DIAGNOSIS AND PREVENTION OF PERIPROSTHETIC JOINT INFECTIONS CLINICAL PRACTICE GUIDELINE

Adopted by the American Academy of Orthopaedic Surgeons Board of Directors

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Disclaimer

This clinical practice guideline was developed by a physician volunteer clinical practice guideline development group based on a formal systematic review of the available scientific evidence and accepted approaches to care. This clinical practice guideline is not intended to be a fixed protocol; some patients may require more or less treatment or different means of diagnosis. Patients in a given clinical scenario may not necessarily be the same as those found in a clinical trial. Patient care and treatment should always be based on a clinician's independent medical judgment, given the individual patient's specific circumstances.

Disclosure Requirement
In accordance with AAOS policy, all individuals whose names appear as authors or contributors to this clinical practice guideline filed a disclosure statement as part of the submission process. All panel members provided full disclosure of potential conflicts of interest prior to voting on the recommendations contained within this clinical practice guideline.

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SUMMARY OF RECOMMENDATIONS

RISK FACTORS FOR PJI

A. Moderate strength evidence supports that obesity is associated with increased risk of PJI.

Strength of Recommendation: Moderate ★★★☆
Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

B. Limited strength evidence supports that patients in which one or more of the following criteria are present are at an increased risk of periprosthetic joint infection after hip and knee arthroplasty:
- **Cardiac disease (arrhythmia, CAD, congestive heart failure, other)**
- **Immunocompromised status (other than HIV), including transplant, cancer**
- **Peripheral vascular disease**
- **Inflammatory arthritis**
- **Prior joint infection**
- **Renal disease**
- **Liver disease (hepatitis, cirrhosis, other)**
- **Mental health disorders (including depression)**
- **Alcohol use**
- **Anemia**
- **Tobacco use**
- **Malnutrition**
- **Diabetes**
- **Uncontrolled diabetes**

Strength of Recommendation: Limited
Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

C. In the absence of reliable evidence, it is the opinion of this work group that in the case that one or more of the following conditions are present, the practitioner should carefully consider the risk before proceeding with surgery:
- **Active infection (strongly caution against proceeding with surgery given the risks)**
- **Anticoagulation status, active thromboprophylaxis (proceed only after careful consideration of the risks)**
- **Autoimmune disease (proceed only after careful consideration of the risks)**
- **HIV status (proceed only after careful consideration of the control and risks)**
- **Institutionalized patients (proceed only after careful consideration of the risks)**
- **Prior bariatric surgery (proceed only after careful consideration of the risks)**

Strength of Recommendation: Consensus ★☆☆☆
Description: There is no supporting evidence. In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion

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D. In the absence of reliable evidence, it is the opinion of this work group that the following conditions have an unclear effect on risk of PJI:
- **Age (conflicting evidence)**
- **Dementia (insufficient evidence due to imprecise confidence intervals)**
- **Poor dental status (insufficient evidence for a recommendation)**
- **Asymptomatic bacteriuria (conflicting evidence)**

Strength of Recommendation: Consensus ★★★★

Description: There is no supporting evidence. In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion

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INJECTIONS PRIOR TO ARTHROPLASTY

Limited evidence suggests intra-articular injection performed prior to total joint arthroplasty may have a time-dependent association for increased risk of PJI.

Strength of Recommendation: Limited ★★★★

Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

BLOOD TESTS FOR PREOPERATIVE DIAGNOSIS

A. Strong evidence supports the use of the following to aid in the preoperative diagnosis of prosthetic joint infection (PJI):
- **Serum erythrocyte sedimentation rate (ESR)**
- **Serum C-reactive protein (CRP)**
- **Serum interleukin-6**

Strength of Recommendation: Strong ★★★★

Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention.

B. Moderate strength evidence does not support the clinical utility of the following to aid in the diagnosis of PJI:
- **Peripheral blood leukocyte count**
- **Serum tumor necrosis factor-α**

Strength of Recommendation: Moderate ★★★★

Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

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DIAGNOSIS OF INFECTED JOINT REPLACEMENTS

SYNOVIAL FLUID TESTS

A. Moderate strength evidence supports the use of the following to aid in the diagnosis of prosthetic joint infection (PJI):
- **Synovial fluid leukocyte count and neutrophil percentage**
- **Synovial fluid aerobic and anaerobic bacterial cultures**
- **Synovial fluid leukocyte esterase**
- **Synovial fluid alpha-defensin (α-defensin)**
- **Synovial fluid C-reactive protein (CRP)**
- **Synovial fluid nucleic acid amplification testing [e.g., polymerase chain reaction (PCR)] for bacteria**

Strength of Recommendation: Moderate ★★★☆
Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

INTRAOPERATIVE TESTS

B. Strong evidence supports the use of histopathology to aid in the diagnosis of PJI.

Strength of Recommendation: Strong ★★★★
Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention.

C. Moderate strength evidence supports the use of the following to aid in the diagnosis of prosthetic joint infection (PJI):
- **Multiple aerobic and anaerobic bacterial periprosthetic tissue cultures**
- **Implant sonication fluid aerobic and anaerobic bacterial cultures**
- **Implant sonication fluid nucleic acid amplification testing (e.g., PCR) for bacteria**

Strength of Recommendation: Moderate ★★★☆
Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

D. Limited strength evidence supports that periprosthetic tissue nucleic acid amplification testing for bacteria is not useful in the diagnosis of PJI.

Strength of Recommendation: Limited ★★☆☆
Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

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DIAGNOSTIC IMAGING

A. Limited strength evidence supports the use of the following to aid in the diagnosis of PJI:

- **^{18}F-FDG PET/CT**
- **^{18}F-NaF PET/CT**
- **CT**

Strength of Recommendation: Limited ★★☆☆

Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

B. Limited strength evidence supports the clinical utility of nuclear imaging to aid in the diagnosis of PJI.

Strength of Recommendation: Limited ★★☆☆

Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

C. In the absence of reliable evidence for gallium-67 imaging it is the opinion of this work group that this radiopharmaceutical does not have a role in the workup of PJI.

Strength of Recommendation: Consensus ★☆☆☆

Description: There is no supporting evidence. In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

GRAM STAIN

Update of 2009 CPG Recommendation

Moderate strength evidence supports that the practitioner avoid the use of intraoperative gram stain to rule out periprosthetic joint infection.

Strength of Recommendation: Moderate ★★★☆

Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

AVOIDING ANTIMICROBIALS TWO WEEKS PRIOR TO OBTAINING INTRA-ARTICULAR CULTURE TO IDENTIFY A PATHOGEN FOR THE DIAGNOSIS OF PJI

Update of 2009 CPG Recommendation

Limited evidence supports withholding antimicrobials for a minimum of two weeks prior to obtaining intra-articular culture to establish the diagnosis of PJI.

Strength of Recommendation: Limited ★★☆☆

Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

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AVOIDING INITIATING ANTIMICROBIALS PRIOR TO OBTAINING INTRA-ARTICULAR CULTURE IN PATIENTS SUSPECTED OF HAVING PJI

Update of 2009 CPG Recommendation

Moderate evidence supports avoiding administration of antimicrobials in patients suspected of having a periprosthetic joint infection until cultures have been obtained and a diagnosis has been established.

Strength of Recommendation: Moderate ★★★☆
Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

ANTIBIOTICS WITH LOW PREOPERATIVE SUSPICION OF PJI OR ESTABLISHED PJI WITH A KNOWN PATHOGEN

Update of 2009 CPG Recommendation

Strong evidence supports that preoperative prophylactic antibiotics be given prior to revision surgery in patients at low preoperative suspicion for periprosthetic infection and those with an established diagnosis of periprosthetic joint infection of known pathogen who are undergoing reoperation.

Strength of Recommendation: Strong ★★★★
Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention.

PERIOPERATIVE ANTIBIOTIC SELECTION

A. Limited strength evidence supports the use of any of the following perioperative antibiotics in reducing risk of PJI, though no studies reviewed were powered to detect a significant difference among those listed:
- **1st generation cephalosporin (e.g. cefazolin)**
- **2nd generation cephalosporin (e.g. cefuroxime)**
- **Glycopeptide (e.g. vancomycin)**

Strength of Recommendation: Limited ★★☆☆
Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

B. In the absence of reliable evidence comparing other antibiotics and antibiotic combinations, including those listed in the guideline, it is the opinion of this work group that perioperative antibiotics should be selected based on principles of responsible stewardship, balancing the risk of PJI and antibiotic resistance. Selection should reflect the antibiogram of the individual institution, the individual risk factors of the patient, and multidisciplinary support of institutional infection control experts. There is no current reliable evidence to support one antibiotic versus the other (examples provided in the rationale).

Strength of Recommendation: Consensus ★☆☆☆
Description: There is no supporting evidence. In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion

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ANTIBIOTIC CEMENT

A. Limited evidence suggests the routine use of antibiotics in the cement does not reduce the risk of periprosthetic joint infections for patients undergoing cemented TKA.

Strength of Recommendation: Limited ★★☆☆
Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

B. Limited evidence suggests the use of antibiotics in the cement may reduce the risk of periprosthetic joint infections for patients undergoing cemented THA.

Strength of Recommendation: Limited ★★☆☆
Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

PREOPERATIVE SCREENING AND DECOLONIZATION

A. Limited strength evidence supports the use of universal preoperative chlorhexidine cloth decolonization to reduce PJI after total hip arthroplasty (THA) and total knee arthroplasty (TKA).

Strength of Recommendation: Limited ★★☆☆
Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

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B. In the absence of reliable evidence for screening and nasal decolonization, it is the opinion of this work group that preoperative nasal mupirocin decolonization is a low-risk, reasonable option prior to hip and knee arthroplasty in patients who are MRSA carriers.

Strength of Recommendation: Consensus ★★★★
Description: There is no supporting evidence. In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion

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INTRAOPERATIVE TECHNICAL FACTORS

In the absence of reliable evidence for the use of an antiseptic wash during total hip or knee arthroplasty, it is the opinion of this work group that dilute betadine lavage be used as a method to decrease infection risk in hip or knee arthroplasty.

Strength of Recommendation: Consensus ★★★★
Description: There is no supporting evidence. In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

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INTRODUCTION

OVERVIEW

This clinical practice guideline is based on a systematic review of published studies regarding the diagnosis and prevention of hip and knee periprosthetic joint infection (PJI) in patients over the age of 18. In addition to providing practice recommendations, this guideline also highlights limitations in the literature and areas that require future research.

The guideline is intended to be used by all qualified and appropriately trained providers and surgeons involved in the management of patients undergoing hip or knee arthroplasty and in the evaluation of those patients for a possible diagnosis periprosthetic joint infection. It is also intended to serve as an information resource for decision makers and developers of practice guidelines and recommendations.

GOALS AND RATIONALE

The purpose of this clinical practice guideline is to help improve perioperative care for hip and knee arthroplasty and facilitate diagnostic evaluation based on the current best evidence. Current evidence-based medicine (EBM) standards demand that providers use the best available evidence in their clinical decision making. To assist them, this clinical practice guideline consists of a systematic review of the available literature regarding the prevention and diagnosis of periprosthetic joint infection of the hip and knee. The systematic review detailed herein was conducted between March 2017 and June 2018 and demonstrates where there is evidence, where evidence is lacking, and what future research must target in order to improve perioperative care in an effort to mitigate the risk of PJI and aid in the diagnosis of PJI for hip and knee replacement patients. In March 2017, PubMed, EMBASE and The Cochrane Central Register of Controlled Trials were searched for articles published after 1970, and an updated search was done in December 2017 to identify recently published articles. AAOS staff and the physician work group systematically reviewed the available literature and subsequently wrote the following recommendations based on a rigorous, standardized process.

Musculoskeletal care is provided in many different settings by many different healthcare providers. We created this guideline as an educational tool to guide qualified providers through a series of management and diagnosis-related decisions to improve the quality and efficiency of care. This guideline should not be construed as including all proper methods of care or excluding methods of care reasonably directed to obtain the same results. The ultimate judgment regarding any specific management must be made considering all circumstances presented by the patient and the needs and resources unique to the locality or institution.

INTENDED USERS

This guideline is intended to be used by orthopaedic surgeons and providers managing hip and knee replacement patients. Typically, orthopaedic surgeons will have completed medical training, a qualified residency in orthopaedic surgery, and some may have completed additional sub-specialty training. Adult primary care physicians, geriatricians, hospital-based adult medicine specialists, infectious diseases specialists, pathologists, clinical microbiologists, radiologists, nuclear medicine specialists, emergency medicine providers, nurse practitioners, physician assistants, and other healthcare professionals who routinely see this type of patient in various practice settings may also benefit from this guideline.

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Periprosthetic joint infection prevention and diagnosis assumes that decisions are predicated on the patient and / or the patient's qualified heath care advocate having physician communication regarding available management options and procedures applicable to the individual patient. Once the patient and or their advocate have been informed of available care options and have discussed these options with his/her physician, an informed decision can be made. Clinician input based on knowledge and experience increases the probability of selecting the most appropriate intervention for each individual patient.

