PROCEDIMIENTOS E INDICACIONES EN LA INFECCIÓN PROTÉSICA

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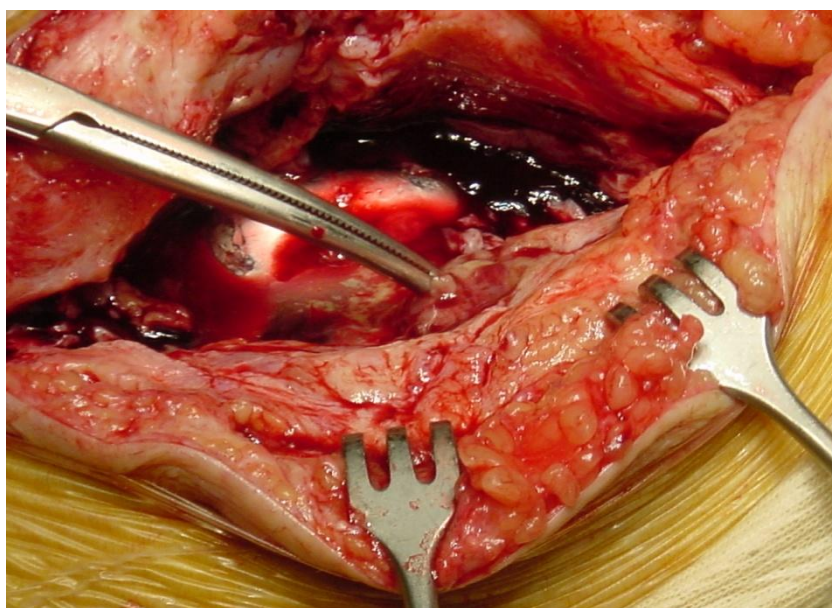
Management of prosthetic joint infections. Clinical practice guidelines by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)

Javier Ariza Cardenal [a], Javier Cobo Reinoso [b,*], Josu Baraia-Etxaburu Artetxe [c], Natividad de Benito Hernández [d], Guillermo Bori Tuneu [e], Javier Cabo [f], Pablo Corona Pérez-Cardona [g], Jaime Esteban Moreno [h], Juan Pablo Horcajada Gallego [i], Jaime Lora-Tamayo Morillo-Velarde [j], Óscar Murillo Rubio [k], Julián Palomino Nicás [l], Jorge Parra Ruiz [m], Carlos Pigrau Serrallach [n], José Luis del Pozo León [o], Melchor Riera Jaume [p], Dolores Rodríguez Pardo [q], Mar Sánchez-Somolinos [r], Álex Soriano Viladomiu [s], María Dolores del Toro López [t] y Basilio de la Torre Escuredo [u]

[a] *Coordinator, Servicio de Enfermedades Infecciosas, Hospital Universitari de Bellvitge, IDIBELL, Barcelona*
[b] *Coordinator, Servicio de Enfermedades Infecciosas, Hospital Universitario Ramón y Cajal, IRYCIS, Madrid*
[c] *Servicio de Enfermedades Infecciosas, Hospital Universitario de Basurto, Bilbao*
[d] *Unidad de Enfermedades Infecciosas, Hospital de la Santa Creu i Sant Pau, Barcelona*
[e] *Servicio de Cirugía Ortopédica y Traumatología, Hospital Clínic, Barcelona*
[f] *Servicio de Cirugía Ortopédica y Traumatología, Hospital Universitari de Bellvitge, Barcelona*
[g] *Servicio de Cirugía Ortopédica y Traumatología, Hospital Universitari Vall d'Hebron, Barcelona*
[h] *Departamento de Microbiología Clínica. Hospital Universitario Fundación Jiménez Díaz, Madrid*
[i] *Servicio de Enfermedades Infecciosas, Hospital del Mar, IMIM, Barcelona*
[j] *Unidad de Enfermedades Infecciosas, Hospital Universitario 12 de Octubre, Madrid*
[k] *Servicio de Enfermedades Infecciosas, Hospital Universitari de Bellvitge, Barcelona*
[l] *Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospital Universitario Virgen del Rocío, Sevilla*
[m] *Servicio de Enfermedades Infecciosas, Hospital Clínico San Cecilio, Granada*
[n] *Servicio de Enfermedades Infecciosas, Hospital Universitari Vall d'Hebron, Barcelona*
[o] *Área de Enfermedades Infecciosas y Microbiología Clínica, Clínica Universitaria de Navarra, Pamplona*
[p] *Servicio de Medicina Interna-Infecciosas, Hospital Son Espases, Palma de Mallorca*
[q] *Servicio de Enfermedades Infecciosas, Hospital Universitari Vall d'Hebron, Barcelona*
[r] *Servicio de Microbiología y Enfermedades Infecciosas, Hospital General Universitario Gregorio Marañón, Madrid*
[s] *Servicio de Enfermedades Infecciosas, Hospital Clínic, Barcelona*
[t] *Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospital Universitario Virgen Macarena, Sevilla*
[u] *Servicio de Cirugía Ortopédica y Traumatología, Hospital Universitario Ramón y Cajal, Madrid*

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.

Tratamiento de las infecciones de prótesis articulares. Guía clínica práctica de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC)

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).

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 2nd step, 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).

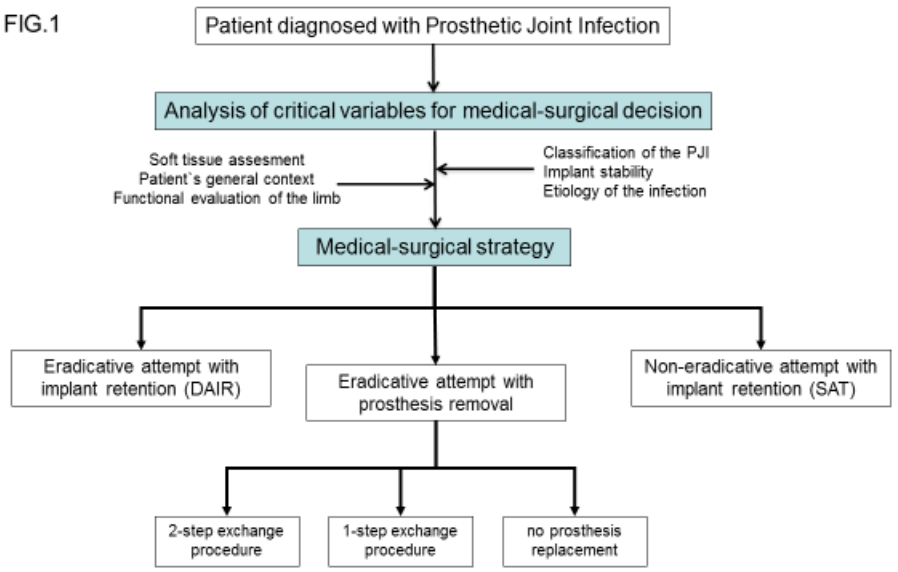**Attempted eradication without implant removal**

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

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.