Consensus document

Management of prosthetic joint infections. Clinical practice guidelines by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)

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On behalf of the Spanish Network for the Study of Infectious Diseases and the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC, Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica) along with expert orthopedic surgeons from the Spanish Group of Septic Pathology of the Locomotive System (GEPSAL, Grupo de Estudio de Patología Séptica del Aparato Locomotor).

ABSTRACT

The incidence of prosthetic joint infection (PJI) is expected to increase in the years to come. PJI pose serious consequences for patients and high costs for the health system. The complexity of these infections make it necessary to organize the vast quantity of information published in the last years to help professionals of orthopaedic surgery, infectious disease specialists, internal medicine physicians, microbiologists, and all other health professionals responsible for the everyday management of patients with PJI. The present guidelines have been developed from a flowchart that includes the different medical-surgical strategies available to treat patients with PJI. The authors selected clinically relevant questions and then reviewed the available literature in order to give recommendations according to a predetermined degree of scientific evidence. The absence of randomized-controlled trials is remarkable; therefore, recommendations are mainly based on observational studies and data from animal studies. Before its final publication, the manuscript was made available online so that all members of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) were able to read it and make comments and suggestions.

ARTICLE INFORMATION

Keywords:
Prosthetic joint infection
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RESUMEN

Se prevé un incremento de la incidencia de infección de las prótesis articulares (IPA) en los próximos años. Las IPA plantean graves consecuencias para los pacientes y un alto coste para el sistema sanitario. La complejidad de estas infecciones hace que sea necesario organizar la inmensa cantidad de información publicada en los últimos años para ayudar a los cirujanos ortopedas, infectólogos, internistas, microbiólogos y otros especialistas involucrados en el cuidado diario de los pacientes con IPA. Estas guías se han desarrollado partiendo de un algoritmo que incluye las diferentes estrategias médico-quirúrgicas disponibles para tratar a los pacientes con IPA. Los autores seleccionaron las preguntas clínicamente relevantes y revisaron la bibliografía disponible con el fin de proporcionar recomendaciones de acuerdo con un grado de evidencia científica predeterminada. Resulta llamativa la ausencia de ensayos clínicos

aleatorizados, por lo que las recomendaciones están basadas principalmente en estudios observacionales y datos de estudios realizados en animales de experimentación. Antes de su publicación el manuscrito estuvo abierto a comentarios y sugerencias de los miembros de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC).

Palabras clave:
Infección de prótesis articular
Infección de artroplastia

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Rationale for these clinical guidelines

The incidence of prosthetic joint infection (PJI) is expected to increase in the years to come[1,2]. The occurrence of a PJI dramatically raises the economic costs of an arthroplasty and it is also catastrophic for the patient[2-5]. The algorithm proposed by Zimmerli represents a notable step forward in the management of these infections, and subsequent publications have confirmed its clinical usefulness[6-9].

The vast quantities of data on PJI published in recent years, along with the inherent complexity of these infections, make it necessary to organize and analyse the available information. The French and Italian guidelines were published more than five years ago[10,11] and, while the Infectious Diseases Society of America (IDSA) guidelines are more recent[12], they do not deal with many important aspects of antimicrobial therapy[13].

In Spain, a consolidated group of research on PJI, including centers in the Spanish Network for Research in Infectious Diseases (REIPI, http://reipi.org), has generated an impressive body of scientific knowledge on the subject. The idea for preparing the clinical practice guidelines presented here originated in this group, in collaboration with expert orthopaedic surgeons from the Spanish Group of Septic Pathology of the Locomotive System (GEPSAL, Grupo de Estudio de Patología Séptica del Aparato Locomotor) and the Spanish Society of Orthopaedic Surgery and Traumatology (SECOT, Sociedad Española de Cirugía Ortopédica y Traumatología).

Scope

The present guidelines focus on the management of PJI by classifying all the possible therapeutic scenarios according to clinical presentation. The indications for the choice of a given surgical strategy and the correspondent antimicrobial therapy are specifically reviewed.

These guidelines are addressed to professionals of orthopaedic surgery, infectious disease specialists, internal medicine physicians, microbiologists, and all other health professionals responsible for the everyday management of patients with PJI. They may also be useful for other specialists who participate less frequently in the treatment of these patients, such as geriatricians, rheumatologists, physical therapy specialists, and plastic surgeons.

Methods

Two authors (JA, JC), both infectious disease specialists, coordinated the contributions of the other authors (infectious disease specialists, internal medicine physicians, clinical microbiologists and orthopaedic surgeons). The recommendations of the Spanish National Health System Manual for the Writing of Practice Guidelines (http://www.guiasalud.es/emanuales/elaboracion/index-02.html) were followed, as well as the regulations of the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC, Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica) and the *Agree collaboration recommendations* (http://www.guiasalud.es/contenidos/documentos/Guias_Practica_Clinica/Spanish-AGREE-II.pdf) regarding the methodological quality of practice guidelines.

A "choice chart" was set up for the creation of these guidelines, including five possible clinical scenarios (fig. 1) which raised several clinical questions of interest. Each scenario was assigned to a working team of authors, who reviewed all the literature published since 1970 in order to answer these questions with a predetermined degree of scientific evidence (Table 1)[14]. The manuscript was reviewed by all authors at various stages. The more controversial aspects were debated and the final composition was agreed at an *ad hoc* meeting. All the authors approved the final version of the guidelines. Before its final publication, the manuscript was made available online so that all SEIMC members were able to read it and make comments and suggestions.

Initial assessment of a patient with PJI

What are the goals of treatment?

The aims of the treatment of a patient with PJI are to eradicate the infection, alleviate the pain and, at the same time, restore the joint's function[15]. This makes PJI different from other infections in which the eradication of the infection alone may be sufficient for evaluating a given therapeutic strategy. In the case of PJI, all three goals must be considered in combination, since sometimes achieving one of these targets (i.e., eradication of the infection) may interfere with another (i.e., achieving a satisfactory functional outcome). This situation increases the complexity of the management of these patients, has a deep impact on the therapeutic decisions, and makes the interpretation of the literature difficult, since there is no standardized definition of therapeutic success[16].

What should the care of patients with PJI involve?

Given the complexity of PJI and other types of bone and joint infection, these patients should be attended at multidisciplinary units staffed by orthopaedic surgeons, infectious disease specialists, microbiologists, plastic surgeons, physiotherapists and physical therapy specialists, as well as specifically trained nurses[17-19]. A specialized microbiology laboratory must also be available.

RECOMMENDATION

1. Due to the complexity of patients with PJI, they should be attended at multidisciplinary units (C-III).

What are the medical and surgical options for patients with PJI?

The management of patients with PJI often requires the removal of the prosthesis in order to eradicate the infection. This must be followed, if possible, by the insertion of a new arthroplasty. In some acute infections, however, retention of the prosthesis may be attempted by means of an exhaustive surgical debridement and prolonged antimicrobial therapy, which must be active against biofilm-embedded microorganisms. This strategy has been named DAIR (debridement, antibiotics, implant retention)[20]. Some patients may be considered unsuitable for implant removal, either because they present with too many baseline conditions, or because a poor functional outcome is foreseen. In these patients, prolonged or indefinite antimicrobial therapy aiming to control the infection may be considered. This strategy is known as SAT (suppressive antimicrobial therapy)[21].

Thus, the main medical and surgical strategies to be considered in a patient with PJI are:

a) Attempted eradication with implant retention and antibiotics (DAIR).
b) Attempted eradication with implant removal and antibiotics:
    - With prosthesis replacement (in a 1-step or a 2-step exchange procedure).
    - Without prosthesis replacement (arthrodesis or resection arthroplasty).
c) Implant retention and long-term suppressive antibiotics (SAT), without attempted eradication.

What are the critical aspects influencing the choice of a particular medical and surgical strategy in a given patient?

The decision regarding the most appropriate medical and surgical strategy for a given patient should consider features of the prosthesis, the patient's baseline condition, his/her previous functional performance, life expectancy, desires and expectations, and also the surgical risk involved.

With regard to the prosthesis, the duration of the infection before initiating treatment is of paramount importance, because this is narrowly related with the biofilm's maturity and complexity, and thus with the difficulty of eradicating the infection. Two time points are used for evaluating the duration of the infection: the time when the prosthesis is placed (for post-surgical cases only), which is an objective measure; and the moment when the symptoms begin, which may be more difficult to establish.

The microorganisms responsible should be borne in mind as well as their susceptibility to antibiotics, especially those with a high activity against biofilm-embedded bacteria. The anatomical location of the PJI is another important factor, as well the condition of the surrounding soft tissue (e.g., the possible presence of sinus tracts, blisters, necrotic tissue) and periprosthetic bone (radiological signs of prosthetic loosening, bone stock).

Tsukayama's and Zimmerli's classifications of PJI are both helpful for guiding medical and surgical decisions in a given patient. These classifications are based on similar criteria, which take into account pathogenic aspects, the time of infection, and the diagnostic circumstances (Table 2)[6,22].

When is attempted eradication with implant retention (DAIR) indicated? What are the results?

Eradication of the infection with implant retention is an attractive and ambitious option, which may potentially save bone stock and avoid the need for more complex surgeries. However, this strategy runs a higher risk of failure (Table 3)[20,22-41]. The available data are very heterogeneous regarding patients, etiologies and antimicrobial treatments, with success rates ranging from 18% to 94%. An optimized surgical and medical approach and good identification of the most appropriate candidates for this conservative management are key in order to maximize the likelihood of success and to avoid unnecessary surgeries[26].

This strategy has a higher chance of success in patients with acute infections, short duration of symptoms, a stable prosthesis and surrounding soft tissues in good condition, especially if antibiotics with good activity against biofilm-embedded bacteria can be used. Zimmerli's algorithm takes into account all these parameters, which have been shown to be relevant in the analysis of several retrospective cohorts[6,28,42,43]. The observation of these criteria is helpful for identifying the patients with a greater likelihood of benefiting from prosthesis retention. However, the opposite situation (i.e., not meeting Zimmerli's criteria) does not unambiguously predict the failure of this strategy; as a result, strict application of the algorithm may deprive some patients of benefiting from this approach[42-44]. Due to the complexity of the condition of patients with PJI, tailored treatments and collegiate multidisciplinary decisions are advisable.

Although the majority of the studies have observed a higher likelihood of failure with longer duration of symptoms, the precise cut-off is variable[23-26,30,31,33,34,38,39,43]. Indeed, in staphylococcal infections treated with β-lactams, Brandt *et al* found that the patients undergoing debridement delayed more than 48 hours had a worse prognosis[25]. Subsequent studies using fluoroquinolone and rifampin combinations showed good results with longer periods of time[26,40,43]. The 21-day limit of symptom duration suggested by Zimmerli *et al* is based on a clinical trial published in 1998 in which all patients included underwent debridement within this time period[45]. In any case, caution is required when evaluating the importance of symptom duration, because it may be a surrogate parameter of clinical presentation and severity: acute cases in ill patients usually carry a worse prognosis, but precisely for this reason they may undergo debridement earlier[20,31,36]. Equally, it is sometimes difficult to determine the precise moment when the symptoms began.

The concept of 'acute infection' includes both early post-surgical infections and haematogenous infections. The latter have a worse prognosis[43,46], but clinical diagnosis is usually straightforward[6,22]. In the case of post-surgical infections, it is reasonable to think that the longer the time elapsed since the prosthesis placement, the more complex and mature the biofilm will be, and therefore the less likely attempts at DAIR are to succeed. Indeed, several studies have shown a higher risk of failure associated with the age of the prosthesis[20,40,44,47]. The cut-off for considering a poor prognosis has been

suggested to be one month after the prosthesis placement[22,47], but a limit of three months is probably more suitable[15,20,33,42].

The value of prescribing antibiotics with high activity against biofilm-embedded bacteria has been well established in staphylococcal infections treated with rifampin plus fluoroquinolones[37,45,48] and also in infections caused by Gram-negative bacilli (GNB) treated with ciprofloxacin[35,39,42]. The usefulness of administering these treatments in the context of streptococcal and enterococcal infections is uncertain[49,50]. In some etiologies (for instance, fungal infections), authors have argued against attempting DAIR[51,52].

