromboelastography

The ROTEM and TEG are gaining attention as diagnostic adjuncts in the management of PJI. Tsantes et al. [23] reported that ROTEM's FIBTEM-MC exhibited diagnostic accuracy for persistent infection, with a sensitivity of 100% and specificity of 73.4%. Yuan et al. [24] showed that TEG's maximum amplitude had an AUC of 0.895, showing good sensitivity and specificity, especially when combined with markers like ESR. Qiao et al. [25] supported these findings, that TEG combined with CRP and ESR accurately diagnoses persistent infection and guides reimplantation, though further validation is needed.

Interleukin-6

Hoell et al. [26] found significantly elevated IL-6 levels in patients who have persistent PJI (17 pg/mL) compared to those who do not have it (three pg/mL), with a cutoff value of $\geq$ 13 pg/mL providing a high positive predictive value (90.9%) before second-stage reimplantation. However, Krueger et al. [27] reported that IL-6 has moderate specificity and lower sensitivity compared to other markers. Qu et al. [28] also reported that IL-6 lacked the ability to effectively differentiate between patients who have and do not have persistent PJI. Thus, while IL-6 may enhance diagnostic accuracy when used in combination with other serological markers, its standalone utility remains limited.

Next-generation sequencing

The diagnostic value of NGS for persistent PJI compared to culture and Musculoskeletal Infection Society (MSIS) criteria was evaluated by Kildow et al. [29] in 57 patients. The NGS showed fair agreement with culture (kappa 0.27) and moderate agreement with MSIS (kappa 0.42), but its diagnostic accuracy was

insufficient to replace traditional methods. Further research is needed to validate NGS's role in PJI diagnosis and treatment.

Frozen section analysis

The FS analysis has been evaluated for predicting persistent infection during second-stage reimplantation. George et al. [30] found that FS had high specificity (94%) but low sensitivity (50%), making it more reliable for confirming infection. Fu et al. [31] observed FS > five PMNs/high powered field (HPF) and had higher sensitivity (90%) and specificity (83.1%) than CRP and ESR. Xu et al. [32] combined greater than five PMNs/HPF and greater than10 PMNs/HPF on FS with ESR and CRP, achieving moderate AUC values (0.709 and 0.697). While FS offers high specificity, its limited sensitivity underscores the need for integration with other diagnostic tools. Qiao et al. [33] found that positive FS increased reimplantation risk, while Kilicarslan et al. [34] noted low sensitivity (25%) and specificity (45.5%) when inflammatory markers were unclear.

Positive culture

Akgun et al. [35] found that positive cultures at reimplantation increased failure risk (29.6 versus 14.7%), while Tan et al. [36] reported that positive cultures doubled the risk of reinfection, despite bacterial differences between explantation and reimplantation. However, Puhto et al. [37] found no significant outcome difference, with a 94.4% success rate, suggesting other factors must be considered along with positive culture.

C-Reactive protein, erythrocyte sedimentation rate

The diagnostic value of ESR and CRP in PJI two-stage revision is debatable. Several studies have highlighted their limited diagnostic performance in predicting persistent infection. Xu et al. (2019) [32] and Johnson et al. [38] reported poor diagnostic utility. Johnson et al. [38] reported low AUC values of 0.47 (ESR) and 0.57 (CRP). Klemt et al. [39] linked high ESR and CRP before reimplantation to higher reinfection rates. Ghanem et al. [40] and Seetharam et al. [22] suggested that these markers, when combined with synovial markers like WBC count or absolute neutrophil count, aid in decision-making. Stambough et al. [41] and Benda et al. [42] found that changes in these markers over time did not reliably predict persistent infection. Li et al. [21] suggested that syCRP is more reliable than seCRP for PJI diagnosis. Oe et al. [43] used CRP to guide two- and multi-stage revision THAs, achieving 85% 10-year survival and 97% infection control. A CRP ratio greater than 4.0 between two to three weeks indicated failure, suggesting the limited adjunctive role of ESR and CRP in PJI management.

Globulin-related markers

Shang et al. [44] studied inflammatory markers related to globulin and found that combining platelet-related markers with traditionally used inflammatory markers, ESR and CRP, improved the diagnostic accuracy of PJI. Globulin-related markers demonstrated diagnostic value comparable to ESR and CRP, indicating that combining multiple markers offers a more robust approach to diagnosing PJI.

Timing of reimplantation

Delayed reimplantation increases the risk of failure and reinfection. Vielgut et al. [45] suggested a second-stage surgery between four and 11 weeks for optimal outcome, with 90% of patients remaining infection-free. Fu et al. [31] found that reimplantation within 12 to 16 weeks resulted in the lowest failure rates, while delays beyond 16 weeks significantly increased the risk of failure. Borsinger et al. [46] and Rezaie et al. [47] noted higher failure rates for delays longer than 18 and 26 weeks, respectively. Puetzler et al. [48] reported increased reinfection risk after 94 days.

Conclusions

The diagnosis of persistent infection should consider a combination of biomarkers. The LE test shows high specificity but inconsistent sensitivity, making it an adjunct rather than a standalone primary marker. The AD tests have limited utility because of their low sensitivity. Standalone plasma D-dimer levels show variable reliability. The ROTEM and TEG enhance diagnostic performance when integrated with other biomarkers, but their diagnostic value, even as adjuncts, needs to be validated. Interleukin-6 and NGS have demonstrated efficacy, but their diagnostic value is inconsistent. The FS offers high specificity in predicting persistent infection, with limited data suggesting the timing of reimplantation. Serological tests, in combination, more reliably guide reimplantation, and combining D-dimer levels with SF-WBC and SF-PMN percentage in the milieu of clinical healing and declining ESR and CRP, put into a score, can reasonably predict the risk of persistent infection.

Question 2: Do the thresholds for serum and synovial tests used for the diagnosis of periprosthetic joint infection (PJI) also apply to reimplantation?[2]

Response/Recommendation

No. Based on limited data, the thresholds for serum and synovial tests used to diagnose PJI should not be used to determine the presence/absence of infection for reimplantation in patients undergoing two-stage exchange arthroplasty.

Level of Evidence: Weak

Delegate Vote: Agree: 93%, Disagree: 5%, Abstain: 2% (Total Consensus, Unanimity)

Rationale:

A two-stage exchange procedure is widely regarded as the preferred surgical strategy for the management of patients who have chronic PJI, with reported success rates of up to 90% [49]. However, significant heterogeneity exists in how studies evaluate persistent PJI at reimplantation.

There were four studies that retrospectively assessed the established serum C-reactive protein (CRP) threshold of one mg/dL at reimplantation via comparison against intraoperative microbiology, recurrence of PJI, and Delphi Criteria [50–53], with sensitivity from 17 to 67% and specificity from 40 to 82%. A wide variety of studies investigated optimal thresholds for serum CRP. They identified optimal cutoffs from 0.33 to 5.2 mg/dL. However, those that employed a threshold greater than one mg/dL demonstrated a trend toward increased specificity, rendering it potentially useful as a rule-in test [54–69].

When evaluating the standard erythrocyte sedimentation rate threshold of 30 mm/h at reimplantation, Lindsay et al. observed a sensitivity of 75% and a specificity of 100% in 21 cases, using recurrent infection after reimplantation as the outcome. However, Pannu et al. identified a sensitivity of 30% and specificity of 67% through retrospective analysis of 44 cases and comparison against Delphi Criteria [52], while Ghanem et al. found a sensitivity of 65%

[2] These authors contributed to Question 2: Christoph Böhler, Jennifer Straub, Derek Amanatullah, Tiziana Ascione, Bernd Fink, Jason M Jennings, Jay Lieberman, Valeri Murylev, James Powell, Jong-Keun Seon

and specificity of 32.4% when retrospectively applying the established threshold in 109 knees [50]. There were ten other studies [54,57–63,69,70] that identified optimal cutoffs based on varying outcome measures ranging from 29 mm/hour (sensitivity: 64%, specificity: 88%) [62] to 102 mm/hour (sensitivity: 29%, specificity: 89%) [63], indicating an overall trend toward higher cutoffs at reimplantation.

There were none of the identified studies that directly assessed the standard D-dimer threshold of 860 ng/mL, with optimal thresholds ranging from 600 to 3,070 ng/mL and no clear trend in sensitivity or specificity, leaving its value at reimplantation unclear [52,58,61,62,71–74].

Regarding synovial white blood cells (WBCs), no study directly assessed the established cutoff, but six of them identified thresholds below the standard of 3,000 cells/μL, most of which used intraoperative cultures as an outcome measure for failure [56,57,59,60,63,75–79]. Seven out of the ten studies report cutoff values below the current standard for initial diagnosis, ranging from 640 [60] to 2,733 cells/μL [77] with variable diagnostic performance. Further, Boelch et al. found noteworthy differences in synovial WBC cutoff when comparing against histology for polymorphonuclear (PMN) cells (3,250 cells/μL) or intraoperative tissue culture (4,450 cells/μl) in 94 revision knees [78].

Similar to WBCs, optimal PMN% thresholds in the literature all range below the established > 80% limit when compared against a variety of outcome measures. These results indicate a possible need for lowering limits at reimplantation [57,59,60,63,73,75,77,79]. Thresholds ranged from 52% (sensitivity 82%, specificity 78%) in a study from Ascione et al. [79] to 79% (sensitivity 78%, specificity 82%) identified by Kusuma et al. [57], with consistently good diagnostic performance. However, due to the heterogeneity of outcome measures, no definitive recommendation or cutoff could be established.

When assessing cultures of aspirated synovial fluid, a single positive culture sample was generally considered a positive test result and, in most studies, compared against intraoperative microbiology and/or histology or MSIS criteria. Throughout all identified studies, specificity was consistently much higher than sensitivity, with values ranging from 85 to 100%, indicating its potential as a rule in tests with at least one positive sample as the threshold [56,75,76,78,80–83].

Recently, a study by Li et al. was the first one to prospectively assess synovial CRP at reimplantation. They identified a reasonably high sensitivity of 78% and specificity of 89% at a threshold of 0.89 mg/dL when comparing it against the emergence of a new sinus tract infection or positive cultures as an outcome [67]. However, further evidence is needed to fully support this threshold as opposed to the established 0.68 mg/dL [84].

There were three studies that evaluated the diagnostic value of leukocyte esterase strips at reimplantation, all interpreting grades > + as positive per the current MSIS criteria [84]. Through prospective comparison against treatment failure after one year, as defined by the Delphi Consensus, Bielefeld et al. found a negative leukocyte esterase result in all 18 patients, yielding a sensitivity of 0% and a specificity of 100% [65]. Kheir et al. retrospectively applied the same threshold and endpoint and found a sensitivity of 26% and specificity of 100% at a mean follow-up of just under two years in 77 patients [70]. A third study by Logoluso et al. showed an outstanding sensitivity of 82% and specificity of 99% through comparison against MSIS criteria at reimplantation or PJI recurrence at a minimum follow-up of 16 months [66]. Although these studies suggest that the previously established threshold for leukocyte esterase strips may be reasonable for reimplantation, further research is needed to confirm its reliability and optimize diagnostic accuracy.

In terms of synovial alpha-defensin, divergent evidence exists when compared against (modified) 2018 MSIS criteria at reimplantation, with Stone et al. reporting a 71% sensitivity [85], while Owens et al. found 0% sensitivity [86], both showing near-perfect specificity. When assessed for failure after at least 1 year, three studies comparing synovial alpha-defensin to the Delphi Consensus showed extremely low sensitivity but almost absolute specificity [65,87,88]. Thus, its clinical utility at reimplantation cannot be supported based on current evidence.

A recent systematic review and meta-analysis by Sabater-Martos et al. [89] assessed 24 studies regarding positive intraoperative cultures at reimplantation and subsequent failure. The number of reported samples ranged from one to eight, and one positive culture was considered a positive result at reimplantation in the vast majority of studies, as defined in the postoperative section of the 2018 MSIS criteria [84]. The overall risk of failure with positive cultures was significantly higher in the antibiotic holiday group (i.e., the group pausing antibiotics before reimplantation, odds ratio of 4.8) as well as the non-holiday group (odds ratio, 2.2). However, studies directly assessing the optimal number of samples needed are still required to fully support this evidence.

The Feldman criterion (≥ five PMN in ≥ five high-power fields) is currently used by both the MSIS and European Bone and Joint Infection Society (EBJIS) criteria as the standard for intraoperative histology [84,90]. Using it, Bori et al. demonstrated a sensitivity of 29% and specificity of 100% when compared to positive intraoperative microbiology as the gold standard. Alternatively, the application of the Athanasou criterion (≥ one PMN per high-power field, on average, in 10 fields) showed a shift toward increased sensitivity (71%) and lowered specificity (64%) in the same cohort [91]. There were two other studies that also found low sensitivity (0 to 38%) and high specificity (83 to 91%) with the Feldman criterion compared to infection recurrence [92,93]. George et al. considered intraoperative frozen sections as positive if ≥ five PMN were seen in ≥ three high-power fields, resulting in a sensitivity of 59% and specificity of 94% in comparison to the MSIS criteria at reimplantation [94]. Further, Straub et al. found a sensitivity of 29% and specificity of 76% with a cutoff of ≥ 23 PMN per 10 high-power fields and treatment failure defined as tier 3B or 3D according to the MSIS reporting tool [95]. In total, no cutoff can be fully supported, with the previous ones primarily useful for ruling in infection.

In a study by Nelson et al., sonication cultures were performed on 36 patients who had a sensitivity of 82% and specificity of 50%, with an average antibiotic-free duration before reimplantation of seven weeks. When considering only sonication results with more than 20 colony-forming units as positive, the sensitivity decreased to 63% and the specificity increased to 78%, respectively [96]. Another study by Sorli et al. applied a threshold of at least five colony-forming units in 55 patients but did not report sensitivities or specificities [97]. Similarly, a study by Bereza et al. [80] assessed sonication results but reported neither colony-forming unit cutoffs nor sensitivity and specificity.

Therefore, thresholds established at explantation cannot be fully supported at reimplantation due to variability in diagnostic performance and lack of standardization across studies [98]. The established serum and synovial test thresholds for the diagnosis of PJI showed lower overall performance at reimplantation in a 2-stage revision. While some thresholds, such as those for CRP, erythrocyte sedimentation rate, or synovial WBC, may provide insights, they show inconsistent sensitivity and specificity across studies. Although some established thresholds seem beneficial for ruling in infection, their clinical relevance is highly diminished by the lack of standardization in study protocols, antibiotic

Table 1
The Cochrane Risk of Bias 2 and Risk of Bias in Nonrandomized Studies Of Interventions Assessments.

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall Risk of Bias
Bernard et al. (2021)	Low - Centralized, computer-generated randomization - Comparable baseline characteristics	Low - Open-label design - Outcomes assessed by blinded committee - No protocol deviations reported	Low - Minimal loss to follow-up - Handled with sensitivity analyses	Low - Objective outcome definitions used - Reinfection assessed by blinded clinical experts using objective criteria	Low - Predefined protocol and outcomes reported - No selective reporting detected	**Low**

Study	Bias due to Confounding	Bias in Selection of Participants	Bias in Classification of Interventions	Bias due to Deviations from Intended Interventions	Bias due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of Reported Results	Overall Risk of Bias
Ma et al. (2020)	Serious	Serious	Low	Serious	Low	Moderate	Moderate	**Serious**
Hsieh et al. (2009)	Serious	Serious	Low	Low	Moderate	Moderate	Moderate	**Serious**
El Helou et al. (2011)	Moderate	Moderate	Low	Low	Low	Low	Low	**Moderate**
Mittal et al. (2007)	Serious	Serious	Moderate	Serious	Moderate	Moderate	Moderate	**Serious**

management, and outcome measures, making it difficult to recommend specific cutoffs.

Question 3: What is the optimal duration of antimicrobial treatment between stages for patients undergoing two-stage exchange for implant-associated infections?[3]

Response/Recommendation

Unknown. There is limited to no evidence to help determine the optimal duration of antimicrobial treatment between stages for patients undergoing two-stage exchange arthroplasty for the management of PJI.

Level of Evidence: Limited

Delegate Vote: Agree: 73%, Disagree: 19%, Abstain: 8% (Strong Majority, Moderate Consensus)

Rationale

PJI is a serious complication following total joint arthroplasty that requires individualized management [99,100]. Although two-stage exchange arthroplasty is a popular treatment option for patients who have chronic PJI, the optimal duration and route of antimicrobial administration between the two stages remain undefined and unstandardized. Existing guidelines recommend durations that vary from four to 12 weeks, with six weeks being the most commonly utilized duration for antimicrobial treatment. To address the posed question above, we conducted a comprehensive systematic review of the literature using MeSH terms developed by librarians. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol to review the optimal duration of antibiotic treatment between the first and second stages of two-stage revisions for PJI in total knee arthroplasty (TKA) and total hip arthroplasty (THA). Following deduplication, 1,620 records were available for title and abstract screening, with 104 advancing to full-text review. All single-arm observational studies were excluded due to high risk of bias and low-quality evidence. A randomized controlled study and four retrospective studies that directly compared different antibiotic durations and their impact on success rates at final follow-up were included [101–105]. Risk of bias was evaluated using the Cochrane risk of bias tool 2.0 and the Risk of Bias in Nonrandomized Studies of Interventions (Table 1).

Bernard et al. [101], in the only randomized controlled trial, 325 PJI cases (hip and knee) were assigned to either a 6- or 12-week antibiotic treatment group, with one to two weeks of intravenous (IV) therapy followed by oral administration. A subgroup

[3] These authors contributed to Question 3: Frank Kolhoff, Koji Yamada, Armen Daniliyants, Daniel H. Taupin, Svetlana A. Bozhkova, Oscar Murillo, Martin Pietsch, Ashok Rajgopal, Vinay K. Aggarwal

analysis of 40 patients (six weeks) and 41 patients (12 weeks) undergoing two-stage procedures showed a nonsignificant reinfection risk difference within two years post-treatment (risk difference: 10.1, 95% confidence Interval (CI) [−3.1 to 23.3]), with low risk of bias. Reinfection occurred in six of 40 patients (15.0%) in the 6-week group and two of 41 patients (4.9%) in the 12-week group.

Meanwhile, Ma et al. [102] reviewed 64 THA PJI cases, comparing a systemic antibiotic treatment duration of ≤ one week (n = 21) with a four- to 6-week treatment duration (n = 43), which included IV followed by oral antibiotics between the first and second stages. The mean follow-up was 75 months (range, 24 to 133). An adjusted odds ratio for reinfection of 0.051 (95% confidence intervall [0.002 to 1.122], $P = 0.059$) was reported for the short-course group compared to four to six weeks, with serious risk of bias. In addition, the 5-year implant survival rate, defined as the absence of revision or chronic antibiotic use, was 85.2% in the short-duration group compared to 74.0% in the longer-duration group, though this difference did not reach statistical significance ($P = 0.317$).

Similarly, Hsieh et al. [103] assessed 99 THA PJI cases, retrospectively comparing success rates of two-stage revisions between a 1-week IV antibiotic course and a 4- to 6-week IV treatment group with a mean follow-up of 43 months (range, 24 to 60). Again, no statistically significant difference in overall success rate was found between the 1-week group (89%; 47 of 53) and the four- to 6-week group (91%; 42 of 46) ($P = 0.67$), with serious risk of bias.

El Helou et al. [104] reported the outcome of four weeks of IV antibiotics versus six weeks of IV antibiotics, reviewing 208 PJI cases (THA: n = 99; TKA: n = 109). Using the Cox proportional hazards model adjusted for propensity scores, they found no significant difference in treatment failure rates between patients treated with six versus four weeks, hazard ratio = 1.4, 95% confidence interval [0.7 to 2.7], $P = 0.31$ (moderate risk of bias)). However, the results of this study should be interpreted with caution, as not all confounders, such as the causative organism, were controlled for, with all methicillin-resistant *Staphylococcus aureus* PJIs being assigned to the 6-week group.

Mittal et al. [105] observed 37 TKA PJI cases caused by methicillin-resistant *Staphylococcus aureus* or methicillin-resistant *Staphylococcus epidermidis* and retrospectively categorized them into two groups based on antibiotic treatment duration: < 42 days and ≥ 42 days of IV therapy. The success rate of infection control of the initial resistant microorganism was 13 of 15 in the < 42 days group compared to 90.9% (20 of 22) in the ≥ 42 days group at a mean follow-up of 51 months (range, 24 to 111). However, the success rate was 12 of 15 in the less than 42 days group compared to 63.6% (14 of 22) in the ≥ 42 days group when the definition of success was considered free of infection, including infections caused by new microorganisms, and free of chronic antibiotics at follow-up.

Due to the lack of a standardized definition of success and the variations in methodologies, we were not able to combine the data and perform a meta-analysis. From our review, none of the comparative studies reported statistically significant differences between shorter and longer durations of antimicrobial treatment. However, it is important to note that the definition of shorter duration and success varied among studies. Moreover, these results were based on limited sample sizes and exhibited strong heterogeneity in study design, outcome definition, and patient populations, which complicates direct comparisons and restricts the feasibility of a robust meta-analysis.

Conclusions

There is little to no high-quality evidence related to the optimal duration of antimicrobial treatment between the first and second stages of a two-stage exchange revision for patients with PJI of the hip and/or knee. Although there are several comparative studies, the heterogeneity among available studies and the lack of standardized definitions of success make it difficult to perform a meta-analysis. Future research should focus on prospective randomized trials comparing different antibiotic durations, with standardized and comprehensive definitions of success rates with long-term follow-up, to improve our understanding of this issue.

Question 4: Is there a role for a two-week antibiotic holiday in patients undergoing two-stage exchange arthroplasty for periprosthetic joint infection (PJI)?[4]

Response/Recommendation

There is no conclusive evidence that a 2-week antibiotic holiday improves the outcome of two-stage exchange in patients who have a PJI. On the other hand, continuous therapy may result in better outcomes for some, such as immunocompromised patients.

Level of Evidence: Limited

Delegate Vote: Agree: 90.7%, Disagree: 7.0%, Abstain: 2.3%

Rationale

An "antibiotic holiday" period can be observed before reimplantation in a two-stage exchange procedure for PJI to identify patients who have a latent infection before reimplantation. This approach was first described by Insall et al. in 1984 as a strategy to address the risk of infections that may be suppressed but not eradicated before reimplantation [106]. Building on Insall's work and other early reports, the practice of a 2-week antibiotic holiday emerged, theoretically allowing latent infections to become clinically evident before reimplantation [107,108]. However, the absence of reliable thresholds for serological markers to indicate infection control or persistence, as well as the low accuracy of microbiologic investigations in predicting infection recurrence, remains an unsolved challenge in this field [109]. In addition, withholding antibiotics for two weeks can extend the interval between surgical stages, potentially leading to worse treatment outcomes [110].

A meta-analysis was completed utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol to review the effect of an antibiotic holiday versus continuous antimicrobial therapy on treatment failure. Following de-duplication, 1974 records were available for title and abstract screening, of which 185 proceeded to full-text screening. There were no randomized controlled studies available. There were six retrospective cohort studies that were identified to have directly compared treatment failure rates between patients who underwent an antibiotic holiday and those who were subjected to continuous antibiotic therapy [111–116]. There were three of the six included studies that were at serious risk of bias, and the remaining three were at moderate risk of bias (Table 2). Ascione et al. [111] found that the absence of an antibiotic holiday predicted a favorable outcome in terms of treatment failure ($P = 0.029$). Lee et al. [114] found that the lack of an antibiotic holiday was a risk factor for treatment failure. Mont et al. [115] reported a benefit to the use of an antibiotic holiday. Chang et al. [113], Castellani et al. [112], and Van Dijk et al. [116] found no difference.

Random-effects meta-analysis calculated a risk ratio of 0.77 (95% confidence interval 0.40 to 1.46) for the outcome of treatment failure with the use of an antibiotic holiday (Figure 1). This

[4] These authors contributed to Question 4: Andrew Fraval, Daniel Gould, Bülent Atilla, Jose Luis Del Pozo, Elizabeth Gancher, Anders Odgaard, Jakrapun Pupaibool, Tiziana Ascione

Table 2
Critical Appraisal.

Study ID	Bias due to confounding	Bias due to participant selection	Bias due to intervention classification	Bias due to deviation from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias due to selection of reported result	Overall risk of bias
Ascione 2019 (6)	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Castellani 2017 (7)	Serious	Serious	Low	Moderate	Moderate	Low	Low	Serious
Chang 2019 (8)	Moderate	Low	Low	Low	Moderate	Moderate	Low	Moderate
Lee 2022 (9)	Serious	Serious	Low	Moderate	Moderate	Low	Low	Serious
Mont 2000 (10)	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Van Dijk 2022 (11)	Serious	Serious	Low	Moderate	Moderate	Low	Low	Serious

indicates that there is a comparable risk of treatment failure between patients who underwent an antibiotic holiday and those who underwent continuous antibiotic therapy between stages [117]. The I^2 value was 63.1% (95% confidence interval 10.6 to 84.8%), and the prediction interval was 0.13 to 4.44, indicating substantial heterogeneity [118–121].

Ascione et al. [111] reported the largest comparative cohort study of the outcomes of continuous antimicrobial therapy versus an antimicrobial holiday, involving 196 patients who had a minimum follow-up of 96 weeks. Those undergoing continuous therapy had a significantly better success rate of 91% (104 of 114) compared to those undergoing an antimicrobial holiday, 79% (65 of 82) ($P = 0.029$). This study was the only one to find a statistically significant difference between the groups and found that immunocompromised patients had the highest advantage with continuous therapy.

Van Dijk et al. [116] reported on a cohort of 105 patients undergoing a two-stage exchange. Infection control rates were comparable between patients who had an antibiotic-free period (87%) and those who had continuous antibiotics (82%), with no statistically significant difference ($P = 0.6$). Similarly, Castellani et al. [112] reported on the outcomes of 75 patients who underwent a two-stage exchange and found no difference in treatment success between continuous therapy versus the use of an antimicrobial holiday (nine of 47 versus three of 16 failures; $P = 1$). This finding is limited by the small number of patients undergoing continuous therapy. Chang et al. [113] reported on 58 patients, of whom 31 were receiving an antimicrobial holiday and 27 were

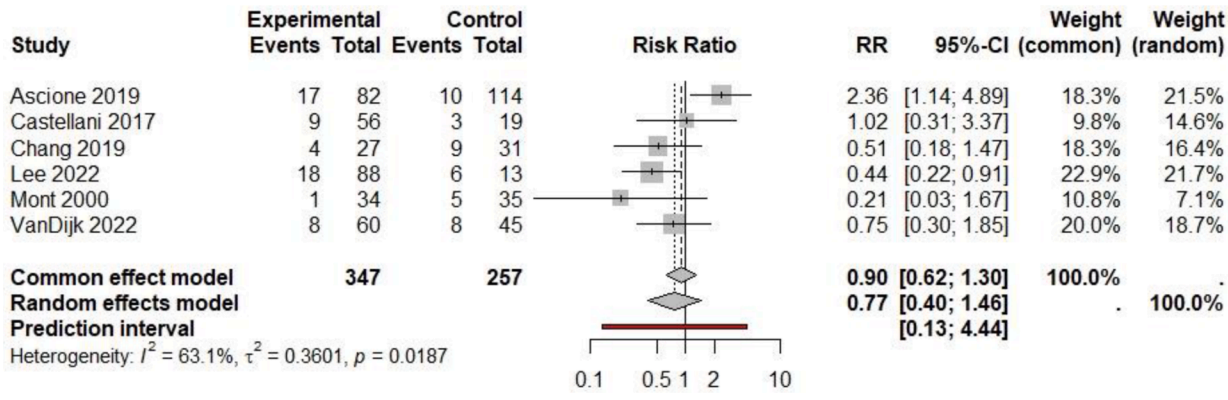

Figure 1. Forest plot: values to the right side of the line of no effect (risk ratio = 1) indicate increased risk of failure with antibiotic holiday. RR, risk ratio; CI, confidence interval.

receiving continuous therapy. While the 2-year survival rate was higher in the antimicrobial holiday group (89.3 versus 78.8%), this failed to reach statistical significance ($P = 0.263$). Furthermore, patients undergoing an antibiotic holiday period before reimplantation had an overall lower C-reactive protein at the end of the antibiotic treatment period, suggesting better infection control in this group. Of note, in addition, is the fact that this study employed long intervals of 4.5 to 6.5 months between the first and second stages, limiting its generalizability.