This guideline is not intended for use as a benefits determination document.

PATIENT POPULATION
This document addresses interventions employed to mitigate the risk for periprosthetic joint infection in primary hip and knee arthroplasty and explores the tools available to diagnose PJI. This guideline does not address the prevention or diagnosis of superficial infections nor is it intended to address the treatment of patients with confirmed PJI of the hip or knee.

BURDEN OF DISEASE
The economic burden (represented by hospital costs) of periprosthetic joint infection in the United States was $566 million in 2009 and is estimated at an annual cost of $1.62 billion (CI $1.53-1.72 billion) in 2020 (Kurtz et al. JoA 2012). These data did not include the cost of surgeon or other provider services and do not include the post-acute care or patient's lost work productivity making the societal costs for PJI remarkably high.

Costs to be considered include:
1. Direct Medical Costs
2. Post-acute Care Costs
3. Long-term Medical Costs
4. Potential Lost Work / Disability Costs

ETIOLOGY
Periprosthetic joint infections of the hip and knee are caused by a variety of microorganisms and can be influenced by a myriad of host, technical, and environmental factors throughout the continuum of care. These infecting microorganisms may be introduced at the time of surgical intervention, through hematogenous or contiguous spread from another site, or from recurrence of a previously septic joint (ref 22 from 2009 CPG – Della Valle et al. CORR 2004).

INCIDENCE AND PREVALENCE
With the aging population and continued advancement in joint arthroplasty, the demand for hip and knee replacement is expected to continue to rise (Kurtz et al. JBJS 2007; p. 780-785; Cram et al. JAMA 2012) With this demand for these surgeries is also an expectation for an increased prevalence of periprosthetic joint infection requiring revision arthroplasty (Kurtz et al. JBJS 2007, suppl 3; p144-151).

Defining the incidence and prevalence of PJI has been difficult with unclear definitions for diagnosis of PJI in the literature until recently (Parvizi et al. CORR 2011; Osmon et al. 2013).

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The reported prevalence of PJI out to 2 years following hip replacement is 1.63% (Ong et al. JoA 2009) and following knee replacement is 1.55% (Kurtz et al. CORR 2010). Both procedures likely have a prevalence over 2% at 10 years (Ong et al. JoA 2009, Kurtz et al. CORR 2010).

RISK FACTORS
Risk factors for developing PJI of the hip or knee include a complex interplay of host, technical, and environmental conditions.

EMOTIONAL AND PHYSICAL IMPACT
Hip and knee arthroplasty patients with periprosthetic joint infection are at risk for:
1. Increased rate of mortality (Zmistowski, 2013): 26% mortality 5 years after revision surgery for PJI.
2. Increased risk for morbidity (Boddapati, 2018)
3. Decreased quality of life (Helwig, 2014)
4. Potential for impaired joint function / decreased level of mobility and ambulation (Cahill, 2008)

POTENTIAL BENEFITS, HARMS, AND CONTRAINDICATIONS
Most invasive and operative treatments are associated with some risk for infection. Hip and knee arthroplasty are no exception (Ong et al. JoA 2009; Kurtz et al. 2010). The impact to the patient and healthcare system are significant. The impetus to employ strategies and make clinical decisions focused on mitigating the risk of periprosthetic joint infection cannot be overstated. Furthermore, the ability to accurately diagnose the presence or absence of PJI also has far-reaching consequences to the patient and healthcare system. This guideline comprehensively evaluates the available evidence regarding recommendations for prevention and diagnosis of PJI. Effort has also been made to identify potential harms that may be associated with implementing each individual recommendation. Most critically with respect to hip and knee arthroplasty is access to care. Specifically, an ethical fine line exists with improved understanding of patient-related risk factors for infection. As the evidence continues to unfold, the guideline has taken care to identify shortcomings in knowledge to ensure the recommendations serve to guide constructive communication between provider and patient regarding options for care and associated individualized risks with and circumstances related to that care. The intent is not to define proscriptive barriers to care. The individual patient will influence management decisions. Moreover, clinician input based on experience increases the probability of identifying who will benefit from specific management options. Once the patient has been informed of available therapies and has discussed these options with their physician, an informed decision can be made. The guideline should be used as a tool within the context of the dynamic relationship between provider and patient.

FUTURE RESEARCH
Consideration for future research, when identified, is provided for each recommendation. Review of the published literature does indicate two overarching themes: (1) complex and interrelated modifiable / non-modifiable patient factors as an important aspect in understanding risk for PJI, and (2) ongoing challenges in accurately ruling in or ruling out PJI. Given the severe consequences of this disease process, the workgroup strongly suggests that future, high-quality research focus on continued development of validated risk assessment tools specific to hip and

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knee replacement not only to identity individual risk but also guide additional research efforts to mitigate the risks. Specifically, the effect of preoperative risk factor modification or correction prior to a patient undergoing hip or knee arthroplasty surgery must be elucidated. Additionally, focused research to develop highly accurate and timely diagnostic tools, including those that can be used at the point of care, is critical to facilitate diagnostic accuracy and efficiency in the evaluation of patients suspected of PJI. This ideally can lead to better management, in addition to shortened work-up times and decreased cost by allowing providers access to immediate diagnosis.

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METHODS

The methods used to perform this systematic review were employed to minimize bias and enhance transparency in the selection, appraisal, and analysis of the available evidence. These processes are vital to the development of reliable, transparent, and accurate clinical recommendations for diagnosis and prevention of periprosthetic joint infections. To view the full AAOS clinical practice guideline methodology please visit www.aaos.org/cpg.

This clinical practice guideline evaluates the effectiveness of diagnostic modalities and prevention strategies for periprosthetic joint infections in hip and knee arthroplasty. The AAOS approach incorporates practicing physicians (clinical experts) and methodologists who are free of potential conflicts of interest relevant to the topic under study, as recommended by clinical practice guideline development experts (Institute of Medicine, 2011).

This clinical practice guideline was prepared by the AAOS Diagnosis and Prevention of PJI Clinical Practice Guideline physician development group (clinical experts) with the assistance of the AAOS Clinical Quality and Value (CQV) Unit in the Department of Research, Quality and Scientific Affairs (methodologists). To develop this clinical practice guideline, the clinical practice guideline development group held an introductory meeting on November 14, 2017 to establish the scope of the clinical practice guideline. As the physician experts, the clinical practice guideline development group defined the scope of the clinical practice guideline by creating PICO Questions (i.e. population, intervention, comparison, and outcome) that directed the literature search. The AAOS Medical Librarian created and executed the search (see PJI CPG eAppendix 1 for search strategy).

BEST EVIDENCE SYNTHESIS
We included only the best available evidence for any given outcome addressing a recommendation. Accordingly, we first included the highest quality evidence for any given outcome if it was available. In the absence of two or more occurrences of an outcome at this quality, we considered outcomes of the next lowest quality until at least two or more occurrences of an outcome had been acquired. For example, if there were two 'moderate' quality occurrences of an outcome that addressed a recommendation, we did not include 'low' quality occurrences of this outcome. A summary of excluded articles can be viewed in the PJI CPG eAppendix 2. All of the detailed data for each recommendation can be found in the pages following each recommendation.

LITERATURE SEARCHES
The medical librarian conducted a comprehensive search of PubMed, Embase, and the Cochrane Central Register of Controlled Trials based on key terms and concepts from the workgroup-defined PICO questions (PJI CPG eAppendix 1). Bibliographies of relevant systematic reviews were hand searched for additional references. All databases were last searched on December 12, 2017 with limits for publication dates from 1970-2017 and English language.

DEFINING THE STRENGTH OF THE RECOMMENDATIONS
Judging the strength of evidence is only a stepping stone towards arriving at the strength of a clinical practice guideline recommendation. The strength of recommendation (Table 1) also takes into account the quality, quantity, and the trade-off between the benefits and harms of a treatment, the magnitude of a treatment's effect, and whether there is data on critical outcomes. Table 2 addresses how to interpret the strength of each recommendation.

VOTING ON THE RECOMMENDATIONS
The recommendations and their strength were voted on by the guideline development group members during the final meeting. If disagreement between the guideline development group

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occurred, there was further discussion to see whether the disagreement(s) could be resolved. Recommendations were approved and adopted in instances where a simple majority (60%) of the guideline development group voted to approve; however, the guideline development group had consensus (100% approval) when voting on every recommendation for this guideline.

INTERPRETING THE STRENGTH OF EVIDENCE
Table I. Strength of Recommendation Descriptions

Strength	Overall Strength of Evidence	Description of Evidence Quality	Strength Visual
Strong	Strong	Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention.	★★★★
Moderate	Moderate	Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.	★★★☆
Limited	Low or Conflicting Evidence	Evidence from two or more "Low" quality studies with consistent findings **or** evidence from a single "Moderate" quality study recommending for against the intervention or diagnostic or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.	★★☆☆
Consensus*	No Evidence	There is no supporting evidence. In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion. Consensus statements are published in a separate, complimentary document.	★☆☆☆

Table II. Clinical Applicability: Interpreting the Strength of a Recommendation

Strength of Recommendation	Patient Counseling (Time)	Decision Aids	Impact of Future Research
Strong	Least	Least Important, unless the evidence supports no difference between two alternative interventions	Not likely to change
Moderate	Less	Less Important	Less likely to change
Limited	More	Important	Change possible/anticipated
Consensus	Most	Most Important	Impact unknown

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PEER REVIEW

Following the final meeting, the clinical practice guideline draft undergoes a two-week peer review for additional input from external content experts. Written comments are provided via an electronic structured review form. All peer reviewers are required to disclose their conflicts of interest.

PUBLIC COMMENTARY

After modifying the draft in response to peer review, the clinical practice guideline was subjected to a two-week period of "Public Commentary." Commentators consist of members of the AAOS Board of Directors (BOD), members of the Council on Research and Quality (CORQ), members of the Board of Councilors (BOC), and members of the Board of Specialty Societies (BOS). The clinical practice guideline is automatically forwarded to the AAOS BOD and CORQ so that they may review it and provide comment prior to being asked to approve the document. Members of the BOC and BOS are solicited for interest. If they request to see the document, it is forwarded to them for comment. Based on these bodies, over 200 commentators have the opportunity to provide input into this clinical practice guideline. To view comments, 668 visit the PJI CPG Peer Review and Public Comment Report via www.aaos.org/qualityprograms.

THE AAOS CLINICAL PRACTICE GUIDELINE APPROVAL PROCESS

This final clinical practice guideline draft must be approved by the AAOS Committee on Evidence Based Quality and Value Committee, the AAOS Council on Research and Quality, and the AAOS Board of Directors. These decision-making bodies are described in the PJI CPG eAppendix 1. Their charge is to approve or reject its publication by majority vote.
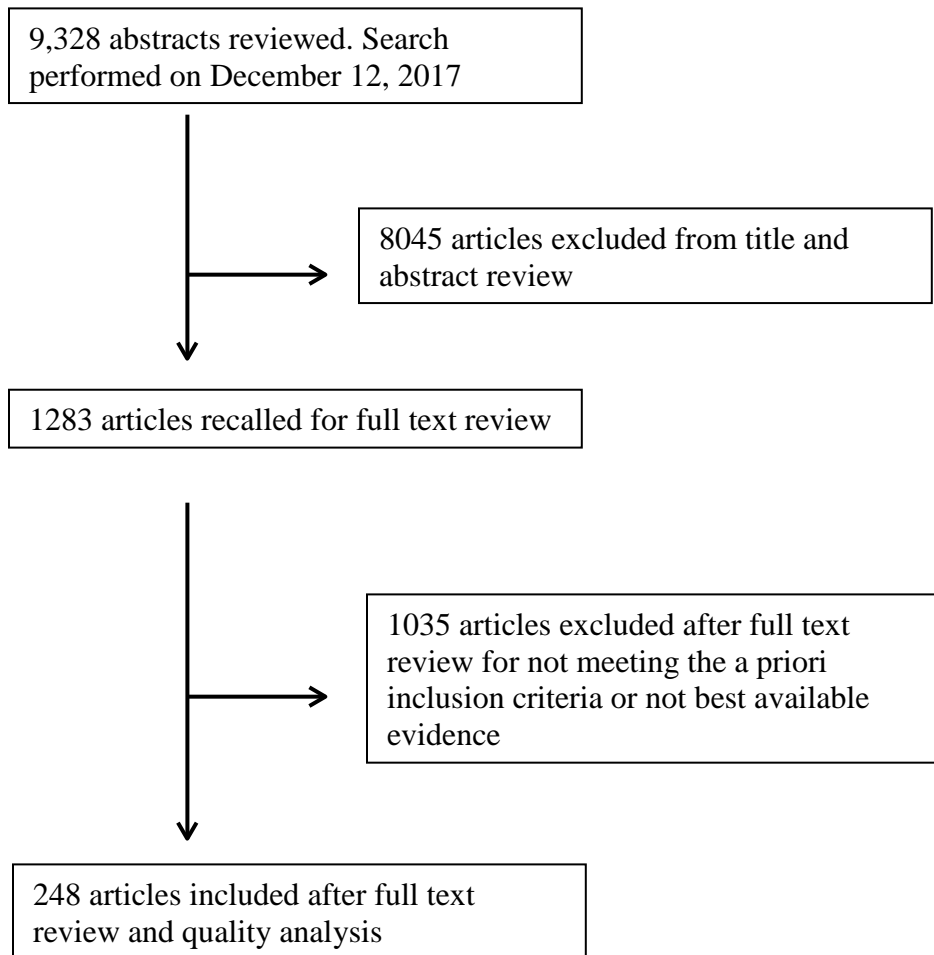
REVISION PLANS

This clinical practice guideline represents a cross-sectional view of current diagnostic and prevention strategies and may become outdated as new evidence becomes available. This clinical practice guideline will be revised in accordance with new evidence, changing practice, rapidly emerging treatment options, and new technology. This clinical practice guideline will be updated or withdrawn in five years.