RECOMMENDATIONS

1. The best candidates for attempting eradication treatment with implant retention are those who:
    a) Have an early post-surgical (up to three months after the placement of the prosthesis) or haematogenous infection (A-II), with a stable implant, and surrounding skin and soft tissues in good condition.
    b) Have a short duration of symptoms (≤3 weeks) (B-II).
c) Can be treated with rifampin (staphylococcal infections) or fluoroquinolones (infections caused by GNB) (A-II).
2. Some patients who do not strictly meet the above criteria may still benefit from this strategy, but its implementation should be considered on an individualized basis, since there is a higher likelihood of failure (B-II).

In what cases of PJI should a strategy including the removal of the prosthesis be offered? What results are to be expected?

The removal of the prosthesis facilitates the control and eradication of the infection: The elimination of foreign bodies and necrotic tissue enhances antibiotic activity. However, prosthesis removal also requires various complex surgical procedures which may deplete bone stock and reduce joint function. The removal of the implant should be considered as an eradication strategy in the setting of chronic infections, in cases of prosthetic loosening, when the surrounding skin and soft tissue are in poor condition, and when no antibiotics with good activity against biofilm-embedded bacteria are available.

The 2-step exchange procedure, which was first described in 1983[53], is the classic treatment of choice for chronic PJI, and it is still frequently applied at most centers. In the first step, the prosthesis and all foreign material (including the bone cement) are removed, and an exhaustive debridement of all non-viable tissues is performed, as well as synovectomy, generous irrigation of the surgical site, reaming of the medullary canal, and the placement of a cement spacer which locally elutes antibiotics. Then, systemic antimicrobials are prescribed for a certain period of time. Once the antibiotic therapy is finished, and if the infection is considered cured, the second step (prosthesis re-implantation) is performed. The rate of failure in hip prosthesis after re-implantation is 0-10%, and slightly higher (5-15%) in studies with 5-10 years of follow up[5,18,54-57]. In the case of knee prosthesis, the rates of failure range are from 0-18% when follow up is short, and from 9-34% if it is longer[58-61]. The 2-step exchange procedure is also the

commonest surgical management in cases in which DAIR has been attempted but has failed, as well as in acute PJI when a DAIR strategy is unsuitable.

In the context of a 2-step exchange procedure, antibiotics were traditionally administered intravenously for six weeks, in accordance with the recommendations of the American school. However, the role of systemic antimicrobial therapy in this setting and its choice, route, and duration are controversial, as well as the indication for rifampin in infections caused by Gram-positive microorganisms. The best moment for performing the 2nd-step surgery is not well defined, nor is the need for monitoring the values of C-reactive protein (CRP) in order to take this decision. Other areas of uncertainty include the choice of the antimicrobial prophylaxis for the new implant, the need to obtain samples for microbiology during the 2ndstep, and the question of how these cultures should be interpreted.

In recent years, the performance of a 1-step exchange procedure has emerged as an attractive possibility, especially in infected hip prosthesis. This practice consists in removing the implant and, in the same surgical procedure, re-implanting a new prosthesis (Table 4)[62-86]. The technique is half way between DAIR (also a single surgical procedure, but offering a more thorough eradication of the infection) and the 2-step exchange procedure, in which the prosthesis is implanted with a higher guarantee of sterility in the surgical site. The 1-step exchange procedure may be considered in non-immunosuppressed patients with a chronic PJI, with surrounding soft tissues in good condition, with sufficient bone stock, and if the infection is caused by low-virulent microorganisms susceptible to antimicrobials with activity against sessile (biofilm-embedded) bacteria. This strategy may also be considered in some cases of acute PJI in which the removal of the prosthesis and later re-implantation is not excessively complex.

Finally, the removal of the prosthesis without further placement of a new implant is another option, which may be considered in patients for whom re-implantation is not viable due to the anatomy of the joint, the patient's baseline condition or his/her functional ability. In Girdlestone's resection arthroplasty, the femoral diaphysis is fitted in the acetabulum[87]. The knee arthrodesis may be performed by external fixation[88] or by intramedullary nailing[89]. In highly complex surgical scenarios, or in patients with a short life expectancy, the placement of a permanent cement spacer may be considered[90]. Lastly, in some exceptional cases amputation may be necessary.

RECOMMENDATIONS

1. The prosthesis should be removed in cases of chronic PJI (A-II).
2. A 2-step exchange procedure is recommended in patients with chronic PJI (A-II).
3. In patients with acute PJI who are not candidates for eradication treatment with implant retention, a 2-step exchange procedure is recommended (B-II).
4. The performance of a 1-step exchange procedure may be considered in non-immunosuppressed patients if they have good bone stock, if the prosthetic surrounding soft tissues are in good condition, and if the infection is caused by microorganisms susceptible to antibiotics with good activity against sessile (biofilm-embedded) bacteria (B-II).
5. In patients with acute PJI in whom the removal of the prosthesis is not very complex, a 1-step exchange procedure is recommended as long as the causative

microorganisms are susceptible to antibiotics with good activity against biofilm-embedded bacteria (C-III).

In what cases of PJI should implant retention without attempted eradication be considered? What results should be expected?

SAT is seen as an alternative strategy for cases of PJI in which the surgical treatment cannot be performed or will be insufficient for eradicating the infection. SAT consists in the indefinite administration of antibiotics; the goal is not to eradicate the infection but to alleviate the symptoms and to prevent (or slow down) the progression of the infection. This situation should be distinguished from cases in which it is considered that prolonging antimicrobial therapy will actually eradicate the infection.

In the two case series which reported the proportion of patients with PJI treated with this strategy, SAT was an infrequent therapeutic option (5-8%)[91,92]. However, it may be chosen in up to 36.5% of patients over the age of 80 years[93]. SAT may be considered in patients with acute PJI in whom DAIR has failed and salvage prosthesis removal has been ruled out, or in chronic PJI if no prosthesis removal is to be performed, for any of the following reasons: the functional results are expected to be unsatisfactory; the risks or potential consequences after surgery are disproportionate to the present symptoms; the patient presents another condition that argues against or delays the surgery; life expectancy is short; there is a major surgical contraindication, or the patient refuses to undergo surgery.

The use of SAT may also be considered in situations in which the likelihood of failure after surgical and medical therapy is very high. Possible examples are: 1) chronic PJI with partial exchange of the prosthetic components (nevertheless, good results have recently been reported after the exchange of only the femoral stem in selected cases, with no need for SAT)[94]; 2) acute PJI managed with DAIR and a high likelihood of failure (and/or severe potential consequences if failure actually occurs); i.e., immunosuppressed patients or patients undergoing chemotherapy, or debridement performed by arthroscopy and/or without exchange of removable components, or use of suboptimal antimicrobial therapy. Alternatively, these patients could be followed up closely, reserving the possibility of starting SAT at any moment if signs of relapse are observed.

The following conditions need to be met for the indication of SAT:

a) Identification of the microorganism causing the infection.
b) Availability of oral antibiotics which are not toxic when administered over long periods of time. The use of SAT with parenteral antibiotics with long half-life has been reported, but this strategy is very rarely applied[95].
c) Possibility of a close follow-up of the patient.

In addition, it should be considered that pain due to looseness or implant instability will be not reverted by SAT.

It is difficult to determine the effectiveness of SAT, although an idea can be obtained by indirect means. In a cohort of cases with PJI managed with DAIR and prolonged antimicrobial therapy for more than one year, the rate of failure among

patients stopping treatment was 4-fold higher than those who continued[20]. Although the majority of patients who stopped antibiotics did not fail (meaning that the infection was actually eradicated), the occurrence of failure in some of them indicated that a proportion of those who were not cured by a DAIR strategy did in fact benefit from antimicrobial therapy and thus avoided or delayed failure, which mainly occurred within the first four months of antibiotic withdrawal. Another more recent retrospective cohort study has shown that SAT achieved better results than avoiding long-term antibiotics in a group of patients with high risk of failure after DAIR or after a 2-step exchange procedure (68.5% vs. 41.1%)[96]. The reasons for prescribing SAT in that study are not clear, but it adds evidence regarding the usefulness of SAT. In addition, the experience of SAT as salvage therapy in cases of failure in some patients treated with other strategies[38,93,97], and the occurrence of failure after stopping SAT[31], argue in favour of its use.

The efficacy of SAT is uncertain, because of the difficulties in performing research in this particular area. No controlled trials have been performed, observational studies include patients with acute PJI in whom the use of SAT may not be necessary, and there are certain differences in the definition of endpoints between studies. Indeed, while some authors consider SAT to be successful if surgery is finally avoided (even if surgical samples yield no microorganisms)[91,98], others also require the relief of symptoms as a criterion of success[20,92,97,99]. With this heterogeneity, success rates range between 23% and 84%. Series showing the best results included patients with early infections[20,92,99], many of whom probably did not need SAT. In the study published by Marculescu *et al*[31], the 2-year rate of success was 53% (95%CI: 42-64%) when considering only the 78 patients who were actually followed during the period. By contrast, in the works by Segreti[92] and Byren[20], after excluding early infection, the outcome was favourable in 75% and 68% of cases (with 4 and 2 years of follow-up respectively). Few authors have analysed the parameters predicting failure of SAT, but it seems that the presence of a sinus tract and infection caused by *S. aureus* carry a worse prognosis[31,99].

Bearing all these considerations in mind, and also the implications of long-term antimicrobial therapy, the indication for SAT must be carefully weighed up. The use of SAT in patients with early PJI managed with prosthesis retention should be avoided if no clear factors for failure are present. In the same way the temptation to use this strategy and thus avoid the need for complex but potentially eradicative surgery should be resisted.

RECOMMENDATIONS

1. Treatment with SAT may be considered in situations in which medical and surgical strategies are unlikely to cure the patient, and non-toxic long-term antimicrobials are available (B-II).
2. Treatment with SAT is not indicated in acute PJI managed early, with appropriate debridement and optimized antimicrobial therapy (E-II).

Attempted eradication without implant removal

When should eradication with prosthesis retention be attempted, and what surgical technique should be used?

The importance of performing the debridement as soon as possible has already been stressed. The quality of the debridement is a key point in this strategy. Ideally, the patient must be stable from a hemodynamic, respiratory and metabolic point of view, so that s(he) is in the best possible condition to undergo surgery. In addition, the debridement should be performed by an expert surgical team[15,25,100]. If possible, antibiotics should be withheld until the time of surgery to ensure that the samples taken yield representative microorganisms; the presence of severe sepsis or septic shock is an exception.

Surgical debridement must be performed by open arthrotomy[101]. The evidence available discourages the use of arthroscopy in this setting, because the debridement it obtains is of poorer quality and does not permit the exchange of removable components. The results appear to be far worse when the debridement is performed by arthroscopy than when it is performed by open arthrotomy[20,102]. Nonetheless, some series including very selected patients have showed that arthroscopy could be considered as initial surgical treatment[103,104].

In the first phase of debridement (the "dirty" part of the procedure), cleaning must be very aggressive and methodical. Correct visualization is required, therefore the need for a wide surgical approach using the previous incision. All infected and necrotic tissues must be extensively debrided, as well as the synovial tissue. The loosening of the components of the prosthesis must be ruled out[101].

The importance of the exchange of the removable components of the prosthesis and its final impact in the outcome are controversial. The availability of spare parts is sometimes a matter of concern. Nevertheless, there are strong arguments in favour of this practice: the exchange of removable components allows the debridement of spaces of the joint which are difficult to reach, it facilitates the cleaning of the hidden surface of these components (*undersurface*), and it obtains a more effective detachment of the bacterial biofilm. In addition, the removed components may be sonicated, thus increasing the efficiency of the microbiological diagnosis. Finally, some recent studies have proven that exchanging the removable components of the prosthesis improves prognosis[44,105].

