The Journal of Arthroplasty xxx (2018) 1–13

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Hip and Knee Section, Treatment, Antimicrobials: Proceedings of International Consensus on Orthopedic Infections

Craig A. Aboltins [1], Ruben Anemüller [2], Katherine Belden [3], Barry Brause [4], Mustafa Citak [3], Jose L. Del Pozo [5], Lars Frommelt [6], Thorsten Gehrke [6], Angela Hewlett [7], Carlos A. Higuera [4], Harriet Hughes [2], Michael Kheir [8], Kang-il Kim [8], Sujith Konan [6], Christian Lausmann [2, 3, 6, 9], Dorothy Ling [1], Camelia Marculescu [1, 9], Laura Morata [5], Isabel Ramirez [7], Markus Rossmann [9], Randi Silibovsky [8], Alex Soriano [5], Gina Ann Suh [2], Charles Vogely [4], Andrea Volpin [6], Jean Yombi [1, 9], Akos Zahar [3], Werner Zimmerli [3]

ARTICLE INFO

Article history:
Available online xxx

Keywords:
antibiotics
antibiotic therapy
antimicrobial treatment
antibiotic duration
antibiotics for single-stage exchange
antibiotic treatment monitoring
erythrocyte sedimentation rate (ESR)
C-reactive protein (CRP)
D-dimer
presepsin
Infectious Diseases Society of America guidelines (IDSA)
antibiotic guidelines
antibiotic dose
antibiotic type
infective organism
route of administration
antibiotic indications
staphylococcal periprosthetic joint infection (PJI)
debridement, antibiotic, implant retention (DAIR)
debridement and implant retention
single-stage exchange
biofilm
fluoroquinolone
culture-negative periprosthetic joint infection (PJI)
broad-spectrum antibiotics
rifampin
vancomycin
ceftriaxone
fosfomycin
tigecycline
daptomycin
combination antimicrobial therapy
enterococcal periprosthetic joint infection (PJI)
antibiotic susceptibility
methicillin-resistant *Staphylococcus aureus* (MRSA)
multidrug-resistant bacteria

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2018.09.032.

[1] Question 4.
[2] Question 7.
[3] Question 6.
[4] Question 5.
[5] Question 9.
[6] Question 1.
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Question 1: What is the recommended duration of antibiotics after a single-stage exchange for periprosthetic joint infections (PJIs)?

Recommendation:

In the setting of single-stage exchange arthroplasty, intravenous antibiotics should be administered for 10 to 14 days followed by oral antibiotics. Generally, the overall duration of antibiotics of 4 to 6 weeks is sufficient.

Level of Evidence: Limited

Delegate Vote: Agree: 73%, Disagree: 23%, Abstain: 4% (Super Majority, Strong Consensus)

Rationale:

The 2-stage exchange arthroplasty is the preferred method for treatment of chronic periprosthetic joint infections (PJIs). However, the single-stage exchange procedure has been gaining popularity

https://doi.org/10.1016/j.arth.2018.09.032
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and demonstrates comparable outcomes regarding infection control, and offers various benefits for patients compared to 2-stage exchange [1–3]. Unfortunately, there are limited studies examining the issues of antibiotic administration following 1-stage exchange arthroplasty. In addition, the duration of antibiotic treatment after 2-stage exchange arthroplasty is not well determined either.

Most studies related to 1-stage exchange arthroplasty highlight the importance of preoperative identification of the infective organism [4–11]. This is important for numerous reasons, including the ability to add the appropriate antibiotics to methylmethacrylate cement during reimplantation as well as administering the appropriate antibiotics after the procedure. Antibiotic therapy following single-stage revision surgery usually starts with an intravenous agent, based on the antibiogram of the infective agent. Intravenous antibiotics are usually administered for a few days, and then replaced by oral agents, if available. In the postoperative period, antibiotics are adjusted to the susceptibility reports from intraoperative samples. In a similar fashion to 2-stage exchange arthroplasty, antibiotics are selected in accordance with organisms and sensitivities and are subsequently continued for 4-6 weeks [6,10,12–14].