CLINICAL PRACTICE GUIDELINE DISSEMINATION PLANS

The primary purpose of the present document is to provide interested readers with full documentation of the best available evidence for various procedures associated with the topic of this review. Publication of most clinical practice guidelines is announced by an Academy press release, articles authored by the clinical practice guideline development group and published in the Journal of the American Academy of Orthopaedic Surgeons, and articles published in AAOS *Now*. Most clinical practice guidelines are also distributed at the AAOS Annual Meeting in various venues such as on Academy Row and at Committee Scientific Exhibits. The final guideline recommendations and their supporting rationales will be hosted on www.OrthoGuidelines.org.

Selected clinical practice guidelines are disseminated by webinar, AAOS Online Learning, Orthopaedic Video Theater (OVT), Media Briefings, and by distributing them at relevant Continuing Medical Education (CME) courses and at the AAOS Resource Center.

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STUDY ATTRITION FLOWCHART

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9,328 abstracts reviewed. Search
performed on December 12, 2017
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↓ →
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8045 articles excluded from title and
abstract review
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1283 articles recalled for full text review
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↓ →
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1035 articles excluded after full text
review for not meeting the a priori
inclusion criteria or not best available
evidence
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248 articles included after full text
review and quality analysis
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RECOMMENDATIONS

RISK FACTORS FOR PJI

A. Moderate strength evidence supports that obesity is associated with increased risk of periprosthetic joint infection (PJI).

Strength of Recommendation: Moderate ★★★☆

Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

B. Limited strength evidence supports that patients in which one or more of the following criteria are present are at an increased risk of periprosthetic joint infection (PJI) after hip and knee arthroplasty:
- **Cardiac disease (arrhythmia, CAD, congestive heart failure, other)**
- **Immunocompromised status (other than HIV), including transplant, cancer**
- **Peripheral vascular disease**
- **Inflammatory arthritis**
- **Prior joint infection**
- **Renal disease**
- **Liver disease (hepatitis, cirrhosis, other)**
- **Mental health disorders (including depression)**
- **Alcohol use**
- **Anemia**
- **Tobacco use**
- **Malnutrition**
- **Diabetes**
- **Uncontrolled diabetes**

Strength of Recommendation: Limited ★★☆☆

Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

C. In the absence of reliable evidence, it is the opinion of this work group that in the case that one or more of the following conditions are present, the practitioner should carefully consider the risk before proceeding with surgery:
- **Active infection (strongly caution against proceeding with surgery given the risks)**
- **Anticoagulation status, active thromboprophylaxis (proceed only after careful consideration of the risks)**
- **Autoimmune disease (proceed only after careful consideration of the risks)**
- **HIV status (proceed only after careful consideration of the control and risks)**
- **Institutionalized patients (proceed only after careful consideration of the risks)**
- **Prior bariatric surgery (proceed only after careful consideration of the risks)**

Strength of Recommendation: Consensus ★☆☆☆

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Description: There is no supporting evidence. In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion

D. In the absence of reliable evidence, it is the opinion of this work group that the following conditions have an unclear effect on risk of PJI:
- **Age (conflicting evidence)**
- **Dementia (imprecise effect estimates)**
- **Poor dental status (inadequate evidence for a recommendation)**
- **Asymptomatic bacteriuria (conflicting evidence)**

Strength of Recommendation: Consensus ★☆☆☆
Description: There is no supporting evidence. In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion

RATIONALE

Out of 143 studies which met inclusion criteria for this recommendation, there were no high strength studies, and only ten were considered moderate strength. The remaining studies were considered low strength. Many of these studies evaluated multiple variables as it applied to either PJI directly, or to other perioperative complications, necessitating the use of various statistical methods to attempt to control for these variables. These methods were frequently constrained in doing so. Additionally, based on the available literature, whether a risk factor is "modifiable" or if optimization of a listed condition affects the risk of infection remained unclear. No specific threshold value could be endorsed for most listed conditions, but instead the simple binary presence or absence of the condition as defined by the individual study criteria affected the risk of PJI. Furthermore, many of the studies were based on national payor databases or registries, whose data is only as accurate as the data being input. As such, there is often no way to verify that an individual diagnosis or the definition of the diagnosis is accurate, though the sheer numbers in such databases may help correct for errors in diagnosis. Finally, definitions and clarity of location of infection introduced ambiguity between studies, some clearly indicating PJI, and others with variations of "deep infection," "deep surgical site infection," or "involves deep soft tissue," among other delineations.

Of the listed and reviewed conditions, obesity was the only risk factor for periprosthetic joint infection that met moderate strength criteria for increased risk of periprosthetic joint infection. The rest are based on single moderate strength and/or low strength studies with either conflicted or limited data, with each condition or risk factor individually discussed below.

Moderate Strength:

Obesity – There were three *moderate*-quality studies assessing the risk of PJI in obese patient undergoing TKA or THA. Lubbeke and associates (Lubbeke, A, 2016) compared 5 categories each of BMI (<24.9, 25-29.9, 30-34.9, 35-39.9, and ≥40) and weight (<60, 60-79, 80-99, 100-119, and ≥120) with a mean follow-up of 6.5 years. They identified similar PJI rates in BMI categories less than 35, but twice as high in patients with BMI 35-39.9, and 4 times as high with BMI 40 or greater. Weight greater than 100 kg was also associated with an increased risk of infection, with a hazard ratio of 2.1.

In a moderate-quality study assessing the effect of BMI on 30-day outcomes following joint replacement, Alvi et al (Alvi, HM, 2015) queried the ACS-NSQIP database and stratified 13,250 patients into 5 matched groups based on BMI. Compared to patients with BMI 18.5-25, hip patients with BMI 25-30, 30-35, and 35-40 had a 2.92-, 4.82-, and 6.4-fold increased risk of deep incision or organ space infection, respectively. Hip patients

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who had a BMI of 40 or higher had a 12.85 times higher risk of deep incision/organ space infection (NSQIP database tracks CMS definitions of infection, not clearly defining as PJI).

The final moderate-quality study by Wagner and associates (Wagner ER 2016) also identified a higher risk of deep incisional infection in TKA patients. In their single-institution registry, 22,289 consecutive knee replacements were analyzed, demonstrating a hazard ratio of 1.08 per unit of BMI over 35 kg/m² in favor of deep infection.

Of the 32 included *low* quality studies, 14 suggested no effect on the risk of hip or knee infection. Of the other 18 demonstrating increased risk of infection, 5 indicated increased risk of PJI in *both* hip and knee patients. Two additional studies found increased risk of PJI in obese TKA patients; one study deep infection (Namba, R.S. 2013); and one deep surgical site infection (Frisch, N, et al 2016). Five low quality studies indicated higher risk of *PJI* in obese patients undergoing THA, two indicated higher risk of *deep infection*, and one found a higher risk of *septic revision*. An additional study identified a higher risk of *deep infection for re-revision* THA in obese patients.

Limited Strength:

Alcohol – Only low-quality studies met inclusion criteria. Four of these six studies suggested an increased risk of hip and knee PJI in patients with history of alcohol abuse. Two others demonstrated no effect. Wu and associates (Wu, 2014) performed a multivariate conditional logistic regression analysis on a cohort of 297 patients, identifying a nearly 3-fold increase (odds ratio 2.95, p=0.039) in risk of PJI in patients with alcohol abuse. However, the study did not provide definition of alcohol abuse, including whether this was current abuse, or a history of abuse. Rotevatn et al (Rotevatn, 2017) queried the Danish Anesthesia Database, identifying 30,799 patients, and stratified *self-reported* current alcohol consumption. Their findings suggest that patients who consume 168 to 252 grams of alcohol per week (14 grams of alcohol is typical of 1 beer or 1 glass of wine for reference) had a 1.55 hazard ratio for PJI versus those who did not report consumption of alcohol. But there was a significant portion missing data for tobacco use, not fully controlled for by the study.

Preoperative anemia – One moderate quality study by Greenky and associates (Greenky M, 2012) demonstrated increased risk of PJI in patient with anemia, defined as hemoglobin <12 g/dL in women, and <13 g/dL in men. This single-center study of 15,221 hip and knee patients identified an odds ratio of 1.95 for PJI in patients who were anemic, using a propensity score adjusted model, though the study does not disclose the specific variables that were controlled for. Of seven additional low-quality studies, Lu et al (Lu, M, 2017) identified a higher risk of deep infection in both hip and knee patients with anemia, two (Bozic 2012 and Lee 2015) showed increased risk in knee patients alone, and one (Bozic 2012) demonstrated increased PJI risk in hip patients alone. But one (Bozic 2014) demonstrated no effect in hip patients, and two others identified no effect on either hip or knee patients. These conflicting conclusions between low-quality studies, and paucity of any better-quality studies qualifies as limited evidence.

Cardiac disease (arrhythmia, CAD, congestive heart failure, other) – Fourteen low quality studies evaluating cardiac disease as it applies to PJI met inclusion criteria. Of these, four identified no increased risk of PJI in hip and knee patients, two in hip patients alone, and two in knee patients alone. However, this was in conflict with five other studies that suggested higher risk of PJI. Three studies demonstrated an increased risk in knee patients, including Lee and associates (Lee, 2015) who suggested a 5 times higher risk of PJI in patients with "cardiac disease"; Long et al, (Long, 2016) who identified 2.1 higher risk in patients with atrial fibrillation; and Bozic and associates, who identified a 1.28 hazard ratio in patients with congestive heart failure. In another study, Bozic et al identified an adjusted hazard ratio 1.30 in favor of PJI in hip patients with

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cardiac arrhythmia. Aggarwal and associates (Aggarwal 2013) showed a 9 times higher risk of hospital admission for PJI in both hip and knee patients with history of atrial fibrillation versus those without atrial fibrillation. Finally, one retrospective study (Tabatabae 2015) actually demonstrated a reduced risk of in-hospital wound healing complications (hematoma or seroma) in patients having undergone coronary revascularization (CABG, stenting).

Diabetes – One moderate strength study and 36 low strength studies evaluating the effect of diabetes and/or uncontrolled diabetes met inclusion criteria. In the 2010 moderate strength study, Pedersen et al evaluated the effect of diabetes and diabetes with associated comorbidities on the rate of revision for deep infection in 57,575 patients in the Danish Hip Arthroplasty Registry, who underwent THA from 1996 to through 2005. Type 1 diabetics had a clinically insignificant higher risk of *revision for deep infection*, versus those without (rate ratio 1.01), while type 2 diabetics had a 1.49 times higher risk. Diabetic patients with history of complications in general related to their disease state had a 2.11 times higher risk than patients without diabetes, and those with cardiovascular comorbidities and diabetes had a 2.35 higher risk. It was unclear as to whether all important confounding variables were accounted for sufficiently.

Four low strength studies revealed increased risk of PJI in both diabetic hip and knee patients. Jiang et al (Jiang, 2014) identified a 1.32 times higher risk of PJI based on diagnosis of diabetes in a study based on national and state-level databases of over 800,000 THA and TKA patients. In contrast, Wu and colleagues performed a hospital-based case-control study, including 297 patients, predicting a 5.47 odds ratio in favor of PJI for patients with diabetes, versus case controls in patients undergoing THA or TKA in China. In insulin-dependent diabetics, the odds ratio was lower than diabetics in general, at 3.69. In a study evaluating the risk of PJI in hip and knee arthroplasty patients with preoperative asymptomatic leucocyturia, Gou et al (Gou, 2014) incidentally found that 6 out of the 7 patients with early PJI – a out of a total of 739 patients – had diabetes, representing a significant logistic regression odds ratio of 69.65. Finally, Jamsen et al (Jamsen, 2010) reviewed the one-year incidence of PJI in a single-center series of 7181 primary hip and knee arthroplasties performed for osteoarthritis, evaluating the effect of obesity, diabetes, and preoperative hyperglycemia. They found that patients with preoperative diagnosis of diabetes had an associated odds ratio of 2.31 for PJI. Even patients without diagnosis of diabetes, but with preoperative blood glucose of 124 mg/dL or higher had an adjusted odds ratio for PJI of 3.3 versus those with a blood of less than 124. Aside from this one numeric value, none of these four studies provided parameters on the diagnosis and severity of disease (e.g. blood glucose, hemoglobin A1C, etc.).