Experience learnt in traumatological surgery of open wounds[106-108] indicates that debridement must be followed by generous irrigation of the joint, but there is no consensus regarding the precise technique[109,110]. With the evidence available, the recommendation is to irrigate a large volume of saline (at least 9 L) using a low-pressure system[101,106,107,111,112]. There is no evidence supporting the use of antiseptics or local antibiotics during the surgical cleaning.

After debridement and irrigation, the "clean" phase of the procedure begins. The surgical field and surgical instruments must be replaced with new sterile materials. The surgical team must change their gloves and gowns, and antiseptics must be re-applied in the surgical field.

RECOMMENDATIONS

1. Surgical debridement must be performed promptly by an expert surgical team, with the patient in the best possible condition (C-III).

2. The surgical approach must be performed by open arthrotomy. Arthroscopy should only be considered in selected cases, and performed by expert surgeons (A-II).
3. The surgical debridement must be aggressive, methodical and exhaustive.

a) If feasible, the removable components of the prosthesis should be exchanged (B-II).
b) Copious irrigation (≥9 L of saline) is recommended with no additives, performed by a low-pressure system (C-III).

What empirical and definitive antimicrobial treatment is recommended?

Prior considerations regarding planktonic and sessile bacteria in the setting of PJI, and their importance in antimicrobial therapy

Foreign-body infections are characterized by the presence of sessile (biofilm-embedded) bacteria in a stationary phase of growth. However, it is also important to consider planktonic bacteria (in a logarithmic phase of growth) in these infections, especially when they are acute. Actually, most failures observed in the setting of an acute PJI managed with implant retention occur within the first days or weeks after surgical debridement[25,34,35,40,42,44]. Consistent with these results, several studies have shown a worse prognosis for episodes of PJI with a high inflammatory load (fever, high C-reactive protein, bacteraemia, high leukocyte count), as well as for those needing a second debridement[25,35,40,43,49].

Therefore, prioritizing a treatment which focuses only on slow-growing sessile bacteria is debatable, at least in the first days or weeks after debridement. Specifically, rifampin may have an antagonistic effect on β-lactams and other antimicrobials with good activity against rapidly-growing bacteria, and may thus reduce their efficacy[113-115]. In addition, the use of rifampin or fluoroquinolones in a context of high bacterial inoculum increases the odds of resistance and may undermine these valuable antibiotics at a later stage in the treatment, when their anti-biofilm activity is crucial[116].

In summary, surgical debridement is an important element in the efforts to reduce the bacterial inoculum. An optimized initial antibiotic treatment with good activity against rapidly-growing planktonic bacteria should be provided, ideally based on intravenous β-lactams, lipopeptides, or glycopeptides administered for at least 7 days. Once the most inflammatory component of the infection and the initial bacterial inoculum have been reduced, the treatment can focus on the biofilm-embedded bacteria. Table 5 summarizes the recommendations for the treatment of patients managed with implant retention.

RECOMMENDATIONS

1. After surgical debridement, antibiotics with good activity against rapidly-growing planktonic bacteria should be provided, ideally based on β-lactams, lipopeptides, or glycopeptides (B-III).
2. This initial treatment must be administered intravenously for at least 7 days before switching to an optimized antimicrobial therapy focused on the treatment of biofilm-embedded bacteria (C-III).

Staphylococcal infections

The most important microorganism in this context is *Staphylococcus aureus*. Coagulase-negative staphylococci (CNS) are less frequent (but not rare); their treatment is based on the extrapolation of the results of clinical and experimental studies of *S. aureus*.

The fundamental initial treatment (during the logarithmic phase of growth) for methicillin-susceptible *S. aureus* (MSSA) is cloxacillin (cefazolin is an alternative, offering similar efficacy), although its activity is suboptimal when there is a high bacterial inoculum. The addition of daptomycin may provide synergy, as shown by *in vitro* studies and animal experimental models, and it possesses good activity against biofilm-embedded bacteria[117]. Given the difficulties of this scenario this combination may be considered, but at present no clinical experience is available.

For methicillin-resistant *S. aureus* (MRSA), vancomycin has been the standard of treatment, but its bactericidal ability and the clinical results obtained are unsatisfactory[118]. *In vitro* studies and experimental animal models have shown daptomycin to be more bactericidal[119-122]. If daptomycin is to be used, high doses (8-10 mg/kg/d) and a combination with a second drug are recommended in order to increase the efficacy and to avoid the emergence of resistant subpopulations[123-125]. Combinations of daptomycin with cloxacillin or with fosfomycin have been shown to be synergistic and effective in experimental animal models of MRSA foreign-body infection, but there is no clinical experience[126]. Although there are no clinical comparative data, the authors of these guidelines favour the use of daptomycin plus cloxacillin as the initial treatment for PJI by methicillin-resistant strains.

Rifampin has excellent activity against staphylococcal biofilms, but it should not be administered alone due to the high risk of resistance development during therapy[127,128]. Rifampin-based combinations are the treatment of choice against slow-growing biofilm-embedded bacteria, ideally in combination with fluoroquinolones[15,37,43-45,103,129,130]. Levofloxacin is intrinsically more active than ciprofloxacin and is less likely to develop resistance[131,132]. Moxifloxacin is less frequently used: although its intrinsic anti-staphylococcal activity is higher[133], experimental models have failed to prove a higher efficacy[134]. In addition, rifampin induces the metabolism of moxifloxacin, therefore limiting the usefulness of this combination[135].

When fluoroquinolones cannot be used, the best alternative rifampin-based combination remains uncertain. Daptomycin plus rifampin is an attractive alternative based on experimental studies and a limited clinical experience[129,136-138]. The combination of fosfomycin and rifampin showed similar efficacy in an animal experimental model[139]. Other options with rifampin (or oral sequential treatments following the above combinations) include the addition of linezolid[140], fusidic acid[33,141], co-trimoxazole[142,143], or clindamycin[144]. There is also limited experience with combinations of rifampin and minocycline[97]. The clinical relevance of the ability of rifampin to induce the metabolism of the other antibiotics is not well known[145-147]. The choice of one or other treatment should be individualized after taking account of the potential adverse events, the drug-to-drug interactions, and the advantages of oral over intravenous administration.

In some instances, it will not be possible to use rifampin (because of toxicity, drug-to-drug interactions, or resistant strains). In these cases, the best treatment is not well defined at present. The combinations of daptomycin with fosfomycin[139], with linezolid[148], with co-trimoxazole[149,150], or with levofloxacin[151] have shown good activity in *in vitro* studies and experimental animal models. Monotherapy with a

fluoroquinolone, co-trimoxazole, or linezolid, or other combinations of antimicrobials may be an alternative[114,133,152,153]. There is also some experience with the combination of fusidic acid and antimicrobials other than rifampin[154,155].

RECOMMENDATIONS

1. Initial treatment (antibiotics against planktonic bacteria):

a) Methicillin-susceptible strains: cloxacillin (or cefazolin) (B-II), or cloxacillin + daptomycin (C-III).
b) Methicillin-resistant strains: daptomycin + cloxacillin, or daptomycin + fosfomycin (C-III), or vancomycin (B-II).

2. Subsequent treatment (against biofilm-embedded bacteria):

a) Treatment of choice: rifampin + levofloxacin (A-II).
b) If fluoroquinolones cannot be used: combinations of rifampin with co-trimoxazol (B-II), linezolid (B-II), clindamycin (B-II), fusidic acid (B-II), or daptomycin (B-III).
c) If rifampin cannot be used: combinations of daptomycin with fosfomycin (B-III), cloxacillin (B-III), linezolid (B-III), co-trimoxazol (C-III), or levofloxacin (C-III); or combinations of 2 oral antibiotics or monotherapy with levofloxacin (B-III), or moxifloxacin (B-III), co-trimoxazol (BIII), or linezolid (B-III).

Streptococcal infections

The recommended therapy for streptococcal PJI is based on β-lactams (ceftriaxone or penicillin), both for the initial phase of treatment and later for sessile microorganisms[12,15]. Although β-lactams are known to have poor activity against biofilm-embedded bacteria, this may be less important in infections which are believed to have a better prognosis. However, the actual experience is scarce and heterogeneous, with a wide range of cure rates (42-94%)[27,29,156-158]. Some authors have suggested that patients treated with fluoroquinolones or rifampin-based combinations may have a better prognosis, especially in infections caused by virulent streptococci[159,160].

RECOMMENDATIONS

1. For initial treatment (planktonic phase): penicillin or ceftriaxone (B-II).
2. Subsequent treatment (biofilm-embedded bacteria): penicillin or ceftriaxone (B-II), followed by amoxicillin (B-II), either in combination with rifampin or not (B-III); alternatively, levofloxacin (B-III) either in combination with rifampin or not (B-III), or monotherapy with clindamycin or linezolid in the case of allergy to fluoroquinolones (C-III).

Infections caused by Enterococcus faecalis

Ampicillin is the treatment of choice[12,15]. The addition of aminoglycosides has been questioned: they have not shown any advantage in clinical studies, and they may increase the risk of ototoxicity and nephrotoxicity[161]. By contrast, there is some clinical experience supporting the use of rifampin[50] or the addition of ceftriaxone or ceftaxime[162,163]. As alternatives, vancomycin[161], teicoplanin[164-166], or linezolid[167,168] may be used.

RECOMMENDATIONS

1. The treatment of choice is ampicillin, followed by oral amoxicillin (B-II).
2. It can be administered in combination with ceftriaxone (B-III) or rifampin (B-III).
3. Teicoplanin or linezolid are possible alternatives (C-III).

Infections caused by GNB

A β-lactam with activity against the specific GNB is indicated during the initial phase of treatment (planktonic bacteria): a 3rd-generation cephalosporin for *Enterobacteriaceae*, or ertapenem for extended-spectrum β-lactamase (ESBL)- producing or AmpC β-lactamase-producing GNB, or an anti-pseudomonal β-lactam for *Pseudomonas aeruginosa*.

For the subsequent treatment of biofilm-embedded bacteria, the possibility to administer fluoroquinolones (ciprofloxacin) is decisive, because this treatment significantly improves the prognosis of these infections and is therefore the treatment of choice in all cases of PJI caused by GNB[34,35,39,42,169]. For infections caused by *P. aeruginosa*, it is reasonable to administer two antibiotics, including a β-lactam and a fluoroquinolone[169].

If there is resistance to fluoroquinolones, the prognosis of the infection relies on β-lactams, which may be insufficient in this phase of slow-growing biofilm-embedded bacteria. In this regard, and bearing in mind that fluoroquinolones resistance is an increasing problem, more studies evaluating the efficacy of alternative antibiotic regimes are needed. The combination of colistin with β-lactams may be an option, given its activity on biofilm-embedded bacteria in specific targets within the biofilm structure which are different and complementary to those of other antibiotics[170-172]. Colistin also increases the permeability of the bacterial membrane, thus facilitating the activity of other antimicrobials[173,174]. Several experimental and clinical studies have demonstrated higher activity in colistin-based combinations than in monotherapies[175-177]. Still, more studies supporting the use of colistin are required; its potential disadvantages (complex pharmacokinetics, uncertain dosage, intravenous route, and significant risk for nephrotoxicity) need to be considered.

Fosfomycin combined with β-lactams may also be an alternative, given its synergistic effect, its activity against biofilm-embedded bacteria[175] and its good bone diffusion[178], but there is no clinical experience with this treatment. Tigecycline may be considered as part of a combination in the salvage treatment of infections caused by multi-drug resistant microorganisms[179]. Finally, co-trimoxazole is considered as a minor antibiotic compared with fluoroquinolones, but it may have a role in prolonging therapy via the oral route.

RECOMMENDATIONS

1. For initial treatment (planktonic phase): a β-lactam (a 3rd-generation cephalosporin for *Enterobacteriaceae,* a carbapenem for ESBL or AmpC β-lactamase producing GNB, and an anti-pseudomonal β-lactam for *P. aeruginosa*) (B-III).
2. Subsequent treatment (biofilm-embedded bacteria):

a) Treatment of choice: a fluoroquinolone (ciprofloxacin) (A-II).
b) If fluoroquinolones cannot be used (due to resistance, toxicity…): continue treatment with a β-lactam (B-III) combined or not with colistin (B-III) or fosfomycin (C-III), or monotherapy with co-trimoxazole (C-III).