Several studies have reported negative findings with respect to treatment success when continuous therapy is employed. Mont et al. [115] reported on 69 patients who underwent a two-stage exchange, 35 receiving the continuous therapy and 34 receiving an antibiotic holiday period. They found a higher rate of treatment failure in the continuous therapy group compared to the antibiotic holiday (14% (five of 35) versus 3% (one of 34); $P < 0.05$). There were, however, methodological discrepancies between groups. Routine joint aspiration occurred before the second-stage reimplantation in the antibiotic holiday group, while the continuous therapy group did not undergo aspiration. Negative cultures led to reimplantation, while positive cultures prompted additional debridement, which may have led to lowered reinfection rates in the antibiotic holiday group. Lee et al. [114] reported that the lack of an antimicrobial holiday was a risk factor for treatment failure in their series of 101 patients undergoing a two-stage exchange. Only 13 patients in this series received continuous therapy with a reported failure rate of 46.4%. The treatment methodology in this series stated that antibiotic regimens were individualized and dependent on response to treatment. If the clinical condition improved and C-reactive protein levels declined, the patient was switched to oral antibiotics or antibiotic treatment was discontinued. If recurrence of PJI was suspected, the patient would receive further debridement and spacer exchange. This may explain the finding in this series of a higher failure rate for those receiving continuous therapy.

The wide prediction interval calculated in this meta-analysis represents the range within which the true effects of 95% of future studies, conducted under similar conditions as those included in this meta-analysis, are expected to fall [121]. This suggests that there may be settings in which an antibiotic holiday may be beneficial in terms of treatment failure and settings in which it may be harmful; however, based on published literature, it is not known which factors or their magnitude. As such, this meta-analysis should be interpreted cautiously in the context of substantial multifactorial heterogeneity, which renders interpretation of the independent effect of antibiotic holidays on treatment failure rate difficult and complex. Given the heterogeneity of the data, further research is needed to clarify the optimal approach.

Question 5: Should prolonged antimicrobials be given to patients who have undergone recent reimplantation surgery with all cultures being negative?[5]

Response/Recommendation

There is a weak signal in the literature suggesting that administration of prolonged oral antibiotics after reimplantation may reduce the risk of reinfection. However, the evidence is insufficient to make any conclusive recommendation.

Level of Evidence: Weak

Delegate Vote: Agree: 91.0%, Disagree: 2.9%, Abstain: 6.2% (Super Majority, Strong consensus)

Rationale

Reimplantation after a two-stage exchange arthroplasty has a reported subsequent reinfection rate of 6 to 20% [122–127]. Prolonged oral antibiotic prophylaxis following reimplantation offers a potentially simple and cost-effective strategy to address the risk of reinfection, a complication that would be otherwise challenging and costly to treat [125,127]. However, current guidelines lack any specific recommendations for antibiotic use following reimplantation when cultures are negative, leaving the decision to the discretion of the treating surgeon or infectious disease specialist [127].

Reimplantation is usually carried out after six or more weeks of high-dose antibiotic therapy, once the patient is presumed to be cleared of infection [124]. Despite the absence of clinical or histological signs of infection, it is possible that some latent microorganisms may remain in the joint or may be introduced during the second-stage procedure [124,127]. Patients undergoing multiple operations in the same joint may be more vulnerable to early reinfection [127–129].

There are a limited number of publications assessing the benefit of using extended oral antibiotic prophylaxis following reimplantation; only six studies met our criteria for inclusion in this review [130–135]. The most rigorous of these studies was an unblinded multicenter randomized controlled trial comparing the reinfection rates in patients given a 3-month course of antibiotics following reimplantation to a control group who received preoperative antibiotics, but no prolonged antibiotics following reimplantation. The trial results in 185 patients reported a reduction in the “treatment failure rate” (defined as an infection due to a further infection as per MSIS criteria) from 28.6% in the control arm to 12.5% in the treatment arm, with a mean follow-up of 3.3 years [131]. Of note, the relapse rate of 28.6% in patients in the control arm of this trial was substantially higher than the approximately 6 to 20% rate reported in the literature. Furthermore, there were several methodological issues with the trial, including high loss to follow-up, a lack of power, and a fragility index of 2 (meaning if two patients in the treatment arm had developed reinfection, the statistical significance would be lost).

The other five relevant studies are all retrospective in nature; four of these reported a benefit from extended postreimplantation oral antibiotic use. Johnson et al. found a 0% reinfection rate in 22 patients who had a 1-year follow-up and received a mean 36 days (minimum 14 days) postoperative oral antibiotic course, compared to a 14% reinfection rate in 44 patients receiving antibiotics for only one to three days postoperatively [130]. Zywiel et al. observed a 4% reinfection rate in 28 patients treated with a 28-day antibiotic course versus a 16% reinfection rate in 38 patients who did not receive prolonged antibiotic therapy (relative risk = 0.23). [132]. In contrast, Kelly et al. found no difference in outcome with a mean follow-up of 2.2 years between 158 patients who received prolonged oral antibiotics following reimplantation as compared to 53 patients who did not [134].

The two retrospective studies were designed to compare the outcomes of different treatment durations following reimplantation. In the largest study to date assessing this intervention, Ryan et al. evaluated 444 patients and found that treatment with oral antibiotics following reimplantation (this consisted of two groups, those who received antibiotics for more than two weeks and others for less than two weeks) was associated with a reduction in the relapse rate compared to giving no antibiotics at all but reported no difference with respect to the

[5] These authors contributed to Question 5: Rajeev K Sharma, Bryan Hess, Dominic Meek, Joshua Davis, Katherine Belden, Michael Henry, Michael Neufeld, Poorani Sekar, Udit Vinayak

duration of post-reimplantation antibiotic therapy [135]. Fang et al. noted comparable reinfection rates of 4.7% in 41 patients who received antibiotics for more than a month post-reimplantation versus 7.3% ($P = 0.676$) in 64 patients who were treated for less than a month [133].

Based on these studies, the optimal duration of prolonged antibiotics remains unclear. There were three months of prophylactic antibiotics that were given in the only randomized controlled trial [131]. However, the four retrospective studies reporting benefit suggest that a much shorter course could be equally beneficial; the duration of prophylaxis in these studies ranged from under two to five weeks. The two studies that compared longer courses to shorter courses of prophylaxis found no therapeutic advantage of the longer course over a shorter course; however, their role in preventing early postoperative infection remains uncertain [133,135].

The primary role of prolonged antibiotics remains prophylactic rather than treating an already existing infection [136–138]. However, reinfections following two-stage exchange, even when postreimplantation oral antibiotics are not given, are frequently caused by new or undetected latent organisms, as shown by Yang et al., where 85% of reinfections involved new microorganisms, and Zmistowski et al., where 68.5% of reinfections were attributed to new pathogens [131,139]. Studies evaluating the benefit of extending antibiotic prophylaxis after primary joint arthroplasty, aseptic revision, and spinal fusion surgery have shown conflicting results [140–143]. It may be that patients undergoing reimplantation for PJI are at a uniquely higher risk for early new infection and are more likely to benefit.

Despite its potential benefits, prolonged antimicrobial therapy has limitations. Complications include the risk of adverse effects, patient non-compliance, and the risk of promoting antibiotic resistance [131,132,144]. The risk for the development of antibiotic-resistant infections was highlighted in the study by Kelly et al. In addition to reporting no significant advantage in reducing infection relapse rates with postreimplantation antibiotics, the authors also found a sharp increase in infection with antibiotic-resistant organisms in patients who relapsed after being treated with postreimplantation oral antibiotics. Antibiotic resistance was defined as any organism resistant to the oral antibiotic given following reimplantation. Fifteen percent of patients receiving prolonged antibiotics experienced infection relapse, with 67% developing infection with an antibiotic-resistant organism. In comparison, 21% of patients who did not receive post-reimplantation antibiotics relapsed, but with 0% multidrug resistance [134].

Conclusions

The use of prolonged antibiotic prophylaxis following reimplantation in two-stage exchange arthroplasty offers a potentially promising strategy to reduce the risk of reinfection. There are relatively few studies assessing this intervention, but several, including a multicenter randomized trial, have found that extended oral antibiotics significantly lower reinfection rates. The duration of postreimplantation antibiotics required to achieve this benefit is unclear; as few as two weeks may provide equivalent benefit to longer courses. And while prolonged antibiotics may offer improved outcomes, their application must balance the risks of complications, patient compliance challenges, and the potential for the development of antibiotic resistance. Well-designed randomized controlled trials are essential to determine if there is, in fact, a benefit of postoperative antibiotic prophylaxis in this context.

Table 3
Prognostic Value of Positive Cultures at Reimplantation.

Study, Y	Design	Level of Evidence	Number of Joints, (n)	(+) Cultures (n,%)	(+) Cultures Considered Pathogens (n,%)	ATB[a]	(+) Cultures, Failure (n,%)	(−) Cultures, Failure (n,%)	(+) Cultures, Predictor of Failure
Murillo 2007	Prosp.	III	25 (10 hips, 14 knees, 1 shoulder)	15/25 (60)	7/15 (47)	6 to 8	0/7 (0%)	2/18 (11)	NA
Bejon 2009	Retrosp.	III	152 (71 hips, 77 knees, 4 elbow)	21/152 (14)	19/21 (91)	6 to >52	NA[b]	NA	$P = 0.6$
Cabo 2011	Prosp.	III	41 (18 hips, 23 knees)	18/41 (44)	4/18 (22)	4 to 6	4/18 (22%)	1/23 (4)	NA
Mortazavi 2011	Retrosp.	III	117 knees	19/117 (16)	NA	NA	6/19 (32%)	27/98 (28)	$P = 0.33$
Sorli 2012	Prosp.	III	55 (17 hips, 37 knees, 1 shoulder)	14/55 (25)	11/14 (79)	NA	7/11 (64)	11/44 (25)	$P = 0.021$
Puhto 2013	Retrosp.	IV	107 (61 hips, 46 knees)	5/97 (5.2)	5/5 (100)	8 to 12	1/5 (10)	4/92 (4)	$P = 0.24$
Nelson 2014	Prosp.	III	36 (7 hips, 29 knees)	18	9/18 (50)	N/A	9/18 (50)	2/18 (11)	$P = 0.0189$
Tan 2016	Retrosp.	III	267 (81 hips, 186 knees)	33/267 (12)	25/33 (76)	6 to 12	15/33 (45)	49/234 (21)	$P = 0.02$
Akgun 2017	Retrosp.	III	163 (84 hips, 79 knees)	27/163 (17)	15/27 (56)	12	8/27 (30)	20/136 (15)	$P = 0.049$
Xu 2019	Retrosp.	III	117 hips	23/117 (20)	23/23 (100)	6 to 10	6/23 (26)	6/94 (6)	$P = 0.022$
Xu 2019	Meta-analysis	III	925 joints	141/925 (15)	NA	2 to 12	58/141 (41)	116/784 (15)	$P < 0.001$
Theil 2020	Retrosp.	III	204 (93 hips, 111 knees)	51/204 (25)	12/51 (24)	2 to 6	17/51 (33)	25/152 (16)	$P = 0.014$

Prosp., prospective; Retrosp., retrospective; NA, not available., CI, confidence interval.
[a] Antibiotic duration after reimplantation (wk).
[b] Reported Cox univariate analysis: hazard ratio 1.3 (95% CI 0.4 to 3.7).

Question 6: Should patients undergoing reimplantation surgery in whom intraoperative cultures isolate organism(s) be treated with antimicrobials?[6]

Search Methods/Results

There were two databases searched for relevant terms: PubMed and Scopus. There were 65 studies identified—32 from PubMed, 22 from Scopus, and 11 by citation searching of identified studies. There were eight duplicate studies removed. Of 57 studies screened, 24 were irrelevant, 33 underwent full-text review, with 22 excluded (11 wrong setting, nine wrong patient population, one wrong outcome, one wrong indication), leaving 11 included studies.

Response/Recommendation

Based on available data, patients undergoing reimplantation surgery in whom positive cultures are detected should be treated with antimicrobials if two or more cultures detect the same organism, a single positive culture is identified that is the same as the first-stage findings, or if there is high clinical concern for infection. The optimal duration for antimicrobial therapy is unknown, and four to six weeks may be appropriate in many cases.

Strength of Recommendation: Moderate

Delegate Vote: Agree: 93.8%, Disagree: 1.6%, Abstain: 4.7% (Super Majority)

Rationale

The diagnosis of persistent infection and need for extended antibiotics in patients undergoing two-stage exchange arthroplasty for PJI is challenging, especially when a positive culture at reimplantation is detected. How to best differentiate isolates representing contamination from pathogens is unclear, especially when a new organism is identified that differs from the first stage of microbiology. This review examines the role of intraoperative cultures at the time of reimplantation in the management of implant-related infection.

There were 11 identified studies and one meta-analysis performed in 2019 [145] that examined the association of positive reimplantation cultures with treatment outcomes (Table 3). There were seven reviewed studies that were included in the meta-analysis of 11 studies by Xu et al. [145–151] Of the identified studies, one evaluated hips alone [145], one evaluated knees alone [152], six evaluated both hips and knees [146–149,151,153], two evaluated hips, knees, and shoulders [150,154], and one evaluated hips, knees, and elbow [155]. There were eight studies that confirmed that an antibiotic-free period occurred between resection and completion of antimicrobial therapy and reimplantation [145,147–149,151,152,154,155]. There were five studies that considered positive cultures as a real infection if two or more cultures identified the same organism or if a single culture found the same organism as that detected at first-stage resection [146,147,150,151,153]. There were two studies that considered two or more positive cultures with the same organism as significant [149,154], one study considered growth of more than 20 colony-forming units as significant [148], and three studies considered any positive culture as significant [145,152,155]. Included studies reported a wide range of positive cultures at reimplantation (5.2 to 60%) and those that were considered significant (24 to 100%). Three studies examined the role of spacer sonication cultures in the detection of subclinical infection, with two reporting improved sensitivity with this technique compared to tissue culture alone [147,148,150]. The majority of positive cultures differed from first-stage cultures, suggesting that superinfection is more common than persistence of initial infection. Failure was defined by clinical parameters in 11 studies [145–155], by the need for extended oral antibiotic suppression in two [146,148], and by reimplantation cultures in one study [147].

There were six studies found that positive cultures at reimplantation significantly increased the chance of subsequent failure [145,146,148,150,151,153]. Xu et al. performed both a retrospective study of 117 patients who have hip PJI correlating a positive culture at reimplantation with failure [145] and a meta-analysis of 11 studies that included 141 cases with positive cultures at reimplantation and 784 cases with negative cultures, finding that positive cultures were significantly associated with failure as compared to negative cultures (26.1 versus 6.4%, $P = <0.001$) [145]. Several studies reported an increased risk of failure with a single positive culture [146,151,153]. Conversely, three studies found no correlation between positive cultures at reimplantation and subsequent failure [5,8,11]. Two studies provided descriptive results only, with one finding a greater number of infections in positive culture cases and the other finding the opposite [147,154].

There were eight studies that reported the duration of administered antimicrobial therapy in cases with positive cultures, with most treatment courses ranging from four to 12 weeks [145–147,149,151,153,154] [147,149,151,153,154], but one extending to over a year [155]. As the majority of patients who have positive reimplantation cultures considered significant received antimicrobial therapy, the benefit and optimal treatment duration are not well examined. The meta-analysis by Xu et al. reported as a subgroup analysis that pooled data from five studies found that treatment with at least 6 weeks of antibiotics in cases with positive cultures decreased the risk of subsequent failure [145].

The interpretation of positive cultures at the time of reimplantation remains difficult. Direct comparisons between reviewed studies are limited by variation in study design, identification of cultural significance, definition of failure, and length of follow-up. Nevertheless, while three studies did not significantly correlate positive cultures with failure, six did find a significant association, underscoring the potential relevance of positive findings and the role of antimicrobial therapy. Most studies distinguished relevant culture results from contaminants by the finding of the same organism in multiple samples. This is common in clinical practice and likely to continue as a means to identify higher-risk patients. Other considerations factoring into management include the persistent detection of the organism identified during first-stage surgery, the identification of a virulent organism such as *Staphylococcus aureus* in a single culture, and clinical concern for infection.

Conclusions

Persistent infection as a complication of two-stage exchange arthroplasty for the management of PJI is a serious event, and future work should better define infection at the time of reimplantation. The optimal duration of antimicrobial therapy in cases with positive cultures that are considered significant remains unknown, and the role for treatment beyond four to 6 weeks (with the potential for adverse antibiotic effects) is not well examined.

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The Journal of Arthroplasty 41 (2025) S399–S401

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Hip and Knee

2025 ICM: End-Stage or Intractable Cases

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ARTICLE INFO

Article history:
Available online 27 October 2025

Keywords:
knee arthrodesis
amputation
knee
prosthetic joint infections
intractable

Question 1: Is there a difference in outcome when arthrodesis versus above-the-knee amputation (AKA) is performed in patients who have intractable periprosthetic joint infection (PJI) of the knee?

Recommendation

Both knee arthrodesis and above-knee amputation yield similar results in infection eradication and complications. However, knee arthrodesis may offer a slightly better function overall with a lower mortality rate compared to amputation.

Level of Evidence: Moderate

Delegate Vote: Agree: 84%, Disagree: 8%, Abstain: 8% **(Super Majority, Strong Consensus)**

Rationale

Multiple total knee arthroplasty (TKA) revisions performed for management of periprosthetic joint infection can lead to loss of soft tissue, extreme bone defects, as well as deficiency of the extensor mechanism. If successful reconstruction and/or control of infection using revision TKA may no longer be possible, salvage options, namely knee arthrodesis (KA) or above-the-knee amputation (AKA), are often the only treatment options.

The aim of this systematic review was to assess differences in outcome, if any, between KA and AKA, performed in patients who have intractable periprosthetic joint infection of the knee.

Literature Overview and Potential Limitations

An extensive search of the literature was performed. All relevant publications were screened to determine those eligible for final inclusion. A total of 51 retrospective studies were included, of which 37 studies reported on KA [1–37] and eight on AKA [38–45]. Of these, only six [46–51] directly compared KA to AKA in patients who have failed septic revision knee arthroplasty. The mean weighted age was comparable between KA (67 ± 7.1 years) and AKA (66 ± 9.2).

Fusions were performed using modular prostheses/intramedullary nails [1–27,46–48,51], external fixators [24,28–37], or plate and screw fixation [24,28,51]. Importantly, KA results are mostly mixed between the separate techniques of KA, suggesting that each one should be compared to AKA rather than the umbrella term of KA.

An inherent limitation is the quality of the studies available. All were retrospective case series and case-control studies, often missing detailed data. Moreover, definitions of complications and outcomes differ among studies.

Eradication of Infection

Data regarding infection control after either AKA or KA following septic failure of TKA are heterogeneous and contrasting. Trouillez et al. [48] reported no significant difference in recurring infection between the two groups. In their study, 10% of patients were revised for abnormal wound healing (dehiscence and persistent discharge) after AKA, whereas 21.8% of patients in the arthrodesis group required revision surgery for recurrent infection. Hungerer et al. [47] observed a comparable rate of recurrence of infection (22% after KA versus 35% after AKA). Schnetz et al. [46] observed a reinfection rate of 37% after AKA and 11.5% after KA.

No author associated with this paper has disclosed any potential or pertinent conflicts which may be perceived to have impending conflict with this work. For full disclosure statements refer to 10.1016/j.arth.2025.08.039.

https://doi.org/10.1016/j.arth.2025.08.039
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Similar reinfection rates were reported when comparing different arthrodesis techniques [32–34].

Complications

The literature highlights heterogeneous definitions of complications, leading to variance in reported outcomes. Schnetz et al. [46] reported a similar rate of systemic complications (pneumonia, urinary tract infection, cardiovascular complications) between AKA and KA. Hungerer et al. [47] observed a similar rate of local major complications, which required surgical revision (in 36% after KA and 35% after AKA). Apart from the recurrence of infection, the most frequent complications observed after KA were implant loosening, peri-implant fracture, and pseudoarthrosis/nonunion. In patients requiring AKA, wound healing complications of stumps were the most frequent complication. Complication rates were higher in the case of fusion obtained through an external fixator, including nonunion and pin-site infections.

Functional Outcomes

The literature highlights heterogeneous functional results after AKA and KA. However, a slightly better functional outcome has been reported for KA. The mean weighted short-form-12 (SF-12) scores were slightly higher in the KA group (physical 38.8 and mental 51.3) compared to AKA (physical 31.2 versus 48.4). Chen et al. [51] directly compared AKA to KA, observing different SF-12 results between the two groups. Both the SF-12 physical and mental scores were markedly higher for patients who had fusion versus AKA. However, Hungerer et al. [47] showed no significant difference in SF-12 scores between the procedures. Similarly, the mean weighted SF-36 scores were slightly higher in the KA group (physical 30.9 and mental 61.0) compared to AKA (physical 28.3 and mental 47.0). Interestingly, Chen et al. [51] reported a significantly higher incidence of nonambulatory patients after AKA compared to KA (33.3 versus 5.0%). In addition, some KA techniques are associated with substantial limb-length discrepancy (mean weighted 26.6 mm limb-length discrepancy in the fused knee). Postoperative pain was comparable after either KA or AKA, with a mean visual analog score of 3 in both groups.

Mortality

The selected studies reported a higher mortality rate after AKA (18.9%) compared to KA (14.0%). This was also confirmed by a series that directly compared AKA and KA. Schnetz et al. [46] observed a mortality rate of 13.0% in AKA at six to 12 months post-surgery compared to 1.9% in KA. Hungerer et al. [47] reported that 4% of patients died postoperatively after KA compared to 13% after AKA, with a minimum follow-up interval of 12 months.

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The Journal of Arthroplasty 41 (2025) S402–S406

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Hip and Knee

2025 ICM: Diagnostic Techniques: Histology

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ARTICLE INFO

Article history:
Available online 27 October 2025

Keywords:
periprosthetic joint infection
PJI
histology
diagnosis
total knee arthroplasty
total hip arthroplasty

Question 1: Is there a role for histopathological testing of joint tissue in the diagnosis of periprosthetic joint infection (PJI)?[1]

Response/Recommendation

Histopathological analysis of deep tissue samples can be useful as a confirmatory criterion for diagnosing PJI of the hip and knee. Although frozen sections showed slightly lower sensitivities with similar specificities compared to permanent sections, it can be supported as an intraoperative confirmatory criterion, especially when preoperative results are inconclusive.

Level of Evidence: Strong

Delegate Vote: Agree: 92.5%, Disagree: 4.4%, Abstain: 3.1% (**Total Consensus: Unanimity**)

Rationale

Histopathological analysis of deep-tissue samples is a well-established test method for the intra- and postoperative diagnosis of PJI. Multiple studies have demonstrated a strong correlation between the presence of polymorphonuclear neutrophils in periprosthetic tissue and PJI. Hence, the European Bone and Joint Infection Society (EBJIS) [1] and the Infectious Diseases Society of America (IDSA) [2] defined positive histology as a confirmatory criterion in their PJI definition, while it is a minor criterion in the Musculoskeletal Infection Society (MSIS) definition of 2011 [3] and 2013 [4], and the International Consensus Meeting (ICM) infection definition of 2018 [5].

Permanent Sections

In our systematic review and meta-analysis of 22 studies evaluating permanent sections (formalin fixation and paraffin embedding) in 2,697 patients who had PJI or aseptic failure of total hip or knee arthroplasty [6–27], the pooled sensitivity, specificity, diagnostic odds ratio (DOR), and summarized area under the curve (sAUC) were calculated with 78.7% (95% confidence interval [CI]: 77.1 to 80.3), 96.1% (95% CI: 95.3 to 96.8), 119.1 (95% CI: 59.95 to 236.63), and 0.962 (SE: 0.01), respectively. However, a limitation of most studies is the reference standard they utilized to diagnose PJI. There were 12 studies [8,9,11–15,20–22,26,27] that used institutional criteria, and six [6,7,10,18,19,23] used positive cultures to classify PJI. Only four studies [16,17,24,25] applied standardized infection definitions such as IDSA, MSIS, ICM, or EBJIS. When only considering these four studies (n = 428, PJI = 214 of 428) using standardized criteria, the pooled sensitivity, specificity, DOR, and sAUC were 90.7% (95% CI: 87.5 to 93.2%), 88.8% (95% CI: 85.4 to 91.6%), 98.3 (95% CI: 42.6 to 226.6) and 0.959 (SE: 0.01), respectively. Thus, standardized criteria revealed higher sensitivities but at the cost of specificity. Overall, good diagnostic accuracy was

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to 10.1016/j.arth.2025.08.038.

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https://doi.org/10.1016/j.arth.2025.08.038
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demonstrated regardless of the chosen PJI definition, suggesting that histopathological analysis is a reliable test method for diagnosing PJI and can be recommended as an intraoperative or postoperative confirmatory criterion. Other benefits in revision settings include that a pathologist can not only discriminate between septic and aseptic failure, but can also provide detailed information about other causes of inflammation or implant-related pathologies (particle-associated immunological and inflammatory reactions, prosthesis-related arthrofibrosis, bone pathologies, etc.) [28,29].

A better sensitivity of the permanent section was observed in the knees than in the hips. There were six studies [7,8,10,22,23,26] that analyzed histopathology in only the hips. The pooled sensitivity, specificity, DOR, and sAUC in hips were 69.0% (95% CI: 65.7 to 72.1), 98.9% (95% CI: 98.0 to 99.5), 136.7 (95% CI: 27.4 to 682.3), and 0.966 (SE: 0.03), and in knees 92.5% (95% CI: 87.5 to 95.9), 98.3% (95% CI: 95.0 to 99.6), and 434.9 (95% CI: 1.2 to 157,309.9), respectively. However, only two studies [8,13] investigated the diagnostic utility of histopathology for diagnosing knee PJI alone. Therefore, sAUC could not be calculated for the knees. Given the available results and limited evidence, no definitive conclusion can be drawn concerning the impact of the site of intervention (hips versus knees) on the performance of histopathology.