In patients with uncontrolled diabetes, three studies of low strength demonstrated increased risk of PJI in both hips and knees, and two in knees alone. Chrastil et al (Chrastil, 2015) found that hemoglobin A1C (HbA1c) did not perfectly correlate with PJI risk, but perioperative hyperglycemia with maximum preoperative blood glucose level of 194 or higher had a hazard ratio of 1.44 in their study of 13,372 Veterans Affairs patients. Additionally, patients with history of diabetic complications had an HR of 1.113. Shohat et al (Shohat, 2017) looked at serum fructosamine in evaluating risk of PJI in diabetic patients, identifying that patients with a serum fructosamine of 292 mmol/L or higher had more than 6 times the risk of PJI (odds ratio 6.2) than those under 292 mmol/L. However, there was concern that use of a stepwise regression model without validation could increase the likelihood that there was inadequate control of confounders. The authors note that the benefits of use of fructosamine include its low cost and its reflection of mean glycemic control over a shorter time period than HbA1c. In the final study, reported in 2017, Tarabichi et al (Tarabichi, 2017) performed a retrospective multicenter study of 1645 diabetic patients undergoing primary THA or TKA, evaluating HbA1c levels as a predictor for adverse events. Their stepwise logistic regression analysis suggested that an HbA1c of 7.7%

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(ROC with AUC 0.65) was associated with an increased rate of PJI, from 0.8% with HbA1c less than 7.7, to 5.4% with HbA1c $\geq$7.7, with AUC of 0.65.

Three additional studies on uncontrolled diabetes found no difference in either PJI or wound complications in hips or knees, and two found no difference in PJI or deep infection in knees alone. Five studies demonstrated increased risk of PJI in patients with diagnosis of diabetes alone, in TKA only, and two in THA, with an additional study (Song 2012) indicating increased risk of "deep incisional and/or organ space infection" in THA, and one (Namba 2013) "deep" infection in knee patients. The remaining 20 low strength studies demonstrated no significant differences in occurrence of various extent of infection.

Immunocompromised status other than HIV, including transplant, cancer – There were 12 included low strength studies evaluating the effect of immunocompromised status (other than HIV, see below) on risk of PJI. Three of these indicated higher risk of PJI in hip and knee patients, and one identified higher PJI incidence in knee patients. According to the findings of Klement et al (Kelment, 2016), kidney, liver, heart or pancreas transplant recipients undergoing hip replacement had higher risk of PJI, at relative risk of 1.56, 1.6, 1.82, and 1.31, respectively. In a review of 2,579,694 patients from the Nationwide Inpatient Sample (NIS) between 1993 and 2011, Cavanaugh et al (Cavanaugh, 2015) identified a higher risk of in-hospital wound healing complications in hip and knee patients with history of heart, lung, or pancreas transplant versus no history of transplant, with an odds ratio of 2.13. The remaining six studies identified no difference in PJI in patients with history of transplant.

Inflammatory arthritis – There were 22 included studies assessing risk of PJI as a function of inflammatory arthritis. In the single moderate strength study by George et al (George, 2017), timing of infliximab cessation was assessed in patient with inflammatory arthritis in over 4288 patients in a Medicare database. While there was no significant difference in PJI risk in patients at various stoppage times before surgery, there was increased risk in patients with inflammatory arthritis using glucocorticoids (hazard ratio 2.7, in favor of PJI). Out of the 21 low strength studies, one demonstrated increased risk of PJI in TKA and THA (Bongartz 2008), one for TKA alone (Bozic 2012), two for THA alone (Bozic 2012, Triantafyllopoulos 2016), and eight others demonstrated increased risk of various delineations of infection, including several that indicated higher rates of late revision for infection ($\geq$6 years).

Malnutrition – One study on the effect of malnutrition on risk of PJI was of moderate strength, and demonstrated no increased risk of deep infection in TKA patients. In this study, Wagner and associates (2016) reviewed data from 22,289 consecutive knees from their institutional joint registry, finding that TKA patients with BMI less than 18 had nearly twice the risk of deep infection (hazard ratio 1.96[95% CI .42 to 9.14]). Four low strength studies evaluated malnutrition in the primary joint arthroplasty population. Manrique et al (Manrique, 2017) found TKA patients with BMI less than 18.5 at an over 23 times higher risk of deep infection (odds ratio 23.3), but also note a higher incidence of rheumatoid arthritis in their study population than the general population, potentially confounding the result. One by Gramatico-Guillon et al (Gramatico-Guillon, 2015) identified increased risk of PJI in TKA and THA patients. In a study of 4551 patients undergoing right TKA in the NSQIP database, Kamath and associates (Kamath, 2016) identified that patients with preoperative albumin levels below 3.5 mg/dL were at an increased risk of deep incisional (odds ratio 2.3) and deep organ space infection (odds ratio 3.79) than those with albumin 3.5 or higher. Zorrilla and colleagues (Zorrilla,2006) identified that patients with low serum zinc had a higher incidence of delayed wound healing after total hip arthroplasty. Huang and associates (Huang, 2013) evaluated hip and knee patients and found that those with low albumin or transferrin levels had greater odds of acute infection within 3 months of surgery (odds ratio of 2.37[95% CI .73 to 7.76]), which was statistically insignificant, but the study was likely underpowered due to a low event rate.

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Mental health disorders, including depression – Three included low strength studies evaluated at least one component of mental health. Bozic and colleagues reported on 587 unilateral THA at 5 clinical sites, identifying an adjusted hazard ratio of 1.96 for PJI in patients with diagnosis of depression (Bozic 2014). Using the Medicare 5% sample claims database,40,919 patient who underwent THA between 1998 and 2007 were evaluated by Bozic et al (Bozic 2012) reporting a hazard ratio of 1.38 with concomitant diagnosis of depression and 1.48 for psychosis. Finally, using similar methods and the same database, this time for 83,0111 TKA performed between 1998 and 2007, they reported a 1.28 hazard ratio for depression, and a similar 1.26 for psychosis.

Liver disease (hepatitis, cirrhosis, other) – Fourteen low strength studies assessed the effect of liver disease on PJI, and one moderate strength study specifically evaluated the risk of deep PJI in patients with cirrhosis. Most seemed to indicate a roughly two-fold higher rate of PJI in patients with liver disease. The moderate strength study by Deleuran et al (Deleuran, 2015) compared PJI rates for TKA and THA in 363 patients with cirrhosis versus 109,159 patients without cirrhosis in the Danish healthcare registries, identifying twice the rate of infection (hazard ratio 2.1) in patients with cirrhosis. As is a frequent issue with registry data, comorbidities were measured retrospectively through diagnosis codes, whose validity is unclear. Additionally, alcohol consumption was not a measured variable and not controlled for, though authors identify that cirrhotic patients currently drinking would not have been offered joint replacement in their setting. Nonetheless, the remaining low strength studies also favored a higher risk of PJI in patients with liver disease, with higher rates of hip and knee PJI in patients with presence of *viral hepatitis* in two studies (Jiang et al 2014, Kildow 2017), as well as knee PJI in another (Kuo 2016). Three studies predicted higher risk of PJI with *presence* of liver disease in both hip and knee patients (Grammatico-Guillon 2015, Kao 2017, and Cai 2014). Grammatico-Guillon et al found a hazard ratio of 2.88 in patients with diagnosis code of liver disease based on a French database of 32,678 patients. A low strength study of all 255,568 Taiwanese residents who underwent TKA or THA between 1997 and 2009 by Kao and associates identified a similar 2.09 adjusted hazard ratio in favor of PJI in patients with diagnosis of chronic liver disease. In a case-control study of 903 patients undergoing TKA or THA, Cai and associates identified an odds ratio of 7.03 for PJI in patients with liver disease versus those without. The remaining 8 low strength studies found no significant difference for patients with liver disease, and no study identified a lower risk of PJI.

Peripheral vascular disease – Six low strength studies evaluated peripheral vascular disease (PVD) as a risk factor for PJI. One demonstrated increased risk in THA and TKA patients (Jiang 2014), one for TKA patients alone (Bozic 2012), and one for THA patients alone (Bozic 2012). The remaining three showed no difference.

Prior joint infection – There was one moderate strength study and one low strength study identifying increased risk of PJI in patients with history of prior prosthetic joint infection. In the moderate quality study Bedair and colleagues reported a 21 times higher relative risk of PJI in subsequent joint replacements when a patient had a history of PJI in a previously replaced hip or knee (Bedair, 2015). Intuitively, Mortazavi and associates demonstrated a higher risk of infection after revision for infection than for those with aseptic revisions (Mortazavi, 2010).

Renal disease – Data from one moderate and fourteen low strength studies were conflicting as it applied to renal disease, but three of the low strength studies (Bozic 2014, Grammatico-Guillon 2015, Bozic 2012) indicated *higher* risk of PJI in hip, hip & knee, and knee patients, respectively. An additional low strength study by Tan and associates (Tan, 2016) identified a higher risk of *revision* for PJI in hip and knee patients. In the one included moderate strength study, Miric and associates (Miric, 2014) reported on the results of 20,720 patients who underwent hip replacement from an integrated healthcare system database. Defining deep SSI as attributable to index THA up to 365 days post-operatively, they found no statistically significant difference

between those patients with chronic kidney disease (CKD) or end stage renal disease (ESRD), and those without renal disease, but were unable to adjust for confounding variables. This was true of many of the studies, and many patients with more advanced stages of renal disease seemed to have higher incidences of other comorbidities. There were no studies that predicted a lower risk of PJI in patients with renal disease.

Tobacco – All twelve studies that met inclusion criteria for tobacco and associated risk of PJI were considered low strength. One study indicated higher risk of "deep soft tissues or any part of the anatomy," including organ space in hips, but not knees (Sahota 2018). Two studies demonstrated increased risk of "deep infection" (not specifically PJI) in hip and knee patients who use tobacco, and another found increased risk of wound healing complications, including dehiscence and deep wound infection (Duchman 2015).

Potentially increased risk for PJI, but not enough data:

Active infection – Even though only one low strength study (Song 2012) evaluated active infection at other anatomical sites – finding increased risk of deep incisional and/or organ space infection – it is intuitive that a patient with an active infection is more likely to become bacteremic, increasing the risk of PJI.

Anticoagulation/active thromboprophylaxis status at the time of surgery – Three low strength studies met inclusion criteria, all by Bozic and associates. Of the three, one study (Bozic, 2012) identified a higher risk of PJI in those undergoing hip replacements with coagulopathy (hazard ratio 1.58) based on an administrative database. The other two, including one on knee replacement and the other in 2014 (Bozic, 2014) on hip replacement, identified no increased risk of PJI. However, all three studies were performed using the same database, with limited ability to control for confounding variables, and the accuracy of diagnosis (for or against) in question by the nature of the database.

HIV (diagnosis only) – Five low strength studies assessed the effect of HIV status on risk of PJI. Only one study, by Kildow et al (Kildow, 2017), identified a higher risk of PJI in HIV patients undergoing knee replacement at 2 years (odds ratio 2.51). However, as was true of other included studies, no stratification of the HIV patients in terms of CD4 count or detectable viral load was conducted. Lin and associates (Lin 2013) identified higher risk of need for irrigation and debridement in hip patients with HIV, but no such increased risk for knees, and no increased risk of PJI or wound healing complications in hip or knee patients. Issa and associates (Issa, 2017) did indicate that "all patients with HIV underwent thorough preoperative optimization with their primary care physician and infectious disease specialist," and noted no difference in risk of PJI for HIV-infected TKA patients. In a study evaluating long-term results of primary TKA in patients with hemophilia, Silva and associates (Silva, 2005) recorded the HIV status and CD4 count in 53 of the 90-patient cohort, identifying no effect on PJI, but given expected incidence and total number of patients in this study, it was likely underpowered.

Prior bariatric surgery - Only three *low* quality studies on those having undergone bariatric surgery for obesity were included. Of these, only one (Nickel BT, 2016) indicated higher risk of PJI in TKA, with significant concern for confounding variables. The other two identified no difference in risk. As such, no reliable evidence is available to support increased risk of PJI in patients with history of bariatric surgery undergoing THA or TKA. However, given significant nutritional shifts associated with bariatric procedures and known effects of malnutrition on tissue healing, caution is still advised.

Institutionalization and autoimmune disease - There was one low strength study involving institutionalized patients that were habitual residents of a healthcare center, which did indicate a higher risk of PJI in such

patients (Gallardo-Calero et al 2016). But with only one study, it did not meet inclusion criteria for recommendation. Likewise, an isolated low strength study (Jiang et al 2014) evaluated the effect of **autoimmune disease** on PJI, including rheumatoid arthritis, lupus, or ankylosing spondylitis. They identified an increased risk of PJI in both hip and knee patients, with a hazard ratio of 1.55. We advise caution in these patients.