Culture-negative PJI

A microbiological isolate may be absent in 5-9% of cases of PJI, especially if patients have received antibiotics prior to sampling[38,180-182]. The performance of clinical and experimental studies in this scenario is difficult by definition, and the best antimicrobial regime has not been defined. In spite of the uncertainty and the challenge they represent, these infections do not carry a worse prognosis even if no antibiotics with activity against multi-drug resistant microorganisms are used[180]. In this situation, it seems reasonable to administer antimicrobials with activity against the most frequent microorganisms (i.e., staphylococci, streptococci, and GNB)[179]. The inclusion of MRSA in the antimicrobial spectrum of the regime chosen depends on the clinical context of the patient. It also seems logical to keep the antibiotic spectrum as similar as possible to the one the patient was receiving before sampling, given that it may have interfered with the culture results.

RECOMMENDATIONS

1. If possible, the use of antibiotics prior to a valid sampling (i.e., joint aspirate, and/or intraoperative cultures) should be avoided (B-III).
2. The antimicrobial treatment must be active against the most prevalent microorganisms. The need for antibiotic activity against multi-drug resistant microorganisms must be considered in accordance with the patient's clinical and epidemiological context (C-III).
3. If antibiotics have been administered prior to the sampling and they are considered as potentially responsible for the absence of microbiological diagnosis, the antimicrobial spectrum of this treatment should be considered when choosing the new antibiotic regime (C-III).

What is the optimal duration of the antimicrobial treatment?

The initial antimicrobial treatment, which is intended to reduce the planktonic component of the infection, should be based on β-lactams, glycopeptides or lipopeptides administered intravenously for at least seven days. Then, the oral route may be used as long as antibiotics with high bioavailability are prescribed, such as levofloxacin, rifampin, co-trimoxazole, linezolid, or clindamycin. Otherwise, it will be necessary to prolong intravenous administration of the drug.

A long treatment was empirically recommended for PJI cases managed with implant retention, ranging from 3 to 6 months[15]. However, long treatments increase the risk of adverse events, have an impact on the patient's microbiota and environment, and have a higher economic cost[183-186]. Several retrospective studies have suggested a similar rate of success for shorter treatments[32,35,40,43,187], and a recent multicenter randomized clinical trial showed that an 8-week course of levofloxacin plus rifampin was as effective as 3-6 months in acute staphylococcal PJI[188].

The value of CRP as an acute phase reactant and for follow-up is relative. Persistently high values of CRP after the first weeks of debridement may suggest persistence of the infection, but many patients present abnormally high values of CRP

for a long time. Thus, the normalization of CRP is not a criterion for extending the antimicrobial therapy beyond the recommended duration[179,189].

RECOMMENDATIONS

1. For acute staphylococcal PJI managed with rifampin and levofloxacin, an 8-week schedule of treatment after debridement appears sufficient for most patients (B-I).
2. For PJI caused by other microorganisms treated with antibiotics with good activity against biofilm-embedded bacteria (i.e., ciprofloxacin for PJI caused by GNB, 8 weeks is also a reasonable duration) (B-III).
3. In other clinical scenarios, the most appropriate duration of treatment remains uncertain. A variable period between 8 and 12 weeks may be adequate (B-III).
4. Monitoring of CRP during the follow-up is advisable; the persistence of high values is suggestive of treatment failure (B-III), but its total normalization must not be a condition for deciding the end of therapy (B-II).

How should patients be followed up and for how long?

During the antibiotic treatment (8-12 weeks) a close follow up performed by an expert in antimicrobial therapy is recommended, in order to guarantee observance and to monitor potential toxicity, drug interactions, and other adverse events of the treatment. Failure after surgical debridement usually occurs within the first 6 months, and is rare after 1 year of follow-up[20,23,28,37,43,130,190]. Overall, it is reasonable to follow the patients closely during the antimicrobial treatment and during the first weeks after withdrawal of antibiotics. The frequency of visits may then decrease progressively during the first year, and become annual, or once every two years, after the first 2 years of follow up.

RECOMMENDATIONS

1. During antimicrobial therapy, a close follow up of observance and potential adverse events of the treatment is recommended, performed by a clinician with expertise in antibiotics (C-III).
2. During the first 6 months after the end of a treatment aiming at eradication, patients must be followed up closely (B-III).
3. The frequency of follow-up visits may decrease afterwards. Follow-up should last at least one year (B-III).

Attempted eradication with prosthesis removal and a 2-step exchange procedure

What is the role of systemic antimicrobial treatment? What is the most appropriate length and route?

The management with a 2-step exchange procedure is complemented by antimicrobial treatment, the goal being to provide high concentrations of antibiotics at the site of infection. This may be achieved by administering systemic antibiotics, or using cement spacers loaded with antibiotics and placed at the surgical site, or with the combination of the two, which is the most common strategy. A study including 68 cases of hip PJI proved the use of combined antimicrobial therapy (local and systemic) to be superior to systemic antibiotics alone[191]. Systemic antibiotics have classically been administered

intravenously over a period of 6 weeks between the first and second surgical step. Nevertheless, recent studies have questioned the value of such long treatments if antibiotic-loaded cement spacers are used (as long as the local antimicrobials are active against the microorganism isolated in the first-step surgery)[192-198].

The possibility of only providing local antibiotics is limited by the reduced availability of antimicrobials for loading the cement spacers (not all can be used), and by potential risks such as superinfection by other microorganisms (indeed, the cement spacer is a new foreign-body in the surgical site), or the selection of difficult-to-treat phenotypical variants of bacteria (i.e., staphylococcal small colony variants)[199]. As a consequence, at present there is not enough evidence to abandon the prescription of systemic antibiotics, although shortening the length in the setting of PJI caused by low-virulent microorganisms (i.e., CNS) might be considered. For the management with a 2-step exchange procedure of PJI caused by more virulent microorganisms, and/or suppurative and inflammatory infections (i.e., PJI caused by *S. aureus*) administration of a prolonged treatment is reasonable.

Systemic antibiotics are begun after the first-step surgery. If the etiology has been identified during the pre-surgical evaluation, a targeted antibiotic may be used. Otherwise, wide-spectrum antimicrobial therapy is recommended while waiting for the microbiological results after the first-step surgery. In the case of chronic PJI caused by CNS, a lower rate of positive cultures during the second-step surgery (re-implantation) has been observed when anti-staphylococcal antibiotics with a *universal* spectrum have been administered (i.e., glycopeptides, daptomycin, or linezolid)[200,201].

While the American school has classically recommended that the intravenous route be maintained throughout the treatment, in the recent IDSA guidelines and the international recommendations on PJI there is a consensus on administering part of the antibiotics orally (as long as the antimicrobial has a good bioavailability), after a short intravenous schedule of 7-14 days[12,21]. Some studies also support this practice[202-206].

The isolation of microorganisms in samples taken during the second-step surgery is interpreted in a similar way to the "positive intraoperative cultures" category in Tsukayama's classification (Table 2). Most authors have prescribed 4 to 6 weeks of antibiotics in order to avoid the contamination of the new implant[200,201,207]. However, little evidence is available on the usefulness of this treatment, or on the most appropriate duration.

RECOMMENDATIONS

1. The two-step exchange procedure should include a targeted intravenous antimicrobial treatment for 4 to 6 weeks (A-II), or 1-2 weeks of intravenous antibiotics followed by oral antimicrobials with good bioavailability for a total duration of 6 weeks (B-II).
2. In chronic PJI caused by CNS, "universal" anti-staphylococcal antimicrobial therapy (i.e., glycopeptides, daptomycin, or linezolid) may be considered after the first-step surgery (prosthesis removal), because this carries a lower rate of positive cultures during the second-step surgery (re-implantation) (C-III).
3. Shortening the systemic antimicrobial treatment could be considered for cases of PJI due to low-virulent microorganisms, such as CNS or *Propionibacterium acnes,* as long as the first-step surgery has included a thorough and exhaustive debridement of the

joint, and a cement spacer loaded with antibiotics active against the microorganism responsible for the infection has been used (B-II).

4. When samples taken during the second-step surgery yield a microorganism, a new 4-6 weeks course of antibiotics is recommended (B-II).

Is rifampin necessary in staphylococcal infections managed with a 2-step exchange procedure?

Rifampin is one of the most active antibiotics against slow-growing biofilm-embedded bacteria. In addition, the combination of rifampin with fluoroquinolones decreases the likelihood of the emergence of resistance to both antibiotics[131]. However, the usefulness of rifampin has not been proven in the setting of a 2-step exchange procedure[12,16].

In most case series reporting the efficacy of a 2-step exchange procedure, rifampin was not included in the antimicrobial treatment and cure rates were near 90%. Therefore, there is not enough evidence to evaluate this antibiotic in this scenario. Theoretically, the complete removal of the prosthesis and a thorough surgical debridement would be able to eradicate all the biofilm (in both the prosthesis and periprosthetic bone), and the role of rifampin would be less relevant. Nevertheless, rifampin may still be of benefit in cases in which the surgery was not optimal and where fragments of cement and osteitic bone may remain. Likewise, in cases presenting a significant inflammatory load or those caused by *S. aureus*, it is reasonable to administer a rifampin-based combination, as long as the microorganism is susceptible and there are no toxicity or drug-to-drug interactions. In these cases, there is no reason for delaying the administration of rifampin after surgery, since in the majority of cases the bacterial inoculum will not be high and there will be no bacteremia.

RECOMMENDATIONS

1. At present, it is not clear whether rifampin should be administered to treat staphylococcal infection managed with a two-step exchange procedure.

a) The indication of rifampin in a chronic non-inflammatory infection should be based on the thoroughness of the surgical debridement (C-III).

b) Rifampin is recommended in cases with a significant inflammatory presentation, especially those caused by *S. aureus* (C-III).

What is the role of local antimicrobial treatment (cement spacers)? Which kind should be used?

During the first-step surgery, once the prosthetic material and foreign bodies have been removed and the joint and bone debrided, an acrylic cement spacer loaded with antibiotics (ALS) is put in place. The main goals of the ALS are: to occlude the hollow space left after the prosthesis removal; to stabilize the joint; to maintain joint mobility as much as possible before the second-step surgery is performed, as well as the limb function; and to avoid muscle contracture and joint shortening[208]. The spacers may be static or dynamic, and both types achieve similar eradication rates[21].

The role of the local antibiotic provided via ALS in eradicating infection is not well defined. Theoretically, its activity depends on the eluted concentration of the antibiotic,

which should be higher than the microorganism's MIC over a sufficient period of time[198,209-213]. Aminoglycosides (gentamicin and less frequently tobramycin) were the antibiotics initially added to ALS, and so they have been the most frequently used[214,215]. Later, other antimicrobials such as clindamycin or erythromycin were added in order to include Gram-positive microorganisms in the antimicrobial spectrum[216-218].

The elution of antibiotics from the cement is maximal (≥30 mg/L) during the first 48 hours. Later, it decreases progressively over the next 15-30 days[213,219]. *In vitro* data suggest that the concentrations achieved are sufficient to avoid neo-formation of biofilm on a sterile surface, but not to eradicate a pre-formed biofilm on that surface[220].

The selection of resistant microorganisms has been observed on the surface of gentamicin-loaded cement spacers or cement beads[201,221,222]. This phenomenon is predominant in CNS, but it has also been observed in GNB. The combination of vancomycin and gentamicin in the spacer, which was introduced a decade ago[223], offers theoretical advantages over aminoglycosides alone because of the vancomycin-gentamicin synergy against Gram-positive microorganisms. The combination also includes a wider antimicrobial spectrum, thus offering protection against the development of resistant microorganisms which may be responsible for superinfection during the second-step surgery[201,222]. There is very little information comparing the results of these two options (monotherapy vs. combination in ALS). A retrospective study including 146 patients who underwent a 2-step exchange procedure and the placement of an ALS (83 with gentamicin alone and 63 with vancomycin-gentamicin) showed a lower rate of positive cultures during the second-step surgery in the combination group (2.8% vs. 13.4%)[224]. In our opinion, while waiting for more comparative studies specifically addressing this question, it is reasonable to use vancomycin-gentamicin loaded spacers, for the reasons outlined above. The recent publication by the International Consensus on Prosthetic Joint Infection supports the use of a spacer combining vancomycin and gentamicin or tobramycin for most infections[21].