Some authors continued the antibiotic therapy until inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) as well as nutritional markers, such as plasma albumin concentration, return to stable limits (levels normalized in 90% of cases) [10]. Normal levels for serological markers are thought to be an erythrocyte sedimentation rate of 30 mm/h, C-reactive protein of 10 mg/L, and albumin of 35-50 g/L.

Other investigators believe that the type, course, and duration of antibiotic treatments for patients undergoing 1-stage exchange arthroplasty need to be determined by a designated infectious disease consultant [4]. In this study, the average duration of the antibiotic treatment was 14 days (range 10-17). Duration was determined by wound healing and laboratory infection parameters. No prolonged oral antibiotic therapy was administered in all 70 cases.

The importance of the local delivery of antibiotics during 1-stage exchange arthroplasty has not been well studied. Some surgeons, including those at the ENDO Klinik, believe that the addition of antibiotics to cement during reimplantation plays a major role in infection control. There are 2 studies that point to the potential importance of antibiotics in cement [12,15]. In the latter study, the infection-free rate was under 60% for patients undergoing 1-stage exchange arthroplasty. Culture-specific antibiotics were given for at least 6 weeks to all the patients, but the single-stage exchange arthroplasty was performed with cementless total hip arthroplasty without local antibiotics. It is important to mention that the findings of low infection control could relate to other factors (eg, how the surgery was performed), and may not be related to local antibiotic delivery at all.

Despite the paucity of concrete evidence with no randomized clinical trials available on the subject of antibiotic treatment after 1-stage exchange arthroplasty, the use of antibiotic therapy following single-stage revision procedure is a universal practice. However, there is a lack of evidence for the duration of therapy. Currently, the orthopedic community feels that a few weeks of antibiotic treatment following 1-stage or 2-stage exchange arthroplasty is needed. Whether this will stand the test of time remains to be seen. In the absence of evidence to the contrary, we believe that patients undergoing 1-stage exchange arthroplasty for the management of PJIs should receive 4-6 weeks of antibiotic treatment, which can be started as intravenous for a few days, and switched to oral antibiotics soon after. We also feel that the dose, duration, and type of antibiotic therapy should be individualized for most patients based on numerous metrics that influence the outcomes of treatment of PJIs, including the host type, organism virulence, the complexity of the procedure, and soft tissue status.

Question 2: Are there any tests that can guide antimicrobial treatment in patients with PJIs and allow stopping these agents?

Recommendation:

No. There are no tests that can be used to guide therapies and monitor responses to treatments in patients with periprosthetic joint infections (PJIs). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are considered useful for monitoring responses to treatments, however, sustained elevations after treatment does not predict persistent infections. Emerging biomarkers, such as D-dimer and presepsin, have shown promising results. Nevertheless, more studies are required to assess their role in monitoring response to treatment in patients with PJIs.

Level of Evidence: Moderate

Delegate Vote: Agree: 89%, Disagree: 8%, Abstain: 3% (Super Majority, Strong Consensus)

Rationale:

The diagnosis of periprosthetic joint infections (PJIs) remains a challenge. Currently, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the most commonly used serological markers used for diagnosis. More recently, serum molecular biomarkers such as D-dimer and presepsin have emerged as potential diagnostic tools. However, determining whether the infection is controlled after surgical and antimicrobial treatment is even more difficult. There are limited studies assessing the roles of biomarkers in the follow-up periods of these patients; most of these studies have focused on diagnostic performance. No studies were found to specifically assess the role of biomarkers for guiding the antibiotic treatment protocols. However, there are studies that evaluate the roles of these markers in determining reimplantation timing and prognosis of PJIs.

Of the 11 published studies that were found to be relevant to this topic, 9 were prospective nonrandomized trials that focused on comparing the levels of biomarkers at the time of diagnosis and reimplantation. These studies have shown that serum ESR and CRP are poor predictors of persistent infections, and that they are frequently abnormal even when the infection has been controlled. New markers, such as the cytokines in synovial fluid, leukocyte esterase (LE), and serum D-dimer, tend to normalize at the time of reimplantation. However, more studies are required to show their trends with antimicrobial treatments.