No increased risk for PJI, or conflicting data:

Recent UTI and/or asymptomatic bacteriuria – Four low strength studies evaluated the effect of the the presence of asymptomatic urinary tract infection (UTI) on the risk of PJI (Gou 2014, Honkanen 2017, Singh 2015, Sousa 2014). The Singh and Honkanen studies evaluated bacteriuria, and Gou used leucocyturia as measures of asymptomatic UTI. Only Souza et al found that the odds of PJI were significantly higher in those with asymptomatic bacteriuria (OR 3.95(1.52-10.26)). The other three studies did *not* show a significant increase in PJI risk. Bozic and associates, in two large database studies (both in 2012, one hip and one knee) attempted to link urinary tract infection to PJI. However, given the nature of the database, "urinary tract infection" (e.g. symptomatic vs. asymptomatic) is not clearly defined, and multiple other variables may be inadequately controlled. The role of symptomatic versus asymptomatic bacteriuria or leucocyturia in the risk of PJI remains unclear.

Age, dementia and poor dental health - Three moderate strength studies assessed **age** as a risk factor for PJI, with none indicating increased risk of PJI or infection. The remaining thirty low strength studies demonstrated very mixed results, with some even suggesting a decreased risk of PJI, but most without a difference. There were four low quality studies evaluating the effect of **dementia** on risk of PJI, all of which found no difference in risk of PJI. However, the confidence intervals were wide and imprecise in the dementia studies (possibly due to low event rates), and therefore the evidence strength was downgraded from limited to consensus. The one low strength study assessing diagnosis of **poor dental health** showed no difference in risk of PJI (Wu 2014). Despite the lack of evidence individually, the practitioner is encouraged to consider that these may be markers of other comorbidities, which could increase the overall risk of infection or other complication.

POSSIBLE RISKS AND HARMS OF IMPLEMENTATION

Candidacy for surgical intervention is at once, one of the most essential and complex decisions in surgical practice, ethically balancing the degree of pathology and risk of the operation, with the positive benefits to the patient and society at large, in a shared decision-making process between patient and surgeon. The positive effect of indicated lower extremity arthroplasty on quality of life and reduced morbidity is well established. However, its cost to the health care system has been the subject of increased scrutiny. Surgeons are under increasing pressure from payors, health care systems, and peers alike to provide highest value care, balancing the overall cost of care with excellence in patient outcomes. As such, delay or denial of surgical care based on any one or multiple factors in order to avoid one of the most devastating complications of one of the best value surgeries ever practiced should not be taken lightly. Given that all risk factors listed – with the exception of obesity – are supported with only low strength or conflicting evidence, the decision to proceed is individual, and based on myriad other factors, including but not limited to the ability of the system in which the surgeon practices to handle varying degrees of complexity, volume and experience of the surgeon and system, and other confounding factors not herein assessed. Additionally, at this time it is unclear based on the literature if modification of any risk factor, including obesity, actually reduces the risk of PJI. Payors and healthcare systems alike should understand that though tactics to reduce cost may include delaying or avoiding operating on patients with these risk factors, such practice may deny surgery to a much larger proportion of patients who may otherwise significantly benefit and not endure PJI.

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FUTURE RESEARCH

Despite the volume of literature addressing risk factors for periprosthetic joint infection, there is a paucity of moderate-quality studies, and complete absence of high-quality studies. Future research must attempt to better control for individual confounding variables prospectively, with better delineation of disease states. For example, though BMI may not be the best measure of obesity overall, its stratification in many studies has helped allow for better comparison between groups, improving the quality of data available. Simply identifying whether or not a disease process is present based off an individual entry of a diagnostic code from the patient's potentially remote past medical history does not ensure best quality data. Unfortunately, the relatively low incidence of PJI requires large numbers for appropriate statistical power, making registries and large healthcare databases an optimal target for research. Better quality abstraction for such databases is therefore necessary to help de-confound. Additional assessments of markers of disease status and their associated thresholds may also help the clinician further and more accurately stratify risk. Finally, identification of risk associated with a condition or stage of comorbidity does not by itself afford the provider the ability to proselytize for change, as the effect of modification and optimization of the status of a listed condition is still unclear. Future research endeavors should specifically be designed to determine if risk factor modification truly results in a reduction in the risk for PJI after hip or knee arthroplasty surgery. Given frequently conflicting conclusions among studies, the individual system and even provider-specific management of comorbidities – which was typically not delineated – may account for such discrepancies. Prospective, appropriately controlled studies incorporating these considerations will better afford surgeon and patient the ability to predict and potentially minimize risk of periprosthetic joint infection.

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INJECTIONS PRIOR TO ARTHROPLASTY

Limited evidence suggests intra-articular injection performed prior to total joint arthroplasty may have a time-dependent association for increased risk of PJI.

Strength of Recommendation: Limited ★★☆☆
Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

RATIONALE
One low strength study (Ravi et al. 2015) reported an association between intra-articular hip injection within 1 year prior to hip replacement and the development of periprosthetic hip infection). Another low strength study (Schairer et al. 2016) confirmed this association but only when the injection was within 3 months or less of the surgery. Kaspar et al (2005) also raise the concern for an increased risk for revision surgery due to infection in hips that had intra-articular steroid injections prior to replacement. A moderate strength study (Chambers et al. 2017) evaluated the effect of multiple steroid injections versus a single injection within the 12 months preceding hip replacement and found an increased risk for periprosthetic joint infection in the multiple injection cohort. The cohorts in this study were dissimilar in that the multi-injection cohort on average had injections closer to the time of hip replacement than the single cohort. Other low strength studies have shown no risk for infection when injections preceded hip arthroplasty (Meermans 2012, Sreekumar 2007, McIntosh 2006)

With respect to injections prior to knee arthroplasty, two low strength studies (Papavasiliou et al. 2006, Bedard et al. 2017) reported on an increased risk for deep infection if the patient had received an intra-articular steroid injection within 6 to 7 months (Bedard et al 2017) or within 12 months (Papavasiliou et al. 2006) prior to surgery. Other low strength studies have found no correlation between preoperative intra-articular injection and periprosthetic knee infection (Khanuja 2016, Amin 2016, Desai 2009). Looking at multiple preoperative injections in knee replacement patients, Kokubun et al (2017) conducted a low strength study that found no difference in infection risk between subjects with 4 or more injections versus those with 3 or less injections.

The studies on this topic are subject to the bias associated with retrospective design, numerous variables related to type and timing of injections, small sample size, and inconsistent definition of infection making firm conclusions difficult.

POSSIBLE HARMS OF IMPLEMENTATION
A possible harm to this recommendation is that patients could be inappropriately denied reconstruction of end stage joint disease if they had a prior intra-articular injection. It is important to note that the exact interval between an injection and surgery that may increase risk is not clear. Additionally,even though the risk was higher in injected patients in some studies, the overall event rate was still low.

FUTURE RESEARCH
With conflicting reports in the literature, a prospective and randomized study comparing injection versus no injection at a defined time interval and in a large patient cohort is needed. The ubiquitous nature of preoperative injections for symptomatic management of hip and knee arthritis deserves further investigation as to the possibility of an association with periprosthetic joint infection.

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BLOOD TESTS FOR PREOPERATIVE DIAGNOSIS

A. Strong evidence supports the use of the following to aid in the preoperative diagnosis of prosthetic joint infection (PJI):
- **Serum erythrocyte sedimentation rate (ESR)**
- **Serum C-reactive protein (CRP)**
- **Serum interleukin-6**

Strength of Recommendation: Strong ★★★★
Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention.

B. Moderate strength evidence does not support the clinical utility of the following to aid in the diagnosis of PJI:
- **Peripheral blood leukocyte count**
- **Serum tumor necrosis factor-α**

Strength of Recommendation: Moderate ★★★☆
Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

RATIONALE

There were two high quality studies, eight moderate and one low quality study evaluating serum ESR (Della Valle 2007; Greidanus 2007; Alijanipour 2013; Bottner 2007; Buttaro 2010; Cipriano 2012; Elgeidi 2014; Kamme 1981; Savarino 2004; Schinsky 2008; Kwon 2016).

There were two high quality studies, eleven moderate and one low quality article evaluating serum CRP (Della Valle 2007; Greidanus 2007; Alijanipour 2013; Bottner 2007; Buttaro 2010; Cipriano 2012; Elgeidi 2014; Fernandez-Sampedro 2017; Fink 2008; Fink 2013; Savarino 2004; Schinsky 2008; Yuan 2015; Kwon 2016).

If both ESR and CRP were negative, the combined tests were strong at ruling out PJI (negative LR=0 to .06). If both tests were positive, the tests were also useful for ruling in PJI (positive LR range=4.34 to 13.5).

There is concern that ESR and CRP may be elevated in the early postoperative period, which could affect the reliability of these tests. Three included studies evaluated these biomarkers for PJI in the early postoperative period. A moderate quality study by Fernandez-Sampedro (2017) found CRP (13.5mg/L) to be a weak test for diagnosing PJI in hip and knee patients within 3 months of surgery (positive LR=3.52; negative LR=0.24), with the test result producing a small (but sometimes important) change in probability PJI. Another moderate quality study (Alijanipour 2013) of hip and knee patients showed CRP (23.5mg/L) to be a strong rule in test (positive LR=14.5), and moderately good rule out test (negative LR=.14) within 4 weeks of surgery. The same study found that ESR (54.5 mm/hr) was a strong rule in test (positive LR=11.4), but a weak rule out test (Negative LR=.21) for early PJI. Finally, a low-quality study of hip patients by Yi (2014) found ESR (44 mm/hr) was a moderately good rule out test within six weeks of surgery but was poor for ruling in PJI (positive LR=1.96; negative LR=.15). The same study found CRP to be a strong rule in test (positive LR=66.76) and a moderate

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rule out test (negative LR=.12), although it should be noted that the positivity threshold of 93 mg/L was much higher than the other CRP studies in this recommendation.

Another concern is that ESR and CRP tests could be elevated by other inflammatory conditions. Cipriano (2012) evaluated ESR (30mm/hr) and CRP (17 mg/L) in hip and knee patients with inflammatory arthritis. ESR was a weak rule in test (positive LR=2.34), indicating that a positive test produced a small, but sometimes important change in probability of PJI. However, a negative ESR test strongly decreased the probability of PJI (negative LR=.09). CRP also was a weak rule in test, but a strong rule out test (positive LR=3.32; negative LR=.07). Kwon (2016) evaluated ESR (22mm/hr) and CRP (31.3mg/L) in hip patients with dual taper modular implants who underwent revision for adverse local tissue reaction due to taper corrosion. ESR was a strong rule in test in these patients (positive LR=10.48) but was a weak rule out test (negative LR=.45). CRP was a weak rule in test (positive LR=3.93) and a poor rule out test (negative LR=.77).

One moderate quality hip study (Buttaro 2010) and two moderate quality hip/knee studies (Bottner 2007; Elgeidi 2014) evaluated serum IL-6. IL-6 was a moderately strong rule-in test (positive LR range=7.03 to 9.67) and may be useful as a rule-out test (negative LR=0-.67).

In arthroplasty failure, it is important to distinguish PJI from non-infectious causes because the surgical and medical management varies. Blood is easy to collect, and a number of biomarkers can be tested. Some are useful for PJI diagnosis, whereas others are not. Of the listed biomarkers, only ESR and CRP are commonly performed and have strong evidence supporting their use. Serum interleukin-6 has been studied in a smaller number of studies and its use is supported, though it is not widely available, and what it adds to ESR and CRP, which are more commonly performed, has not been defined. Conversely, moderate evidence supports not using tumor necrosis factor-α or peripheral blood leukocyte count for PJI diagnosis, because they were poor at ruling out PJI (Bottner 2007; Elgeidi 2014; Savarino 2004; Spangehl 1999; Yuan 2015; Claassen 2016; Trampuz 2007).

POSSIBLE HARMS OF IMPLEMENTATION

Neither CRP nor ESR is perfectly accurate for PJI diagnosis. These biomarkers may be elevated as a result of inflammatory conditions not related to PJI; conversely, they are not always positive in cases of PJI. Therefore, they should not be used as the sole tests to diagnose PJI. None of the listed biomarkers defines the microbiology of PJI, which is important to inform appropriate management.

FUTURE RESEARCH

As noted in the subsequent recommendation, the goal of testing for PJI is to rule in or rule out this diagnosis. No test should be used alone. In most cases, a diagnosis can be achieved without using all of the testing listed, and testing should be deployed in an algorithmic fashion; defining such an algorithm is beyond the scope of this guideline. Novel blood-based biomarkers, including procalcitonin, are currently being explored. The relative value of biomarker testing (e.g., CRP, interleukin-6) on serum *versus* synovial fluid remains to be defined.