Spacers may be industrially pre-formed or created manually during the surgery. In pre-formed spacers, the antibiotic is homogeneously distributed; the biomechanical characteristics comply with the ISO rules, but only the following antimicrobials are available: gentamicin, clindamycin plus gentamicin, and vancomycin plus gentamicin. By contrast, manually-made spacers allow an individualized design and choice of the antibiotic to be used according to the microorganism causing the infection and its antibiotic susceptibility profile, the patient's renal function and his/her allergies or intolerances[198]. No studies to date have evaluated the ideal dosage of antibiotics to be mixed with the cement so that it is effective but does not perturb the resistance of the cement. However, an amount of antibiotic equivalent to 1-10% of the cement weight is accepted (vancomycin 0,5-4 g or gentamicin 0,25-4.8 g per 40 g of acrylic cement)[21]. The risk of nephrotoxicity after a two-step exchange procedure has been highlighted in a recent review[225]. Nevertheless, the authors acknowledge the limitations of the published studies for attributing the responsibility for the adverse event to the antibiotics absorbed, and stress the need for well-designed prospective studies.

Not all antibiotics can be mixed with acrylic cement. The characteristics required are thermostability (heat may inactivate some antimicrobials, such as echinocandins), hydrosolubility (non-hydrosoluble antimicrobials have poor elution), a high, progressive,

and maintained elution, and hypoallergenity.[198,226] The antibiotics used in acrylic cements are shown in Table 6.

Some controversy exists regarding the use of ALS in PJI caused by multi-drug resistant microorganisms. Some authors have stressed that the spacer behaves as a foreign body, thus facilitating the persistence of the infection, and recommend a two-step exchange procedure without the ALS[15,199]. Nevertheless, the use of the ALS may be still considered, as long as it is loaded with an antimicrobial active against these multi-drug resistant microorganisms[227].

RECOMMENDATIONS

1. Antibiotic-loaded spacers are recommended in the two-step exchange procedure (B-II).
2. The dose of local antibiotic ranges between 0,5 and 4 g of vancomycin, and 0,25 and 4.8 g of gentamicin or tobramycin (per every 40 g of acrylic cement) (C-III).
3. The use of combined local antibiotics (vancomycin-gentamicin) is recommended until further evidence specifically addressing this topic is available (C-III).
4. In PJI caused by multi-drug resistant microorganisms, spacers may be still used as long as they are loaded with antibiotics active against these microorganisms (C-III).

When is the best time to perform the second-surgical step?

The final goal of a 2-step exchange procedure is the placement of a definitive prosthesis in a sterile surgical site. No randomized controlled trials have been performed to establish the best moment for re-implantation. In old cohort studies, re-implantation within the first three weeks after prosthesis removal was associated with a higher rate of failure[228]. Some European cohort studies have shown good results performing re-implantation within 2 to 6 weeks after prosthesis removal, as long as the infection was caused by microorganisms other than MRSA, enterococci, or multi-drug resistant GNB[15].

Currently, the most widely accepted strategy is to perform the re-implantation after 4 to 6 weeks of antimicrobial therapy plus an antibiotic-free period of 2 to 8 weeks[229-232]. An excessive period of time (>6 months) between prosthesis removal and re-implantation may have a negative impact on the functional prognosis of the new prosthesis[209].

The absence of symptoms during and after the antimicrobial therapy is not diagnostic of eradication of the infection, but most experts consider that an antibiotic-free period increases the safety margin of infection control and also on the efficacy of the antimicrobial treatment. In addition, an antibiotic-free period before the second-step surgery may help to restore the patient's skin microbiota and reduce the risk of superinfection of the new prosthesis. In the absence of more scientific evidence, a period of 2 to 8 weeks between the end of therapy and the placement of a new prosthesis has been classically used[59,233].

The optimal time for placing the new prosthesis is chosen according to clinical local signs, laboratory tests, intraoperative inspection, and the histopathological study at the time of re-implantation. The IDSA guidelines recommend assessing erythrocyte sedimentation rate (ESR) and CRP in order to evaluate the success of treatment before reimplantation[12]. Both these parameters have traditionally been monitored, along with

the improvement of clinical signs[234]. However, several recent studies have observed that the CRP and ESR values before the second-step surgery are not helpful for predicting the persistence of the infection[235-237]. This is why some authors argue against delaying second-step surgery even in the presence of high values of these parameters[198]. Nevertheless, notable changes in these markers not attributable to other reasons may indicate the persistence of the infection or a superinfection. Therefore, ESR and CRP values, the possible need for an extra debridement before the second-step surgery, and the best time for re-implantation must be interpreted in the context of the entire clinical scenario[235-237].

Analysis and culture of the synovial fluid obtained from a joint aspirate before re-implantation have been proposed by some authors in some doubtful cases[236-239]. However, as discussed below, this culture has a low sensitivity for predicting persistence of the infection[239]. More highly-powered studies are needed in order to evaluate the value of new markers and techniques, including the role of molecular biology procedures in this context[240].

RECOMMENDATIONS

1. In the two-step exchange procedure, an antibiotic-free period of 2 to 8 weeks and clinical stability before the second-step surgery is recommended (C-III).
2. The monitoring of ESR and/or CRP is recommended. The persistence of values above the normal range does not necessarily indicate the persistence of the infection, and sore-implantation should not be delayed (B-II). However, significant changes in these serum markers may imply the persistence of the infection or a superinfection (C-III).

Is it necessary to take new samples for microbiological analysis before and/or during the second-step surgery? How should the results be interpreted?

The two-step exchange procedure does not totally guarantee a sterile surgical site during prosthesis replacement. Therefore, sampling at this time is a common procedure in order to certify the eradication of the initial infection and the absence of superinfection. The sampling is usually performed during the second-step surgery, after a minimal antibiotic-free period of 2 weeks[238,239,241-243]. Overall, studies have shown good sensitivity for finding microorganisms, ranging between 10 and 25%. The microorganisms isolated in the second-step surgery are usually resistant to the antibiotics locally used in the spacer, and also to those administered systemically[200].

The isolation of CNS during the second-step surgery, which usually occurs in infections originally also caused by CNS, is even more difficult to interpret (i.e., whether it represents contamination or infection) and to define whether they imply a new infection or the persistence of the previous infection. Some genotypic studies highlight the difficulty of this analysis compared with other studies which are only based on the phenotypical features of CNS and cannot assess the possibility of a polyclonal infection[76,200,201,238,244,245]. As already mentioned, the frequency of microorganisms during the second-step surgery is lower if the anti-staphylococcal therapy administered after the prosthesis removal is “universal” (glycopeptides, daptomycin, or linezolid)[200,201].

In spite of the clinical implications of the presence of microorganisms in the second-step surgery, there is no solid evidence regarding the interpretation of this phenomenon and its management. Generally, the criteria defined by Atkins *et al* for the microbiological diagnosis of chronic PJI are applied[246].

Murillo *et al* reviewed their experience with positive cultures taken during second-step surgery. Patients with positive cultures received supplementary antibiotics for a mean of 30 days and did not present relapse during follow-up[200]. Likewise, Bejon *et al* observed that patients with positive intraoperative cultures from samples taken during re-implantation and treated with antibiotics for a prolonged time did not have worse prognosis than the group with negative cultures[233]. Therefore, in the case of diagnosis of a persistent infection or a superinfection, a targeted antimicrobial during a period of 4 to 6 weeks appears reasonable.

The presence of a cement spacer between the first and second-step surgery has been associated with the possibility of perpetuating the infection, since it is a foreign body[221,247]. Some studies advocate performing cultures of this material in order to rule out the persistence of infection. Nelson *et al* showed that 50% of patients with a positive culture of the sonicated cement spacer presented subsequent infection relapse, as compared with only 11% of cases with a negative culture.[248] Similar results were observed by Sorli *et al*[207] Other authors argue that the result of the culture of the spacer should be evaluated as an additional sample along with the ensemble of samples taken during the second-step surgery, and so Atkins' criteria should be applied to the whole of samples (tissues and spacer) [201]. More studies are required to evaluate the culture of the spacer or the liquid obtained after its sonication.

In a retrospective study, a group of patients undergoing systematic sampling before re-implantation were compared with another group without systematic sampling. In the first group, 9% of cases had positive pre-surgical cultures; these patients again underwent debridement, cement spacer exchange and a new course of antibiotics before re-implantation, after which there was only one case of infection relapse (3%). By contrast, the second group managed with no sampling before re-implantation presented an infection recurrence rate of 14%[238].

Nevertheless, there is no consensus on the usefulness of sampling the joint aspirate before the second-step surgery; the sensitivity of this practice is low, so its systematic performance is not recommended[198]. Nonetheless, bearing in mind the specificity of a positive result, it could be useful in cases with a clinical and analytical suspicion of poor prognosis (persistent local signs of inflammation, persistently high biological markers) or in cases of difficult treatment (i.e., multi-drug resistant GNB or fungi).

RECOMMENDATIONS

1. Sampling of tissues and the cement spacer during the second-step surgery of a two-step exchange procedure is recommended in order to guarantee the sterility of the surgical site where the new prosthesis is to be placed (B-II).
2. Culture of the joint aspirate before the second-step surgery is not systematically recommended, although it may be of some use when the clinical and analytical evaluation of the patient suggests poor evolution, or in difficult-to-treat episodes caused by multi-drug resistant microorganisms or fungi (C-II).

3. Cultures of samples taken during the second-step surgery may be considered as positive if ≥1 or ≥2 of them yield a microorganism, depending on its pathogenicity (C-III).

What is the best prophylaxis for the second-step surgery and how long should it be prescribed?

Antimicrobial prophylaxis must be administered in this setting (actually, it is indicated for any surgery with placement of orthopedic hardware)[249], but guidelines do not specify the type or the length.

Only two studies have addressed the issue of antimicrobial prophylaxis for the second-step surgery in the setting of a two-step exchange procedure. In a case-control study of patients with knee prosthesis, 28 patients were administered oral *prolonged prophylaxis* for 28-43 days using various antibiotics (67% co-trimoxazole, 14% linezolid) while 38 were given a *standard prophylaxis*. Whether or not this prophylaxis was targeted and took in consideration the initial etiology of the infection was not specified. Notable differences were observed after one year of follow up: the rate of reinfection was only 1/28 (4%) in cases treated with prolonged oral prophylaxis, but 6/38 (15.8%) in the controls[250].

In another retrospective study, the effect of prolonged vs. standard prophylaxis was evaluated in chronic hip PJI managed with a 2-step exchange procedure. None of the 22 patients receiving *prolonged prophylaxis* presented relapse, compared with six out of 44 patients who received *standard prophylaxis*. In four of these, the etiology was the same as the one that caused the original infection. These results were compared with a control group of patients undergoing prosthesis revision for aseptic reasons, in which only two out of 410 patients developed infection[251].

In addition, in three supplementary studies[238,252,253] the microorganism causing infection after the second-step surgery was identical to the original etiology in 18/19, 8/9, and 2/11 cases respectively, thus supporting the idea that antimicrobial prophylaxis should target the initial etiology of the infection. Moreover the isolation of CNS from samples obtained during the second step is not a rare event[200,201,248], and good results have been obtained when these isolates are treated (in the case they are interpreted as significant)[200,233,235]. For this reason, the use of a glico-lipopeptide from the second step until cultures are known (pre-emptive treatment) seems reasonable.

Nevertheless, superinfection by a different microorganism is an alternative cause of failure when exchanging the prosthesis[201,248,254]. These microorganisms are probably part of the patient's skin microbiota, which is likely to have been modified by previous antimicrobial pressure and by the nosocomial environment. All these factors support the use of wide-spectrum antimicrobials for prophylaxis during the second-step surgery. Tandel and Patel's review acknowledges as common practice the use of antimicrobial prophylaxis in the second step until cultures are negative[182].