Frozen Sections

In our meta-analysis of 25 studies assessing frozen sections in 3,137 patients who had PJI or aseptic failure of the hip and knee [17–19,27,30–50], the pooled sensitivity, specificity, DOR, and sAUC were 67.8% (95% CI: 66.1 to 69.4), 94.3% (95% CI: 93.4 to 95.1), 47.1 (95% CI: 27.7 to 80.2), and 0.960 (SE: 0.01), respectively. Of these, 12 studies [18,19,30–32,34–37,40,43,44] used positive cultures, six [27,33,45,47–49] institutional infection criteria, and seven [17,38,39,41,42,46,50] standardized infection definitions (EBJIS, IDSA, MSIS, or ICM) as the gold standard reference. When only considering the seven studies (n = 1,341, PJI = 197 of 1,341) using standardized criteria, the pooled sensitivity, specificity, DOR, and sAUC showed only marginal differences compared to the overall meta-analysis on frozen sections calculated with 66.9% (95% CI: 64.3 to 69.4), 95.5% (95% CI: 94.2 to 96.5), 69.0 (95% CI: 32.8 to 145.4) and 0.953 (SE: 0.02), respectively.

Although frozen sections demonstrated slightly lower sensitivity with similar specificity compared to permanent sections, their relatively high accuracy and quick turnaround make them a reliable test method for diagnosing PJI; therefore, they can be endorsed as a confirmatory criterion. In a study of 101 revision hip or knee arthroplasties, the utilization of frozen section analysis demonstrated a capability to identify 81% of preoperatively inconclusive cases that ultimately received a definitive septic diagnosis based on intraoperative findings [46]. Therefore, frozen sections can help surgeons during the intraoperative decision-making process, especially in unclear preoperative cases. Notably, frozen sections showed a similar or even superior diagnostic value compared to other intraoperatively available tests [17,38,46].

In hips (13 studies), the pooled sensitivity, specificity, DOR, and sAUC were calculated with 64.2% (95% CI: 61.8 to 66.6), 93.6% (95% CI: 92.3 to 94.8), 36.1 (95% CI: 14.9 to 87.7), and 0.963 (SE 0.03). Only four studies analyzed frozen sections for diagnosing PJI after total knee arthroplasty. The pooled sensitivity, specificity, DOR, and sAUC of these four knee studies were 66.4% (95% CI: 62.5 to 70.2), 96.6% (95% CI: 94.9 to 97.9), 82.1 (21.6 to 312.3), and 0.983 (SE: 0.02). Based on these results, a similar performance of frozen sections in hips and knees can be assumed.

Overall, histopathological analysis of deep tissue samples is an inexpensive and accurate test method for diagnosing PJI. Furthermore, the pathologist cannot only discriminate between septic and aseptic complications, but also provide the surgeon with detailed information about other causes of failure, such as adverse tissue local reaction, gout, inflammatory diseases, arthrofibrosis, and bone pathology, suggesting clear advantages compared to other test methods. Therefore, histology can be firmly integrated into the clinical workup of PJI.

Question 2: What thresholds for neutrophils in histopathological sections should we use in the diagnosis of periprosthetic joint infections (PJIs)?[2]

Response/Recommendation

The optimal threshold of polymorphonuclear neutrophils (PMN) in histopathological sections for diagnosing periprosthetic joint infections (PJI) is still a matter of debate. A threshold of ≥ five PMN/high-power field [HPF] in each of at least five HPFs is recommended to differentiate infected from aseptic hip and knee cases in frozen and permanent histopathological sections of deep tissue samples.

Level of Evidence: Moderate

Delegate Vote: Agree: 94.2%, Disagree: 4.5%, Abstain: 1.3% (**Total Consensus: Unanimity**)

Rationale

Thresholds of either five PMN/HPF or 10 PMN/HPF in each of five HPFs were recommended in the International Consensus Meeting (ICM) guideline of 2018 for diagnosing PJI [51], and a threshold of ≥ five PMN/HPF in each of five HPFs in the European Bone and Joint Infection Society (EBJIS) definition of PJI [52]. The three most commonly used thresholds in the literature are ≥ 23 PMN/10 HPF, ≥ five PMN/HPF, and ≥ 10 PMN/HPF. However, high-quality studies on the optimal threshold for PMN in histopathological sections for diagnosing hip and knee PJI are scarce.

To address the posed question, we conducted a comprehensive systematic review. Relevant studies were identified using the Medical Subject Headings terms developed by librarians. After screening the initial studies, articles that met the inclusion criteria were reviewed in detail, and data were extracted.

Permanent Sections

In our meta-analysis of 16 studies (2,308 patients undergoing revision surgery following total hip or knee arthroplasty) reporting the used threshold for permanent sections of intraoperatively collected samples [53–68], five studies [53–57] presented the diagnostic value of histopathological analysis when using the threshold of ≥ 23 PMN/10 HPF, 11 studies [57–67] when applying the threshold of ≥ five PMN/HPF, and four studies [57,58,67,68] when using the threshold of ≥ 10 PMN/HPF. The threshold of ≥ 23 PMN/10 HPF showed a pooled sensitivity, specificity, diagnostic odds ratio, and summarized area under the curve (sAUC) of 80.7% (95% confidence interval (CI): 78.0 to 83.3), 94.9% (95% CI: 93.3 to 96.3), 162.4 (95% CI: 36.4 to 725.7), and 0.957 (SE 0.02). When considering the threshold of ≥ five PMN/HPF, they were 82.0% (95% CI: 80.0 to 84.0), 94.7% (95% CI: 93.5 to 95.8), 133.5 (95% CI: 41.6 to 428.6), and 0.963 (SE: 0.02); and 88.8% (95% CI: 84.6 to 92.2), 89.2% (95% CI: 85.0 to 92.5), 67.1 (95% CI: 39.0 to 115.3), and 0.950 (SE: 0.01) when the threshold of ≥ 10 PMN/HPF was used. In this meta-analysis, a threshold of ≥ five PMN/HPF showed the best performance. However, several limitations need to be highlighted: the majority of studies (13 of 16) did not use a standardized infection definition. The gold standard reference in five studies [58,59,64,66,68] was a positive culture, and in eight studies [53–56,60,61,65,67], institutional criteria (including clinical features, microbiology, and/or histology). In only three studies

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[57,62,63], a standardized infection definition was applied. Many studies included histology in their infection definition, leading to an incorporation bias. Furthermore, no uniform histopathological investigation (e.g., different numbers of HPFs) was performed, making a comparison between studies difficult. These limitations may also explain the unusually higher pooled sensitivity and lower pooled specificity in studies utilizing the higher threshold of ≥ 10 PMN/HPF compared to studies using the threshold of ≥ five PMN/HPF, indicating low reliability of the available studies.

Only one study investigated different thresholds with standardized infection definitions and histopathological analyses [57]. In this retrospective study of 119 patients undergoing revision hip or knee arthroplasty, a threshold of ≥ five PMN/HPF was recommended. Nevertheless, the effective threshold depended importantly on the chosen infection definition, with more PJI cases identified when using the EBJIS definition. When the ICM or Infectious Diseases Society of America definitions were used as a reference for PJI, ≥ 10 PMN/HPF showed a better diagnostic value compared to ≥ five PMN/HPF. However, when applying the EBJIS definition, no difference was observed between the latter two thresholds (AUC 0.89 versus 0.90; $P = 0.916$), but higher sensitivities were seen with a threshold of ≥ five PMN/HPF (93 versus 86%) at the cost of lower specificity (84 versus 93%). Due to the better sensitivity when applying the more sensitive EBJIS infection definition, the threshold of ≥ five PMN/HPF was recommended to ensure accurate infection diagnosis. In addition, the threshold of ≥ 23 PMN/10HPF showed a significantly poorer outcome in comparison to ≥ five PMN/HPF and ≥ 10 PMN/HPF regardless of the used infection definition (EBJIS, Infectious Diseases Society of America , ICM 2018) [57].

Frozen Sections

In our systematic review and meta-analysis of 22 studies (2,904 patients who had septic or aseptic failure after a total hip or knee arthroplasty) describing the used threshold for frozen sections [63,64,67–86], three studies [69–71] reported the diagnostic value of histopathological analysis when using the threshold of ≥ 23 PMN/10 HPF, 16 [63,64,67,72–84] when applying the threshold of ≥ five PMN/HPF, and six studies [64,67,68,83,85,86] when using the threshold of ≥ 10 PMN/HPF. The threshold of ≥ 23 PMN/10 HPF showed a pooled sensitivity, specificity, diagnostic odds ratio, and summarized area under the curve (sAUC) of 81.0% (95% CI: 74.9 to 86.1), 95.6% (95% CI: 91.8 to 98.0), 83.3 (95% CI: 19.7 to 352.9), and 0.940 (SE 0.12). When using the threshold of ≥ five PMN/HPF, performance values were 69.4% (95% CI: 67.5 to 71.3), 94.4% (95% CI: 93.3 to 95.3), 56.2 (95% CI: 30.4 to 103.7), and 0.964 (SE: 0.01); and when applying the threshold of ≥ 10 PMN/HPF, 62.0% (95% CI: 58.3 to 65.6), 96.1% (95% CI: 94.4 to 97.4), 50.7 (95% CI: 20.4 to 126.1), and 0.892 (SE: 0.05), respectively. However, similar limitations were observed in these studies: There was no standardized infection definition used in 15 studies (only positive culture: n = 10, institutional criteria: n = 5) [64,67,68,71–74,76,79–83,85,86]. Many studies included histology in their infection definition, and no uniform histopathological analysis (e.g., different numbers of HPFs) was performed among studies. It needs to be highlighted that only three studies with overall 205 patients, including 60 PJIs, investigated the threshold of ≥ 23 PMN/10 HPF, while 16 studies with 2,256 patients (378 PJIs) evaluated the threshold of ≥ five PMN/HPF, and seven studies with 697 patients (133 PJIs) evaluated the threshold of ≥ 10 PMN/HPF. All these drawbacks make a comparison between studies difficult.

High accuracies are reported in the literature, and despite the listed limitations, a threshold of ≥ five PMN/HPF in each of at least five HPFs can be recommended to differentiate septic from aseptic failure in frozen and permanent histopathological sections of deep tissue samples. At least five HPFs should be investigated and the mean PMN count calculated [57]. However, it needs to be emphasized that a threshold of ≥ 10 PMN/HPF can be used as well, but with a risk of missing some (low-grade) PJIs. In addition, the presence of only one to five PMN/HPF cannot exclude infection. In these cases, a careful interpretation in conjunction with other diagnostic test methods within the infection definition is recommended.

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The Journal of Arthroplasty 41 (2025) S407–S411

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Hip and Knee

2025 ICM: Diagnostic Techniques: Molecular Tests

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Question 1: Is there a role for the use of molecular techniques in the isolation of infective organisms causing periprosthetic joint infection?[1]

Response/Recommendation

Yes. Molecular techniques are promising adjuncts to conventional methods for diagnosing periprosthetic joint infection (PJI) and isolating infective organisms. These techniques may be of particular benefit in culture-negative cases, when rapid pathogen identification is critical, when rare pathogens are suspected, or in high-risk patients, such as those who have a history of recurrent PJI.

Level of Evidence: Moderate

Delegate Vote: Agree 92.5%, Disagree 3.8%, Abstain 3.8% (Total consensus, Unanimity)

Rationale

Of the many challenges associated with treating a periprosthetic joint infection (PJI), one is making a timely and accurate diagnosis while also identifying the causative pathogen. The use of microbial culture remains the gold standard for pathogen identification when treating a patient with a PJI. However, over the last several years, numerous studies have evaluated the diagnostic efficacy of molecular techniques, such as next-generation sequencing (NGS) and polymerase chain reaction (PCR). Consequently, a comprehensive literature search using PubMed and Embase was conducted on October 15th, 2024. A total of 642 articles were identified. Following initial screening and after excluding duplicates and abstract review, 267 articles entered the full-text screening phase. At this stage, two independent reviewers screened the full text of the included studies, and ultimately, 50 articles were selected for data extraction and evaluation.

In a study by Huang et al., NGS was utilized to detect pathogens from the synovial fluid of patients undergoing revision hip and knee arthroplasty for PJI. The authors found the sensitivity (95.9%) of NGS to be significantly higher than microbial culture (79.6%). In addition, they reported that NGS identified pathogens in all 10 of their culture-negative PJI cases, as well as 15 additional pathogens from five of their culture-positive cases. However, they did note that seven pathogens identified by cultures were missed by NGS, and specificity was similar compared to culture (95.2 and 95.2%, respectively) [1]. Shi et al. also found NGS to have a higher sensitivity (89.1 versus 67.4%) and the same specificity (94.7 versus 94.7%) when compared to microbial culture, while also identifying 17 potential pathogens in 14 culture-negative PJI cases [2].

The utilization of NGS for pathogen identification in culture-negative PJIs was further investigated in a prospective multi-institutional study by Goswami et al. In their cohort of 85 culture-negative patients, NGS identified opportunistic pathogens in 65.9% of cases. In addition, they found that NGS revealed a polymicrobial infection in 91.1% of culture-negative PJI cases [3]. Mei et al. investigated the clinical value of NGS in the diagnosis of polymicrobial PJI and found this technique to have greater sensitivity (85.7 versus 57.1%), but lower specificity (60 versus 100%) and accuracy (65.2 versus 91.3%) when compared to conventional culture [4]. Additional studies have also supported these findings, suggesting that NGS is m ore sensitive than conventional culture, useful for detecting rare and unculturable organisms, beneficial for culture-negative PJIs, and can reduce the turnaround time needed to identify a pathogen [5–22].

In contrast to the above findings, a retrospective study by Kildow et al. found the culture to be more sensitive (76.9%) and specific (95.3%) than NGS (sensitivity: 60.9%; specificity: 89.9%) [23]. Similarly, Kildow et al. sought to evaluate the diagnostic accuracy of NGS in patients with antibiotic spacers before reimplantation and found that NGS did not provide sufficient agreement when compared with culture or MusculoSkeletal Infection Society criteria [24].

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.085.

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https://doi.org/10.1016/j.arth.2025.10.085
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The type of sample used to be evaluated by NGS has also become a topic of interest. Tan et al. assessed the diagnostic value of NGS across synovial fluid, prosthetic sonicate fluid, and periprosthetic tissue among patients with PJIs and found the sensitivity (90.7%) and specificity (94.4%) of prosthetic sonicate fluid to be superior for pathogen detection when compared to synovial fluid (sensitivity: 83.7%; specificity: 94.4%) and periprosthetic tissue (sensitivity: 81.4%; specificity: 100%) [25]. These findings support prior work, which has also demonstrated that NGS using sonication fluid can improve the detection rate of pathogenic organisms [26,27]. However, in instances when an adequate sample of sonication fluid is not obtainable, or if the prosthesis is not removed, NGS of periprosthetic tissue has been shown to have a higher sensitivity (95.5%) and specificity (90.91%) than periprosthetic tissue microbial culture (sensitivity: 72.7%; specificity: 77.3%) [28].

Preoperative synovial fluid cultures can help diagnose PJI and guide antimicrobial therapy, although the sensitivity of culture is low when an inadequate sample is obtained. Fang et al. sought to evaluate if NGS could detect bacteria in such instances and found that with a low volume of synovial fluid (one ml), NGS had higher sensitivity (92%) and the same specificity (91.7%) when compared to preoperative synovial fluid culture (sensitivity: 52%; specificity 91.7%) [29]. In another study by Fang et al., they found that the results from preoperative synovial fluid NGS could be used to guide the optimization of intraoperative cultures to increase their sensitivity, further highlighting another potential benefit of NGS in the preoperative period [30].

Zhang et al. evaluated if serologic NGS could provide diagnostic value for the detection of PJI and found that serologic NGS had a higher sensitivity (86%) and specificity (96%) when compared to bacterial culture obtained from drainage fluid (sensitivity: 47%; specificity: 95%) [31].

The effect of antibiotics on the results of NGS has also been investigated. In their series of 52 suspected patients with PJI, Yu et al. reported a higher sensitivity (69.5%) for diagnosis and pathogen detection compared to culture (23.1%) in PJI patients who had received antibiotic treatment within two weeks of sample collection [32]. Similarly, Hao et al. found NGS to have a positivity rate of 90.5% when antibiotics were discontinued more than 14 days before surgery, 96.4% when discontinued between four and 14 days before surgery, and 77.8% when discontinued between zero and three days [33].

Multiple studies have also explored the diagnostic efficacy of PCR. Gardete-Hartmann et al. evaluated a multiplex PCR (mPCR)-based system (BioFire Joint Infection Panel, bioMérieux, France) in patients with unclear conventional microbiological results and reported a sensitivity and specificity of 41.4 and 91.1%, respectively [34]. In addition, Esteban et al. evaluated this same technology and found that although it has 31 targets and eight antimicrobial resistance markers, the system has lower accuracy in detecting PJI in chronic cases due to the absence of relevant targets such as *Staphylococcus epidermidis* and *Cutibacterium acnes* [35]. Malandain et al. compared a different automated mPCR (Unyvero i60, Curetis, Germany) cartridge system to optimized culture or 16S rRNA PCR and found the concordance rate of mPCR with culture to be 58.1% and the concordance rate with 16S rRNA PCR to be 70.1% [36]. Sebastian et al. evaluated 16S rRNA gene PCR of periprosthetic tissue and found it to be more sensitive (86%) than periprosthetic tissue culture (79.4%), while maintaining the same specificity (100%) as culture and also establishing the etiology of PJI in 31% of culture-negative cases [37]. Lausmann et al. investigated the utility of mPCR and found an overall sensitivity of 78.8% and specificity of 100%. In addition, they found mPCR to have a higher accuracy (87.5%) for acute infections when compared to chronic PJI (76.9%) and noted that the results were obtained within five hours (average: one hour), whereas the mean time for cultures was 6.4 days [38]. Fang et al. analyzed RNA-based quantitative polymerase chain reaction (qPCR) and DNA-based qPCR and reported the sensitivity and specificity of RNA-based qPCR to be 73.6 and 100%; the sensitivity and specificity of DNA-based qPCR to be 81.5 and 84.8%; and the sensitivity and specificity of culture to be 65.7 and 100%, while also noting these PCR methods to be beneficial in detecting bacteria after patients received antibiotics [39]. Moshirabadi et al. [40] performed a multicenter study utilizing PCR with the restriction fragment length polymorphism technique and found the sensitivity (97.4%) to be higher than culture (31.6%), with both techniques having 100% specificity.

In contrast to the above studies, some studies have not found PCR to be efficacious [41–43]. Suda et al. found multiplex PCR to have a sensitivity of 30.8% and a specificity of 100%, which differed significantly from conventional methods in their cohort of patients [44]. Mariaux et al. evaluated whether PCR analysis of sonication fluid from bone cement spacers could improve bacterial detection and help predict whether a patient will present with a persistent infection, but were unable to find a benefit [45]. Fink et al. investigated the role of preoperative PCR synovial fluid analysis and reported a sensitivity and specificity of 55.6 and 82%, which was lower than the combined sensitivity (77.8%) and specificity (95.5%) of joint fluid culture and serologic C-reactive protein [46]. However, despite these findings, multiple recent studies supported the use of PCR technologies of variable sensitivity and high specificity; mPCR has been recommended in combination with traditional culture and other molecular diagnostic technologies in certain patient populations in culture-negative scenarios and unclear clinical scenarios [47–56].

In conclusion, the literature supports the use of molecular techniques as adjuncts to conventional methods for the isolation of infective organisms in the setting of PJI. These techniques may have particular utility in culture-negative cases, when rapid pathogen identification is needed, when rare pathogens are suspected, or in patients with a high probability of infection, such as those with a history of recurrent PJI.

Question 2: What is the diagnostic relevance of molecular techniques for polymicrobial periprosthetic joint infections?[2]

Response/Recommendation

Molecular diagnostics can enhance the diagnosis of polymicrobial periprosthetic joint infections (PJI). Multiplex PCR and NGS are the two most extensively studied molecular diagnostic technologies in recent years. The average sensitivity of molecular diagnostics for diagnosing polymicrobial PJI is higher than that of conventional microbial culture; however, the average specificity is lower compared to culture. A combination of culture and molecular diagnostics is recommended when polymicrobial PJI is suspected, as originally diagnosing and treating polymicrobial PJIs as monomicrobial is associated with worse outcomes.

Level of Evidence: Limited

Delegates Vote: Agree 82.6%; Disagree 13.1%; Abstain 4.4%

Rationale

We conducted a comprehensive literature review across two databases (PubMed and Cochrane Library), utilizing the MeSH terms developed by our librarians. After screening the potentially

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eligible studies, we included 1,315 studies for full review and data extraction, ultimately selecting 75.

Periprosthetic joint infections are considered polymicrobial when at least two different organisms are isolated from synovial fluid or intraoperative tissue cultures [57].

Polymicrobial PJIs account for up to 46% of all PJIs [58,59]. Historically, polymicrobial PJIs have demonstrated a lower success rate than monomicrobial PJIs due to the increased morbidity, costs, and complications typically associated with modern polymicrobial PJI treatments [60]. Understanding the microbiological profile of the causative organisms remains central to the treatment strategy, as several species of pathogens are notoriously difficult to eradicate, as they reside in a biofilm rather than in a more metabolically active planktonic form.

There is no consensus on the typical microorganisms responsible for polymicrobial PJIs. Yapar et al. [61] reported an average of 2.4 microorganisms in their series of polymicrobial PJIs. In the same study, those authors identified *Staphylococcus epidermidis* and *Cutibacterium acnes* (well-known low-virulence bacteria) as the leading pathogens in polymicrobial PJIs. In contrast, Wouthuyzen-Bakker et al. [62], Löwik et al. [63], and Li et al. [57] suggested that additional organisms with relatively low or variable virulence (e.g., *Enterococcus spp*., anaerobes) or high-virulence organisms (e.g., *Staphylococcus aureus*, gram-negative bacilli) were more often responsible for polymicrobial PJIs.

To counteract the high negativity rate associated with culture (ranging from 0 to 41% in some reports) [64,65], molecular diagnostic technologies (both DNA-based and RNA-based) have recently been introduced to the market for the rapid identification of infecting microorganisms [66] and their associated antibiotic resistance [67]. Among these, mPCR [68] and NGS [69], including metagenomic NGS (mNGS) [70,71,72], have demonstrated the highest accuracy in identifying polymicrobial PJIs.

The utility of broad-range PCR with Sanger sequencing was lower for polymicrobial infections compared to standard culture or NGS techniques, as the presence of multiple organisms resulted in overlapping reads that were difficult to interpret [73]. The sensitivity of multiplex PCR in diagnosing monomicrobial PJI ranged between 33 and 85% [74,75], while its specificity ranged between 91 and 100% [76,77]. Only a few authors [75,76] supported the diagnostic role of mPCR in polymicrobial PJIs. Lausmann et al. [75] identified additional microorganisms in 12.5% of their intraoperative samples from infected joints analyzed using a new generation mPCR system. Gardete-Hartmann [76] recommended mPCR as an intraoperative test during a 2-stage revision to rule out an incomplete initial diagnosis of complex polymicrobial infection that was not initially captured by culture.

Several authors have compared standard microbial cultures with NGS in systematic reviews and meta-analyses. Kato et al. [78] examined the detection rates of pathogens between NGS and microbial cultures using synovial fluid samples taken from replaced joints; the detection rate for NGS was significantly higher than that for culture (odds ratio: 4.52). Different findings emerged from Kildow et al. [79], who analyzed samples from 116 patients suspected of having PJI. They demonstrated that NGS did not yield superior sensitivity or specificity results compared to traditional culture methods. Hantouly et al. [80], in a systematic review and meta-analysis, compared the sensitivity and accuracy of NGS and

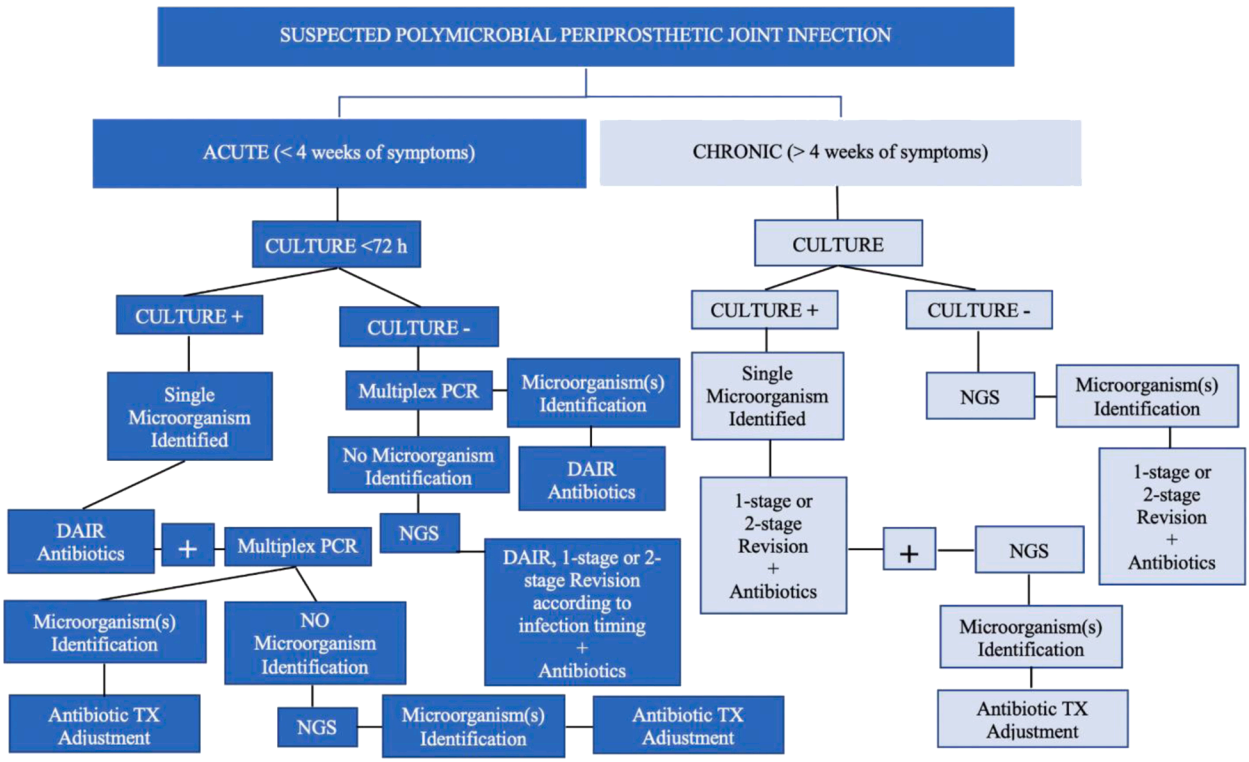

Figure 1. Diagnostic flowchart for suspected polymicrobial PJI when molecular techniques (multiplex PCR; NGS) are available at the treating institution. The distinction between acute and chronic PJI has been made according to the 2018 ICM criteria [84]. Acute PJI: Debridement, antibiotics, and retention of the implant (DAIR) are recommended only if symptoms persist for less than 4 weeks with the possible identification of the microorganism; contraindications to DAIR also include the presence of a sinus tract, difficult-to-treat (DTT) infections, loosening of the implant, and antibiotic availability [85,86]. In culture-negative PJI with the presence of a sinus tract, the use of molecular diagnostics must be supported by future research. Chronic PJI: Contraindications to a 1-stage revision also include the presence of sepsis, an infection caused by drug-resistant bacteria or DTT, the presence of a sinus tract, severe soft-tissue deficiency over the joint, and a history of multiple revisions [60,87,88]. PCR, polymerase chain reaction; PJI, periprosthetic joint infection; NGS, next-generation sequencing.

standard culture: data from 341 patients (seven studies) were reviewed, revealing an overall pooled sensitivity of NGS at 94%, while the pooled specificity was 89%; conversely, the pooled sensitivity of culture was 70%, and the specificity was 94%. In the same study [80], the accuracy of NGS and culture was reported as 91.9 and 80.5%, respectively. Unfortunately, most of these studies [74–76] did not assess the performance of molecular diagnostics in general or NGS specifically for diagnosing polymicrobial PJIs.