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DIAGNOSIS OF INFECTED JOINT REPLACEMENTS

SYNOVIAL FLUID TESTS

A. Moderate strength evidence supports the use of the following to aid in the diagnosis of prosthetic joint infection (PJI):
- **Synovial fluid leukocyte count and neutrophil percentage**
- **Synovial fluid aerobic and anaerobic bacterial cultures**
- **Synovial fluid leukocyte esterase**
- **Synovial fluid alpha-defensin (α-defensin)**
- **Synovial fluid C-reactive protein (CRP)**
- **Synovial fluid nucleic acid amplification testing [e.g., polymerase chain reaction (PCR)] for bacteria**

Strength of Recommendation: Moderate ★★★☆

Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

INTRAOPERATIVE TESTS

B. Strong evidence supports the use of histopathology to aid in the diagnosis of PJI.

Strength of Recommendation: Strong ★★★★

Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention.

C. Moderate strength evidence supports the use of the following to aid in the diagnosis of prosthetic joint infection (PJI):
- **Multiple aerobic and anaerobic bacterial periprosthetic tissue cultures**
- **Implant sonication fluid aerobic and anaerobic bacterial cultures**
- **Implant sonication fluid nucleic acid amplification testing (e.g., PCR) for bacteria**

Strength of Recommendation: Moderate ★★★☆

Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

D. Limited strength evidence supports that periprosthetic tissue nucleic acid amplification testing for bacteria is not useful in the diagnosis of PJI.

Strength of Recommendation: Limited ★★☆☆

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Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

RATIONALE

Description of Evidence:

There was one high, five moderate and four low quality studies evaluating synovial fluid leukocyte count (Della Valle 2007; Cipriano 2012; Ghanem 2008; Trampuz 2004; Schinsky 2008; Spangehl 1999; Choi 2016; Higuera 2017; Chalmers 2015; Kwon 2016). Seven studies obtained synovial fluid preoperatively, and three intraoperatively. There was one high, five moderate and three low quality studies evaluating synovial fluid neutrophil percentage (Della Valle 2007; Cipriano 2012; Ghanem 2008; Schinsky 2008; Spangehl 1999; Trampuz 2004; Balato 2017; Higuera 2017; Kwon 2016). Seven studies used fluid obtained preoperatively, and two used intraoperatively-collected fluid. Most of the studies found both tests to be moderate to strong at ruling in and ruling out PJI.

There were two high, seven moderate and one low quality studies evaluating the diagnostic accuracy of preoperative aspiration culture for bacteria (Della Valle 2007; Eisler 2001; Barrack 1993; Fink 2008; Fink 2013; Glithero 1993; Malhotra 2004; Mulcahy 1996; Williams 2004; Parvizi 2006). Every study evaluated preoperatively-collected synovial fluid, except the Parvizi 2006 study which used synovial fluid obtained operatively. A meta-analysis of the preoperative aspiration studies found it to be a good rule-in test [pooled positive LR=10.09 (6.74,15.09)]. Although slightly weaker as a rule-out, the test was still useful [negative LR=.29 (.22,.40)]. The intraoperatively-collected synovial fluid culture study found the test to be strong at ruling in, and moderately strong at ruling out PJI.

Three moderate quality studies evaluated the synovial fluid leukocyte esterase test (Koh 2017; Shafafy 2015; Parvizi 2011). Two studies used preoperatively-collected and one used intraoperatively-collected synovial fluid. The test was useful for ruling in (positive LR range=4.25 to 80) and ruling out PJI (negative LR range= 0 to .2). Three moderate and three low quality studies evaluated synovial fluid α-defensin testing (Kasparek 2016; Suda 2017; Bonanzinga 2017; Berger 2017; Deirmengian 2014; Bingham 2014). The strength of evidence is rated as moderate, although it is important to note that relevant conflicts of interest were present in five out of the six α-defensin studies. Three of the studies used synovial fluid obtained intraoperatively, and the other three used synovial fluid obtained preoperatively. The test was useful for ruling in (positive LR range=4.36 to 32.33) and ruling out PJI (.03 to .36).

One moderate and two low quality studies evaluated synovial fluid CRP using synovial fluid obtained preoperatively (Tetreault 2014; Omar 2015; Vanderstappen 2013). The positivity thresholds in these studies ranged from 1.8 to 14.1 mg/L. One additional moderate quality study used intraoperatively-collected synovial fluid for CRP in combination with leukocyte count and neutrophil percentage analysis (Sousa 2017). Synovial fluid CRP alone was a moderate to strong rule-in test and a moderate to strong rule-out test (positive LR range=5.86-15; negative LR range=0 to.19). When used in combination with synovial fluid leukocyte count or neutrophil percentage, it was very a strong rule-in test (positive LR range=39.88 to77.42), but a weaker rule-out test (negative LR=.23 to.4).

One moderate knee (Melendez 2016) and one moderate hip/knee study (Morgenstern 2017) evaluated synovial fluid PCR using synovial fluid obtained preoperatively. Morgenstern evaluated multiplex PCR and Melendez used a genus and group specific rapid PCR assay panel designed to target *Staphylococcus* species, *Enterococcus/Granulicatella/Abiotrophia* species, *Proteus* species, *Enterobacteriaceae*, *Bacteroides fragilis*

group, *Pseudomonas aeruginosa*, streptococci, *Corynebacterium* species, *Propionibacterium*/*Cutibacterium*/*Actinomyces* species, and anaerobic Gram-positive cocci. PCR was moderately strong as a rule-in test (positive LR range=5.55-6.82), and was of use for ruling out PJI (negative LR range=0.45-0.48).

There were three high quality studies, six moderate and one low quality study evaluating histopathology (Della Valle 2007; Frances 2007; Ko 2005; Banit 2002; Boettner 2016; Fehring 1994; Kasparek 2016; Lonner 1996; Nunez 2007; Suda 2017). The studies used various thresholds, but most had positive likelihood ratios in the moderate to strong rule-in test range. There were enough studies to meta-analyze thresholds of at least 5 and 10 neutrophils/high powered field (HPF). Both meta-analyses revealed both thresholds were strong at ruling in PJI [(5 neutrophils/HPF LR+=13.82(7.29, 26.19); 10 neutrophils/HPF in 5 fields= 56.5(20.3,157.2)]. As rule-out tests, results were more inconsistent and were unable to be pooled, but indicated the test may be of some use for ruling out PJI (negative LR range=.05 to .91).

There was 1 high, 5 moderate and 1 low quality study that evaluated periprosthetic tissue cultures (Aggarwal 2013; Atkins 1998; Schafer 2008; Spangehl 1999; Trampuz 2006; Trampuz 2007; Parvizi 2006). A meta-analysis was conducted using a threshold of 2 or more positive samples, which was revealed to be a very good rule-in test [positive LR=28.9(14.3, 58.6)] and was somewhat useful as a rule-out test [negative LR=0.34(0.27, 0.43)].
One high and three moderate quality studies evaluated sonication fluid cultures (Greenwood-Quaintance 2014; Janz 2013; Trampuz 2006; Trampuz 2007) using various cutpoints for positivity. The studies, in general, found the test to be moderate to strong at ruling in PJI (positive LR=4.25 to 172.25, and to be useful as a rule-out test (Negative LR=.11 to .32). A meta-analysis was conducted which revealed an area under the curve of .90 (.87-.92).

One high and three low quality studies evaluated sonication fluid PCR (Greenwood-Quaintance,K.E., 2014; Cazanave 2013; Gomez 2012; Ryu,S.Y., 2014). The test was good at ruling in PJI (positive LR range=8.71-78.26) and was also useful for ruling it out (negative LR range=0.19-0.30). There was 1 moderate and one low quality study (Suda,A.J., 2017; Ryu,S.Y., 2014) evaluating periprosthetic tissue PCR. The test was weak at ruling in (positive LR range=2.92-4.84), but very poor at ruling out PJI (negative LR range=0.77-0.87).

Clinical Considerations:
It is important to distinguish PJI from non-infectious causes of arthroplasty failure because of divergent surgical and medical management. In addition, in cases of PJI, the infecting microorganism(s) should ideally be defined to direct antimicrobial therapy; only cultures and microbe-directed molecular diagnostics are able to define the infecting microorganism(s). Preferably, a diagnosis should be established pre-operatively to allow for pre-surgical planning. If feasible, preoperative arthrocentesis is recommended, with fluid submitted for leukocyte count and differential, as well as aerobic and anaerobic cultures. There are varying methods for performance of synovial fluid cultures; culture in blood cultures bottles may be helpful, although there is no United States Food and Drug Administration (FDA) approved/cleared system for this approach. No evidence supports routine fungal and mycobacterial cultures of synovial fluid.

It should be noted that interpretive criteria for synovial fluid leukocyte counts and differential vary from those applied to native joint septic arthritis, that some studies suggest that different cutoffs be applied for hip *versus* knee arthroplasties, and that cutoffs may vary with the time post-arthroplasty. Definition of appropriate cutoffs for synovial leukocyte count and differential are beyond the scope of this guideline.

Synovial fluid leukocyte esterase strip tests may be applied to synovial fluid as a rapid diagnostic for PJI, but no assay is United States FDA approved/cleared for this indication and this testing may be redundant with leukocyte count and neutrophil percentage determination. Likewise, synovial fluid α-defensin and CRP may be used but are also not FDA approved/cleared at this time and may be redundant with leukocyte count and neutrophil percentage determination, and serum CRP, respectively. Several studies have examined microbial nucleic acid amplification tests (e.g., PCR) applied to synovial fluid; none of these tests are FDA-approved/cleared and this type of testing may be redundant with cultures and does not provide phenotypic susceptibility test results. In addition, not all nucleic acid amplification tests are equivalent. Some may target specific microorganisms (and not "all" PJI-causing organisms), whereas others may be more broad-range in nature, targeting, for example, a conserved bacterial gene (e.g., 16S ribosomal RNA gene).

If a preoperative diagnosis of PJI has been established and the microbiology defined, intraoperative testing for PJI may not be needed. Alternatively, if this is not the case, efforts should focus on determining whether or not the arthroplasty is infected and on defining the infecting microorganism(s). Histopathology is recommended, and when performed as frozen section histopathology, can provide a result during the operative procedure. Multiple periprosthetic tissues should be submitted for aerobic and anaerobic bacterial culture. Definition of the ideal number of periprosthetic tissues to be submitted to bacterial cultures is beyond the scope of this guideline. If implant components are being resected, they may be submitted for sonication, with aerobic and anaerobic bacterial cultures performed on the resultant sonication (or sonicate) fluid. No evidence supports routine fungal and mycobacterial cultures of periprosthetic tissues or sonication fluid. Several studies have examined microbial nucleic acid amplification tests (e.g., PCR) applied to periprosthetic tissues as well as sonication fluid; none of these tests is FDA-approved/cleared and this type of testing may be redundant with cultures and may be best reserved for culture-negative cases. One possibility to achieve this is to collect and reserve a sample for future molecular testing, if needed. The same caveats vis-à-vis lack of equivalency between such tests as detailed for synovial fluid apply to nucleic acid amplification tests applied to periprosthetic tissues and sonication fluid. Overall, sensitivity of nucleic acid amplification testing is better for sonication fluid than periprosthetic tissues. While nucleic acid amplification tests performed on periprosthetic tissue may be useful in ruling in PJI, they are not useful for ruling out PJI, and therefore not routinely recommended on this specimen-type. Swab cultures are not recommended because swabs sample a small amount of material, and alternative specimens, as detailed above, are easily collected, providing lower rates of false negative diagnoses.

POSSIBLE HARMS OF IMPLEMENTATION

There is no perfect test for diagnosis of PJI. Lack of sensitivity of the above-listed tests can lead to missed diagnoses and conversely, lack of specificity (either a false-positive diagnosis of PJI or detection of a microorganism which is not causing PJI) can lead to inappropriate surgery and/or use of unneeded antibiotics, increased cost of care, selection for antibacterial resistance, toxicity and/or dysbiosis. Additionally, not all test options are available at each center which may have resource, access to care, and cost implications not fully delineated in these recommendations.

FUTURE RESEARCH

While multiple tests are listed, the goal, as stated above, should be to rule in or rule out PJI and if ruled in, define its microbiology. In most cases, this can be achieved without using all of the testing covered. Ideally, testing should be deployed in an algorithmic fashion; defining such an algorithm is beyond the scope of this guideline but is needed. The field of molecular microbiology diagnostics, including organism-specific, multiplex panels, 16S ribosomal RNA gene or other broad-range bacterial PCR followed by Sanger sequencing of amplification products, targeted metagenomic sequencing and shotgun metagenomic sequencing, is rapidly developing, which will likely impact future recommendations. Future research should address the most

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appropriate type of advanced diagnostic(s), which specimen-types are ideal or such testing, the ideal number of specimens to be tested, and when, in the course of testing and under which scenarios this type of testing is most appropriate (i.e., develop algorithms for appropriate test utilization).

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DIAGNOSTIC IMAGING

A. Limited strength evidence supports the use of the following to aid in the diagnosis of PJI:
- **^{18}F-FDG PET/CT**
- **^{18}F-NaF PET/CT**
- **CT**

Strength of Recommendation: Limited ★★☆☆

Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

B. Limited strength evidence supports the clinical utility of nuclear imaging to aid in the diagnosis of PJI.

Strength of Recommendation: Limited ★★☆☆

Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

C. In the absence of reliable evidence for Gallium-67 imaging it is the opinion of this work group that this radiopharmaceutical does not have a role in the workup of prosthetic joint infection.