RECOMMENDATIONS

1. Wide-spectrum antibiotic prophylaxis including nosocomial microorganisms that may potentially cause superinfection of the new prosthesis is recommended for the second-step surgery of a 2-step exchange procedure (C-III).

2. "Preemptive treatment" including microorganisms that could be isolated during the second-step surgery (usually multi-drug resistant SNC) is recommended: vancomycin (or another glycopeptide or lipopeptide) during the first 5 days after re-implantation or until confirmation that the samples taken during the second-step surgery yield no microorganisms (C-III).

Attempted eradication with prosthesis removal and a 1-step exchange procedure

What is the antimicrobial treatment for patients undergoing a 1-step exchange procedure?

There is no consensus on the best antimicrobial treatment for patients undergoing a 1-step exchange procedure, since no randomized or comparative studies have been carried out in this setting. Our evaluation of the literature includes 28 studies (Table 4), but few specify the antibiotic therapy or report the use of various treatment regimens; therefore, no recommendations are forthcoming[62-84,86,255,256]. In spite of this heterogeneity, the cure rates reported were higher than 80%, suggesting that the efficacy of this strategy depends mostly on the surgeon's ability to perform an exhaustive debridement and removal of all foreign bodies and necrotic tissues.

In the majority of reports, antimicrobial treatment begins at the time of prosthesis removal. However, some authors start antibiotics some time (one week to several months) before the surgical procedure[81,83,86], in order to reduce the bacterial load and lower the risk of contamination of the new prosthesis. This seems reasonable, especially in cases with a highly inflammatory clinical presentation or those caused by pathogenic and virulent microorganisms such as *S. aureus* or GNB. In these cases, active antibiotics administered for 3 to 5 days prior to the procedure may be sufficient. It is very important to establish the microbiological diagnosis of the infection before-hand in order to be able to target the antibiotic therapy.

If there is no microbiological diagnosis at the time of the procedure, wide-spectrum antibiotic therapy should be initiated after the sampling and maintained until the results of these cultures are available. This empirical antimicrobial therapy should include a glycopeptide (vancomycin or teicoplanin), daptomycin, or linezolid, in combination with a β-lactam with anti-pseudomonal activity (ceftazidime or cefepime, or else meropenem in patients colonized or with previous infections by ESBL-producing *Enterobacteriaceae,* or in those presenting with risk factors for infection by these microorganisms). Once the etiology is known, a tailored specific antimicrobial treatment may be administered, following the same criteria as in the management of PJI with implant retention (Table 5).

Regardless of the decision regarding the time to start antibiotics, it is crucial to meet the fundamental principles of antimicrobial prophylaxis for the new prosthesis and to include a high antimicrobial concentration at the surgical site throughout the procedure[257]. Two studies have suggested that the administration of antibiotics prior to intraoperative sampling does not reduce the sensitivity of the cultures[258,259], but this is still a matter of controversy. The recommendation is to delay the infusion of antibiotics until the samples have been taken. This issue is less important if the etiological diagnosis

is already available and a targeted antimicrobial therapy has been decided in the days prior to the procedure.

As mentioned above, high antibiotic concentrations must be achieved at the surgical site throughout the procedure. Therefore, the antibiotic dose must be repeated if the operation lasts for more than twice the antibiotic's half-life or if the blood loss is greater than 1.5 L[260].

RECOMMENDATIONS

1. Beginning an antimicrobial therapy 3 to 5 days prior to the 1-step exchange procedure is recommended if the etiological diagnosis has already been made, especially in infections caused by *S. aureus* or GNB (C-II).
2. Regardless of the decision regarding when to start antibiotics, an appropriate antimicrobial prophylaxis throughout the procedure must be guaranteed (A-I).
3. If no antimicrobial therapy has been initiated before the procedure, it should be delayed until the intraoperative sampling has been performed (C-III).

How long should antimicrobial treatment last?

A tailored antimicrobial therapy should be administered once the results of the cultures taken during surgery are available, the goal being to complete the treatment of peri-prosthetic osteomyelitis that may still persist after the prosthesis exchange. The authors with the most experience with 1-step exchange procedure[261] report a cure rate of 80% after following a protocol that only includes 10-14 days of intravenous antibiotics, usually without rifampin. These results may be due to the performance of a thorough debridement and the use of cement loaded with antibiotics during the procedure. In contrast, in the setting of staphylococcal infections the IDSA guidelines recommend intravenous antibiotics for a period of 2 to 6 weeks, then switching to a rifampin-based combination for a total of 3 months of antimicrobial therapy[12].

The overall success of this medical and surgical strategy depends not only on the surgeon's ability to thoroughly eradicate the lifeless tissues and the inert material, but also on the administration of an appropriate antimicrobial therapy that prevents the new prosthesis from being colonized. The total length of therapy (including intravenous and oral antibiotics) reported in the literature varies widely, from 10 days to 6 months (Table 4). These studies do not take into consideration the degree of inflammation that finally leads to the prosthesis exchange or the etiology of the infection. The 1-step exchange procedure strategy is halfway between DAIR (indicated in acute cases of infection, with a high degree of inflammation and usually caused by virulent microorganisms) and the 2-step exchange procedure (chronic or subacute PJI, rarely suppurative, and caused by less virulent microorganisms). Thus, it seems reasonable that the length of therapy in this scenario will vary according to these parameters.

RECOMMENDATION

1. A minimum of 7 days of intravenous antibiotics with activity against the microorganisms causing the infection is recommended (dosage summarized in Table 5), followed by oral antibiotics for a total of 4-8 weeks (B-II).

What is the role of the local antimicrobial treatment (cement)?

There are no comparative studies evaluating the efficacy of mixing antibiotics with cement during 1-step exchange procedure. In our review of the literature (Table 4), we found five studies reporting 237 patients who underwent prosthesis exchange with no local antibiotics, with a cure rate ranging between 83 and 100%, while there were 22 papers including 1,704 cases in which cement with antibiotics was used, with cure rates between 72-100%. The data reported in the literature support the practice of 1-step exchange procedure with non-cemented prosthesis, thus with no possibility of using local antibiotics. Still, in these cases bone allograft or calcium sulfate beads may be used as carriers of local antibiotics[82]. It is the surgeon who decides whether the prosthesis should be cemented or non-cemented. If a cemented prosthesis is selected, the usual antibiotics are gentamicin, tobramycin, and vancomycin. The accumulated experience suggests that these local antibiotics are safe, have minimal toxicity, and do not disrupt the cement's consistency in the long term.

RECOMMENDATION

1. If it has been decided to use a cemented prosthesis, a local antibiotic with activity against the microorganism causing the infection is recommended. If the etiology is unknown at the moment of the exchange procedure, the combination of vancomycin plus gentamicin is recommended (C-III).

What is the treatment for the 'positive intraoperative cultures' (PIOC) category of Tsukayama's classification?

The PIOC category described by Tsukayama (Table 2) includes patients submitted to a 1-step exchange procedure due to the loosening of a prosthesis which was assumed to be non-infectious, but in which the samples taken during surgery finally yielded microorganisms. Actually, these patients are very similar to those with a chronic PJI undergoing a 1-step exchange procedure; however, they have very subtle or non-existent symptoms, and so do not receive antimicrobials except for the standard surgical antibiotic prophylaxis.

The interpretation of these cultures and the management of this scenario are quite controversial, and reconsideration of the whole clinical picture and complementary data is needed: pre-surgical CRP and ESR, patient's age and condition, data on synovial fluid, histological information, and so on. In some cases these cultures are just read as contaminants, especially if there is one single positive culture[262], and in other cases the surgical debridement and irrigation are considered to be sufficient treatment. Nevertheless, some patients have later developed an infection of the new prosthesis, caused by the microorganisms isolated during the previous prosthesis exchange (PIOC)[263].

In spite of the absence of contrasted evidence in this setting, when the cultures are considered to be significant most authors support the use of antibiotics during 4-6 weeks and see no need for additional surgery. Broadly speaking, they follow the same

principles as for PJI managed with a 1-step exchange procedure. The outcome after an antimicrobial therapy is satisfactory in most cases[22,264].

RECOMMENDATION

1. In the case of PIOC (Tsukayama's classification) an antimicrobial treatment of 4 to 6 weeks is recommended. There is no need for further surgery. The same protocol is followed as in cases of PJI managed with a 1-step exchange procedure (B-III).

What is the treatment for cases in which no new prosthesis is to be inserted after the removal of the infected one?

The difficulty of treatment is significantly reduced when the infected prosthesis is not to be replaced. The same antibiotics and dosages used in DAIR (Table 5) may help the choice of the antimicrobial treatment, but the length of treatment may be shortened to 4-6 weeks, depending on the clinical follow-up.

RECOMMENDATION

1. For cases in which the infected prosthesis is not to be replaced after its removal, the same antibiotics as those used for DAIR may be administered (Table 5) (B-II).
2. In these cases, the length of therapy may be shortened to 4 to 6 weeks (C-III).

Implant retention and long-term suppressive antibiotics (SAT) without attempted eradication

Is it necessary to perform a surgical debridement before initiating SAT?

It is reasonable to think that reducing the bacterial inoculum and debriding the infected tissues may favour the success of SAT. Indeed, in most series of PJI managed with SAT, patients underwent surgical debridement. However, in many of these cases the decision to initiate SAT may well have been taken after performing the debridement. The difficult decision to starting SAT is considered in clinically stable patients, with few symptoms, and especially if the surgical risk is high. Indeed, in a case series of elderly patients with PJI managed with SAT, only 24% underwent surgery[93]. Another important advantage of performing surgical debridement is the possibility of obtaining valuable samples for culture. Access to reliable cultures in this setting is particularly important, since the samples taken from sinus tracts are not really representative. If the patient cannot undergo surgical debridement, obtaining a valid sample via joint aspirate or synovial biopsy should be considered.

RECOMMENDATIONS

1. A surgical debridement before beginning SAT is recommended, if feasible (C-III).
2. Obtaining a valid sample for culture before starting SAT is particularly important (C-III).

What are the most appropriate antibiotics for SAT? Are combinations of antimicrobials convenient or necessary? What is the role for rifampin?

In published case series, the most frequently reported antibiotics are the combination of minocycline plus rifampin or β-lactams alone[91-93,99]. Other less frequently antibiotics used are co-trimoxazole, clindamycin, and fluoroquinolones. It is difficult to draw recommendations from the literature regarding the usefulness of these antibiotics for SAT.

RECOMMENDATIONS

1. For the choice of the specific antibiotic for SAT, the antimicrobial susceptibility of the microorganism causing the infection, the safety of the drug and the observance of the treatment must be considered. Except for the initial stages of SAT, these aspects must prevail over the optimization of the antimicrobial treatment (C-III).
2. Except for some particular cases, the use of combinations (and therefore the use of rifampin) is not recommended (D-III).

Is it necessary to administer intravenous antibiotics at the beginning of SAT?

In most published series, patients were initially treated with intravenous antibiotics for several weeks. This was very likely done in the setting of the standard protocol of PJI management at each center, and not necessarily as a consequence of choosing a SAT strategy. In addition to the surgical debridement, an initial intravenous antimicrobial treatment may contribute to reducing the bacterial inoculum, thus favouring good evolution. Nevertheless, it seems unlikely that prolonged intravenous treatment is really relevant for the success or failure of SAT, since its efficacy is based on its indefinite administration.

RECOMMENDATION

1. In cases undergoing surgical debridement, an initial intravenous treatment for at least 7 days is recommended. Nevertheless, prolonged intravenous treatment is not necessary when deciding on SAT management (C-III).

Is it possible to have defined periods with no antimicrobial treatment?

Antibiotic-free periods are not reported in any of the series undergoing with SAT. Some of these studies report the occurrence of failure after antibiotic withdrawal, usually within the first 4 months after discontinuation[20].

RECOMMENDATIONS

1. If it is necessary to stop or change the antibiotics due to the occurrence of adverse events, long periods without antibiotics are not recommended (D-III).

