DESBRIDAMIENTO CON RETENCIÓN IMPLANTE

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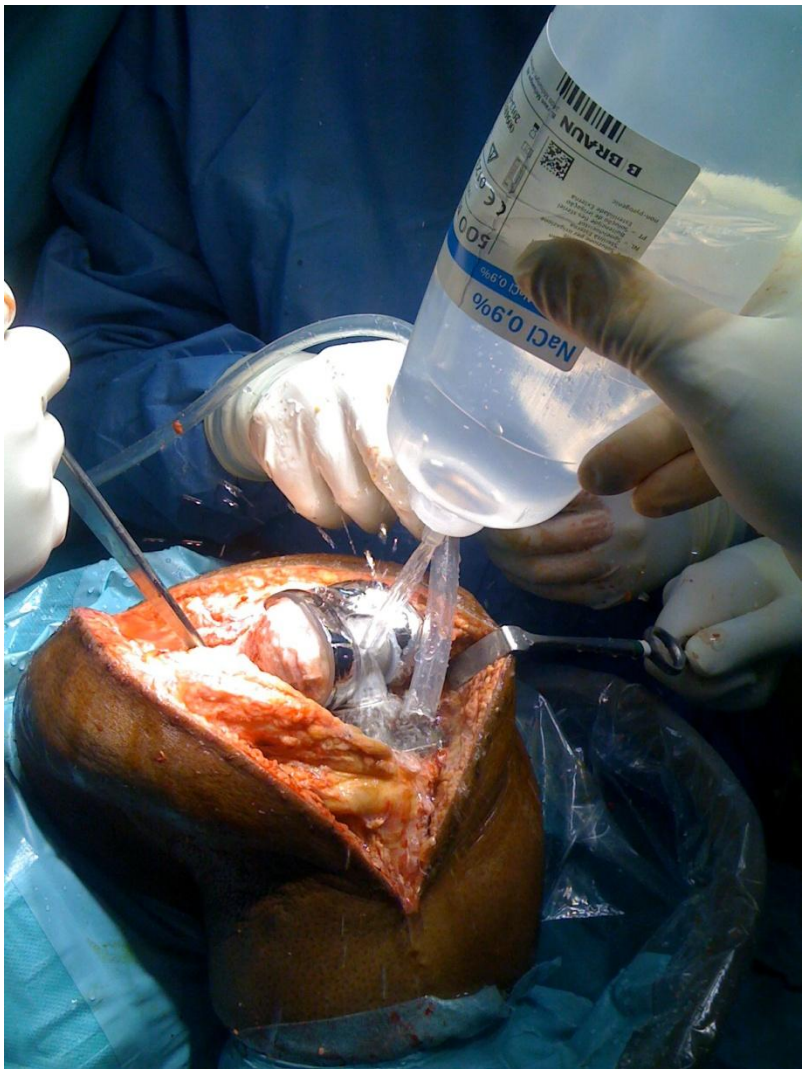

When should eradication with prosthesis retention be attempted, and what surgical technique should be used?

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

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.