Sanzén [16] studied the performance of serum ESR in 76 patients with PJI and found that in treated infections, ESR decreased to a lower value compared to the initial assessment. In those with persistent infections, there was a nonsignificant increase in ESR after 6 weeks, 3 months, 6 months, and 12 months; the average ESR was above 30 mm/h, and, in resolved cases, ESR was lower than 20 mm/h. However, the authors did not take into account patients who had inflammatory diseases. Likewise, George et al [17] evaluated the values of ESR and CRP in 14 infected arthroplasties in patients with inflammatory arthritis, finding that these markers remained elevated in the infected group. Shukla et al, Ghanem et al, Tornero et al, Hoell et al, and Kusuma et al, all showed that ESR and CRP remained elevated in more than one-third of cases in which the infection was eradicated, demonstrating that ESR and CRP often fail to normalize and do not reflect infection eradication [18–22].

Frangiamore et al [23] evaluated cytokine profiles of the synovial fluid between the first and second stage of a 2-stage exchange protocol for PJIs, in order to determine the cytokines that can indicate resolved infections. The reimplantation (second stage revision) was performed after symptom resolution, completion of antibiotic treatment (3-16 weeks, mean of 6 weeks), and normalization of CRP and ESR, in addition to negative cultures by aspiration. Interleukin-1B and interleukin-6 had the best performance for determination of infection eradication.

Kheir et al [24] assessed the leucocyte esterase (LE) strip test for its ability to predict persistent infections in patients with PJIs.

Patients were evaluated at the time of reimplantation with the LE strip test, considering 2+ as a positive read. The LE test was negative in all reimplantations that did not fail. The authors found higher failure rates in those who had positive test results at the time of reimplantation.

A single prospective multicenter study by Marazzi et al [25] evaluated the trends of presepsin and chemokine (C-C motif) ligand 2 in 30 patients with PJIs. The authors found a gradual decrease in the first week after surgery, and reaching values similar to the control group (patients without PJIs) in the first month and 3 months after the first revision. Another prospective study conducted by Shahi et al [26] evaluated the utility of D-dimer in the diagnosis of PJIs, and also examined its role in determining the timing of reimplantation. The authors found that serum D-dimer levels fell below the diagnostic threshold at the time of reimplantation in resolved cases. Furthermore, serum D-dimer was able to indicate the persistence of infection at the reimplantation time if the values were greater than 850 ng/mL (the recommended cutoff). Whether serum D-dimer levels can guide antibiotic treatment and have a consistent trend in response to antibiotics remains to be evaluated.

In conclusion, there is no single test or a gold standard that can indicate infection eradication in patients with PJIs. Although there are several studies on biomarkers for diagnosis, studies on responses to antibiotic treatments in patients with PJIs are lacking.

Question 3: Does the International Consensus Group (ICG) agree with the Infectious Diseases Society of America (IDSA) guidelines regarding the recommended duration of antibiotic therapy in orthopedic infection?

Recommendation:

There is some disagreement between what the International Consensus Group (ICG) and the IDSA recommends regarding the duration of antibiotic treatments for different infective organisms. The differences between the two organizations reside on the duration of oral antibiotic therapy following a pathogen-specific intravenous (IV) antimicrobial therapy.

Level of Evidence: Moderate

Delegate Vote: Agree: 82%, Disagree: 3%, Abstain: 15% (Super Majority, Strong Consensus)

Rationale:

The optimal length of antibiotic treatment following surgical treatment of periprosthetic joint infections (PJIs) by resection arthroplasty, 1-stage exchange arthroplasty, or debridement, and implant retention remains unknown. There are numerous studies related to this subject, and during the last meeting of the International Consensus, it was felt that antibiotic treatments between 2 and 6 weeks appeared to be sufficient for patients with PJIs.

The last International Consensus Group (ICG) found no conclusive evidence regarding the ideal duration of antibiotic therapy when considering treatment following resection arthroplasty due to PJIs. They found that ideal duration of antibiotic therapy, either intravenous (IV) or combined with oral medications, was unknown. Cost and resistance were lower when decreasing the time of antibiotic regimens [7,27–31]. Most of the literature, at the time, recommended antibiotic therapy between 6 and 12 weeks, although Bernard et al found that 1 week of an IV antibiotic regimen plus a following 5 weeks with oral regimen was sufficient to control infection. This study involved irrigation and debridement, single-stage exchange arthroplasty, and 2-stage exchange arthroplasties [30]. Stockley et al [32] used a short 2 weeks of IV-only antibiotic therapy following irrigation and debridement and placement of an antibiotic-impregnated cement spacer, and noted an 87% success rate. Nevertheless, the ICG strongly recommends a course of 2-6 weeks of antibiotics.