Is SAT safe? What about its effect on the microbiota?

Safety issues in the setting of antimicrobial therapy scheduled for long periods (like SAT) are of paramount importance. Although information is very scarce, the safety data published for case series of SAT indicate a low rate of antibiotic withdrawal due to adverse events[31,92,99]. However, caution is required when interpreting these results: the rate of antibiotic withdrawal within the first weeks or months of treatment may have been underestimated, since patients who discontinued treatment early were probably removed from the series.

Nevertheless, information on the safety of prolonged antimicrobial therapies can be obtained not only from SAT in the setting of PJI or other bone and joint infections, but from other clinical scenarios as well, such as antibiotic prophylaxis in immunosuppressed hosts, infections requiring long treatments (multi-drug resistant tuberculosis, actinomycosis, endocarditis caused by *Coxiella*…), or diseases that also need long antibiotic therapies due to a natural history in which bacterial infection and colonization have a significant role (chronic obstructive pulmonary disease, cystic fibrosis, acne, and so on).

The analysis of the diversity of protocols, patients, and antibiotics is overwhelmingly complex. Table 7 summarizes the most interesting information for the management of PJI for each antibiotic separately.

RECOMMENDATIONS

1. The prescription and control of a SAT must be performed by an expert in antimicrobial therapy, who will periodically follow up the clinical evolution of the infection and assess the possible occurrence of adverse events (B-III).
2. The use of linezolid is discouraged in SAT due to high risk of toxicity, which limits its prolonged administration (E-I).
3. The use of β-lactams, or low doses of co-trimoxazole, is recommended. Alternatively, other antimicrobials such as minocycline or clindamycin may be administered (C-III).

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Conflict of interests

JA has served as speaker for and has received fees for advisory boards from Pfizer and Novartis.

JC has served as speaker for Astellas, AstraZeneca, MSD, Novartis and Angellini, and has received fees for advisory boards from Astellas, Pfizer, AstraZeneca and MSD.

JE has received fees for lectures from Laboratorios Leti and support for attending conferences from Pfizer, bioMérieux, Alere, Laboratorios Leti and Novartis

JPH has served as speaker for MSD, Astellas, Novartis, Pfizer, and Astra Zeneca and also has received fees for advisory boards from MSD, Astellas, Novartis, Pfizer, Angelini, Basilea and Astra Zeneca

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DRP has received lecture fees, travel support for attending meetings and fees for advisory boards from Novartis, Astellas, Merck and Pfizer.

AS has received fees as speaker from Pfizer, Novartis, MSD and Astellas.

The rest of the authors declare no conflict of interests.

Apendix 1. Abbreviations

ALS: acrylic cement spacer loaded with antibiotics.
CNS: Coagulase-negative staphylococci.
CRP: C-reactive protein.
DAIR: debridement, antibiotics, implant retention.
ESBL: extended-spectrum β-lactamase.
ESR: erythrocyte sedimentation rate.
GNB: Gram-negative bacilli.
IDSA: Infectious Diseases Society of America.
MSSA: methicillin-susceptible *S. aureus.*
MRSA: methicillin-resistant *S. aureus.*
PIOC: Positive intraoperative cultures.
PJI: prosthetic joint infection(s).
SEIMC: Spanish Society of Clinical Microbiology and Infectious Diseases.
SAT: suppressive antimicrobial therapy.

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Tables

Table 1
System from rankings recommendations in clinical guidelines[14]

Level of scientific evidence	
I	Evidence obtained from ≥1 randomized clinical trial
II	Evidence obtained from ≥1 well-designed non-randomized clinical trial, or cohort studies, or case-control-studies, especially if they have been performed in more than one centre, from multiple time-series; or from dramatic results for uncontrolled experiments.
III	Evidence obtained from documents or opinions of experts, based in clinical experience descriptive sudies or reports of expert committees
Grades of recommendation	
A	Good evidence to recommend the use of a measure or practice
B	Moderate evidence to recommend the use of a measure or practice
C	Poor evidence to recommend the use of a measure or practice
D	Moderate evidence to discourage the use of a measure or practice
E	Good evidence to discourage the use of a measure or practice

Table 2
Classifications of prosthetic joint infections (PJI)

Author	Type of PJI	Definition
Tsukayama[22,230]	Early post-surgical	Symptoms of infection begin within the first month after the placement of the prosthesis
	Late chronic	Symptoms of infection begin insidiously beyond the first month after the placement of the prosthesis
	Hematogenous	Symptoms of the infection emerge acutely as a consequence of a bloodstream infection (either suspected or proven)
	Positive intraoperative cultures	≥2 positive intraoperative cultures taken during a 1-step exchange procedure for an assumed aseptic prosthetic loosening
Zimmerli[6]	Early	Symptoms of infection emerge within the first 3 months after the placement of the prosthesis
	Delayed	Symptoms of infection begin within 3 months and 2 years after the placement of the prosthesis
	Late	The infection occurs beyond 2 years after the placement of the prosthesis, as a consequence of a

		bloodstream infection (either suspected or proven)

Comment: Tsukayama's categories *positive intraoperative cultures* (PIOC) and *late-chronic* infection actually reflect the same clinical scenario: a loosened prosthesis inserted months or years previously, the difference being that, at the time of diagnosis, in the PIOC category a new prosthesis has already substituted the infected one (the surgeon did not observed signs of infections during surgery).
Also, these categories are equivalent (except for the limitation in the calendar) to Zimmerli's *Delayed* category. Finally, Tsukayama's *hematogenous* category has the same definition as Zimmerli's *late* category (again, except for the time limit, set at 2 years). From a practical point of view, early post-surgical infections and hematogenous infections (*late*, according to Zimmerli's classification) may be considered as acute infections, whereas *late chronic* and *delayed* PJI correspond to chronic infections.

Table 3
Selection of representative cohorts of patients with prosthetic joint infection managed with implant retention

Ref	Centers	Patients submitted to DAIR	Success	Significant parameters and comments	Time to failure
Schoifet, 1990[23]	One center	N = 31 TKP, various microorg.	23%	Predictors of failure: *S. aureus*, age, duration of symptoms	252 days (max 1008 days)
Burger, 1991[24]	One center	N = 39 TKP, various microorg.	18%	Predictors of success: short duration of symptoms, susceptible microorganisms, no radiological signs of infection, no problems of the surgical wound	
Tsukayama, 1996[22]	One center	N = 41 THP, 90% *Staphylococcus*	68%	Predictors of failure: non-cemented prosthesis, hematogenous infections	
Brandt, 1997[25]	One center	N = 33, all *S. aureus*	31%	Predictors of failure: duration of symptoms >2 days	81 days (range 15-614)
Tattevin, 1999[26]	One center	N = 34, various microorg. (74% *S. aureus*)	38%	Predictors of failure: duration of symptoms	
Meehan, 2003[27]	One center	N = 19, all *S. agalactiae*	89%	8 cases treated with SAT (if considered as failures, 53% global success)	At 114 and 204 days
Berdal, 2005[28]	One center	N = 29 early infections (<3 months). Various microorg. (60% *S. aureus*)	83%	Treatment protocol based in the combination of ciprofloxacin + rifampin	Mean 97 days, max 217 days
Everts, 2004[29]	One center	N =16, all streptococci	94%	Very long treatments, SAT in some patients	
Barberan, 2006[30]	One center	N = 60, all staphylococci	65%	Predictors of failure: duration of symptoms >6 months	
Marculescu, 2006[31]	One center	N = 99, various microorg.	46%	Predictors of failure: sinus tract, duration of symptoms >7 days. Most patients treated for very long times, SAT in some cases	
Soriano, 2006[32]	One center	N = 47, various microorg.	77%	Predictors of failure: infection by methicillin-resistant *S. aureus* or by enterococci	
Aboltins, 2007[33]	One center	N = 20, all *S. aureus*	90%	Treatment protocol based on the combination of rifampin plus fusidic acid	
Byren, 2009[20]	One center	N = 112, various microorg.	82%	Predictors of failure: debridement performed by arthroscopy, revision prosthesis, infection by *S. aureus*	Most failures happened within the first 4 months after antibiotic withdrawal
Hsieh, 2009[34]	One center	N = 27, all Gram-negative microorg.	26%	Large cohort of PJI, including a minority of patients treated with DAIR. Poorer prognosis in patients with a long duration of symptoms	
Martínez-Pastor, 2009[35]	One center	N = 47, all Gram-negative microorg.	75%	Predictors of failure: high C-reactive protein, fluoroquinolone-resistant microorg.	
Rodríguez-Pardo, 2010[36]	Multi-center	N = 34 hematogenous cases, various microorg.	56%	Predictors of success: infection caused by streptococci or Gram-negative bacilli	
Senneville, 2011[37]	One center	N = 41, all *S. aureus*	78%	Majority use of fluoroquinolones and rifampin (94%)	165 days after antibiotic withdrawal
Cobo, 2011[38]	Multi-center	N = 117 early infections (<1 month), various microorg.	57%	Predictors of failure: infection caused by *S. aureus* and cases attended at one particular center	
Aboltins, 2011[39]	One center	N = 17, all Gram-negative microorg.	94%	Protocol of treatment based on the use of fluoroquinolones	
Vílchez, 2011[40]	One center	N = 53, all *S. aureus,* acute post-surgical cases	76%	Predictors of failure: C-reactive protein >220 mg/L and the need for a second debridement	
Zmistowski, 2011[41]	One center	N = 103, 86% *S. aureus*.	46%	Predictors of success: infection caused by Gram-negative bacilli	
Sendi, 2011[157]	Multi-center	N = 20, all *S. agalactiae*	65%	Better prognosis in patients meeting Zimmerli's criteria for undergoing DAIR	
Geurts, 2013[47]	One center	N = 89, various microorg.	83%	Predictors of failure: prosthesis age >4 weeks at the time of debridement. The management included the use of beads loaded with antibiotics	

Lora-Tamayo, 2013[43]	Multi-center	N = 345, all *S. aureus*	55%	Predictors of failure: immunosuppression, bacteremia, high C-reactive protein, polymicrobial infection, need for a 2nd debridement, and not exchanging the removable components	130 days after the end of therapy (max 2528)
Achermann, 2014[190]	One center	N = 55, various microorg. Early infections (<3 months)	80%		Median 219 days (max 329 days)
Ascione, 2015[130]	One center	N = 159, various microorg.	80%		14-63 days after the end of therapy

DAIR: debridement, antibiotics and implant retention; Microorg: microorganism; SAT: suppressive antimicrobial therapy; THP: total hip prosthesis; TKP: total knee prosthesis.

Table 4
Published studies evaluating the efficacy of a 1-step exchange procedure for management of prosthetic joint infection

Author (year)	N	Joint	Local antibiotics	Failure rate (%)	Follow-up
Tibrewal (2014)[62]	50	Knee	Yes	8	126 months
Singer (2012)[63]	63	Knee	Yes	5	36 months
Buechel (2004)[64]	21	Knee	Yes	9	122.4 months
Göksan (1992)[255]	18	Knee	Yes	11	60 months
Freeman (1985)[256]	8	Knee	Yes	0	12-40 months
Von Foerster (1991)[65]	104	Knee	Yes	27	75,5 months
Jenny (2014)[66]	65	Hip	Yes	16,9	37 months
Choi (2013)[67]	17	Hip	Yes	17,6	62 months
Loty (1992)[68]	90	Hip	Yes	17,7	47.3 months
Sanzén (1988)[69]	78	Hip	Yes	23,6	71 months
Wroblewski (1986)[70]	102	Hip	Yes	8,8	38 months
Buchholz (1981)[71]	583	Hip	Yes	23,1	52 months
Carlsson (1978)[72]	59	Hip	Yes	8,4	24 months
Rudelli (2008)[73]	26	Hip	Yes	7,8	42-125 months
Mulcahy (1996)[74]	15	Hip	Yes	0	24-84 months
Callaghan (1999)[75]	24	Hip	Yes	8,3	1-14 years
Hope (1989)[76]	72	Hip	Yes	12,5	5-121 months
Ure (1998)[77]	20	Hip	Yes	0	3.5-17.1 months
Raut (1995)[78]	183	Hip	Yes	15,8	2-13 years
Yoo (2009)[79]	12	Hip	No	16,6	7.2 years
Bori (2014)[80]	24	Hip	No	4,1	44.6 months
Winkler (2008)[81]	37	Hip	Yes	8,1	4.4 years

Winkler (2012)[82]	54	Hip	Yes	9,2	8 years
Zeller (2014)[83]	157	Hip	No	5	41.6 months
Klouche (2012)[84]	38	Hip	No	0	NA
Rudelli (2008) [73]	6	Hip	No	0	138 months
Sofer (2005)[85]	15	Knee and hip	Yes	7	18.4 months
Drancourt (1993)[86]	19	Knee and hip	NA	10.5	9-61 months

NA: not available.