Strength of Recommendation: Consensus ★☆☆☆

Description: There is no supporting evidence. In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

RATIONALE (A)

^{18}F-FDG PET/CT: There were two high strength studies, with conflicting results. In one study (Aksoy) only patients with positive ^{18}F-FDG results were included in the investigation and only the positive predictive value, which was 28%, could be calculated. In the other study (Kumar 2016), patients with both positive and negative results were included and the positive predictive value was 88.2%. Furthermore, the Kumar investigation was limited to hip arthroplasties. In view of the conflicting results, the appropriate strength of the recommendation should be limited.

^{18}F-NaF PET/CT: The one high quality (Kumar 2016) study was limited to hip arthroplasties, so it may not be possible to extrapolate the data to knee arthroplasties and any recommendation should be limited to hip arthroplasties.

One moderate quality hip study evaluated the diagnostic accuracy of computed tomography (CT) (Cyteval 2002). The study used several different measures, including joint distention, fluid-filled bursae, and fluid collection in muscles and perimuscular fat (for the complete list see table 118 of eAppendix 2). CT may be useful for ruling in infection, with positive likelihood ratios (LR's) ranging from poor to strong (positive LR range=.29 to 45.69). Seven of the 11 CT measures had positive LR's over 2 (see table 118 of eAppendix2 for specific measure results), indicating that CT might be useful as a rule in test. The four CT measures under two (indicating a poor rule in test) were: focal low attenuation, bone abnormalities, nonfocal low attenuation and asymmetric position of femoral head.

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However, the study indicated that CT may not be as good of a rule out test (negative LR range=.04 to 1.28). Nine of 11 CT measures had negative LR's over .5, indicating a very low decrease in probability of PJI with a negative test result (see table 118 of eAppendix2 for specific measure results). The only two CT measures without poor negative LR's were soft tissue abnormalities (negative LR=.04, strong rule out test), and joint distention (negative LR=.17, moderate rule out test).

In their recent retrospective MR imaging study in 108 consecutive patients with TKAs who underwent MR imaging within 1 year prior to revision surgery, Li et al. (2016) found different lamellated and hyperintense appearance of the synovium in infected joints which can be differentiated from frondlike and hypertrophied synovium associated with particle-induced synovitis and from homogeneous effusion with the signal intensity of fluid associated with nonspecific synovitis. When compared with surgical and microbiology results as the reference standard, MRI had 65.2-78.3 sensitivity and 97.6-98.8 specificity for infection. The diagnostic accuracy was higher in the index TKA cohort than in the revision TKA cohort. However, the quality of this single article was not sufficient to issue a limited recommendation for or against MRI.

RATIONALE (B)

^{18}F-FDG PET: There were two moderate strength studies, with conflicting results. In one study of 41 patients with hip arthroplasties (Chacko 2002), ^{18}F-FDG was 91.7% sensitive and 96.6% for infection. In another investigation (Stumpe 2004), ^{18}F-FDG PET studies performed on 35 patients were reviewed by two readers independently. Sensitivity of ^{18}F-FDG PET for the two readers was 33% and 22%, and specificity was 81% and 85% respectively.

Combined labeled leukocyte/bone: One moderate strength investigation (Savarino 2004) studied 26 hip arthroplasties with combined bone and techenetium-99m labeled leukocyte imaging and found that the combined test was 31% sensitive, and 100% specific for infection. Thus, the test is good for ruling in, but not for ruling out prosthetic hip infection. It may not be possible to extrapolate these data to knee arthroplasties.

Combined labeled leukocyte/marrow: Moderate evidence supports the use of combined leukocyte/marrow imaging for diagnosing prosthetic joint infection. One moderate strength investigation (Segura 2004) studied 77 lower extremity arthroplasties with combined technetium-99m labeled leukocyte and bone marrow imaging and found that the combined test was 92.8% sensitive, and 98% specific for infection.

Indium-111-labeled leukocyte imaging: In one moderate strength investigation (Rand 1990) studied 38 painful knee arthroplasties and found that the test was 83% sensitive, and 85% specific for infection. In one high strength investigation of 153 scans of lower extremity arthroplasties (Scher 2000) the test was 77% sensitive and 86% specific for infection.

Technetium-99m-labeled leukocyte imaging: There were two moderate strength papers with conflicting results. In one investigation of 77 lower extremity arthroplasties (Segura 2004) the test was 96% sensitive and 30% specific. In another investigation of 40 lower extremity arthroplasties (Chik 1996) the test was 70% sensitive and 100% specific.

Technetium-99m bone imaging: There were five moderate strength papers with conflicting results. Three investigators reported that the test was 100% sensitive (Segura 2004, Chik 1996, Larikka 2001[hip only]). One investigator (Levitsky 1991) reported 33% sensitivity and another (Hill 2017, hips only) reported 29% sensitivity. Specificity varied from 0% to 86% among the five studies.

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RATIONALE (C)

There was one low strength investigation (Kraemer 1993) of hip arthroplasties in which combined bone gallium-67 imaging was performed. Sensitivity and specificity were 38% and 100%, respectively. A search of PubMed identified only 2 subsequent papers on gallium-67 imaging in periprosthetic joint infection. Yapar et al. (Eur J Nucl Med. 2001 Jul;28(7):822-30) studied 22 hip arthroplasties, 6 of which were infected and reported that gallium-67 imaging was 78% sensitive and 100% specific. Piriou et al. (Rev Chir Orthop Reparatrice Appar Mot. 2003 Jun;89(4):287-96) reported on the role of gallium-67 imaging for monitoring treatment response, not for diagnosing periprosthetic joint infection.

POSSIBLE HARMS OF IMPLEMENTATION

There may be a radiation dose associated with imaging of the site but it is small enough to pose no real risk to the patient. Some metal implants are not MRI safe which must be determined prior to imaging. Caution should be used with intravenous administration of iodinated and gadolinium based contrast agents to patients with impaired renal function (https://www.acr.org/Clinical-Resources/Contrast-Manual). Additionally, not all test options are available at each center which may have resource, access to care, and cost implications not fully delineated in these recommendations.

FUTURE RESEARCH

More high-quality evidence is needed to determine if ultrasound and MRI are useful in diagnosis of PJI, and higher quality diagnostic evidence is needed in order to create stronger recommendations.

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GRAM STAIN

Moderate strength evidence supports that the practitioner avoid the use of intraoperative gram stain to rule out periprosthetic joint infection.

Strength of Recommendation: Moderate ★★★☆

Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

RATIONALE

Three moderate (Zywiel et al. 2011, Banit et al. 2002, Spangehl et al. 1999) and one low strength (Parvizi et al. 2006) study evaluated the use of Gram stain to rule out periprosthetic joint infection. Although these studies found a positive gram stain to be a strong rule-in test, all had negative likelihood ratios over 0.5, indicating a negative Gram stain is not a strong indicator of absence of periprosthetic joint infection whether performed on synovial fluid, tissue, or sonicate fluid. One moderate strength study found sonicate fluid Gram stain may have value to rule in PJI but still showed low sensitivity reflecting poor performance in ruling out PJI (Trampuz et al. 2007).

POSSIBLE HARMS OF IMPLEMENTATION

There are no known associated risks or harms with this recommendation.

FUTURE RESEARCH

Based on current evidence, Gram stain does not seem to have utility in ruling out periprosthetic joint infection.

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AVOIDING ANTIMICROBIALS TWO WEEKS PRIOR TO OBTAINING INTRA-ARTICULAR CULTURE TO IDENTIFY A PATHOGEN FOR THE DIAGNOSIS OF PJI

Limited evidence supports withholding antimicrobials for a minimum of two weeks prior to obtaining intra-articular culture to establish the diagnosis of PJI.

Strength of Recommendation: Limited ★★☆☆

Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

RATIONALE

One moderate strength study found that subjects who received antibiotics within two weeks of obtaining an intra-articular culture were at increased risk of false negative culture results (Trampuz et al. 2007). One low quality study failed to find a statistical difference in the risk for false negative culture results between those subjects who did and those who did not receive antibiotics within two weeks of acquiring intra-articular cultures specimens (Shahi et al. 2016).

POSSIBLE HARMS OF IMPLEMENTATION

There may be scenarios where withholding antibiotic treatment may not be appropriate, such as in the case of sepsis. In the case of a hemodynamically stable patient, there are no known associated risks or harms with this recommendation. However, it is recommended that patients remain closely monitored to ensure no worsening of their clinical status during the antibiotic free period.

FUTURE RESEARCH

Periprosthetic joint infection can be caused by a myriad of microorganisms. Whether this recommendation applies to all microorganism-types as well as all antibiotic-types is unknown. Future research is needed to better understand the effect of varying antimicrobial agents on differing organisms and to define the ideal "antibiotic-free" time prior to specimen collection for cultures in patients with suspected PJI.

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AVOIDING INITIATING ANTIMICROBIALS PRIOR TO OBTAINING INTRA-ARTICULAR CULTURE IN PATIENTS SUSPECTED OF HAVING PJI

Moderate evidence supports avoiding administration of antimicrobials in patients suspected of having a periprosthetic joint infection until cultures have been obtained and a diagnosis has been established.

Strength of Recommendation: Moderate ★★★☆
Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

RATIONALE

One moderate strength study (Trampuz et al 2007) addressed whether administration of antibiotic therapy affected the sensitivity of cultures in diagnosing periprosthetic infection. The study found a false negative rate of 55% in patients receiving antibiotics within the previous 14 days, compared to 23% in patients not receiving antibiotics during the same time period. The difference was statistically significant. There is a concern that antibiotics can interfere with isolation of the infecting organism(s), leading to confusion regarding the diagnosis or inability to use organism-targeted antibiotics or antibiotics selected based on organism-specific susceptibility/resistance testing if infection is confirmed. In otherwise stable patients, antibiotic administration prior to definitive diagnosis of or surgical intervention for PJI is unlikely to be associated with benefit. Thus, administration of oral or intravenous antibiotics to patients with a suspected diagnosis of periprosthetic joint infection is discouraged until samples for culture are obtained. An exception, though rare, would be an acutely septic or potentially bacteremic patient, in whom appropriate cultures (e.g., blood, synovial fluid, as appropriate) should be promptly collected and antibiotics started based on clinical judgement. Also, in a patient in whom the infecting organism(s) have been well-defined prior to surgery (e.g. through synovial fluid cultures), the value of withholding antibiotics is lessened.

The finding of only one moderate strength study supporting this recommendation would be evaluated as limited evidence. However, because of the severity of the potential harm to the patient in getting a false negative culture result and the lack of harm in implementing the recommendation, the strength of the recommendation was elevated to moderate by the work group.

POSSIBLE HARMS OF IMPLEMENTATION

There may be scenarios where withholding antibiotic treatment may not be appropriate, such as in the case of sepsis. However, in a hemodynamically stable patient, there are no known associated risks or harms with this recommendation. It is important to note that there is not clear evidence as to the risk of delaying antibiotic treatment in the patient with suspected but undiagnosed periprosthetic infection which argues for expeditious evaluation to make the diagnosis. .

FUTURE RESEARCH

No indications for future research.

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ANTIBIOTICS WITH LOW PREOPERATIVE SUSPICION OF PJI OR ESTABLISHED PJI WITH A KNOWN PATHOGEN

Strong evidence supports that preoperative prophylactic antibiotics be given prior to revision surgery in patients at low preoperative suspicion for periprosthetic infection and those with an established diagnosis of periprosthetic joint infection of known pathogen who are undergoing reoperation.

Strength of Recommendation: Strong ★★★★

Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention.

RATIONALE

Preoperative prophylactic antibiotics mitigate the risk for surgical infection and PJI and thus should be administered prior to revision surgery in patients with low preoperative suspicion for PJI. Additionally, patients with an established diagnosis of PJI and a known pathogen from preoperative synovial aspirate who are undergoing surgery would also benefit from preoperative antibiotic prophylaxis. Two high quality studies (Bedencic et al. 2016, Tetreault et al. 2014) in hip and knee revision patients and two low quality knee studies (Ghanem et al. 2007, Burnett et al. 2010) found no significant difference in false negative rates in their study population when antibiotics were given before surgery versus after intraoperative cultures were obtained. Additionally, two moderate quality randomized controlled trials found that patients not given any antibiotic prophylaxis were at increased risk of PJI compared to those who were given antibiotics preoperatively (Carlsson et al. 1977, Hill et al. 1981).

POSSIBLE HARMS OF IMPLEMENTATION

In the patient with a known diagnosis of PJI and an identified organism, there are no known associated risks or harms with this recommendation. It is possible that implementing this recommendation could mask an occult PJI in a patient is undergoing revision for presumed aseptic causes of failure. In these patients, a preoperative evaluation should have established a low suspicion of PJI prior to undergoing revision surgery. The evidence would suggest that the ability to culture an organism from intraoperative specimens would not be affected by the preoperative antibiotic prophylaxis.

FUTURE RESEARCH

No indications for future research.