Mei et al. [72], in a mid-sized cohort study, were among the few to report that mNGS exhibited high sensitivity (85.7%), but moderate specificity (60%) and accuracy (65.2%) for the diagnosis of polymicrobial PJIs. Interestingly, in that study [72], the specificity, positive predictive value, and diagnostic accuracy of conventional microbial culture for diagnosing polymicrobial PJI were higher than those of mNGS; in contrast, the sensitivity and negative predictive value of conventional microbial culture for diagnosing polymicrobial PJI were lower than those of mNGS. Goswami et al. [81] utilized NGS in a series of culture-negative PJIs: NGS was able to identify a pathogen in 65.9% of the cases. In the same study [81], NGS revealed a polymicrobial PJI in 91% of culture-negative PJIs.

In summary, it is recommended that different testing methods (including standard culture and molecular diagnostics) be combined when polymicrobial PJI is suspected. In clinical practice, the diagnosis of polymicrobial PJI made solely by standard culture may be affected by the concurrent use of antibiotics [82] and the competitive inhibition effects of multiple bacteria during culture [83].

Figure 1 presents a diagnostic flowchart for the suspicion of polymicrobial periprosthetic joint infection (PJI).

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The Journal of Arthroplasty 41 (2025) S412–S422

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Hip and Knee

2025 ICM: Diagnostic Techniques—Serological and Point-Of-Care

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Question 1: Is there a utility for point-of-care tests for diagnosing periprosthetic joint infections?[1]

Response/Recommendation

Yes. Point-of-care (POC) tests can be very useful either definitively or as screening tools for the diagnosis of periprosthetic joint infections (PJIs).

Level of Evidence: III

Delegate Vote: Agree: 80%, Disagree: 12.1%, Abstain: 7.9% (Super Majority, Strong Consensus)

Rationale

Recently, many different synovial fluid biomarkers have been explored for diagnosing PJI. Several of these biomarkers can be determined with different cassette or strip POC tests. The minimal cost per test, wide availability, and immediate results without the involvement of a laboratory during outpatient visits or intraoperatively are the greatest advantages of these POC tests. To date, relatively few POC tests specific to markers useful for diagnosing PJI have been investigated.

This systematic review was conducted independently by two researchers utilizing the PubMed/Medline and Scopus databases. The MeSH terms employed were focused on POC tests and the diagnosis of chronic PJI, resulting in 58 original studies that have been included in this review. Of these, 23 studies concerned leukocyte esterase (LE) [1–23], 21 alpha defensin (AD) [1–3,24–41], 11 calprotectin (CLP) [5,42–51], one D-lactate [52], one interleukin-6 (IL-6) [53], and one C-reactive protein (CRP) [54]. A total of four of these studies investigated two different biomarkers assayed using POC tests. The results are summarized in Table 1.

Leukocyte esterase

The LE strip test is an inexpensive POC method for diagnosing chronic PJI. According to the International Consensus Meeting 2018 (ICM 2018) criteria [55], "-" and "+" are considered negative results, and "++" (250 leu/mL) and "+++" are considered positive. However, it is important to note that the cut-off value "++" can correspond to 125 or 250 leu/mL, depending on the manufacturer of the strips, and this can influence the results [14,52]. The sensitivity reportedly ranges from 66 to 100% and the specificity from 80 to 100%, depending on several factors and conditions associated with testing. The disadvantages of this test are the subjective interpretation of the result, as well as the inability to read the result when the synovial fluid sample is contaminated by blood. To remove any blood, the sample can undergo centrifugation; however, Li et al. [10] revealed that this also has an effect on the accuracy of the LE strip test. Centrifugation resulted in a lighter color of the LE pad, with decreased sensitivity and increased specificity of the test. Similarly, Zheng et al. observed that the results are affected by centrifugation and also by the delay time before reading [22]. They recommend reading the result five minutes before centrifugation or after 10 minutes if centrifugation was done.

Alpha defensin

Alpha defensin is a small peptide mainly released from activated neutrophils in response to the presence of a pathogen. This marker is considered useful for diagnosing PJI [56]. However, the test can be done either as a laboratory test or, recently, as a POC test. The majority of the literature on the usefulness of AD relates to the test being performed in a specialized laboratory. The performance of the POC test has been variable [57]. The latter and the

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.078.

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https://doi.org/10.1016/j.arth.2025.10.078
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Table 1
Summary of the Results Collected From the Analyzed Studies According to the Different Biomarkers Included in This Review.

POC Test	Cut-off Value	AUC Range	Sensitivity Range (%)	Specificity Range (%)	PPV Range (%)	NPV Range (%)
LE [1–23]	≥++ (125 to 250) leu/uL	0.701 to 0.914	92 (66 to 100)	93 (72.4 to 100)	86 (61.8 to 100)	96% (79 to 100)
AD [1–3,24–41]	"–"— negative "+"—positive	0.72 to 0.938	85 (46 to 100)	96 (82.4 to 100)	91 (55 to 100)	92 (78.6 to 100)
CLP [5,42–51]	≥14 to 85.5 (mg/L)	0.71 to 0.996	92 (60 to 100)	84 (61 to 100)	81 (40 to 100)	98 (78 to 100)
DLac [52]	≥22.5 mg/L	0.917	83	100	100	91
IL6 [53]	≥10,000 pg/mL (upper limit)	N/A	100	100	100	100
CRP [54]	≥8 (mg/L)	0.94	90	90.8	85.1	94.5

Results are presented as medians (range).
AUC, area under curve; LE, leukocyte esterase; AD, alpha defensin; CLP, calprotectin; DLac, D-lactate; CRP, C-reactive protein; IL-6, interleukin-6; PPV, positive predictive value, NPV, negative predictive value.

relatively high price are strong disadvantages that limit its use in routine clinical practice. The ICM 2018 and the European Bone and Joint Infection Society (EBJIS) 2021 PJI definitions both include AD testing as one of the criteria [55,58]. AD can be measured in synovial fluid either quantitatively with enzyme-linked immunosorbent assay (ELISA) methods or with a qualitative lateral-flow test (Synovasure) [59]. In a recent meta-analysis, Balato et al. [60] identified no significant differences in diagnostic accuracy between laboratory-based and lateral-flow tests. However, for laboratory-based tests, pooled sensitivity and specificity were higher (97 and 96%, respectively) than for lateral-flow tests (83 and 94%, respectively). In the studies included in this review, the sensitivity and specificity of commercially available POC AD tests ranged from 46 to 100% and 82.4 to 100%, respectively. These results are supported by another meta-analysis [57] and are considered comparable to LE strip tests [61].

Calprotectin

Calprotectin is a heterodimer complex produced and stored in granulocytes and monocytes and released into body fluids as a response to inflammation or infection. Recent studies have emphasized the promising role of this biomarker for diagnosing PJI. The CLP can be measured in synovial fluid with the use of both laboratory-based and POC tests [23,62]. Currently, one commercially available CLP POC test is available and dedicated to the diagnosis of PJIs (Lyfstone Calprotectin) [44–49]. However, several studies have investigated different CLP tests as an off-label use on synovial fluid samples [5,42,43,46,50,51]. For the dedicated CLP test, sensitivity ranges from 60 to 98.2%, and specificity from 61 to 100%. Warren et al. [45] evaluated how diagnostic standards influence test accuracy, and the best performance was observed by applying the ICM 2018 criteria. Other CLP tests are designed mainly for use on fecal samples, and when used off-label on synovial fluid samples, the sensitivity and specificity varied from 86.7 to 100% and 79 to 95%, respectively. Despite the reported efficacy of off-label tests in diagnosing PJI, it is important to note that these tests are validated for solid rather than liquid samples; therefore, unit conversion from μg/g to mg/L is necessary [43].

D-Lactate

Unlike the other laboratory biomarkers used for diagnosing PJI, which are all focused on human inflammatory proteins, D-lactate is instead a molecule produced exclusively by bacteria. Thus, the potential advantage of this pathogen-specific marker is that it should not cause false-positive results in patients who have chronic inflammatory diseases (such as rheumatoid arthritis). For diagnosing PJI, this biomarker was initially investigated with the use of standard laboratory methods [63]. However, in one study, the utility of a semiquantitative colorimetric POC D-lactate strip test was evaluated [52]; when using 22.5 mg/L as the cut-off, sensitivity was 83% and specificity was 100%.

Interleukin-6

Wimmer et al. [53] investigated the IL-6 lateral flow immunoassay (Milenia QuickLine, Gießen, Germany) for synovial fluid samples. In their study, 14 patients were diagnosed as aseptic, and in six cases, PJI was recognized according to the Infectious Disease Society of America (IDSA) criteria. There were no false-positive or false-negative results, and therefore, the sensitivity and specificity, PPV, and NPV were all 100%. In the aseptic group, IL-6 measured via the POC method was 410 pg/mL and was lower than determined by the reference laboratory method (1,219 pg/mL). In the PJI group, the laboratory method revealed a 57,920 pg/mL concentration of IL-6; for the POC test, the upper limit of detection was 10,000 pg/mL, and all patients who had PJI had results above this value.

C-Reactive protein

Only one study examined the accuracy of alternative semiquantitative POC for CRP, evaluating four versions with different cut-off values used off-label on synovial fluid samples, in comparison with laboratory methods [54]. The highest accuracy was demonstrated with the cassette test using a minimum threshold of ≥ eight mg/L. For this particular POC test, sensitivity and specificity were 90 and 90.8%, respectively. Wide availability, low price, and the possibility to perform measurements of CRP using synovial fluid samples contaminated by blood are practical advantages that potentially make these tests most useful in clinical practice.

Conclusions

The POC tests are considered a very useful tool for diagnosing PJIs. While much is dependent upon which specific test is detecting which particular biomarker, each of them has advantages and disadvantages that must be considered. Nevertheless, the generally excellent diagnostic performance of POC tests, comparable with most laboratory methods, encourages their routine use in clinical practice. However, before their routine clinical application, proper validation is mandatory, especially for those used off-label. Moreover, the limitations of individual studies in this review, such as the small groups of included patients, off-label and inconsistent use of the tests, different diagnostic standards, and heterogeneous cohorts, should be particularly noted before analyzing the results. This review confirms POC tests are promising tools with the potential to improve the diagnostic process for PJIs. Further research into their utility and efficacy, while also detecting other biomarkers or those evaluating new tests, including molecular-based (proteomic and genomic), is clearly warranted.

Question 2: Is there a role for antibody testing for microorganisms in the diagnosis of periprosthetic joint infection?[2]

Response/Recommendation

Antibody testing for microorganisms is a potential adjunct for the diagnosis of a PJI. More studies are needed to determine the most appropriate microbial targets for antibody testing and to evaluate the clinical performance of this approach.

Level of Evidence: Moderate

Delegate Vote: Agree: 86.2%, Disagree: 11.7%, Abstain: 2.2% (Super Majority, Strong Consensus)

Rationale

Accurate and early diagnosis of prosthetic joint infection (PJI) is of paramount importance in establishing a management plan for antimicrobial therapy and revision surgery. However, the diagnosis of PJI remains a major clinical challenge, primarily due to the limitations of traditional diagnostic tools, such as microbiological cultures, cell numbers in joint aspirate, imaging, histology, and inflammatory markers (erythrocyte sedimentation rate, ESR; CRP), which can yield inconclusive results, especially in chronic, low-grade, or polymicrobial infections, and are subject to limitations due to specimen collection, low bacterial burden, and prior antibiotic treatment.

Antibody testing for microorganisms in PJI has been explored in recent years for its ability to detect pathogen-specific antibodies, potentially providing a noninvasive diagnostic option. Such a serodiagnostic test should ideally have high specificity to distinguish PJI from aseptic conditions, such as mechanical loosening or aseptic inflammation, and to differentiate between microbial contamination and infection. In addition, it should have a high sensitivity to be able to detect low-grade infections and culture-negative cases. Ideally, it would allow us to monitor secondary bacterial invasion during treatment, indicate the optimal timing of reimplantation, and ultimately guide targeted antimicrobial therapy.

To investigate the potential role of antibody testing for microorganisms and its efficacy in the diagnosis of PJI, a systematic review was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Using the appropriate MeSH terms developed by librarians from Thomas Jefferson University (Philadelphia, Pennsylvania, USA), we conducted a search in PubMed and Embase, which retrieved 873 records (Figure 1). Following the removal of 121 duplicates, the titles and abstracts of 752 records were screened, of which 26 studies met our criteria for full-text review. After excluding eight studies due to wrong publication type (e.g., case report, review, commentary), wrong diagnostic method, or article retraction, data were finally extracted from 18 key studies investigating the sensitivity, specificity, clinical relevance, and diagnostic potential of antibody testing for microorganisms in PJI diagnosis.

Initially, studies evaluated the potential of serological assays using single bacterial antigens for the diagnosis of PJI. Examples were exocellular carbohydrate antigens [64] and poly-N-acetyl-ß-(1,6)-glucosamine [65] from *Staphylococcus epidermidis*, staphylococcal slime polysaccharide antigens [66] and exocellular glycolipid antigen [67] from *S. aureus*, and streptolysin O from *Streptococcus pyogenes* [68]. Using conventional ELISA tests, these studies demonstrated the value of this approach for the diagnosis of PJI and other orthopaedic infections caused by staphylococci and streptococci, respectively.

Including complex protein mixtures led to increased sensitivity of the assay. Using the ELISA method, Wang et al. [69] found that sera from infected guinea pigs and patients who have implant-associated infections had higher levels of immunoglobulin G (IgG) antibodies to extracellular proteins from staphylococcal biofilms than controls. Another study investigated antibody production against several *S. aureus* biofilm-upregulated antigens (SAOCOL0486, glucosaminidase, and SACOL0688) for the detection of chronic *S. aureus* infection using both ELISA and lateral flow assay (LFA) in sera from rabbits with *S. aureus*–mediated osteomyelitis and in synovial fluid from humans who have PJI [70]. The authors demonstrated the clinical diagnostic utility of the SACOL0688 antigen for the diagnosis of *S. aureus* infection with high specificity (100%) and sensitivity (100, 91%) using LFA and ELISA, respectively [70].

Recent advances in the field of infection immunology led to the replacement of conventional ELISA with bead-based multiplex immunoassays based on the Luminex technology, providing a high-throughput platform for studying infection processes. In their 2015 study, Nishitani et al. characterized the antibody response in patients who have *S. aureus* culture-confirmed deep musculoskeletal infections against 14 selected *S. aureus* antigens (Gmd, Amd, SrtA, IsdA, IsdB, IsdH, ClfA, ClfB, FnbpA, coagulase, Hla, SCIN, CHIPS, and Efb) [71]. Using multivariable logistic regression analysis, they combined the IgG titers against all 14 antigens and determined a sensitivity of 80.0% and specificity of 92.5% for detecting patients who have an infection.

Using a similar panel of eight staphylococcal antigens (IsdA, IsdB, IsdH, SCIN, CHIPS, Hla, and the Atl subunits Amd and Gmd), Muthukrishnan et al. [72] found that higher serum antibody levels specific for Amd, Gmd, Hla, SCIN, CHIPS, and IsdH at the time of diagnosis could predict a better outcome of the orthopaedic infection. Interestingly, in another study looking at antibody levels to the same antigens up to 12 weeks after primary total knee arthroplasty (TKA), the authors observed a reduction in anti-staphylococcal antibodies on postoperative day one, which they attributed to blood loss from surgery and hemodilution with intravenous fluid. According to the authors, this observed reduction in humoral immunity may explain early postoperative infections [73].

In a further study, the authors utilized a bioinformatic approach, employing antibodies derived from newly activated, pathogen-specific plasmablasts in human blood (medium enriched for newly synthesized antibodies, MENSAs) to identify six functionally distinct *S. aureus* antigens (IsdB, IsdH, Gmd, Amd, SCIN, and Hla) that can be used as diagnostic biomarkers for *S. aureus* musculoskeletal infections, exhibiting high potential for discriminating between culture-confirmed *S. aureus*–infected patients and healthy controls [74]. Furthermore, the MENSA approach has been shown to have high diagnostic potential for monomicrobial *S. aureus* and *Streptococcus agalactiae* orthopaedic infections [75].

In 2016, Marmor et al. [13] designed a panel including 16 recombinant antigens from different microorganisms commonly associated with PJI, including *S. aureus*, *S. epidermidis*, *S. lugdunensis*, *Streptococcus agalactiae*, and *Cutibacterium acnes*. Utilizing a comparative immunoproteomic approach, the immunoassay demonstrated satisfactory performance, exhibiting a sensitivity of 72.3% and a specificity of 80.7% for detecting staphylococcal infections. Interestingly, the sensitivity increased for staphylococcal infections that occurred more than three months following arthroplasty and among patients exhibiting elevated ESR or CRP levels [76,77].

[2] These authors contributed to Question 2: Dina Raafat, Janosch Schoon, Majd Tarabichi, Jason M Jennings, Kaisa Huotari, Yasuhiro Homma, Vittorio Bellotti, Marjan Wouthuyzen-Bakker

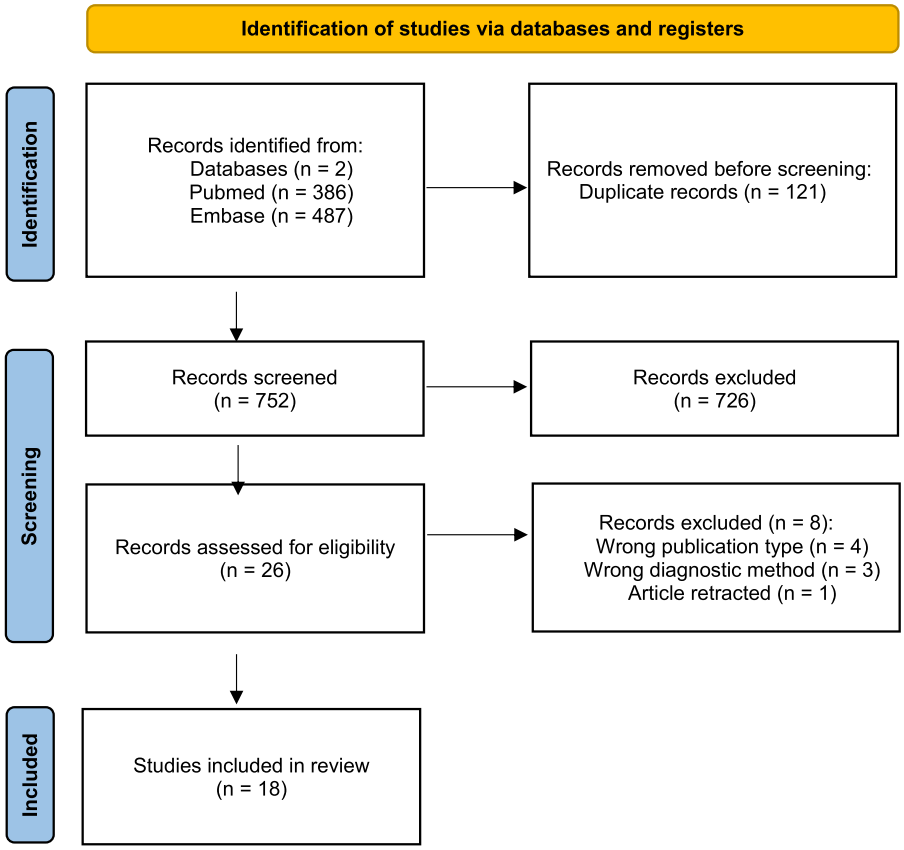

Figure 1. PRISMA flow chart for the systematic review process*. * Page MJ, et al. BMJ 2021; 372:n71. https://doi.org/10.1136/bmj.n71.

Since this multiplex serological test, which had the capacity to detect antibodies against multiple pathogens simultaneously, proved useful in the diagnosis of PJI, it has been commercialized with the aim of providing rapid test results (approximately two hours). This immunoassay has been tested in two different prospective studies [77,78], with the objective of assessing its contribution to the routine diagnosis of chronic PJI. Despite its favorable performance, with sensitivity and specificity rates of 86.7 and 96.2%, respectively [79], the test was unable to definitely confirm the diagnosis of PJI in a multicenter prospective observational study involving 115 orthopaedic patients [77]. However, the approach was deemed useful for the post-therapeutic follow-up of patients who have staphylococcal PJI in a prospective clinical study, where a decrease in the level of antibodies was indicative of successful treatment [79]. Moreover, combining the measurement of serum antistaphylococcal antibodies with synovial fluid culture results improved the ability of preoperative aspiration to diagnose staphylococcal PJI of the replaced hip [80].

The use of species-specific multiplex immunoassays for the identification of causal pathogens in PJI has gained much interest, and Janz et al. [81] have successfully implemented this approach for simultaneous measurement of antibody specificities against 32 pathogens commonly associated with PJI in a prospective pilot study. Utilizing their multiplex approach, they were able to trace the dynamics of the pathogen-specific humoral immune response and employed the decline in pathogen-specific IgG binding as an indication of successful treatment, thus introducing a promising tool for PJI monitoring [81].

While multiplex antibody testing shows promise, it is not without limitations. One challenge is the variability in test performance depending on several factors, such as the infection stage (acute versus chronic infection) [70,76–78], the type of assay used (LFA, ELISA, and multiplex assay) [70,71], the targeted pathogen [75–78], the choice of target antigens (e.g., biofilm antigens) [70], the sample material (serum, synovial fluid, or MENSA) [70,74,75], the inclusion and exclusion criteria of the study subjects (some excluding culture-negative infections), and the immune status of the patient. For instance, patients who have immune deficiencies or those who are on immunosuppressive therapy may have a reduced antibody response, leading to false negatives [74]. Furthermore, it is important to note that antibody testing measures a systemic immune response to a pathogen, but does not indicate the site of infection. This limitation might be addressed through the use of joint aspirates to test for pathogen-specific antibodies [70].

Despite the encouraging results obtained thus far, there is an imperative for further enhancements in the sensitivity of current multiplex assays, particularly in the context of acute infections and those caused by less prevalent organisms. Moreover, the execution of large-scale clinical trials is crucial to substantiate the feasibility of fully incorporating these tests into clinical practice for the diagnosis of PJI across a range of patient populations, including those with comorbidities or prior antibiotic or drug treatment, which may influence antibody production. Furthermore, there is a need to establish the cut-off values required to define serology as positive, as these vary between studies [66–69,81]. In addition, studies examining the impact of antibody testing on patient outcomes, including recovery time, antibiotic stewardship, and surgical decision-making, are essential to fully understand the clinical benefits of these tests. A cost-benefit analysis is also required in order to evaluate the economic usefulness of antibody testing. A combined approach, integrating antibody testing with other

diagnostic tools such as polymerase chain reaction, next-generation sequencing, and advanced imaging techniques, may improve diagnostic accuracy and help tailor more effective treatment strategies for PJI.

Notwithstanding the aforementioned limitations, serum antibody testing for microorganisms still has a role in the diagnosis of PJI. However, it can be used as an adjunct rather than a standalone diagnostic method. It is a noninvasive and rapid tool that could be most effectively used as part of a comprehensive diagnostic strategy that includes microbiological cultures, inflammatory markers, clinical assessment, and imaging, thus enhancing the overall diagnostic accuracy and facilitating earlier detection of infection, particularly in challenging cases, where traditional diagnostic methods fall short, and also to monitor the efficacy of infection resolution [80,81]. Numerous studies have demonstrated the efficacy of antibody testing in a variety of orthopaedic infection settings, including PJI, fracture-related infections, native joint septic arthritis, osteomyelitis, orthopaedic infections in the soft tissue, and diabetic foot infections [68,70,71,74,75]. Multiplex antibody testing could be designed to detect polymicrobial infections, a common challenge in diagnosing PJI. This objective can be realized by incorporating targets from various pathogens to encompass a more extensive range of organisms, as previously documented [76–78,81]. For instance, Sulovari et al. [75] demonstrated that MENSA possesses diagnostic potential for group B Streptococcus polymicrobial musculoskeletal infections. This is of particular importance in cases where microbiological cultures fail to identify all pathogens present. The ability to rapidly detect pathogen-specific antibodies could help clinicians make more informed decisions about treatment, including the selection of appropriate antibiotics and determining the need for surgical intervention [70,81].

Conclusions

The studies reviewed demonstrate that serological tests targeting pathogen-specific antibodies, while unable to localize an infection due to their systemic nature, offer several benefits, including their flexibility, since they can cover a wide spectrum of microbial strains that can be easily expanded according to the choice of targets, as well as their robustness against antimicrobial therapy. As technology and assay sensitivity improve, antibody testing may play an increasingly important role in the diagnosis and management of PJI.

Question 3: Is there a role for neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio in diagnosing periprosthetic joint infections?[3]

Response/Recommendation

Serum neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR) are promising adjunctive diagnostic markers for PJI, but they should not be used as standalone tests. Combining these serum markers with other diagnostic criteria or biomarkers may enhance their clinical utility.