Table 5
Empirical and targeted antimicrobial therapy in the eradicative attempt of management with implant retention

	Recommended therapy	Alternative in patients allergic to β-lactams	Recommended duration
Initial phase of treatment (planktonic bacteria)			
Empirical treatment			
	Vancomycin or daptomycin or cloxacillin iv [&] + ceftazidime or cefepime or meropenem iv	Vancomycin or daptomycin iv + aztreonam iv	Until the results of cultures are available
Targeted treatment			
MSSA/MSSE*	(Cloxacillin or cefalozin) ± daptomycin iv	Daptomycin + fosfomycin iv	7-14 days
MRSA/MRSE*	Vancomycin (alone) or daptomycin + (cloxacillin or fosfomycin) iv	Daptomycin + fosfomycin iv	7-14 days
Streptococcus spp	Ceftriaxone or penicillin iv	Vancomycin iv	7 days
E. faecalis	Ampicillin ± ceftriaxone iv	Vancomycin or teicoplanin iv	7 days
Gram-negative bacilli	β-lactam iv ** [†]	Ciprofloxacin iv	7 days
**consider adding rifampin after the 5th day of treatment*			
*** consider combining an anti-pseudomonal β-lactam plus ciprofloxacin in PJI caused by* P. aeruginosa			
Sequential phase treatment (biofilm-embedded bacteria)			
Staphylococcus spp			
Treatment of choice			

	Rifampin + levofloxacin po	-	Until completing 8 weeks
Alternatives without fluoroquinolones			
	Rifampin po + (daptomycin or fosfomycin) iv	-	2-4 weeks, then oral treat.
	Rifampin + (LNZ, fusidic, CMX, clindamycin, or minocyclin) po	-	Until completing 8 weeks of treat.
Alternatives without rifampin			
	Daptomycin iv + (fosfomycin or cloxacillin) iv	-	2-6 weeks, then oral treat.
	Daptomycin iv + (LNZ or CMX or levofloxacin) po	-	2-6 weeks, then oral treat.
	Levofloxacin + (LNZ, CMX, clindamycin or fusidic) po	-	Until completing 8 weeks of treat.
	LNZ + (CMX or fusidic) po	-	Until completing 8 weeks of treat.
	Clindamycin + fusidic po	-	Until completing 8 weeks of treat.
	Levofloxacin or moxifloxacin or CMX or LNZ po	-	Until completing 8 weeks of treat.
Streptococcus spp			
	(Ceftriaxone or penicillin iv) ± rifampin po	Vancomycin iv ± rifampin po	2-6 weeks, then oral treat.
	Amoxicillin ± rifampin po	Levofloxacin ± rifampin po	Until completing 8 weeks of treat.
	Levofloxacin ± rifampin po	-	Until completing 8 weeks of treat.
E. faecalis			
	Ampicillin ± ceftriaxone iv	Vancomycin or teicoplanin iv	2-6 weeks, then oral treat.
	Amoxicillin ± rifampin po	LNZ ± rifampin po	Until completing 8 weeks of treat.

E. faecium	Vancomycin or teicoplanin iv Linezolid po		2-6 weeks, then oral treat. Until completing 8 weeks of treat.
Gram-negative bacilli			
Treatment of choice			
	Ciprofloxacin po	-	Until completing 8 weeks of treat.
Alternatives without fluoroquinolones			
	β-lactam iv ± colistin iv or β-lactam iv ± fosfomycin iv	Aztreonam iv ± colistin iv	6 weeks, then oral treat.
	CMX	-	Until completing 8 weeks of treat.
Alternatives against multi-drug resistant Gram-negative bacilli			
	β -lactam (CI) iv + colistin iv β-lactam (CI) iv + fosfomycin iv	Aztreonam iv (CI) + colistin iv	6 weeks

[&] The choice of a particular anti-staphylococcal agent may be conditioned by the presence of bloodstream infection, especially in hematogenous infections.

[†] The choice of a particular β-lactam agent against Gram-negative bacilli depends on the species and mechanisms of resistance: ceftriaxone is the treatment recommended for *Enterobacteriaceae*, except if they produce chromosomal β-lactamases (i.e., AmpC) or plasmidic extended-spectrum β -lactamases (ESBL); in these cases, the use of ertapenem will be preferred; in infections caused by *P. aeruginosa*, an anti-pseudomonal β-lactam is recommended.

Abbreviations: x: during; MRSA: methicillin-resistant *S. aureus*; MSSA: methicillin-susceptible *S. aureus*; MRSE: methicillin-resistant *S. epidermidis* (and other coagulase-negative staphylococci); MSSE: methicillin-susceptible *S. epidermidis* (and other coagulase-negative staphylococci). CMX: co-trimoxazole; Fusidic: fusidic acid; LNZ: linezolid; CI: continuous infusion; iv: intravenous treatment; po: *per os* (oral route); treat.: treatment.

Recommended doses (assuming normal renal function): cloxacillin, 2 g/4h iv; vancomycin, 1g/12h iv; daptomycin, 8-10 mg/kg/24h iv; ceftazidime, 2g/8h iv; aztreonam, 2g/8h iv; cefepime, 2g/8-12h iv; meropenem 1-2g/8h iv; ertapenem, 1g/24h iv; ceftriaxone 2g/24h; ampicillin: 2g/6h iv; amoxicillin, 1 g/8h po; rifampin, 600 mg/24h po; levofloxacin, 500-750 mg/24h po; moxifloxacin, 400 mg/24h po; ciprofloxacin, 400 mg/12h iv or 750-1000 mg/12h po; linezolid, 600 mg/12h po; fusidic acid, 500 mg/8h po; fosfomycin, 2 g/6h iv; colistin, 6-9 millions IU/d (8-12h) iv; co-trimoxazole 800/160 mg/8h po; clindamycin, 600 mg/6-8h po; minocycline, 200 mg/d po.

Table 6
Antimicrobials used in cement spacers

Fusidic acid
Amikacin
Amoxicillin
Amphotericin
Ampicillin
Aztreonam
Bacitracin
Cefazolin
Ceftazidim
Cefuroxim
Cephalothin
Cephamandole
Ciprofloxacin
Clindamycin
Colistin
Daptomycin
Erythromycin
Gentamicin
Lincomycin

Linezolid
Meropenem
Novobiocin
Oxacillin
Penicillin
Piperacillin-tazobactam
Polymyxin B
Streptomycin
Tazobactam
Ticarcillin
Tobramycin
Vancomycin
Voriconazol

Table 7
Antibiotics most frequently used as suppressive antimicrobial therapy (SAT)

	Experience in prolonged treatments	Precautions and main adverse events
Beta-lactams	Low toxicity in the treatment of actinomycoses[265,266]. However, hypersensitivity reactions are frequent with the use of penicillin[267]. β-lactams are the most frequently used antibiotics for SAT in various case series of PJI[91-93,99]	Skin rash, hypersensitivity reactions
Clindamycin	Very little experience has been reported: treatment of suppurative hidrosadenitis[268] and bone and joint infections[144,269]. Low toxicity	Skin rash. Digestive intolerance. *C. difficile*-associated colitis
Co-trimoxazole	There is a great deal of experience with its use; low toxicity is reported when low doses are used as prophylaxis of opportunistic infections[270]. The use of high doses in bone and joint infections has frequently led to discontinuation due to digestive intolerance[143,152]	Digestive intolerance, leukopenia, megaloblastic anemia, hypersensitivity reactions. Recently, cases of sudden death on patients being administered co-trimoxazole along with spironolactone or inhibitors of the renin-angiotensin system have been reported[271,272]. In a study addressing the impact of antimicrobials on fecal microbiota, a transitory increase of resistance to co-trimoxazole, amoxicillin, and amoxicillin-clavulanate acid was observed[273]
Macrolides	There is experience of prolonged administration of macrolides for preventing infections in patients with chronic pulmonary obstructive disease, with infrequent adverse events[274,275]	A higher risk of sudden death in patients under treatment with macrolides plus amoxicillin has been reported[276], although it has recently been questioned whether these patients may be affected by other circumstances that could prolong the QT segment[277]

Fluoroquinolones	There is acceptable experience with the use of levofloxacin and ofloxacin in the treatment of multi-drug resistant tuberculosis (although the number of patients is scarce)[278]	The use of fluoroquinolones has been associated with a higher risk of tendinopathy. This risk is increased in elderly patients, renal chronic failure and patients under treatment with corticosteroids[279]
Rifampin	There is experience of long treatments with rifampin for brucellosis or tuberculosis. Short treatments of rifampin are more associated with toxicity	Rifampin must never be used alone due to a high risk of resistance. There are frequent drug-to-drug interactions.
Tetracyclins	There is experience in the treatment of acne. Adverse events are more frequent with minocycline than with doxycycline	Minocycline: skin pigmentation, drug-induced lupus (53 cases per 100,000 treatments) and hepatitis (1 case per 10,000 treatments and month)[280-282]. Doxycycline: drug-induced photosensitivity, digestive adverse events, including esophageal ulcers and erosions.

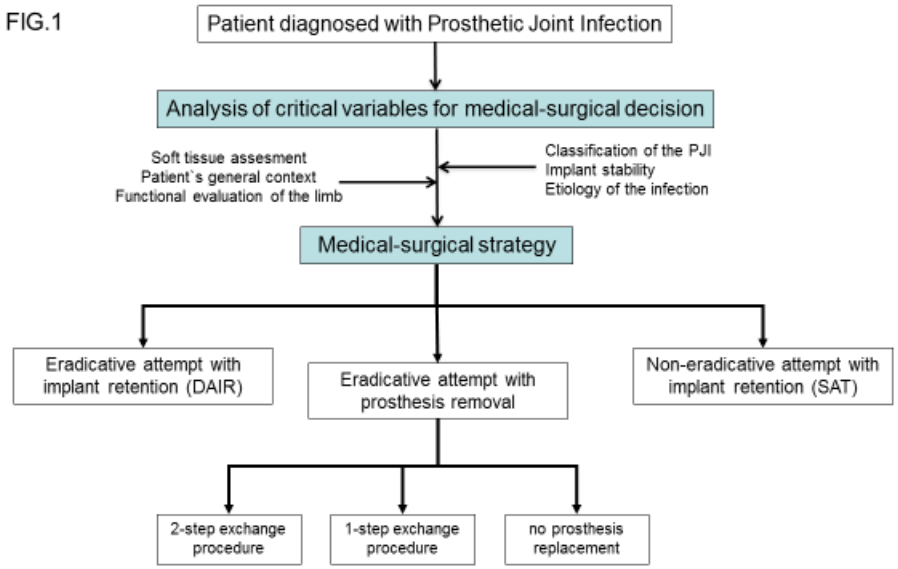
FIG.1
Patient diagnosed with Prosthetic Joint Infection
Analysis of critical variables for medical-surgical decision
Soft tissue assesment
Patient`s general context
Functional evaluation of the limb
Classification of the PJI
Implant stability
Etiology of the infection
Medical-surgical strategy
Eradicative attempt with implant retention (DAIR)
Eradicative attempt with prosthesis removal
Non-eradicative attempt with implant retention (SAT)
2-step exchange procedure
1-step exchange procedure
no prosthesis replacement

Figure 1