RECAMBIO PROTÉSICO EN 2 TIEMPOS

PÁG.. 17-25 Guías SEIMC 2017

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