Level of Evidence: Moderate

Delegate Vote: Agree: 86.3%, Disagree: 9.0%, Abstain: 4.7% (Super Majority, Strong Consensus)

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Rationale

The NLR and MLR have been identified as valuable biomarkers for differentiating between bacterial and viral infections and predicting clinical outcomes [82]. The NLR, in particular, has garnered increasing attention as an inflammatory marker across various diseases due to its prognostic importance. It represents the balance between neutrophils, key mediators of innate immunity that amplify proinflammatory responses, and lymphocytes, which regulate adaptive immune responses. Elevated NLR values reflect a shift toward a proinflammatory state, which may contribute to unchecked systemic inflammation that could impact a vulnerable joint. The NLR has been used to predict prognosis in conditions such as cancer, sepsis, COVID-19, cardiovascular disease, diabetes, and increasingly in PJI [83,84]. The NLR and MLR are inexpensive, readily available from routine white blood cell count differentials, and can be seamlessly integrated into clinical workflows [85]. However, there is limited research specifically examining their relationship with PJI [86,87]. Jiang et al. [88] investigated the role of NLR and MLR in detecting occult infections among septic arthritis patients undergoing total hip arthroplasty (THA) and concluded that these markers are unreliable in this context. In contrast, Varady et al. concluded that serum NLR and synovial fluid neutrophil-to-lymphocyte ratio have superior diagnostic and prognostic ability for septic arthritis compared with current clinical standards [89]. Conversely, Zhao et al. [90] observed elevated NLR and MLR values in patients who have early PJI in a preliminary study, suggesting their potential utility in identifying early postoperative infections. Prior studies evaluating the diagnostic utility of NLR and MLR in PJI have yielded conflicting results. However, recent meta-analyses suggest that these markers can serve as diagnostic markers for PJI following THA or TKA.

The systematic review identified 1,112 studies from three major databases (PubMed, Web of Science, and Scopus) and one additional study from other sources. After removing 401 duplicates, 711 studies were screened based on titles and abstracts, with 669 excluded for not meeting the inclusion criteria. Following this, 42 full-text studies were assessed for eligibility, of which 13 were excluded due to insufficient data (n = one), wrong study design (n = five), wrong patient population (n = one), wrong evaluated parameter (n = one), or ineligible article types such as meta-analyses or reviews (n = six). The final systematic review included 28 studies, with no studies categorized as ongoing or awaiting classification.

A total of 26 studies assessed the role of the serum NLR in the context of PJI [91–116]. The diagnostic criteria for PJI varied among these studies, with 13 using the Musculoskeletal Infection Society (MSIS) criteria, five employing the EBJIS 2020 guidelines, one following the Centers for Disease Control and Prevention/National Healthcare Safety Network criteria, one following the IDSA criteria, and five adhering to the ICM 2018 consensus. Additionally, one study utilized culture results as the diagnostic reference, while two did not specify any diagnostic criteria. Across the pooled data, which included 2,238 PJI patients and 10,177 aseptic loosening patients, NLR levels were consistently higher in PJI cases than in those with aseptic loosening. In the PJI group, the mean NLR values ranged from 2.16 ± 0.58 to 89.72 ± 92.46, while in the aseptic loosening group, they ranged from 1.84 ± 0.59 to 13.80 ± 7.87, reflecting a clear distinction between the two conditions. The analysis indicates that NLR has moderate diagnostic accuracy for distinguishing between PJI and aseptic loosening. The pooled sensitivity (68.4%) and specificity (69.8%) suggest that NLR can moderately identify PJI cases and rule out non-PJI cases. However, the

diagnostic odds ratio (0.995) indicates weak overall discrimination ability. Subgroup analyses revealed that NLR performs consistently across PJI and arthroplasty subtypes, with the highest standardized mean difference observed in TKA subgroups. Heterogeneity was generally low, further supporting the consistency of these findings. Publication bias analysis showed no significant bias based on Begg's test, but Egger's test detected potential asymmetry, suggesting a need for caution in interpreting the results. The funnel plot also indicated mild asymmetry.

Regarding serum MLR, 11 studies assessed the role of the MLR in diagnosing PJI [91–94,96,97,102,112,117–119]. The diagnostic criteria for PJI varied among these studies, with four using the MSIS criteria, two employing the EBJIS 2020 guidelines, two following the IDSA criteria, and two adhering to the ICM 2018 consensus. Additionally, one study utilized culture results as the diagnostic reference. Across the pooled data, which included a total of 1,159 PJI patients and 8,526 aseptic loosening patients, MLR levels were consistently higher in PJI cases compared to those with aseptic loosening. In the PJI group, the mean MLR values ranged from 0.25 to 0.71 ± 0.38, while in the aseptic loosening group, they ranged from 0.2 ± 0.59 to 0.46 ± 0.27, reflecting a distinction between the two conditions. The analysis indicates that MLR has moderate diagnostic accuracy for distinguishing between PJI and aseptic loosening. The pooled sensitivity (67.4%) and specificity (70.6%) suggest that MLR can moderately identify PJI cases and rule out non-PJI cases. However, the diagnostic odds ratio (5.54) indicates only moderate overall discrimination ability. Subgroup analyses revealed that MLR performs similarly across PJI types and arthroplasty subtypes, with the highest standardized mean difference observed in acute PJI and THA subgroups. Heterogeneity was generally low to moderate, further supporting the consistency of these findings. Publication bias analysis showed no major bias based on Begg's test, but Egger's test detected potential asymmetry, suggesting a need for caution in interpreting the results. The funnel plot also indicated mild asymmetry.

There were two studies that evaluated the diagnostic performance of synovial NLR, reporting sensitivities of 74.1 and 52.4%, respectively, and specificities of 80.7 and 88.9%, respectively [114,116].

Conclusion

In conclusion, while serum NLR and MLR are promising adjunctive diagnostic markers for PJI, they should not be used as standalone tests. Combining these serum markers with other diagnostic criteria or biomarkers may enhance their clinical utility. Further high-quality studies are needed to validate these findings and address potential publication bias.

Author contributions

Rares-Mircea Birlutiu: Writing - original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Maryam Salimi**: Writing - original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. Osamu de **Sandes Kimura**: Writing - review & editing, Data curation, Conceptualization. **AliSina Shahi**: Writing - review & editing, Data curation, Conceptualization. **Michael M Kheir**: Writing - review & editing, Data curation, Conceptualization. **Giovanni Balato**: Writing - review & editing, Data curation, Conceptualization. **Vahit Emre Ozden**: Writing - review & editing, Data curation, Conceptualization. **Vittorio Bellotti**: Writing - review & editing, Data curation, Conceptualization. **Razvan-Silviu Cismasiu**: Writing - review & editing, Data curation, Conceptualization.

Question 4: Should serological monitoring of patients receiving antimicrobial treatment for implant-associated infections be performed?[4]

Search Methods/Results

There were two databases searched for studies examining serologic testing and implant-related infections: PubMed and Scopus. There were 307 studies identified from PubMed, 157 from Scopus, and 14 from citation review. There were 72 duplicates removed, and 373 were deemed irrelevant. There were 34 studies that underwent full-text review. There were 19 excluded for wrong setting (10), wrong patient population (4), and wrong study design (5). Ultimately, 15 studies were included in the review.

Response/Recommendation

Individual serum biomarkers should be considered within the context of other available assessments for infection control to guide management of PJI.

Level of Evidence: Moderate

Delegate Vote: Agree: 88.7%, Disagree: 5.7%, Abstain: 5.7% (Super Majority)

Rationale

The CRP, the ESR, and D-dimer have demonstrated a role in the diagnosis of PJI [120]. A noninvasive test accurately predicting the resolution of infection would be valued to guide surgical decisions and antimicrobial duration [121]. The CRP and ESR are often followed during treatment for implant infection and used in management, although their utility in confirming the resolution of infection is unclear [122].

In two-stage exchange arthroplasty for PJI, the risk of recurrent infection increases with spacer duration, underscoring the need for timely reimplantation [123,124]. There were 15 identified studies, including two 2018 systemic reviews/meta-analyses, that examined the prognostic value of serum biomarkers at the time of reimplantation in predicting recurrent infection (Table 2). Studies evaluated knees[123–127], hips [128–130], and both knees and hips [131–137]. The definition of persistent infection after resection arthroplasty and six weeks of antimicrobials is not standardized, and studies assessed different outcome measures, limiting comparisons. There were seven studies that described using positive cultures at reimplantation [126–129,133–136], four that used the need for additional surgery for infection [123,125,126,130], and ten that used infection by MSIS/ICM criteria or other clinical findings as failure/recurrence [124,125,127–132,136,137]. Cut-off values for CRP and ESR were determined by MSIS/ICM criteria in seven studies [125, 126, 130–132,136,137], from receiver operating characteristic curves in five studies [124,127,129,134,135], and not clarified in three studies [123,128,133].

The systematic review and meta-analysis by Bian et al. included eight studies examining CRP (594 joints) with findings of pooled CRP sensitivity 0.45, pooled specificity 0.72, positive likelihood ratio (PLR) 1.77 (1.14 to 2.74), and negative likelihood ratio (NLR) 0.83 (0.66 to 1.04). Of five studies examining ESR (411 joints), findings included pooled ESR sensitivity of 0.57, pooled specificity of 0.50, PLR of 1.26 (0.91 to 1.75), and NLR of 0.81 (0.54 to 1.21) [137]. The systematic review and meta-analysis by Lee et al. included five studies examining CRP (446 joints) with findings of pooled CRP sensitivity of 0.53 and pooled specificity of 0.72. Of the three studies reporting, the pooled CRP PLR was 1.73 (0.82 to 3.65) and NLR 0.79 (0.62 to 1.01). Of three studies examining ESR (272 joints), findings included pooled ESR sensitivity of 0.56, pooled

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Table 2
Prognostic Value of Biomarkers at the Time of Reimplantation.

Study, year	Design	Level of Evidence	Number of Joints (n)	Marker, Cutoffs if Known	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	No Re-Inf, Mean	RE-inf, MEAn	*P*-value
Ghanem 2009	Prosp.	II	109 knees	CRP* 1	66.7	39.7	28	77	2.04	2.62	0.43
				ESR 30	65.2	32.4	23	75	49.2	50.9	0.83
Kusuma 2010	Retrosp.	II	76 knees	CRP** 17.75	17	94	20	7	6.3	4.1	0.56
				ESR 43.5	67	62	13	5	36.8	43.5	0.56
Shukla 2010	Prosp.	III	87 hips	CRP** 5.5	67	55	15	7	11.6	8.4	0.73
				ESR 47.5	78	69	23	4	38.6	53.8	0.03
Mortazavi 2011	Retrosp.	III	82 knees	CRP*	NA	NA	NA	NA	1.96	1.38	0.23
			94 knees	ESR	NA	NA	NA	NA	47	40.3	0.33
Stammers 2014	Retrosp.	IV	51 knees	CRP* 10	73	47	NA	NA	NA	NA	NA
				ESR 30	30	50	NA	NA	NA	NA	NA
Hoell 2015	Prosp.	II	55 (24 knees, 31 hips)	CRP* 2.5	44	92	70	80	0.6	1.65	0.015
				IL-6 >13, <8	67	90	91	92	3	17	0.001
Janz 2015	Retrosp.	III	69 hips	CRP	95	20	36	90	NA	NA	NA
Hoell 2016	Retrosp.	III	115 (59 knees, 56 hips)	CRP* 2.3	42	84	35	88	1.6	2.6	0.08
Muhlhofer 2017	Retrosp.	III	112 (67 knees, 45 hips)	CRP*	43	73	29	83	0.79	1.57	NA
Lindsay 2017	Retrosp.	IV	21 (16 knees, 5 hips)	CRP* 1	50	82	40	88	0.75	2.92	0.0063
				ESR 30	75	100	100	94	15.4	39	0.0015
Stambough 2018	Retrosp.	III	291 (146 knees, 145 hips)	CRP** 10	NA	NA	NA	NA	9#	11#	0.301
				ESR 30	NA	NA	NA	NA	23#	21#	0.876
Lee 2018	Syst. Rev. Meta-an.	III	CRP: 5 studies, 446 joints	CRP	53	72	1.73+	0.79+	NA	NA	NA
			ESR: 3 studies, 272 joints	ESR	56	60	1.58+	0.67+	NA	NA	NA
Bian 2018	Syst. Rev. Meta-an.	II	CRP: 8 studies, 594 joints	CRP	45	73	1.77+	0.83+	NA	NA	NA
			ESR: 5 studies, 411 joints	ESR	57	50	1.26+	0.81+	NA	NA	NA
Li 2021	Retrosp.	III	74 hips	CRP** 10	NA	NA	NA	NA	3.6	20.2	0.008
Ascione 2024	Prosp.	III	153 knees	D-Dimer	74	61	21	94	908#	1420#	0.008
				1110	NA	NA	NA	NA	3.35#	9.3#	0.1
				CRP** ESR	NA	NA	NA	NA	23.5#	31#	0.09

Sens., sensitivity; Spec., specificity; PPV, positive predictive value; NPV, negative predictive value; Re-inf, reinfection; Retrosp., retrospective; Prosp., prospective; Syst.Rev/Meta-an., systematic review/meta-analysis; CRP*, mg/dL; CRP**, mg/L; ESR, mm/h; IL-6, pg/mL; D-Dimer, ng/mL; #, median used instead of mean; +, positive/negative likelihood ratios; NA, not available.

specificity of 0.60, PLR of 1.58 (0.82 to 3.06), and NLR of 0.67 (0.30 to 1.50) [136]. Both meta-analyses concluded that CRP and ESR did not accurately predict the resolution of infection before second-stage surgery. Of the seven reviewed studies not included in these meta-analyses, three reported CRP sensitivities of 0.73 [125], 0.95 [128], and 0.43 [133] and specificities of 0.47 [125], 0.20 [128], and 0.73 [133]. Stammers et al. [125] reported an ESR sensitivity of 0.30 and specificity of 0.50. There were two studies that reported CRP PPV of 36 [9] and 29 [133], and NPV of 90 [128] and 83 [133]. Combining CRP and ESR improved performance in one study of 21 patients, reporting combined sensitivity, specificity, PPV, and NPV all to be 100% [132], while a study of 76 patients reported normalization of both markers in only 37% of patients who did not have recurrent infection [127]. Ascione et al. [124] found a D-dimer sensitivity of 0.74, specificity of 0.61, PPV of 21, and NPV of 94, and proposed a scoring system using D-dimer, synovial fluid cell count, and % polymorphonuclear, with a score > 2 associated with a 58% failure rate. Hoell et al. [135] reported an IL-6 sensitivity of 0.67, specificity of 0.90, PPV of 91, and NPV of 92.

Monitoring CRP and ESR trends is a common practice in patients receiving antimicrobials for PJI. As background, Wu et al. studied normal CRP, ESR, plasma fibrinogen, and D-dimer trends in 53 PJI patients undergoing two-stage exchange, finding that markers peaked postoperatively, CRP and ESR declined significantly at 30 days, and all markers returned to preoperative levels by 90 to 180 days [138]. Ackmann et al. [139] found in a study of 30 two-stage exchange PJI patients that D-dimer levels were not significantly different between resection and reimplantation, while CRP and IL-6 levels were significantly higher before first-stage surgery as compared to second-stage, even though both decreased in three patients who had persistent infection. Bejon et al. [140] examined 109 patients undergoing debridement with implant retention and 151 patients undergoing two-stage revision for PJI, finding in both groups that CRP was a poor test of cure, but an increasing long-term trend was associated with treatment failure. Of the reviewed studies comparing biomarker trends in two-stage exchange patients who have and do not have persistent infection, two found that mean CRP and ESR significantly decreased between stages in patients who did not have recurrent infections, but not in recurrent infections [127,129]. Li et al. [130] reported that a failure of CRP to normalize after the first-stage resection was associated with failure. There are two studies, including 109 and 291 patients, respectively, however, that found that the change in CRP and ESR from resection to pre-reimplantation was not associated with reinfection risk [126,131].

Confirming infection resolution in patients receiving treatment for PJI remains challenging. Accurate tests are needed to detect persistent infection before reimplantation in two-stage exchange arthroplasty and to assess the risk of recurrent infection with all surgical strategies. Within the limitations of this review, including variability in study design, sample size, and outcome measures, the utility of CRP and ESR in assessing response to therapy is not strongly supported. Multiple reviewed studies found that ESR and CRP levels at the time of reimplantation were similar in patients who did and did not have a persistent infection. A decline in serum biomarkers over time may be a better indication of a favorable treatment response, although this was not supported in all studies. The CRP NPV was > 0.8 in five studies, suggesting a possible role as a test of exclusion.

The appeal of CRP and ESR monitoring as noninvasive and relatively inexpensive tests, and the lack of an alternative test with improved performance, suggests that the use of these biomarkers

in managing patients who have a PJI will continue, but should be interpreted with caution. The role of less commonly assessed biomarkers in this setting, including D-dimer, IL-6, and intercellular adhesion molecule-1, is not well defined. D-dimer's overlapping role in thrombosis and pulmonary embolism detection is a limitation. IL-6 is a precursor to CRP, with which it should correlate.

Conclusion

Individual serum biomarkers should be considered within the context of other available assessments for infection control to guide management, including synovial fluid analysis, clinical signs and symptoms, and intraoperative findings.

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The Journal of Arthroplasty 41 (2025) S423–S431

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Hip and Knee

2025 ICM: Surgical Strategy and Approach

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Question 1: Does the surgical approach influence the rate of periprosthetic joint infection after primary total hip arthroplasty?[1]

Response/Recommendation

No. The surgical approach does not appear to impact the risk of periprosthetic joint infection (PJI) in patients undergoing primary total hip arthroplasty (THA). However, recent evidence suggests that the direct anterior approach (DAA) may increase the risk of superficial infection and wound complications when compared to other approaches.

Level of Evidence: Moderate.

Delegate Vote: Agree: 84.5%, Disagree: 11.1%, Abstain: 4.4% (Super Majority, Strong Consensus).

Rationale

A number of surgical approaches for primary THA have been described, with the DAA), posterior approach (PA), and direct lateral approach (DLA) being the most commonly used worldwide [1]. In recent years, the DAA has witnessed a surge in popularity following reports that it results in superior short-term functional outcomes when compared to the PA and DLA. However, we now have substantial evidence to demonstrate that all three approaches are safe and demonstrate excellent results in patients undergoing THA [2,3]. Despite this, the impact of the surgical approach on the risk of developing subsequent PJI in this setting remains unclear, with a recent meta-analysis citing a higher risk for infection with the utilization of the DAA [4].

A systematic review of existing literature on the association between surgical approach and PJI in patients undergoing primary THA was performed using the following databases: Embase, PubMed, and Cochrane. The primary outcome of this review was to determine the risk of developing PJI between the DAA, PA, and DLA. The secondary outcome was to examine whether there was a difference in the odds of developing wound complications between different surgical approaches. A total of 781 records were identified, and 94 studies were considered eligible for full-text review. From these, 34 studies with a comparison group were eligible for inclusion (Table 1).

Over the last two decades, the DAA has gained traction in this setting following reports that it results in the shortest recovery time after surgery [5]. Despite initial enthusiasm, a number of investigations have since suggested that the DAA increases the risk of PJI following primary THA when compared to the PA or DLA [6,7]. Aggarwal et al. [8] found that patients who received the DAA were twice as likely to experience PJI (odds ratio [OR] 2.2; $P = 0.006$) when compared to their counterparts in the non-DAA group. Notwithstanding, it is important to recognize that a

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to doi: 10.1016/j.arth.2025.10.089.

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https://doi.org/10.1016/j.arth.2025.10.089
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Table 1
Studies Included in the Review Article.

Study and Publication Year	Approaches Examined	Level of Evidence
Namba et al., 2012 [12]	DAA, PA, and DLA	III
Lindgren et al., 2012 [23]	DAA and PA	III
Christensen et al., 2014 [20]	DAA and PA	III
Watts et al., 2015 [17]	DAA and PA	III
Malek et al., 2016 [24]	DAA and PA	III
Ilchmann et al., 2016 [25]	DAA and DLA	III
Mjaaland et al., 2017 [26]	DAA, PA, and DLA	III
Triantafillopoulos et al., 2018 [27]	DAA and PA	III
Tissot et al., 2018 [28]	DAA and PA	III
Miller et al., 2018 [11]	DAA and PA	III
Purcell et al., 2018 [29]	DAA and PA	III
Smith et al., 2018 [30]	DAA, PA, and ALA	III
Angerame et al., 2018 [31]	DAA and PA	III
Lenguerrand et al., 2018 [32]	PA and DLA	II
Aggarwal et al., 2019 [8]	DAA, PA, and DLA	III
Klasan et al., 2019 [33]	DAA and ALA	III
Tay et al., 2019 [34]	DAA, PA, and DLA	III
Docter et al., 2020 [35]	DAA, PA, and DLA	III
Adili et al., 2020 [36]	DAA, PA, and DLA	III
Pincus et al., 2020 [37]	DAA, PA, and DLA	III
Hoskins et al., 2020 [15]	DAA, PA, and DLA	III
Huang et al., 2021 [38]	DAA and DLA	III
O'Connor et al., 2021 [39]	DAA, PA, and DLA	III
Shohat et al., 2021 [13]	DAA and DLA	III
Bendich et al., 2021 [40]	DAA and PA	III
Metzger et al., 2022 [41]	DAA and PA	III
Qvistgaard et al., 2022 [42]	DAA, PA, and DLA	III
Acuna et al., 2022 [14]	DAA, PA, and DLA	III
Dockery et al., 2022 [43]	DAA, PA, and DLA	III
Makhdom et al., 2023 [44]	DAA and DLA	III
Salmons et al., 2023 [22]	DAA, PA, and DLA	III
Luger et al., 2023 [45]	DLA and ALA	III
Chalmers et al., 2023 [21]	DAA and PA	III
Wernecke et al., 2024 [46]	DAA and PA	III

DAA, direct anterior approach; PA, posterior approach; DLA, direct lateral approach; ALA, anterolateral approach.

growing body of evidence has demonstrated no difference in the development of PJI between surgical approaches in patients undergoing THA [9,10]. In a meta-analysis that included 164,307 patients, Miller et al. found that patients who received the DAA approach had significantly lower odds for the development of PJI (risk ratio 0.55; $P = 0.002$) than patients who received the PLA [11]. In another study, Namba et al. [12] found no difference in PJI risk between patients who received the DAA and those who received the PA. Moreover, Shohat et al. [13] demonstrated that the DAA for THA did not increase the risk of subsequent PJI (1.3% in the DAA group versus 0.9% in the DLA group, $P > 0.05$). Similarly, Acuna et al. [14] showed that DAA patients had significantly lower odds for the development of PJI than patients who received the PA (OR 0.66; $P < 0.001$) or DLA (OR 0.56; $P < 0.001$). Furthermore, in a study of the Australian National Joint Replacement Registry, Hoskins et al. [15] found that after adjusting for confounding variables, patients in the DAA group had a lower rate of revision for infection than those in the PA group.

Regardless of the surgical approach utilized, increased body habitus and obesity have been shown to be independent predictors of poor outcomes in patients undergoing primary THA. More recently, there has been evidence to suggest that the DAA increases the risk of wound complications in patients who are morbidly obese when compared to the PA and DLA, especially in those who have a large pannus [16–18]. In one study, Shah et al. [19] found that patients in the DAA had significantly higher odds of developing PJI in patients who had a body mass index (BMI) of $\geq$ 35. Similarly, Christensen et al. [20] demonstrated that patients who received the DAA were more likely to require reoperation for wound complications (1.4 versus 0.2%, $P = 0.007$) when compared to their counterparts in the PA group. In another study, Chalmers et al. [21] found that patients who received the DAA had an increased risk of reoperation for superficial infection (risk ratio 2.67; $P = 0.007$). Moreover, Salmons et al. [22] showed that the absolute risk rate of wound complications was higher in the DAA group (3.7 versus 2.6%, $P < 0.001$) than patients in the PA and DLA groups.

Although it is now well-established that the DAA, DLA, and PA all have excellent results, the impact of surgical approaches on the risk of PJI remains a contentious issue. Based on our extensive review of the data, we can conclude that the type of surgical approach is not a risk factor for the development of PJI in most patients undergoing THA. However, the DAA has a higher risk of wound complications in the morbidly obese population, especially in patients who have a large pannus. Future randomized controlled trials are necessary to identify factors that increase the risk of infection and wound complications in patients undergoing THA using the DAA.

Question 2: Should all foreign material be removed during resection arthroplasty for patients who have chronic PJI?[2]

Response/Recommendation

Yes, whenever possible. Complete surgical debridement of the joint with the removal of all components and implants should be the ultimate goal in patients who have chronic PJI.

Level of Evidence: Limited

Delegate Vote: Agree: 64.7%, Disagree: 24.5%, Abstain: 10.8% (Simple, low Consensus)

Rationale

A key characteristic of PJIs, unlike other osteoarticular infections, is the presence of foreign and permanent material in the surgical site (implant). The interaction between this foreign material, the host, and the bacteria creates conditions where a lower bacterial inoculum is required to cause infection. Once the implant is colonized, its removal is often necessary to cure the infection. This phenomenon is well-documented and is driven by bacterial adhesion to the implant surface and subsequent biofilm formation. Despite extensive research into methods for biofilm eradication, no safe and effective *in vivo* method exists to remove mature biofilm from an implant. This inability to effectively eliminate mature biofilm necessitates the removal of all implants (in one or two stages) to manage chronic infections.

In order to answer this question, we performed a comprehensive review of the literature using the Medical Subject Headings (MeSH) terms developed by librarians. A total of 651 studies were initially identified, which were screened by two independent delegates. This resulted in 15 studies meeting the final inclusion criteria. These studies were then reviewed in full for data extraction.

Suzuki et al. [47] reported an increased risk of postoperative infections when prior fixation materials were not fully removed. Similarly, Pfang et al. [48] observed that 16.4% of extracted implants were contaminated, though these were not septic cases. Some authors have reported successful outcomes in retaining implants for acute periprosthetic fractures with infections. However, Karczewski et al. [49] found that

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retaining cerclage wires during septic revision was associated with a significantly higher reinfection risk by the same microorganism (22.2 versus 1.1%) and earlier recurrence (11.1 versus 1.1%).

Although the ability of pathogens to adhere and form biofilm on implant surfaces is well-documented, some researchers argue that osseointegration is a protective factor against bacterial colonization and adhesion. Therefore, properly integrated implants might not be colonized by bacteria, and only components in contact with the joint space may need removal. Nevertheless, Doub et al. [50] recently analyzed biofilm localization in explants from chronic PJI cases and found biofilm present at the bone-implant interface in 100% of cases, irrespective of osseointegration, while only 40% had biofilm in the joint space.

The increasing frequency and complexity of revisions have led to more cases involving septic revisions with fully integrated revision implants, intraosseous osteosynthesis remnants, or patients who have poor biological health, where the surgical morbidity of complete implant removal may far exceed the potential benefits. Subradical resection arthroplasty has been tried in some of these patients, who have acceptable outcomes. The latter is the subject matter of another question in the International Consensus Meeting and will not be covered here extensively.

Shi et al. [51] achieved 100% infection control in 14 high-comorbidity patients undergoing two-stage partial revision (nine femoral components, five acetabular components). However, this study excluded cases with resistant, polymicrobial bacteria or fistulas. Studies not achieving 100% success did not provide a rationale, but analysis revealed similar patient characteristics, including important comorbidities [52] and resistant bacterial infections [53,54]. Chen et al. [54] reported an 81.3% success rate in 16 patients who had a longer follow-up (70 months), consistent with results from El-Husseiny et al. [55] (18 patients, three failures) and Yishake et al. (29 patients). It is important to note that the study by Yishake et al. [56] attributed the success to the use of antibiotics throughout the surgical process and for at least 3 months postoperatively to prevent opportunistic infections. In that sense, the largest series published by Crawford et al. [57] (41 patients) observed eight failures, with a success rate of 80%. However, 15% of patients require suppressive treatment. Both Chen et al. [54] and Crawford et al. [57] attributed higher reoperation rates to high-virulence organisms and uncontrolled infection, necessitating the removal of residual implants.