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PERIOPERATIVE ANTIBIOTIC SELECTION

A. Limited strength evidence supports the use of any of the following perioperative antibiotics in reducing risk of PJI, though no studies reviewed were powered to detect a significant difference among those listed:

- **1st generation cephalosporin (e.g. cefazolin)**
- **2nd generation cephalosporin (e.g. cefuroxime)**
- **Glycopeptide (e.g. vancomycin)**

Strength of Recommendation: Limited ★★☆☆

Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

B. In the absence of reliable evidence comparing other antibiotics and antibiotic combinations, including those listed in the guideline, it is the opinion of this work group that perioperative antibiotics should be selected based on principles of responsible stewardship, balancing the risk of PJI and antibiotic resistance. Selection should reflect the antibiogram of the individual institution, the individual risk factors of the patient, and multidisciplinary support of institutional infection control experts. There is no current reliable evidence to support one antibiotic versus the other (examples provided in the rationale).

Strength of Recommendation: Consensus ★☆☆☆

Description: There is no supporting evidence. In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

RATIONALE

A total of 13 studies met the inclusion criteria to evaluate evidence for the use of one preoperative antibiotic over another in the prevention of hip and knee PJI. Of those, 3 were classified as high-quality studies (Bryan, 1998; Soriano 2008; and Suter, 1994), 5 were classified as moderate quality (Chareancholvanich, 2012; DeBenedictis, 1984; Periti, 1999; Soave, 1986; and Wall, 1998), and 5 were classified as low quality (Josefsson, 1993; Tyllianakis, 2010; Robertsson, 2017; Soriano, 2008; and Wu, 2016).

Three of the studies compared 1st and 2nd generation cephalosporins (Bryan, 1988; DeBenedictis, 1984; and Soave, 1986), and showed no difference in post-operative PJI. Tyllianakis et al found no difference in infection comparing cefuroxime with fusidic acid after THA or TKA. A comparison of 2nd generation cephalosporins cefamandole and cefuroxime with glycopeptides teicoplanin and vancomycin, by Suter et al (1994) and Tyllianakis et al (2010), respectively, also failed to show benefit of one antibiotic class over the other. One RCT evaluated timing of antibiotic relative to tourniquet inflation versus deflation in TKA, finding no significant differences between the two treatment arms (Mensa et al, #3020). Because most of these studies were lacking in statistical power, the strength of this recommendation was reduced to limited, and a definitive statement on the superiority of one antibiotic over another cannot be made.

There is no current reliable evidence to support one antibiotic versus the other:

- Glycopeptide vs. 1st generation cephalosporin
- 2nd generation cephalosporin vs. fusidic acid
- Fusidic acid vs. glycopeptide
- Lincosamides (e.g. clindamycin) vs. penicillinase resistant penicillin

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- Fosfomycin vs 2nd generation cephalosporin

POSSIBLE HARMS OF IMPLEMENTATION

The use of perioperative antibiotics for hip and knee arthroplasty surgery has become the standard of care, and the implementation of this guideline will likely not add risk to the arthroplasty patient population. Preoperative antibiotics should be administered routinely, and the antibiotic selected should reflect the antibiogram of the individual institution, the individual risk factors of the patient, and multidisciplinary support of institutional infection control panels. The inclusion criteria for this guideline excludes in vitro studies. As such, the practitioner should understand the effectiveness of the selected antimicrobial on common pathogens for PJI and specifically consider this with respect to vancomycin as a stand-alone perioperative prophylactic agent.

FUTURE RESEARCH

Future research opportunities on the choice of perioperative antibiotics should focus on the optimal timing and the number of post-operative doses required to reduce the incidence of PJI. The Centers for Disease Control and Prevention (CDC) has issued a recommendation that a single dose of preoperative antibiotic prophylaxis is sufficient prior to lower extremity arthroplasty surgery, but there is concern that the data used to arrive at this conclusion may not be specifically applicable to the hip or knee arthroplasty patient, and as such, this recommendation has been received with a certain degree of reluctance among practicing arthroplasty surgeons (Barríos-Torres, 2017). A multi-center RCT specifically designed to answer this question is currently underway.

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ANTIBIOTIC CEMENT

A. Limited evidence suggests the routine use of antibiotics in the cement does not reduce the risk of periprosthetic joint infections for patients undergoing cemented total knee arthroplasty (TKA).

Strength of Recommendation: Limited ★★☆☆

Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

B. Limited evidence suggests the use of antibiotics in the cement may reduce the risk of periprosthetic joint infections for patients undergoing cemented total hip arthroplasty (THA).

Strength of Recommendation: Limited ★★☆☆

Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

RATIONALE (A)

With respect to the use of antibiotic cement for knee arthroplasty surgery, one high quality randomized controlled trial (RCT) of 2968 primary total knee arthroplasty (TKA) patients showed no overall statistically significant difference in infection rates, as well as no evidence for statistically significant reduction in infection rates involving infection with *Stapylococcus aureus*, *Streptococcus* species, Gram-negative bacilli or *Propionibacterium/Cutibacterium* organisms. A statistically significant difference was noted in rates of infection with coagulase-negative staphylococci for patients treated with Simplex P cement with erythromycin compare with non-antibiotic impregnated cement (Hinarejos, 2013). A moderate quality RCT of primary TKA using Simplex P with cefuroxime showed a reduction in deep infection rates with no significant difference in component loosening rates requiring revision (Chiu, 2002). A RCT of diabetic patients demonstrated no infections in forty-one patients where Simplex P cement and 2 g of cefuroxime was used when compared to 13.5% infection rate in 37 patients where Simplex P alone was used (Chiu et al 2001). Lastly, a RCT of knee revision patients demonstrated a statistically significant reduction in deep infection when Simplex P cement impregnated with vancomycin was compared to Simplex P cement alone, with no difference in component loosening (Chiu 2009).

Observational studies have shown conflicting results, with some studies demonstrating reduced odds of deep infection (Wu 2016), while others showed no difference or increased infection rates when antibiotic cement was used. (Dowsey, 2009; Namba, 2009; Taylor, 2016; Namba, 2009; Namba, 2013).

Most of the RCT evidence in favor of antibiotic cement comes from special populations (diabetics and revision patients) that are not widely applicable to the general primary TKA population, and the primary TKA studies do not support its use.

The importance of this recommendation regards the prevention of infection by using antibiotic cement as additional prophylaxis, which can have significant impact on patient function, and overall morbidity and health.

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RATIONALE (B)

Total hip arthroplasty is commonly done both with and without cement and with a hybrid approach where one component is cemented, and one is not. This recommendation is not intended to imply when cement should be used, but rather only to address the issue of whether antibiotics should be used with cement when cement is used in total hip arthroplasty. There is one randomized controlled study (RCT) evaluating the impact of cefuroxime in cement on deep infection rates after hip and knee replacement with no significant difference in infection rates. (McQueen, 1990). The results of observational studies examining the use of antibiotic cement with total hip arthroplasty have had mixed results. Using deep infection as an outcome, studies have found decreased risk (Schrama, 2015; Dale, 2009). One author compared antibiotic cement to uncemented techniques and reported lower risk of revision for infection in the cement group. (Dale, 2009) Others have failed to show any difference in infection rates when comparing antibiotic and plain cement. (Gandhi, 2009; Dowsey, 2008).

The issue of overall revision risk and implant loosening has been examined as well. One study found the use of antibiotic cement reduced the risk of revision overall and for aseptic loosening when both components were cemented compared with hybrid or uncemented techniques (Engesaeter 2006). However, no difference in revision for infection was noted. Another study found decreased risk of revision for infection when antibiotic cement was used compared to cement without antibiotics (Dale 2012). The use of systemic antibiotics and antibiotic cement compared with systemic antibiotics alone decreased the risk of aseptic loosening, overall revision, revision for infection, and revision for loosening in observational registry studies. (Engesaeter 1997 and 2003)

The importance of this recommendation regards the prevention of infection by using antibiotic cement as additional prophylaxis, which can have significant impact on patient function, and overall morbidity and health.

POSSIBLE HARMS OF IMPLEMENTATION

Indiscrimate use of antibiotic laden cement may have unintended consequences that were not specifically evaluated with this recommendation. Although the studies did not show increased risk of implant loosening, it is possible that cement with higher doses of antibiotics could increase risk of loosening by changing the mechanical properties of the cement fixation. Similarly, there is the potential for other effects such as antimicrobial resistance or increased costs to the healthcare system that should be considered.

FUTURE RESEARCH

Adequately powered randomized controlled trials assessing the impact of antibiotic cement on deep infection, implant survival and other patient outcomes are needed to determine which specific patient groups may benefit from this prophylactic treatment with total knee arthroplasty.

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PREOPERATIVE SCREENING AND DECOLONIZATION

A. Limited strength evidence supports the use of universal preoperative chlorhexidine cloth decolonization to reduce PJI after total hip arthroplasty (THA) and total knee arthroplasty (TKA).

Strength of Recommendation: Limited ★★☆☆

Description: Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.

B. In the absence of reliable evidence for screening and nasal decolonization, it is the opinion of this work group that preoperative nasal mupirocin decolonization is a low-risk, reasonable option prior to hip and knee arthroplasty in patients who are MRSA carriers.

Strength of Recommendation: Consensus ★☆☆☆

Description: There is no supporting evidence. In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion

RATIONALE

Periprosthetic infection after hip and knee arthroplasty is a devastating complication. Limited evidence exists to support the use of routine decolonization. Kapadia (2016) conducted a low quality randomized controlled trial (RCT) which demonstrated preoperative chlorhexidine cloths decrease risk of PJI after hip and knee arthroplasty compared to soap and water baths. Two low quality retrospective studies (Kapadia, 2016, Kapadia 2016) demonstrated the use of preoperative chlorhexidine wipes appeared to reduce the risk of periprosthetic infections after TKA and THA compared to patients who did not use them. Medium and high-risk patients had greater risk reduction in the TKA cohort whereas the THA cohort demonstrated no difference in the infection rate when stratified by risk. Reportedly, these studies were underpowered.

A low quality RCT (Sousa 2016) screened patients prior to undergoing TKA or THA for staphylococcus aureus and decolonized randomly selected carriers. Treated and untreated carriers showed no significant difference in PJI (3.4% vs 4.4%), although the study may not have been adequately powered to detect a difference.

POSSIBLE HARMS OF IMPLEMENTATION

Chlorhexidine skin decolonization appears to be safe with minimal potential risk of dermatitis and rash. There is an associated cost with decolonizing patients but this is relatively inexpensive.

Nasal mupirocin decolonization appears to be safe with minimal potential risk of nasal irritation. There is an associated cost with decolonizing patients but this is relatively inexpensive.

FUTURE RESEARCH

Large multicenter randomized controlled trials that are sufficiently powered to measure a difference in the PJI rate that ideally stratify patients based on risk profile regarding preoperative chlorhexidine, methicillin-susceptible *S. aureus* and MRSA nasal screening and nasal mupirocin decolonization are needed.

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INTRAOPERATIVE TECHNICAL FACTORS

In the absence of reliable evidence for the use of an antiseptic wash during total hip or knee arthroplasty, it is the opinion of this work group that dilute betadine lavage be used as a method to decrease infection risk in hip or knee arthroplasty.

Strength of Recommendation: Consensus ★★★★
Description: There is no supporting evidence. In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

RATIONALE
One low strength study (Brown et al. 2012) evaluated the use of a dilute betadine lavage as a method to reduce the risk of periprosthetic joint infection within 90 days of hip or knee replacement. The study reports a significant decrease in the infection rate following implementation of the betadine lavage protocol. Patients with a documented allergy to iodine were excluded from the study.

POSSIBLE HARMS OF IMPLEMENTATION
There are no known harms associated with implementing this recommendation with the understanding that patients with allergy to iodine / betadine would be excluded from the intervention.

FUTURE RESEARCH
The cited study outlines a specific concentration and protocol for the application of the betadine wash. Further high-quality studies are needed to corroborate the results of this study and to further define the method of use.

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GUIDELINE DEVELOPMENT GROUP DISCLOSURES

Prior to the development of this systematic literature review, systematic literature review development group members disclose conflicts of interest (COI). They disclose COIs in writing to the American Academy of Orthopaedic Surgeons via a private on-line reporting database and also verbally at the recommendation approval meeting.

Disclosure Items: (n) = Respondent answered 'No' to all items indicating no conflicts. 1 = Royalties from a company or supplier; 2 = Speakers bureau/paid presentations for a company or supplier; 3A = Paid employee for a company or supplier; 3B = Paid consultant for a company or supplier; 3C = Unpaid consultant for a company or supplier; 4 = Stock or stock options in a company or supplier; 5 = Research support from a company or supplier as a PI; 6 = Other financial or material support from a company or supplier; 7 = Royalties, financial or material support from publishers; 8 = Medical/Orthopaedic publications editorial/governing board; 9 = Board member/committee appointments for a society.

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CD Diagnostics: Research support ($0) Research grant (Self)
Clinical Infectious Diseases: Editorial or governing board ($0)
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