Studies included patients who have negative cultures and methicillin resistant staphylococcus aureus, as well as those who have previously failed two-stage treatment, resulting in lower success rates [54,58]. Studies with careful patient selection and exclusion of high-risk individuals generally reported lower failure rates, highlighting the importance of adhering to established selection criteria (well-fixed implant, susceptible bacteria to anti-biofilm therapy) for partial two-stage treatment.

The possibility of retaining cement fragments has been widely debated. McDonald et al. [59] reported three recurrences among seven patients when cement was retained, compared to eight recurrences among 75 patients when all cement was removed. Some researchers have proposed a cement-in-cement septic revision technique, provided the cement is preloaded with antibiotics. However, Leijtens et al. [60] observed poor outcomes with this approach, achieving only a 20% cure rate.

In summary, most published studies involving partial septic revisions are highly selective, involving scenarios where complete removal posed major surgical morbidity. The infections in these cases were caused by susceptible bacteria, excluding difficult-to-treat pathogens. Thus, in the absence of concrete evidence, we recommend that the basic principle of revision surgery for infection, namely, removal of all foreign material and meticulous debridement, be adhered to. However, there may be exceptional cases where the morbidity associated with the removal of well-integrated components (usually revision components) outweighs the benefits of their removal. In these specific cases, and in the absence of concrete evidence, retaining parts of implants may be acceptable.

Question 3: Is there a role for subradical exchange (leaving some implants) arthroplasty in patients who have chronic PJIs?[3]

Response/Recommendation

Subradical exchange arthroplasty, that is, leaving parts of implants in place, in this review showed an 83% infection-free rate at a mean final follow-up of four years. Notably, the reinfection rate after two-stage subradical exchange appears to be lower than the one-stage approach. Hence, this technique may be considered during the management of patients with chronic PJIs when a component is proven to be well-fixed and its removal precludes the opportunity for future reconstruction.

Delegate Vote: Agree: 81.0%, Disagree: 12.9%, Abstain: 6.2% (Super Majority, Strong Consensus)

Level of Evidence: Moderate

Rationale

Debate exists as to the optimal treatment of patients who have late, chronic PJI. Removal of all prostheses and foreign materials, whether one-stage with immediate revision or two-stage with delayed reimplantation after an interval of antibiotic therapy, is the current gold standard, even in situations where there is a well-fixed ingrown or well-cemented component on one side of the arthroplasty. However, removal of well-fixed components can result in additional perioperative morbidity and cause iatrogenic bone loss that may compromise subsequent reconstruction. Selectively retaining a well-fixed component while removing only the loosened or suboptimal parts may be an option to avoid compromise of the host bone in the setting of PJI treatment.

Included were studies reporting outcomes in patients managed with subradical exchange for the treatment of infection after hip or knee arthroplasty, either in one or two stages, with partial retention of one or more well-fixed major metallic components. We excluded studies with complete component exchange, revisions for causes other than infection, treatment of septic arthritis before primary hip or knee arthroplasty, studies involving infection of joints other than the hip or knee, studies with complete component retention or exchange of modular parts only, such as hip femoral head and/or acetabular liner or knee insert as part of a debridement, antibiotics, and implant procedure, and studies with removal of metallic cemented components with retention of the cement mantle only. Although we considered both hip and knee studies, subradical exchange is more commonly used in the revision of infected hip arthroplasty. This study was exempt from Institutional Review Board approval because it was a systematic review of published articles and did not involve review of individual patient records or images.

Overall, 550 studies were identified using the search terms supplied across EMBASE and PubMed. After the title and abstract

[3] These authors contributed to Question 3: Adolph V. Lombardi, Jr., Walter Ricioli, Jr., Baochao Ji, Ireneusz Babiak, Erik N. Hansen, Victor M. Ilizaliturri Sánchez, Ali Parsa

review, 40 full-text reviews were performed, reducing the full data extraction to 31 studies published from 1989 to 2024. There were 11 studies from Asia, ten from Europe, nine from North America, and one from South America. There were two articles that were systematic reviews only of studies already included in the current review that were withdrawn from the analysis [62, 84]. There were 27 practice registry studies, one national registry study [70], and one multicenter study with patients from 20 hospitals who underwent one-stage revision arthroplasty with unexpected positive intraoperative cultures [79]. There were three level III evidence studies and 26 level IV, with six case reports, 19 case series, and four case-control series with comparator group(s).

The studies included 591 patients undergoing subradical exchange for the treatment of PJI, with 322 patients (54%; 10 studies) undergoing one-stage exchange (Table 2) and 269 (46%, 19 studies) treated with the two-stage exchange (Table 3). The involved joint was the hip in 580 of 591 patients (97%), with only one study, the multicenter review by Mancheño-Losa and colleagues, that included a small number of patients (11 of 110) with infected total knee or total shoulder arthroplasty undergoing partial revision [79]. Retained components were hip femoral components in 281 (48%) patients, acetabular components in 39 (7%), hip distal stem segments in 16 (3%), and not reported for 255 (43%) patients in four studies, all one-stage exchanges. Fixation of retained components was cementless in 225 (38%) patients, cemented in 24 (4%), and not fully reported in eight studies (342 patients, 58%). Overall, the mean weighted patient age was 66 years (range, 19 to 95; reported in 28 studies), the mean weighted BMI was 28.8 (range, 18 to 58; reported in 11 studies with 205 patients), 51% (302 of 588) of involved joints were in women (range, 42 to 100%; reported in 28 studies), and the mean weighted follow-up was four years (range, 0.3 to 18.5; reported in 28 studies).

The most common infecting organisms cultured were methicillin-sensitive *Staphylococcus aureus* in 81 (13.6%), coagulase-negative *Staphylococcus* in 118 (19.8%), methicillin-sensitive *Staphylococcus epidermidis* in 36 (6.1%), methicillin-resistant *Staphylococcus aureus* in 30 (5.0%), methicillin-resistant *Staphylococcus epidermidis* in nine (1.5%), other *Staphylococcus* in 12 (2.0%), *Streptococcus* species in 27 (4.5%), gram-negative bacilli in 19 (3.2%), gram-positive bacilli in 17 (2.9%), *Enterococcus faecalis* in 18 (3.0%), *Pseudomonas aeruginosa* in 11 (1.8%), *Escherichia coli* in nine (1.5%), *Peptostreptococcus* in six (1.0%), *Propionibacterium* in five (0.8%), four *Enterobacter*, three *Candida albicans,* two gram-negative cocci, seven polymicrobial (1.2%), and one each *Anaerococcus prevotii, Corynebacterium jeikeium, Klebsiella oxytoca, Morganella morgagnii, Proteus mirabilis, Salmonella* group D, *Yersinia enterocolitica*, and *unspecified fungal.* A study with four polymicrobial infections did not specify which organisms were in combination. There were 41 patients (6.9%) who were culture negative. Infecting organisms were not reported in two studies involving 132 patients (22.2%) [70, 73].

For two-stage exchange, the mean weighted interval between stages was 18.1 weeks (range, 0.4 to 96; reported in 17 studies with 253 patients). Most patients (210 of 269; 78%) were treated with articulating spacers made from antibiotic-laden bone cement; static spacers were used in 28 (10%); antibiotic-laden cement beads were used in an early case report [86]; and spacer type was not reported for three studies [73, 74, 85]. The antibiotic most frequently added to the spacers was vancomycin, in doses ranging from two to four grams per unit of cement. Other antibiotics utilized in cement spacers were tobramycin (up to 4.8 grams per unit), gentamicin, cefotaxime, erythromycin, teicoplanin, colistin, cefuroxime, and other organism-specific options. For the one-stage exchange articles, two mention using powdered vancomycin poured into the wound at the time of revision [75, 80].

For patients undergoing one-stage exchange, six of 10 studies reported administration of organism-specific intravenous antibiotics postoperatively, followed by a course of oral antibiotics. Intravenous antibiotic therapy typically lasted for five days to six weeks, while oral treatment extended for up to nine months. For the two-stage exchange studies, most recommended a 6-week course of organism-specific intravenous antibiotics after the first stage, ranging from “discontinued the same day the drainage tube was removed” to 12 weeks, usually followed by a course of oral antibiotics [66]. Some studies also recommended the continuation of intravenous antibiotics after the second stage of reimplantation, followed by oral antibiotic therapy.

For the two-stage exchange, complications during the interval between stages were reported in eight studies. There were eight patients who required further debridement for persistent infection; at least five of these patients had resection arthroplasty without reimplantation. A patient died at three months without reimplantation. Spacer dislocation was reported in four patients, of whom two were treated with closed reduction and two underwent second-stage revision to the definitive implant. There were five patients who refused reimplantation and were satisfied with the pain relief and function achieved with the spacer.

For patients treated with subradical exchange for PJI, the rate of reinfection at one year was 7.8% (26 of 332) overall, with no significant difference between patients undergoing one-stage versus two-stage exchange ($P = 1.00$): 7.6% (5 of 66) of patients in the six one-stage exchange studies reported, and 7.9% (21 of 266) of

Table 2
Studies Reporting Treatment of Periprosthetic Joint Infection With One-Stage Subradical Radical Exchange.

Authors	Year	Country	Source	Number of Patients	Age (Years)	BMI (kg/m^2)	% Women	Follow-Up (Years)	Number Reinfected at Final Follow-Up (%)
Antti-Poka et al. [63]	1989	Finland	Private practice	2	51.5	NR	0	2.7	2 (100)
Bourget-Murray et al. [64]	2024	Canada	Private practice	14	64	32.9	54.4	8.2	5 (38.5)
El-Husseiny & Haddad [69]	2016	United Kingdom	Private practice	18	70.9	25.9	61	7.1	3 (16.7)
Engesæter et al. [70]	2011	Norway	National Registry	129	70	NR	51	2	37 (29)
Ji et al. [75]	2017	China	Private practice	31	54	24.7	42	5	4 (12.9)
Mancheño-Losa et al. [79]	2021	Spain	Multicenter study	110	73	NR	47	3.2	14 (12.7)
Mencia et al. [80]	2021	Trinidad and Tobago	Private practice	1	83	NR	100	1	0
Rahman et al. [83]	2017	Canada	Private practice	15	58.9	30	60	8.6	1 (6.7)
Tleyjeh et al. [87]	2005	United States	Private practice	1	78	NR	0	0.5	0
Wellauer et al. [89]	2024	Switzerland	Private practice	1	68	NR	0	2	0
Total/weighted mean				322	68.7	27.5	50%	3.6	66 (20.5)

BMI, body mass index; NR, not reported.

Table 3
Studies Reporting Treatment of Periprosthetic Joint Infection With Two-Stage Subradical Exchange.

Authors	Year	Country	Source	Number of Patients	Age (Years)	BMI (kg/m^2)	% Women	Interval (Weeks)	Follow-Up (Years)	Number Reinfected at Final Follow-Up (%)
Anagnostakos et al. [61]	2010	Germany	Private practice	13	69	NR	61.5	12.6	4.6	1 (7.7)
Castagnini et al. [65]	2020	Italy	Private practice	28	66.5	NR	46.4	36	5.2	4 (14.2)
Chen et al. [66]	2017	Taiwan	Private practice	16	55.9	NR	50	12.5	5.8	3 (18.8)
Crawford et al. [67]	2019	United States	Private practice	41	62.3	32.7	54	9.3	5.5	8 (19.5)
Ekpo et al. [68]	2014	United States	Private practice	19	60.7	30	47	8.4	4	2 (10.5)
Faroug et al. [71]	2009	United Kingdom	Private practice	2	69	NR	50	3.2	3.5	0
Fukui et al. [72]	2016	Japan	Private practice	5	65.8	26.5	80	12.7	4.2	0
Hannon et al. [73]	2022	United States	Private practice	3	NR	NR	NR	NR	NR	NR
Harmer et al. [74]	2023	United States	Private practice	13	62	33	46	NR	4.3	5 (38.5)
Lee et al. [76]	2013	South Korea	Private practice	19	60.3	NR	63.2	29.2	4	2 (10.5)
Lombardi et al. [77]	2014	United States	Private practice	7	66.8	36	57	7.1	1.6	1 (14.3)
Luk et al. [78]	2023	Hong Kong	Private practice	1	61	NR	0	11	4	0
Moreno-Romero et al. [81]	2023	Spain	Private practice	8	60.8	NR	75	23.5	6.1	0
Otani et al. [82]	2019	Japan	Private practice	5	64	NR	80	13.9	9.1	0
Shi et al. [85]	2020	China	Private practice	14	65.1	27.1	42.9	45.2	6.6	0
Struhl et al. [86]	1989	United States	Private practice	1	45	NR	0	7	1.5	0
Um et al. [88]	2020	South Korea	Private practice	20	68.5	NR	65	10.4	3.2	1 (5)
Yishake et al. [90]	2021	China	Private practice	28	61	23.7	46.4	17.7	4	4 (14.3)
Zhou et al. [91]	2019	China	Private practice	26	65.5	NR	46.2	15	3.7	0
Total/weighted mean				269	62.6	29.7	53%	18.1	4.6	31 (11.7)

BMI, body mass index; NR, not reported.

patients in 18 studies of two-stage exchange. At the final mean overall follow-up of four years (range, 0.3 to 18.1), the overall reinfection rate was 16.5%, observed in 97 of 588 patients. For 322 patients treated with subradical one-stage exchange, reinfection occurred in 20.5% (61) at a mean weighted follow-up of 3.6 years (range, 1.3 to 18.1), while for 266 patients treated with subradical two-stage exchange, results were more favorable with a lower reinfection rate of 11.7% (31 patients, $P = 0.0051$) at a mean weighted follow-up of 4.6 years (range, 0.3 to 18.5).

Potential limitations of this review are that all of the studies included were retrospective in nature; there was a small number of patients overall, with seven articles limited to case reports with one or two patients; a wide variety of methods were utilized, including postoperative antibiotic protocols; and overall, 6.9% of patients were culture negative.

The success rate for patients treated with two-stage partial exchange was significantly higher at a longer final follow-up ($P = 0.0051$), with 88.3% free of reinfection at a mean of 4.6 years compared with 79.5% at 3.6 years for patients undergoing one-stage partial exchange. However, the higher eradication rate must be balanced with the substantial complications observed between the two stages, the interval mean duration of 18.1 weeks, extending up to 96 weeks, and the burden and impact of those factors on the patient's quality of life.

Question 4: What is the optimal management of patients who have prior septic arthritis in a joint that requires arthroplasty?[4]

Response/Recommendation

All patients who have prior septic arthritis should be investigated for the presence of active infection in the affected joint. If active infection is not found to be present, then one- or two-stage surgery can be carried out. For patients who have active septic arthritis, we recommend two-stage arthroplasty. A one-stage surgery may be considered for patients infected with *Mycobacterium tuberculosis* where antituberculosis medications have been commenced.

Level of Evidence: Limited

Delegate Vote: Agree: (85.5%); Disagree: (6.3%); Abstain: (8.2%)—Super majority/Strong consensus

Rationale

The management of patients who have prior septic arthritis in a joint that requires arthroplasty is traditionally performed in one or two stages. A single-stage arthroplasty has the advantage of lower surgical morbidity and decreased hospital expenses. A two-stage arthroplasty may reduce the risk of PJI through two surgical debridements and additional antibiotic therapy between procedures.

Septic arthritis in a native joint may cause extensive damage to the articular cartilage and lead to arthritis [92]. While arthroplasty for patients who have septic arthritis can improve pain and enhance function, there is an elevated risk of subsequent PJI [93,94]. In a meta-analysis of 1,300 total joint arthroplasties (TJAs) performed on joints that have a history of septic arthritis, the reported rate of PJI was 5.96% (95% confidence interval, 4.24 to 7.94), significantly higher than the PJI rate for primary TJA in patients who have osteoarthritis (OA), at around 1% [95,96].

There is an ongoing debate regarding the optimal treatment of patients who have prior septic arthritis. Some surgeons advocate for performing the arthroplasty in a two-stage manner, while others feel that performing the arthroplasty in one sitting is acceptable. To answer the question posed above, we performed a systematic review of the literature. Using MeSH terms developed by the librarians, we ran a search of the PubMed and Embase databases. A total of 1,682 studies were identified in the initial search. After screening the abstracts and full texts, a total of 62 studies met the inclusion criteria for full review and data extraction.

In 2021, Tan et al. [97] investigated whether TJA after septic arthritis can be safely performed. A total of 207 TJAs in patients who have prior septic arthritis undergoing arthroplasty from 2000 to 2017 at five institutions were included. Important data on these patients, including laboratory test results, prior treatment, time

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from the initial infection, and patient characteristics, were recorded. The overall PJI rate was 12.1%. Increasing time from septic arthritis treatment to TJA was not associated with a reduction of PJI risk, whether considering time as a continuous or categorical variable ($P > 0.05$). Although the optimal threshold for the timing of TJA from the initial treatment was 5.9 months, there was no difference in the PJI rate when the overall cohort was dichotomized by this threshold or stratified by single- or two-stage TJA. There was no significant difference in ESR and CRP level before TJA between patients who subsequently developed PJI and those who did not. Aspiration was performed in a small proportion of patients (16.9%), and no conclusions could be drawn on its value.

In 2022, Bettencourt et al. [99] described the outcomes of primary THA following septic arthritis of the native hip. They retrospectively identified 256 THAs in 244 patients following septic arthritis performed between 1969 and 2016 at a single institution. Each case was matched 1:1, based on age, sex, BMI, and year of surgery, to a primary THA performed for OA. The mean age and BMI were 58 years (range, 35 to 84) and 31 (range, 18 to 48), respectively, and 100 (39%) were women. The mean follow-up was 11 years (range, two to 39). The 10-year survival free of any infection was 91 and 99% in the septic arthritis and OA groups, respectively (hazard ratio (HR) = 13; $P < 0.001$). The survival free of PJI at 10 years was 93 and 99% in the septic arthritis and OA groups, respectively (HR = 10; $P = 0.002$). There was a significantly higher rate of any infection at 10 years when THA was undertaken within five years of the diagnosis of septic arthritis than those in whom THA was undertaken more than five years after this diagnosis (14 versus 5%, respectively; HR = 3.1; $P = 0.009$). The mean Harris Hip Scores at two and five years postoperatively were significantly lower in the septic arthritis group than the OA group ($P = 0.001$ for both). The risk of any infection had a strong downward trend as the time interval between the diagnosis of septic arthritis and THA increased, highlighted by a 3.1-fold higher risk when THAs were performed within 5 years of the septic arthritis diagnosis.

Luo et al. [98], in 2023, performed a systematic review with meta-analysis for the treatment of patients who have septic arthritis undergoing single- and two-stage arthroplasty. Theere were seven retrospective studies (Bauer et al. [100]; Bochatey et al. [101]; Hooper et al. [102]; Papanna et al. [103]; Portier et al. [104]; Tan et al. [105]; Zhang et al. [106]) with a total of 413 patients included. Pooled analysis showed no difference in the reinfection rate between single- and two-stage arthroplasty. Subgroup analysis found no difference between the single- and two-stage arthroplasty groups in the incidence of infection of the hip and knee. They also compared the joint function after single- and two-stage arthroplasty for patients who have septic arthritis. The three included studies reported on the postoperative joint function (7, 16, 27). There were two of these studies that evaluated the hip, while one evaluated the knee. The pooled Harris Hip Score results suggested that there was no difference between groups in joint function. However, the pooled results were highly heterogeneous ($I^2 = 94.5\%$) owing to the inclusion of a small number of studies and a small sample size. Therefore, their confidence in the results was low, and they did not report them. The joint function after single-versus two-stage arthroplasty for septic arthritis should be investigated in future studies.

In cases of tuberculosis infection, single-stage arthroplasty is considered a safe option in patients who have prolonged use of antituberculosis medications. [107]. Postoperative infection poses a risk for patients who have untreated disease or those on systemic corticosteroid treatment [108]. In these cases, where sinus tracts are present or extensive, bony destruction with multiple abscesses is predominant, a two-stage approach may be recommended [109,110].

In 2022, Wei et al. [111], performed a retrospective review of 105 TJA patients who had prior septic arthritis. At a mean follow-up of 10.3 years, the PJI rate was 16.2%. The adjusted Cox proportional hazards model showed that men (HR, 9.95; $P < 0.01$), end-stage renal disease (HR, 37.34; $P < 0.01$), debridement surgery greater than three times (HR, 4.75; $P = 0.04$), and polymicrobial infection in primary septic arthritis (HR, 10.02; $P = 0.02$) were independent risk factors for PJI. Neither the types of initial debridement nor one-stage versus two-stage arthroplasty were related to the risk of PJI. There was a higher risk of PJI re-infection by the same microorganisms isolated in prior septic arthritis if TJA was performed within six months after septic arthritis. All patients received a minimum of four weeks of antibiotic therapy. The course of antibiotic treatment depended on the clinical symptoms and signs, ESR, and CRP level. Antibiotic cement use in definitive TJA was not a predictor of success regarding infection rates [HR 2.08 (0.73 to 5.89); $P = 0.17$].

Conclusion

There is limited data related to the optimal management of patients who have prior septic arthritis undergoing TJA. The available evidence, all retrospective, suggests that performing the arthroplasty either in one setting or in two stages does not influence the outcome. The available data suggest that a single-stage arthroplasty is a reasonable treatment strategy in most patients, including for septic arthritis caused by *M. tuberculosis*, where antituberculosis medications have been commenced.

The optimal management of these patients should include investigation for the presence of infection, which should include ordering serological tests, selective preoperative aspiration of the joint, and sending samples of tissue and bone for culture during surgery. Patients who have an active infection, except for *M. tuberculosis*, may best be treated with two-stage arthroplasty. Patients who have an inactive infection can then be treated with arthroplasty in one stage. If any organism, particularly an organism that caused the initial septic arthritis, is isolated by culture, then treatment with an extended course of antibiotics may be required.

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The Journal of Arthroplasty 41 (2025) S432–S436

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Hip and Knee

2025 ICM: Special Cases of Infected Implants

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Question 1: What is the optimal management of an infected hemiarthroplasty of the hip?[1]

Response/Recommendation

The management of patients who have infected hemiarthroplasty of the hip should be individualized. However, in view of the potentially high failure of debridement, antibiotics, and implant retention (DAIR) in this population, consideration should be given to excisional arthroplasty or one- or two-stage exchange with acetabular reconstruction.

Level of Evidence: Limited

Delegate Vote: Agree 88.1% Disagree 9.9% Abstain 2% (Strong consensus, Super Majority)

Rationale

Hemiarthroplasty (HA) of the hip is the most common treatment for displaced neck of femur (NOF) fractures, particularly for elderly patients [1]. The most common reasons for revision HA are infection, instability, and periprosthetic fracture [2]. The rate of periprosthetic joint infections (PJI) after HA ranges from 0.5 to 7% [3–5]. Despite the high incidence, there is a paucity of quality evidence on the management of PJI after HA. Existing literature highlights the complexity and variability of these infections, making it challenging to develop a standardized treatment protocol.

The development of PJI following HA can be influenced by a myriad of risk factors. These factors tremendously impact the success and overall outcome of the procedure. Patient frailty and/or comorbidities, delay to theater, surgical technique and duration, postoperative care, and previous surgical interventions are reported risk factors for PJI after HA [3,4,6,7]. The all-cause mortality at two years after HA PJI is two to three times higher than HA without PJI [2,4,8]. Understanding these risk factors is essential for developing effective prevention strategies and individualized treatment plans to manage PJI after HA.

The most common initial treatment for HA PJI is DAIR, particularly for early acute infections. However, the success of this approach varies and is often compromised by factors such as polymicrobial infection and surgical technique. Modular part exchange, removing and replacing a unipolar or bipolar femoral head, was only reported in 50 to 70% of DAIR procedures performed; as component exchange is essential to DAIR, these studies are therefore more appropriately classified as debridement and lavage. Reported failure rates of the DAIR procedure are high, 18 to 82% [3,4,9–14]. Factors increasing the likelihood of infection after HA included the use of urinary catheterization, concurrent urinary tract infection, and increasing delay to the operating room for treatment of the fracture. However, the culture of any gram-negative organism, polymicrobial infection, and multiple DAIR procedures have been reported to have higher failure rates of DAIR [3,10,12,13].

Surgical alternatives to DAIR include one-stage revision to new HA, one-stage revision to total hip arthroplasty (THA), two-stage revision, and excisional arthroplasty. The available literature does not provide specific data on the success ratio for one- and two-stage treatment for an HA PJI. Bourget et al. reported a case series of 44 infected HA. The ratio of treatment preferences by the surgeon is 13.6% for one-stage revision to new HA, 27.3% for one-stage revision to THA, and 59.1% for DAIR. A one-stage revision to a THA reported lower perioperative complications (16.7 to 33%) and lower 1-year mortality rate (8.3 to 50%) than a one-stage revision to a new HA [9]. This result may be confounded by patient selection.

Excisional arthroplasty is an option in very frail, highly comorbid patients who will not survive a more extensive procedure. It can also be used in those who failed DAIR or revision one- and two-

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.074.

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https://doi.org/10.1016/j.arth.2025.10.074
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stage procedures. The literature reported mixed clinical results for reinfection but a very high 1-year mortality rate after excisional arthroplasty, most likely reflecting patient selection. Nawz et al. reported a 2.2% PJI rate for their series of cementless HA and treated them with excisional arthroplasty, 1.8% with repetitive washout in 1.2%; they did not report any DAIR [15]. Lok et al. compared the rate of PJI between patients undergoing HA for NOF before and after the adoption of a standardized preoperative microbiological screening, perioperative, and postoperative wound care protocol. They reported a reduction of PJI from 3.31 to 1.40% after protocol initiation. Lok et al. reported that of the PJI's, 82.4% were initially treated with "surgical debridement"; however, all patients failed and required excisional arthroplasty [16]. Manoharan et al. also reported 1,445 uncemented Thompson's HA with revision for PJI in 0.83%, with 11 of 12 cases of PJI presenting as early acute infections that were treated by excision arthroplasty [17].

Summary

Current literature is very limited and insufficient to guide a standardized treatment protocol for infected HA. Currently, the Expert Working Group can only agree on available options, including DAIR, revision (in single or two stages), and excision arthroplasty. A DAIR may be considered only for acute infections and should include the exchange of any modular components alongside thorough debridement. Revision surgery may be effective in those patients who are able to tolerate a larger procedure. Excision may be more suitable for frail patients or those at high risk of failure of DAIR or revision procedures. Management should be done by a multidisciplinary experienced team, taking into consideration comorbidities and patient mobility.

Question 2: What is the optimal management of an infected unicondylar arthroplasty of the knee?[2]

Response/Recommendation

Either single- or two-stage revision to TKA is appropriate for infection control and minimizes revision risk compared to debridement and implant retention.

Level of Evidence: Limited

Delegate Vote: Agree 87.5%, Disagree 6.3%, Abstain 6.3% (Super Majority, Strong Consensus)

Rationale

The use of unicompartmental knee arthroplasty (UKA) in the treatment of knee osteoarthritis has steadily increased over the last few decades [18]. With increased utilization, the number of PJIs involving UKAs has also increased [18]. A PJI in the setting of UKA presents a unique therapeutic challenge distinct from TKA PJI, as it presents as both PJI and septic arthritis consequent to the remaining native joint surfaces [18].

Currently, there is limited literature available on the optimal treatment of UKA PJI, with DAIR, two-stage revision, and single-stage revision to TKA being the most utilized treatment strategies [19].

We conducted a comprehensive systematic review to identify pertinent literature using predetermined MeSH terms. A total of 335 studies were initially identified. After initial title and abstract screening, 25 articles were deemed to meet the inclusion criteria. Following a full-text review, eight articles were retained for data extraction and included in the final analysis.

[2] These authors contributed to Question 2: Simon Garceau, Abtin Alvand, Claudia Arias Calderón, Gabriel Baron, Brent Benavides, Camilo Restrepo, Antonio Russo

DAIR

A DAIR is an enticing option in UKA PJI. However, limited literature is available evaluating this approach [19]. Assadollahi et al. evaluated DAIR in the setting of early UKA PJI, demonstrating an 88% 1-year survival free from all-cause revision [20]. At 5-year follow-up, however, 37.5% (n = 6) underwent revision for PJI, with an additional two patients undergoing aseptic revision. This translates to a 57% 5-year survival free of all-cause revision [20]. Brivio et al. reported more encouraging results [21]. The authors reported on 19 patients treated with DAIR following acute PJI, defined as less than eight weeks postoperatively. Overall, 84.2% were free from septic reoperation at a mean of 32.5 months postoperatively. There were three patients (16%) who underwent a second DAIR within 20 days of surgery [21]. There were no patients who had undergone repeat DAIR and required septic reoperation at final follow-up. There was one patient who underwent conversion to TKA for progression of arthritis [21]. Hernandez et al. evaluated 11 patients treated with DAIR, with 64% being free from infection at five years [22]. There were two patients who developed progressive arthritis and underwent conversion to TKA [22]. McCormick et al. reported on a 52-patient series of UKA PJI treated with DAIR. The mean time to DAIR from diagnosis was 11.1 weeks [19]. There were 42 patients (81%) who were infection-free, defined as normal inflammatory markers and no clinical infectious symptoms, at 1-year follow-up. When methiciline-resistant Staphylococcus aureus was the causative organism, DAIR failure was 80% [19]. Notably, of those treated successfully with DAIR, 15% required conversion to TKA secondary to arthritis progression, with 83% undergoing conversion within 1 year [19].

Single-stage revision

A single-stage revision to TKA has shown some promise in small case series, but the available literature remains limited. Kocoaglu et al. reported on 15 patients who underwent single-stage exchange for culture-positive PJI [23]. All patients underwent radical synovectomy and received a hinged TKA. Overall, 93.3% of patients were infection-free at a mean follow-up of eight years. Survival free of any reoperation at five years was 80% [23]. A similar protocol by Labruyère et al. treated nine patients who had chronic PJI and included five patients who had previously undergone failed DAIR [24]. A single-stage exchange to a posterior-stabilized TKA was performed in all cases. At 60-month follow-up, all patients were infection-free, and no septic reoperations were required [24].

Two-stage revision

Although two-stage revision is commonly used in the treatment of TKA PJI, there is limited data for its use in UKA PJI. Cavagnaro et al. reported on 16 patients who had chronic or delayed UKA PJI, defined as per the Zimmerli classification [25]. All patients were treated with a two-stage revision with a minimum of 6 weeks of antibiotics and a 2-week "antibiotic holiday" before second-stage reimplantation [25]. Reimplantation was performed using either a condylar constrained or posterior-stabilized TKA. At 24-month follow-up, the rate of infection control was 100% [25]. Hernandez et al. evaluated two-stage exchange in four patients, achieving a 100% rate of infection eradication at five years postoperatively [22]. There was one patient who required two revisions for aseptic loosening and metallosis. The authors also evaluated three cases of two-stage revision after failed DAIR [22]. Of these, two became reinfected and necessitated further surgical intervention (one repeat two-stage exchange and one DAIR), leading to eventual infection-free status at final follow-up [22].

Conclusions

Available evidence suggests that DAIR should be avoided in the chronic setting or in cases with methiciline-resistant Staphylococcus aureus-positive cultures. In the acute setting, DAIR success is improved. However, 5-year survival free from revision surgery is suboptimal, with a large percentage of patients requiring revision surgery for recalcitrant infection or degenerative arthritis. Available evidence is more promising for the use of single- and two-stage revision, with excellent rates of infection control at 1- and 5-year follow-up. In summary, while UKA PJI remains a condition that is difficult to treat, single- or two-stage revisions provide more robust infection-free and revision-free results compared to DAIR.

Question 3: What is the optimal management of patients undergoing revision arthroplasty for presumed aseptic failure in whom a single culture isolates an organism?[3]

Response/Recommendation

Assuming that the patient undergoing revision had a negative workup for periprosthetic joint infection (PJI) and only one out of at least three cultures turned positive, then the single culture can be ignored. The circumstances when a single positive culture may lead to the need for additional antibiotic treatment are when the isolated organism is the same as the original infective organism, and/or PJI could not be ruled out with confidence before surgery.

Level of Evidence: Limited

Delegate Vote: Agree 85%, Disagree 9%, Abstain 6% (Super Majority, Strong Consensus)

Rationale

Periprosthetic joint infection (PJI) may be present in patients undergoing revision THA and TKA for aseptic failure, even when preoperative workup is negative [26]. Since the treatment of septic and aseptic failure differs markedly, an accurate diagnosis is essential for proper management. Therefore, it is recommended that intraoperative samples be sent for culture in all revision THA and TKA cases, regardless of the suspected cause of failure [27]. Current guidelines define a single positive culture as a "minor criterion" for PJI, contributing two points to a score that classifies a joint as "infected" if it reaches six or more points [28]. Patients who meet the criteria for PJI should be treated accordingly. However, the optimal management of patients undergoing revision arthroplasty for presumed aseptic failure where a single culture isolates an organism (in the absence of other supporting criteria for PJI) remains uncertain.

There were 12 studies that evaluated this patient population. Of the included 10,228 presumed aseptic revisions, single positive cultures occurred in 860 cases (8.4%). The most commonly isolated pathogens were slow-growing bacteria, predominantly coagulase-negative *Staphylococcus* and *Cutibacterium acnes*. There were 10 studies that reported no statistically significant influence on the revision-free survival (RFS) or infection-free survival (IFS) following a single positive culture. Goh et al. conducted a retrospective review of patients at their institution who underwent presumed aseptic revision THA and TKA and compared the outcomes of patients who had a single positive culture (n = 196) or multiple positive cultures for distinct organisms (n = 19) to those who had negative cultures (n = 3,019). No patients who had positive cultures were treated with antibiotics [29]. The authors demonstrated no significant difference in all-cause reoperation (14.0 versus 12.3%, $P = 0.484$) or PJI (3.3 versus 1.9%, $P = 0.151$) between the groups at a mean follow-up of 10.8 years. Furthermore, single culture positivity was not associated with the rate of all-cause reoperation (odds ratio (OR) 0.995, 95% confidence interval (CI) 0.606 to 1.635, $P = 0.985$) or PJI (OR 0.662, 95% CI 0.231 to 1.898, $P = 0.443$) on multivariate regression analyses. In their cohort of single-component THA or TKA revisions, Vargas-Reveron et al. demonstrated that the presence of a single positive culture (n = 35) was not associated with a higher re-revision rate at five years than in those who had negative cultures (n = 97) (5.7 versus 3.1%, $P > 0.05$). There were six patients who had a single positive culture and were treated with antibiotics for four weeks [30]. Leal et al. and Wu et al. each performed a retrospective study of patients who had unsuspected positive intraoperative cultures in presumed aseptic revision THA and TKA using a database from the same single tertiary academic medical center. When comparing 5-year IFS between patients who had a single positive culture with a new organism (hip: n = 59, knee: n = 49) and negative cultures (hip: n = 530, knee: n = 630), there was no difference for both the hip (86 versus 92%, $P = 0.400$) and the knee (89 versus 96%, $P = 0.390$) cohorts. However, patients who had a single positive culture with the same organism from a prior PJI (n = one) had a significantly lower 5-year IFS when compared to patients who had negative cultures (0 versus 92%, $P < 0.001$). Cox proportional hazards regression analysis suggested that a single positive culture did not increase the likelihood of subsequent revision for infection in the hip cohort (hazard ratio = 1.27, 95% CI 0.555 to 2.910, $P = 0.570$), but it did in the knee cohort (hazard ratio = 4.2, 95% CI 1.285 to 13.960, $P = 0.018$). Of the 59 hip patients and 49 knee patients who had single positive cultures, 18 and 13 were treated with postoperative antibiotics, respectively. The one patient who had a single positive culture with the same organism from a prior PJI was not treated with postoperative antibiotics [31,32]. In separate studies, Neufeld et al. retrospectively reviewed patients at their institution who underwent presumed aseptic THA and TKA revisions to assess the impact of unexpected positive cultures on outcomes. There were 62 knee revisions with a single positive culture, 18 of which were treated with postoperative antibiotics (56% oral antibiotics alone, 100% for less than six weeks), and 74 hip revisions with a single positive culture, 15 of which received postoperative antibiotic treatment (40% oral antibiotics alone, 73% for less than six weeks). In the knee cohort, three patients who had a single positive culture developed a subsequent PJI, none of which was caused by the same organism identified at the time of revision. In the hip cohort, eight patients who had a single positive culture developed a subsequent PJI, only two of which were caused by the same organism identified at the time of revision. There was no patient who had a single positive culture and was treated with observation alone who developed a subsequent PJI from the same organism identified at the time of revision. However, they did not include patients who had negative cultures as a control, so comparisons between the groups could not be made [33,34]. For patients undergoing revision TKA after unicompartmental arthroplasty, Lara-Taranchenko et al. demonstrated no difference in the risk of re-intervention between patients who had a single positive culture (n = eight) and those who had negative cultures (n = 254) (0 versus 3.2%, $P = 0.84$) at an average follow-up of 8.3 months. There were no patients who had single positive cultures that were treated with postoperative antibiotics [35]. In their cohort of TKA revisions for presumed aseptic failure, Kloos et al. had 35 patients who had a single positive culture, none of whom received postoperative antibiotics or were re-revised for PJI at two years. Patients who had a single positive culture of a virulent organism were treated as infected in their study [36]. Hoch et al. investigated patients undergoing presumed aseptic revision

[3] These authors contributed to Question 3: Jason M Jennings, Benjamin Ricciardi, Edward Vasarhelyi, Georgios Komnos, George Babis, Rajeev K Sharma, Udit Vinayak, Nicholas C Arpey

arthroplasty in which *Cutibacterium acnes* was identified on a single positive culture. Contamination was defined as a single positive culture in the absence of two or more clinical criteria suggesting infection (elevated inflammatory markers, intraoperative abnormalities, local signs of infection, or a history of two or more prior local surgeries). There were none of the 16 patients who had single positive cultures that were revised for PJI at a minimum 2-year follow-up, irrespective of treatment with postoperative antibiotics [37]. Schwarze et al. also conducted a retrospective review of patients at their institution who underwent presumed aseptic revision THA and TKA. The authors found that a single positive culture had no influence on 2- and 5-year RFS for both hip and knee patients when compared to the cohort with negative cultures (hip: 66.2 versus 76.7 and 59.8 versus 70.6%, $P = 0.13$; knee: 78.4 versus 76.6 and 59.9 versus 63.5%, $P = 0.85$). Similarly, a single positive culture had no influence on 2-year IFS for both hip and knee patients when compared to the group with negative cultures (hip: 90.9 versus 95.4%, $P = 0.17$; knee: 91.9 versus 96.7%, $P = 0.79$). Of the 119 cases of single positive cultures in their cohort, 59 patients received antibiotic treatment. Postoperative antibiotic treatment did not demonstrate a significant influence on IFS at 2-year follow-up (no antibiotic treatment, 95.0% infection-free survival; antibiotic treatment, 85.8% infection-free survival, $P = 0.2$) [38].

The other two studies reported a statistically significant influence of a single positive culture on RFS and IFS. In their retrospective review of presumed aseptic revision THA from a national registry, Milandt et al. found an increased risk for all-cause re-revision (relative risk (RR) 1.73, 95% CI 1.07 to 2.80, $P = 0.020$) and re-revision due to PJI (RR 2.44, 95% CI 1.02 to 5.84, $P = 0.045$) at 1-year follow-up for patients who had a single positive culture compared to patients who had negative cultures. Interestingly, patients who had two or more positive cultures did not have an increased risk of all-cause re-revision (RR 1.52, 95% CI 0.82 to 2.80, $P = 0.180$) or revision due to PJI (RR 2.28, 95% CI 0.81 to 6.43, $P = 0.120$) at 1-year follow-up when compared to patients who had negative cultures. Of the 170 patients who had a single positive culture, 42 were prescribed postoperative antibiotics. Revisions with two or more positive cultures (57 out of 112, 51%) were more likely to be prescribed antibiotics than patients who had a single positive culture (42 out of 170, 25%) or negative cultures (486 out of 2,023, 24%) ($P = < 0.001$). There was no difference in the prevalence of postoperative antibiotic treatment between the single positive-culture patients and negative-culture patients ($P = 0.840$) [39]. Hipfl et al. conducted a retrospective analysis of patients undergoing revision THA for presumed aseptic loosening at their institution and compared outcomes of patients who had a single positive culture with a low-virulence organism (n = 37) or multiple positive cultures for different organisms (n = four) to those who had a low-grade infection (defined as two positive cultures or a single positive culture with a high-virulence organism, n = 36) or negative cultures (n = 197). They demonstrated a 7-year IFS of 87.4% in patients who had a single positive culture, 94.4% in patients who had a low-grade infection, and 97.5% in patients who had negative cultures ($P = 0.021$). There were no patients who had single positive cultures who were treated with postoperative antibiotics, whereas patients with low-grade infections received six weeks of targeted antibiotic treatment [40].

Conclusions

Most studies reviewed demonstrate no statistical difference in RFS or IFS for patients undergoing revision THA and TKA due to presumed aseptic failure, where a single culture isolates an organism in the absence of other supporting criteria for PJI. However, all of the studies are retrospective, the majority utilize a single-institution database, and each has its own approach to postoperative management. Some patients who had single positive cultures are observed, while others are treated with four to six weeks of postoperative antibiotics. It is important to note that two studies demonstrate an increased risk of re-revision for PJI in patients who had single positive cultures, which the authors believe could potentially be reduced if postoperative antibiotic treatment for them was more consistent. While the data clearly suggest that another operation is not necessary for patients who had single positive cultures following revision THA or TKA, the optimal management of these patients (i.e., observation versus antibiotics) is unclear. Treatment is based largely on clinical suspicion and surgeon preference. Care should be taken if a single culture yields a virulent organism or the same organism that was isolated in a prior PJI, as this could represent a true PJI.

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The Journal of Arthroplasty 41 (2025) S437–S442

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Hip and Knee

2025 ICM: Monitoring and Declaring Success

Laurens Manning, Pablo A. Slullitel, Martin A. Buttaro, Theofilos Karachalios, Richard Kuehl, Dominic Meek, Roberto Olivetto, Nicolás S. Piuzzi, Daniel Rienzi, Antonio Russo, Antonio Solano, Danguole Vaznaisiene, Jesse Wolfstadt

Question 1: What tool or instrument should we utilize to determine the success of the treatment of patients who have periprosthetic joint infections (PJIs)?[1]

Response/Recommendation

We recommend that patient-reported outcome measures (PROMs), informed by consumers, should be prioritized over infection eradication, unplanned operations, and ongoing antibiotic use in the next generation of reporting tools for PJI.

Level of Evidence: Low

Delegate Vote: Yes: 86.6%, No: 8.8%, Abstain: 4.4%

Rationale

Standardized reporting of outcomes following PJI is essential to enable comparisons between different treatment modalities and for understanding geographical and temporal trends for PJI outcomes. This need applies to observational, epidemiological, and randomized controlled studies. Numerous approaches to defining 'success' as a dichotomous composite outcome have been proposed, which have variably included infection eradication, the need for ongoing antibiotics, laboratory and radiological findings, or the need for further surgical management as individual components. In preparation for International Consensus Meeting meetings in 2013 and 2018, the Musculoskeletal Infection Society proposed reporting tools, both of which attempted to account for the multidimensional nature of outcomes for managing PJI, largely defined by clinicians and experts [1,2]. To date, PROMs such as joint function or quality of life have not been included as part of standard outcome reporting tools, and (to our knowledge) consumers have not been involved in proposing relevant outcomes.

To evaluate which tool or instrument should be utilized as a reporting tool to determine success, we performed a systematic review. PubMed and Embase databases were searched from 1990 to December 2024. Studies were limited to humans and in English. Randomized controlled trials (RCTs) were included, regardless of language or time period. After being imported into Covidence and deduplication, titles and abstracts were reviewed. Publications were included in the narrative synthesis if they were (1) RCT or large (> 500 participants) prospective observational studies, (2) systematic reviews or comparisons between PJI outcome reporting tools, (3) Delphi or consensus studies proposing outcomes, or (4) studies of consumer preferences of patient-reported outcomes for PJI. Citations within these papers and the 'gray literature' were also searched. There were 15 publications included in the final narrative synthesis (Figure 1). Due to variation in aims and methodologies, no quantitative synthesis was performed. Of note, the search strategy captured only two RCTs [3,4]. However, a systematic review of the design characteristics of the published 15 PJI RCTs highlights the variation in outcome reporting across PJI literature. Terms including 'cure,' 'remission,' 'clinical success,' 'treatment failure,' and 'reinfection' were used as synonyms for a good or poor outcome where a dichotomous outcome was reported, but there was no consistency in how these were determined [5]. Only one trial used a PROM as a primary endpoint [6].

In 2013, a Delphi consensus among clinical experts proposed an outcome reporting tool for success, consisting of all of the following: eradication of infection, no PJI-related mortality, and no subsequent surgical intervention after reimplantation surgery [1]. A critique of this tool is that it only applies to PJI managed with 2-stage revision; patients managed with debridement and implant retention or single-stage revisions are unclassifiable. A subsequent 4-tiered multidimensional tool was discussed at the 2018 International Consensus Meeting [7] and subsequently published in 2019 [2]. This tool achieved strong consensus among the delegates. Success was defined as tiers 1 and 2, which included infection control without and with continued antibiotic therapy, respectively. There were six substrata within tier 3 that were proposed to account for the need for, and timing of, subsequent unplanned operations. Tier 4 is related to all-cause mortality.

In the present review, we identified two retrospective studies that compared success rates between these reporting tools for patients undergoing 2-stage revision procedures [8,9]. Both reported lower 'success' for 2013 (55 and 56%, respectively)

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2025.10.104.

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https://doi.org/10.1016/j.arth.2025.10.104
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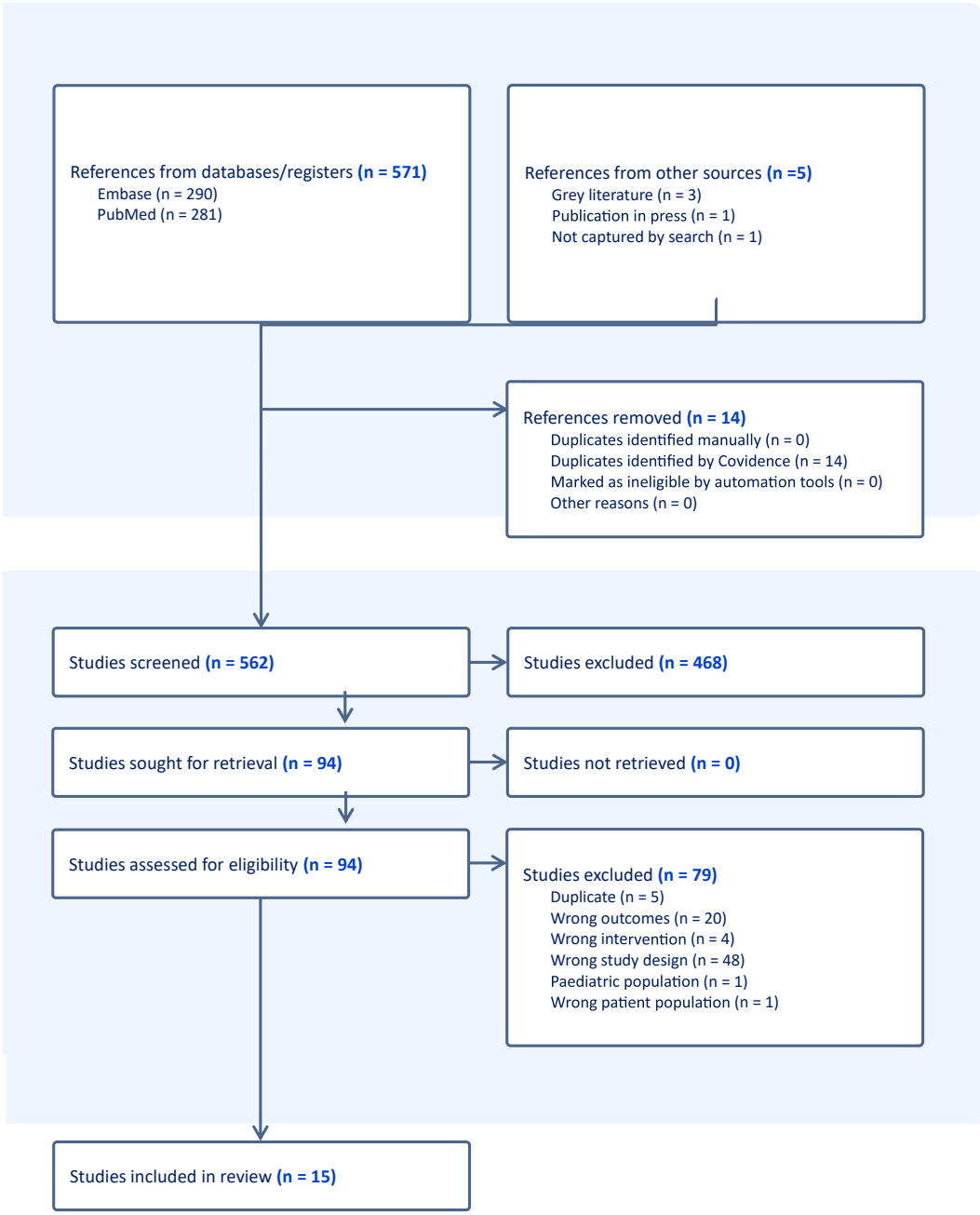

Figure 1. PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

compared with the 2019 reporting tool (70 and 81%, respectively). In another evaluation of the 2019 outcome reporting tool, a recent systematic review extracted data from 245 PJI studies and applied the reported outcomes to the 2019 tool. Across all of these studies, tier 1 (40.7%) and tier 3 (54.5%) are the dominant criteria defining success. After adjusting for other factors, studies with stricter definitions had lower PJI treatment success. Tiers 2 and 4 definitions were infrequently used [10]. The authors also noted that study quality, reflected by the methodological index for non-randomized studies score, did not improve, concluding the need for improved study design and clarification of the definition of treatment success [10].

The negative impacts of PJI on PROMs are well documented but rarely applied as endpoints in clinical studies. One of the challenges in standardizing PROMs as accepted endpoints is the variety of tools available, though Oxford Joint Scores and Western Ontario and McMaster University as joint scores, and SF-12 and EQ-5D as quality of life (QoL) scores, are widely used. The Oxford Scores have a comprehensive evidence base to support their use following arthroplasty, but their use as tools for monitoring the impact and outcomes following PJI is less clear. The QoL scores are normalized to age-adjusted norms, enabling direct comparisons with the general age-matched population. Joint scores may be constrained by a skewed distribution and a ceiling effect.

In this review, we identified analyses from a large prospective study of PJI in New Zealand and Australia, which looked at Oxford Joint Scores [11] and SF-12 scores collected at baseline and 12 months [12]. In addition to reporting absolute values at 12 months and change scores, the authors proposed 'good' dichotomous outcomes, which could be applied in clinical trials. Based on

previously defined thresholds anchored to patient-reported treatment success, a successful outcome at 12 months was defined for knee PJI cases as an OKS at 12 months of > 36 or an improvement from baseline of > nine, and for hip PJI, an OHS of > 38 or an improvement of > 12 [13]. For SF-12 scores, a good QoL was an SF-12 PCS score of > 50 on the SF-12 version 2 (that is, above the age-adjusted population mean) or an increase of > 8.9 or more from baseline. In both, conventional reported success was strongly associated with 'good' PROMs.

We identified a study that reported a Delphi analysis and discrete choice experiments of a desirability of outcome ranking (DOOR) score among clinical experts. In order of importance, the ordinal DOOR score prioritized all-cause mortality, patient-reported joint function, and clinical cure into a 5-point ordinal score that could be applied in comparative observational studies and clinical trials [14].

The importance of patient involvement in defining the most meaningful endpoint is highlighted in a recent manuscript identified as part of the broader search. This methodologically robust qualitative study sought to analyze experiences of patients at least one year from PJI diagnosis. In defining successful PJI management, patients consistently emphasized the importance of function, pain relief, mobility, and independence. There were nine patients (33.3%, $P < 0.001$) who did not agree with their 2019 reporting tool classification of success versus failure, mainly because it did not capture factors associated with their QoL post-treatment [15]. Finally, efforts to define core outcome sets for reporting PJI were identified in the gray literature. The results of these are awaited, but crucially, in these Delphi analyses, consumers who have a lived experience of PJI, as well as clinical experts [16,17].

Defining the optimal tool to define the success of treatment for patients with PJI is difficult due to the multidimensional nature of the goals of therapy, which include infection eradication, optimal function, and QoL, as well as consideration of resource utilization. Currently used reporting tools have been widely used but do not include PROMs and have not been informed by consumers who have lived experience of PJI.

We recommend that PROMs, which are informed by consumers, should be prioritized over infection eradication, unplanned operations, and antibiotic use in the next generation of reporting tools for PJI. We note that defining a 'good' outcome for PROMs may present major challenges. Other approaches, such as an ordinal score (DOOR), which integrates PROMs with traditional measures of success, have promise. In situations where traditional definitions of success are applied, we recommend complete transparency in how each of the dimensions is ascertained. For definitions of success, each component of the composite should be reported separately.

Question 2: How soon after treatment of patients who have periprosthetic joint infection can success be declared?[2]

Response/Recommendation

Failure after surgical management of patients who have periprosthetic joint infection can occur at any time. For assessing the success of surgical treatment, we recommend a minimum follow-up period of five years. For the purpose of comparative efficacy trials or evaluation of novel technologies for regulatory approval, we recommend a minimum of 1-year follow-up.

Level of Evidence: Moderate

Delegate Vote: Agree: 88.7%, /Disagree: 8.5%, /Abstain: 2.8%

Rationale

The definition of success after treatment of prosthetic joint infection (PJI) depends on multiple factors and is irrespective of treatment strategy (one-stage exchange, two-stage exchange, or debridement, antibiotics, and implant retention [DAIR]). Success has been defined in several forms (Musculoskeletal Infection Society Outcome Reporting Tool, Delphi-based consensus definition, microbiological success, implant success, and surgical success), including the combination of normal laboratory and clinical evidence of infection control following treatment and/or the absence of septic revision surgery (with or without implant revision/removal) or infection-related death or unplanned outcome [18–20]. It has been shown that success rates vary dramatically depending on the definition used to evaluate outcomes [19]. Although external validations and agreements on what tool is best to report success after treatment of PJI are still necessary, an issue that has been barely considered in the definition of success is time. Diaz-Ledezma et al. [18] reported that 71% of the participants in a consensus meeting agreed that two years was an acceptable time period after definitive surgery for PJI when considering short-term results. In this study, follow-up durations of two, five, and 10 years were classified as short-, mid-, and long-term, respectively. Tan et al. reported that getting a lengthy follow-up in this patient population is very difficult, with 355 of 570 patients having a 2-year follow-up, 166 of 570 reaching a 5-year follow-up, and only 27 of 570 patients having a 10-year follow-up [19]. In this sense, the follow-up time required to define success remains unknown.

Therefore, to answer the posed question, we performed a systematic review of the literature on the treatment outcomes of DAIR, one-stage, and two-stage exchange treatment strategies with a specific focus on time to failure. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we conducted a systematic search of the online bibliographic databases MEDLINE, Embase, and PubMed from inception through November 2024 to identify studies reporting on survival analysis (Kaplan–Meier, cumulative incidence, Cox regression, or similar analyses) with $\geq$ two years of follow-up after treatment of acute and/or chronic PJI. There was no research ethics board approval necessary. Exclusion criteria consisted of studies reporting outcomes without time-to-event analyses, editorials, commentaries, case reports, reviews, and technique articles. There were two of the authors who independently screened the titles and abstracts of an initial number of 7,746 articles to apply the selection criteria. Disagreements were solved by consensus after reading the full text. We reviewed the full text of 93 articles and finally included 57 articles for analysis.

There were 12 articles reporting on septic events that continued to appear after the first two years of follow-up for all types of PJI treatment strategies [21–32]. In two different studies, Xu et al. showed no substantial improvement in the success rates of PJI treated in a 20-year period [32], highlighting that, given the difficulty with obtaining proper follow-up, a 1-year follow-up was sufficient for an accurate reporting of treatment failure [31]. In the latter study, although Kaplan–Meier curves had an abrupt drop in the initial months and plateaued after 1.09 years (irrespective of treatment type), failures continued to appear even five years after treatment, especially following DAIR surgery [31]. In a retrospective cohort study of 108 polymicrobial PJIs, Tan et al. reported infection-free survival rates of 52.2% (95% confidence interval [CI] 42.1 to 62.3) at the 2-year follow-up, 49.3% (95% CI 39 to 59.6) at the 5-year follow-up, and 46.8% (95% CI 35.9 to 57.7) at the 10-year follow-up [12]. Similarly, Cochran et al. described a retrospective cohort of 16,622 total knee arthroplasty patients, reporting that patients undergoing DAIR had a higher risk of failure when

[2] These authors contributed to Question 2: Pablo A. Slullitel, Nicolás S. Piuzzi, Laurens Manning, Theofilos Karachalios, Daniel Rienzi, Antonio Russo, Antonio Solano, Roberto Olivetto, Martin A. Buttaro

compared to one- and two-stage strategies ($P < 0.001$), with failure rates of 28.2% at one year, 34% at two years, 41.7% at five years, and 43.2% at six years after treatment [21]. Alternatively, the risks of reinfection were 24.6% and 19% at one year and 38.3% and 29.1% at six years for one- and two-stage revisions, respectively [21]. In other words, survival rates continued to decrease in all treatment types during the first five/six postoperative years. In all these studies, risk factors for failure included polymicrobial infections, Gram-negative bacteria, streptococcal and enterococcal infections, and non–biofilm-active antibiotic treatment, all of them irrelevant to time to failure [23–26,31,32].

There were seven studies that focused specifically on the five- to 10-year infection-free survival after one-stage exchange [16–22]. In a study of 87 chronic PJIs treated with one-stage exchange with antibiotic-impregnated allograft, Dersch and Winkler reported an infection-free survival of 93.9% (95% CI 88.8 to 99.1) at one year, 89.9% (95% CI 83.2 to 96.6) at two years, and 81.5% (95% CI 72.1 to 90.9) at five years [33]. In a similar study of 84 cases who underwent single-stage revision total knee arthroplasty, the Kaplan–Meier infection-free survival was 97.6% at one year (95% CI 90.8 to 99.4), 91.1% at five years (95% CI 81.8 to 95.6), and 88.3% at 12 years (95% CI 76.6 to 94.3) [34]. Likewise, Slullitel et al. analyzed 88 one-stage hip revisions and reported a cumulative incidence of septic failure of 8% (95% CI 3.5 to 15) at one year, 13.8% (95% CI 7.6 to 22) at two years, and 19.7% (95% CI 12 to 28.6) at five and 10 years of follow-up [35]. Only Ohlmeier et al. showed that survival rates stayed stable after the first two postoperative years in 101 patients who had infected rotating-hinge knee prostheses, with a survival rate of 90% (95% CI 83 to 97) both at two and six years. Overall, these studies showed that survival curves had most infection relapses occurring within the first five postoperative years, with some additional septic failures occurring between the sixth and tenth years of follow-up [33–39].

There were 27 articles that analyzed the survival rates after two-stage revision surgery [38,40–57]. In two different studies analyzing the long-term results of two-stage revisions, Petis et al. reported a cumulative incidence of reinfection of 10% at one year, 14% at five years, and 15% at 10 and 15 years in chronic hip PJIs; and a cumulative incidence of reinfection of 4% at one year, 14% at five years, 16% at 10 years, and 17% at 15 years in chronic knee PJIs [54,55]. Correspondingly, in a retrospective cohort of 96 chronic hip PJIs, Slullitel et al. reported a cumulative incidence of 14% (95% CI 8 to 22) at one year, 18% (95% CI 11 to 27) at two years, 22% (95% CI 14 to 31) at five years, and 23% (95% CI 15 to 33) at 10 years, highlighting that if there were no recurrent infections within the first five years after a reimplantation, the chances of having a reinfection thereafter were remote [58]. In another study of 97 joints treated with two-stage exchange, Garvin et al. reported that seven out of twelve failures occurred at a late follow-up (> five years after reimplantation), with an estimated 10-year cumulative incidence of reinfection of 14% (95% CI, 7 to 23) [44]. Thus, the authors highlighted that late PJI may recur more than five years after reimplantation, and therefore, patients should be counseled about the importance of ongoing follow-up [44]. In general, all of the included studies on two-stage exchanges showed survival curves with relapses occurring mostly within the first five postoperative years [2,40–65].

There were 11 articles that focused primarily on the survival rates of irrigation and debridement procedures for acute PJIs [66–76]. In two similar studies, Grammatopoulos et al. performed a survival analysis of periprosthetic hip infections treated with DAIR, showing five- and 10-year implant survivals of 85% (95% CI 78 to 92) and 77% (95% CI 68 to 86), and 89% (95% CI 82 to 96) and 78% (95% CI 88 to 98), respectively [69,70]. In a registry study of 5,406 acute PJIs, it was shown that the cumulative incidences of developing an infection-related event were 48% (95% CI 42 to 54) at eight years after a DAIR following a total knee arthroplasty and 42% (95% CI 37 to 46) at four years following a total hip arthroplasty [67]. In addition, Weston et al. analyzed the results of DAIR with chronic antibiotic suppression for infected knee arthroplasties and reported a cumulative incidence of recurrent infection (with death as a competing risk) of 13% at 90 days, 18% at one year, and 34% at five years [76]. Although some have reported that most septic failures after DAIR occur within the first two years of follow-up [71,75,76], it seems clear in the literature that DAIR procedures require a longer-term follow-up in order to fully discard an eventual relapse [66,68,73]. This concept is especially applicable for those requiring chronic suppressive antibiotic therapy, in which failure events continue to appear after the fifth year of follow-up [77].

In conclusion, it seems that a 2-year follow-up is not enough to declare success after treatment of PJI. In fact, one- and two-stage revision surgeries may require at least five years of follow-up, while those undergoing DAIR and in need of chronic suppressive antibiotics might even need longer-term follow-ups. However, for the purpose of comparative efficacy trials or evaluation of novel technologies, especially those requiring regulatory approval, a 1-year outcome may be adequate to assess the efficacy and safety of a given technology in the setting of a randomized controlled trial [78], noting that a thorough power analysis is essential, as multiple failures can occur beyond the 1-year mark, reflecting the potential fragility of results.

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The Journal of Arthroplasty 41 (2025) S443–S447

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Hip and Knee

2025 ICM: Antimicrobial Therapy Options in Special Circumstances

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Question 1: What is the optimal antimicrobial treatment for patients who have culture-negative (CN) periprosthetic joint infections (PJIs)?[1]

Response/Recommendation

For the treatment of CN PJI, the antibiotics should be selected to have a broad-spectrum activity against both gram-positive and gram-negative organisms. Consideration should be given to a combination of multiple drug regimens, including a glycopeptide, for example, vancomycin. The regimen choice should be individualized based on risk factors, previous history, and knowledge of the local epidemiology.

Level of Evidence: Weak

Delegate Vote: Agree: 88.5%, Disagree: 7.6%, Abstain: 3.8%, (Super Majority, Strong consensus)

Rationale

While identifying the causative microorganism is central to the management of PJI, a substantial proportion of cases, CN PJI, fail to yield identifiable pathogens during routine microbiological testing. The reported prevalence of CN PJI ranges from 5 to 42%, reflecting variations in diagnostic protocols, patient populations, and laboratory methodologies [1–3]. This lack of microbiological confirmation poses challenges in choosing effective antimicrobial therapies, increasing the reliance on empirical and often broad-spectrum treatment regimens.

Management of CN PJI after knee and hip arthroplasty generally requires a multidisciplinary approach involving surgical intervention and antimicrobial therapy. Empirical antimicrobial therapy for CN PJI commonly includes broad-spectrum intravenous (IV) antibiotics, such as vancomycin for gram-positive coverage and cephalosporins or fluoroquinolones for gram-negative pathogens. This is typically followed by long-term oral therapy with agents like rifampin and levofloxacin [1,2,4]. The use of local antibiotic delivery through antibiotic-impregnated cement spacers or beads complements systemic therapy by achieving high local drug concentrations and reducing systemic toxicity [1,3]. Despite these strategies, the lack of pathogen-specific guidance often results in longer treatment durations, increased risk of adverse drug reactions, and uncertainty about treatment efficacy.

Current evidence suggests that CN PJI outcomes are comparable to those of culture-positive PJI when robust treatment protocols are employed [3,5]. However, major gaps persist in standardizing diagnostic and therapeutic approaches. Molecular diagnostic methods and multidisciplinary care are essential to advancing the management of CN PJI. This article reviews existing literature to explore the treatment strategies for CN PJI after knee and hip arthroplasty, with a focus on antimicrobial interventions and their respective outcomes.

We included 25 studies in our final analyses [2–4,6–27]. All studies are retrospective cohort studies. Most studies reported CN PJIs in both hip and knee arthroplasties. Cultures were obtained during one- or two-stage resection arthroplasty or even amputations. Tan et al. was the largest cohort (N = 219). They identified the prevalence of suspected CN PJIs as 22%, and according to the modified criteria of the Musculoskeletal Infection Society, the prevalence was 6.4% [3]. The prevalence of CN PJIs can be minimized with adequate culturing techniques [6]. Studies reported preoperative administration of antibiotics in nearly 53 to 68% of CN PJIs [2,4,7–10]. Berbari et al. reported a decrease in the number of CN PJIs with an increase in the duration of antibiotic-free intervals before the sampled culture [2].

The most used postoperative antibiotics were cephalosporins (8 to 85%), vancomycin/teicoplanin (7 to 70%), quinolones (3 to 7.4%), aminoglycosides (e.g., gentamicin) (7%), a combination of

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to doi: 10.1016/j.arth.2025.10.084.

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https://doi.org/10.1016/j.arth.2025.10.084
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antibiotics (7%), and others (e.g., linezolid, piperacillin–tazobactam, meropenem, cefoperazone–sulfbactam, and rifampicin). The antibiotic regimen started with a duration of parenteral therapy (two to six weeks), followed by another duration of oral therapy (12 weeks). The PJI recurrence rate in these studies ranged from 9 to 30.7% at follow-ups ranging from one to five years [2,4,7–11].

Studies by Ji et al. evaluated the role of adding an intra-articular antibiotic infusion to the systemic regimen of IV vancomycin given for a mean of 14 days. They added an intra-articular infusion of 0.5 gram imipenem and 0.5 gram vancomycin, alternately used in the morning and afternoon. This procedure was repeated for 16 days. This intra-articular infusion treatment was guided by serum and synovial markers. They reported that intra-articular vancomycin infusion avoided the systemic toxicity of its IV use and reached a higher level in the joint space, especially in immunocompromised patients and patients who have fungal infections [12,13].

A few studies have compared the results of treatment of CN PJIs to culture-positive PJIs and showed comparable PJI recurrence rates and good prognosis in treatment of CN PJIs with a similar regimen of 1st generation cephalosporin/glycopeptide (e.g., vancomycin or teicoplanin) [11,14,19,20,22]. All studies reported lower serum markers in CN PJIs at the time of presentation and a shorter time required for normalization with treatment. Many reports have chosen the broad-spectrum glycopeptide vancomycin as the first choice in the treatment of CN PJIs, with a no recurrence rate and a high success rate with a lower complication rate [4,28]. Reports also attributed the wide use of vancomycin in the treatment of CN PJIs to the recent high prevalence of methicillin-resistant *Staphylococcus aureus* and methicillin-resistant *Staphylococcus epidermidis* infection [13]. However, the prolonged use of broad-spectrum glycopeptide antimicrobials for extended periods requires further investigation and studies [14]. Antifungal coverage has been rarely described owing to the side effects of antifungal medicines. Li et al. have mentioned the use of meropenem and caspofungin intraoperatively in two-stage revision surgeries of CN PJI patients [15].

Prolonged treatment of PJIs with empirical broad-spectrum antibiotics, especially vancomycin and the piperacillin–tazobactam combination, has been associated with high renal and other complications [29]. The rate of antibiotic-related complications has been shown to be significantly higher in CN PJIs, reaching 59% compared to 11.3% in CP PJIs.

Recent developments in molecular techniques, like next-generation sequencing, hold promise for the identification of causative pathogens in CN PJI patients and delivery of targeted antimicrobial treatment, with the potential to reduce the rate of antibiotic-related complications [17,18,30]. In a study by Wang et al., next-generation sequencing helped the identification of pathogens in CN PJI patients, allowing a targeted antibiotic treatment against a specific pathogen that had a lower antibiotic complication rate and a lower cost compared to the empirical antibiotic-treated group [16]. Also, sonication of implants and disruption of biofilm in patients who have CN PJI have also been proposed as a strategy to help identify the organisms, allowing removal of biofilm and proper microbe identification [3]. On the other hand, positing the high success rate of treatment of CN PJIs, some investigators have argued against the use of expensive technologies like gene sequencing in patients who have CN PJIs and advocated for broad-spectrum empirical antimicrobial treatment [10]. The regimen choice should be individualized based on risk factors, previous history, and knowledge of the local epidemiology [31] and should be discussed in a multidisciplinary team including orthopedic surgeons, medical microbiologists, and infectious disease specialists.

Conclusions

The optimal management of patients who have CN PJI remains challenging and elusive. The antibiotics should be selected to have a broad-spectrum activity against both gram-positive and gram-negative organisms. Consideration should be given to a combination of multiple drug regimens, including a glycopeptide, for example, vancomycin, which plays a pivotal role and may provide a higher success rate in the treatment of CN PJI. However, with the expanding menu of organisms causing CN PJI, including fungi and atypical pathogens, the role of molecular techniques for identification of the causative pathogen and targeted antimicrobial delivery may be justified. In addition, the regimen choice should be individualized based on risk factors, previous history, and knowledge of the local epidemiology and should be discussed in a multidisciplinary team including orthopedic surgeons, medical microbiologists, and infectious disease specialists.

Question 2: Does intra-articular (IA) antibiotic infusion have a role in the management of patients who have periprosthetic joint infection (PJI)?[2]

Response/Recommendation

Yes. Intra-articular antibiotic infusion may be a safe and effective adjunct for managing PJI, delivering high local antibiotic concentrations with minimal systemic toxicity.

Level of Evidence: Moderate

Delegate Vote: Agree: 61.4%, Disagree: 24.6%, Abstain: 14.0% (Simple Majority, Low/No Consensus)

Rationale

Intra-articular antibiotic infusion has become an important adjunctive therapy in treating PJIs. By delivering high concentrations of antibiotics directly to the site of infection, it enhances the eradication of biofilm-associated pathogens while reducing systemic toxicity. Its applications have been explored in the context of both hip and knee arthroplasty, particularly in debridement, antibiotics, and implant retention (DAIR), single-stage revision, and two-stage revision [32].

In DAIR, which aims to retain the existing implant, IA antibiotic infusion has been explored as an effective method for managing acute infections and culture-negative cases. Mu et al. reported an infection control rate of 87.7% in early postoperative infections treated with IA vancomycin infusion combined with systemic antibiotics. This protocol utilized a three-way branch system to deliver antibiotics over 12 to 14 days, achieving high local antibiotic concentrations and supporting effective infection control in early PJI [33]. Similarly, Chaiyakit et al. investigated IA antibiotic infusion in patients who have acute hematogenous PJI following total knee arthroplasty, combined with DAIR. Antibiotics were infused over a 3-week period with dose escalation, achieving an infection control rate of 86.6% [34]. Perry et al. employed a pump system to deliver antibiotics continuously over eight to 15 weeks, reporting an infection control rate of 83.3% [35].

In single-stage revision, IA antibiotic infusion has demonstrated significant efficacy in managing chronic PJI in both hip and knee arthroplasty. Studies from China reported infection control rates ranging from 87.1 to 90.2%, effectively addressing multidrug-resistant organisms, polymicrobial infections, culture-negative PJIs, and patients who have multiple failed surgeries[36–40].

[2] These authors contributed to Question 2: Wenbo Mu, David Campbell, Carolyn Kramer, Li Cao, Stanislav Bondarenko, Oscar Murillo, Wei Huang

Notably, a success rate of 72.7% was achieved in fungal PJIs, underscoring its utility in challenging infections [41]. Particularly impactful in hip arthroplasty with cementless fixation, this approach eliminated reliance on high-dose antibiotic-loaded bone cement. Antibiotics were administered via a three-way branch system over 12 to 14 days, achieving therapeutic vancomycin concentrations in synovial fluid, with peak levels of 14,933.9 μg/mL and trough levels above 5,495.0 μg/mL at 24 hours, exceeding the minimum biofilm eradication concentration [42,43]. The safety profile was favorable, with no major systemic toxicity reported and a low incidence of acute kidney injury [44,45]. Antony et al. reported an 89% clinical cure rate using IA antibiotic infusion via Hickman catheters over four to six weeks combined with aggressive debridement in a single-stage revision [46]. Whiteside's team has employed IA vancomycin infusion via Hickman catheters since 1999, achieving clinical success rates up to 94.4%. Their protocol maintained synovial peak vancomycin concentrations of 9,242 μg/mL, with therapeutic trough levels sustained over six weeks. The infusion began at a low dose and was gradually increased over several days to a maintenance level, administered every 12 or 24 hours based on serum levels and patient tolerance. The safety profile was favorable, with minimal systemic side effects, and catheter-related complications, such as temporary occlusion and leakage, were uncommon [47–50].

In two-stage revisions, a multicenter randomized controlled trial assessed a 7-day IA antibiotic irrigation protocol for chronic PJI. High-dose antibiotics were intermittently delivered via a percutaneous catheter system immediately following debridement and prosthesis removal. The protocol demonstrated effective infection control by reducing inflammatory markers in the joint, preparing optimal conditions for second-stage reimplantation. The regimen was well tolerated, with no systemic toxicity or renal impairment, and all experimental group patients underwent reimplantation within seven to nine days, compared to a longer interval in the control group [51].

Intra-articular antibiotic infusion is a valuable adjunct in PJI management, providing high local antibiotic concentrations while minimizing systemic toxicity. Its efficacy across DAIR, single-stage, and two-stage revisions supports its role as an essential treatment strategy. However, standardization of infusion protocols, including antibiotic selection, dosing strategies, and duration, remains a challenge. Future research should focus on optimizing these parameters and evaluating long-term outcomes through randomized controlled trials.

Question 3: Is there a role for suppressive antibiotic treatment (SAT) only in patients who have periprosthetic joint infection (PJI)?[3]

Response/Recommendation

Yes. Suppressive antibiotic treatment (SAT) is a viable management option for a select group of patients who are not able to undergo definitive medical and surgical treatment for periprosthetic joint infection (PJI). The available literature on this topic is limited, and patients must be carefully selected based on specific medical and surgical criteria, together with careful follow-up to evaluate treatment tolerance and outcomes.

Level of Evidence: Limited

Delegate Vote: Agree: 92.5%, Disagree: 5.0%, Abstain: 2.5%

Rationale

Suppressive antibiotic treatment refers to the indefinite administration of antibiotics to prevent infection progression and to control the patient's symptoms who suffers from periprosthetic joint infection (PJI). The SAT may be appropriate in situations where patient comorbidities, the microbiology of the infection, or the inadequacy of the bone stock and/or soft tissues markedly hinder the possibility of definitive medical and surgical treatment. In such situations, SAT provides an alternative "noncurative" strategy to suppress the infection without removing the implant for as long as possible. To answer the above question (HK102), we conducted a comprehensive literature review across two databases (PubMed and Cochrane) using the Medical Subject Headings terms developed by our librarians. After screening the potentially eligible studies, 31 were included for full review and data extraction; ultimately, 11 articles were selected.

The success rate of the SAT varies widely, ranging from 23 to 86% [52–54]. This reported variability within the literature is due to differences in patient selection, small sample sizes, and a lack of documented adverse effects of antibiotics. The indications vary across different studies, but can be broadly divided into four scenarios.

(1) Elderly or extremely frail patients with significant comorbidities who are not suitable candidates for revision surgery.
(2) Surgical sequelae (or risks) are disproportionate to the symptoms.
(3) Patients who refuse surgery.
(4) Patients who have already undergone surgical treatment but in whom the likelihood of a definitive cure is considered extremely low.

In order to establish guidelines for long-term SAT, a number of criteria must be met. These include knowledge of infection etiology (though it is not essential), ensuring clinical adherence to treatment, monitoring progress, and having access to the appropriate antimicrobials [53]. Around 5 to 43% of patients experience major antibiotic side effects; hence, it is essential that tailor-made antimicrobial therapy is utilized based on the individual needs of patients [53]. Another approach described to avoid systemic side effects includes the use of subcutaneous SAT, local bacteriophages, or phage lysis as potential alternative treatments [55].

Most of the studies reviewed had a previous surgical procedure before receiving treatment with SAT [56]. In 52.2% of the cases where the SAT was utilized, the patients retained their implant [57]. Based on the available but limited evidence, the presence or absence of a sinus tract does not reliably predict treatment success [57]. In addition, SAT appears to have a positive effect on sinus closure [57]. The value of SAT is evidenced by the cases that were "rescued" through the application of SAT following the failure of alternative strategies [57]. In addition, SAT seems to help with pain resolution, but there is no significant difference observed in inflammation.

Suppressive antibiotic treatment failure, characterized by persistent uncontrolled infection symptoms, has an unidentified cause in 52% of patients [53]. In addition, 24% reported poor adherence to treatment, 12% developed resistance to antibiotics, and 11% had unexpected pathogens [53]. Also, SAT failure is approximately four times more common in patients who discontinue antibiotics [53]. The results of the latter study suggest that some patients who were not cured by procedures such as debridement, antibiotics, and implant retention may have benefited from SAT, which could either delay or prevent failure. In complex PJI cases with patients who are at high risk of failure after surgery, those treated with SAT had a better outcome, achieving a 68% success rate at five years [58,59]. In most of these studies,

[3] These authors contributed to Question 3: Claudia Arias, Craig Aboltins, Michael Henry, José Luis del Pozo, Daisuke Inoue, Andrew Porteous, Peng Xu, Koji Yamada

patients had undergone debridement surgery before starting SAT. Some studies demonstrated that the failure of the SAT was not associated with the absence of a previous debridement [55].

When reviewing the microbiological profile of the PJI cases in the available studies, outcomes of SAT appear to be better in patients who have an identified *Staphylococcus* sp. infection. The most commonly used oral antibiotic regimens for SAT were tetracyclines, sulfamethoxazole–trimethoprim, and β-lactams. Combination treatment with rifampin has also been reported, although it is important to remember that rifampicin alone should not be used due to the potential for developing resistance. The combination of rifampicin with β-lactams has been reported to yield better outcomes in large studies [60]. Literature indicates that antibiotic protocols can vary based on geographic region, and combining antibiotics is often not recommended to ensure good patient adherence to treatment [53].

Currently, no studies address the optimal dosage of antibiotics on SAT, nor is there clear guidance on the necessary duration of intravenous treatment. However, cessation of antibiotics for a period of time during SAT is generally not recommended [61,58] due to the risk of treatment failure. Factors associated with failure include age under 70 years, poor adherence to treatment (24%), and the etiology of the infection, such as gram-negative rods, fungi, or negative cultures; however, none of these factors are contraindications for SAT.

Conclusions

The available literature assessing the role of SAT in patients who have PJI and who are not suitable for definitive surgical treatment is limited. All the studies are retrospective in nature, with many reporting on small patient cohorts. Despite the paucity of high-level studies, there is sufficient evidence to suggest that for high-risk patients in whom surgical intervention is not an option, SAT can be a viable option for limb salvage and symptom control. These studies also demonstrate that long-term oral antibiotics can be safely utilized and are well tolerated by patients despite some side effects. The highest success rates are observed in patients who have "primary prostheses" *in situ*, as opposed to revision components. The most commonly used oral antibiotic regimens for SAT are tetracyclines, sulfamethoxazole–trimethoprim, and β-lactams. Some patients can also receive a combination treatment with rifampin for infections caused by gram-positive bacteria. In addition, the presence of a sinus tract does not appear to be a contraindication for the use of SAT. Further research is necessary to establish clear guidelines for the SAT for patients who have undergone previous surgical treatments, as well as those who have not.

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