The ICG then explored how the duration of antibiotic treatments could be determined, agreeing that there was not enough evidence to determine whether biomarkers or clinical symptoms could be used to monitor response to treatment.

Additionally, the ICG attempted to determine the duration of antifungal therapy in the presence of fungal PJIs. The strongly agreed upon consensus stated that systemic antifungal treatment should be initiated before resection, and continued for at least 6 weeks, and stopped before reimplantation, without a need (in most cases) to restart antifungal therapy. For fluconazole, the literature had 3-6 weeks or more (in some studies even 26 weeks) before reimplantation, then no further treatment, or only 2-6 weeks more after reimplantation. For amphotericin B, the duration was often found to be about 6 weeks before reimplantation [33–45].

Infectious Diseases Society of America Guidelines

The Infectious Diseases Society of America (IDSA) guidelines suggest no more than a 6-week course of antimicrobial therapy following resection arthroplasty for PJIs due to more virulent organisms such as *Staphylococcus aureus* [46]. The IDSA recommends 2-6 weeks of pathogen-specific IV antimicrobial therapy, combined with rifampin 300-450 mg given orally twice daily. The treatment should continue with rifampin plus a companion oral drug (ciprofloxacin (A-I), or levofloxacin (A-II), or others), for a total of 3 months for staphylococcal total hip arthroplasty PJI, treated with 1-stage exchange, or with debridement and retention of the prosthesis. The IDSA recommendation for staphylococcal total knee arthroplasty PJI is the same, but for a total of 6 months when treated with debridement and prosthesis retention.

For organisms other than staphylococci, the IDSA guidelines recommend an initial course of pathogen-specific IV therapy for 4-6 weeks, or highly bioavailable oral antimicrobial therapy (B-II). Chronic suppression after fluoroquinolone treatment of Gram-negative bacilli was not unanimously recommended [46]. Longer courses of combination antimicrobial therapies of 6 months or more are recommended for bone infections due to rapidly growing mycobacteria by the current guidelines and reports [47,48].

IDSA guidelines recommend a minimum of 6 weeks of antifungal therapy for fungal PJIs, but a longer course of antifungal therapy has been considered to be an essential factor for the success of fungal PJIs treated with staged reimplantation. Phelan et al [33] administered antifungal therapies after resection arthroplasty for 6 weeks to 9 months in 4 patients who underwent 2-stage reimplantations.

Regarding the IDSA guidelines on the treatment of osteomyelitis due to invasive *Candidiasis*, they recommend treatment duration from 6 to 12 months.

Question 4: Is the type, dose, route of administration, and duration of antimicrobial treatment influenced by the type of infective organism causing periprosthetic joint infection?

Recommendation:

The duration, dose, route of administration, and the type of antibiotic administered to patients with periprosthetic joint infection are determined by the type of infective organism(s) isolated.

Level of Evidence: Limited

Delegate Vote: Agree: 92%, Disagree: 4%, Abstain: 4% (Super Majority, Strong Consensus)

Rationale:

There have been reports showing increased risks of treatment failure reported in patients with a sinus tract [49] and infections due to certain organisms such as *Staphylococcus aureus* [50], methicillin-resistant *Staphylococcus aureus* (MRSA), and Gram-negative organisms [51–59] when not treated with a rifampin combination. For staphylococcal periprosthetic joint infections (PJIs), the Infectious Diseases Society of America guidelines

recommend, based on expert opinion, 2-6 weeks of pathogen-specific intravenous (IV) antimicrobial therapy in combination with rifampicin, followed by rifampicin plus a companion oral drug for a total of 3 months [46].

The duration of antimicrobial therapy for most bacterial PJIs depends on the type of surgical procedure used to treat PJIs (debridement and retention vs 1-stage vs 2-stage exchange, etc.) rather than the infecting microorganism itself.

One retrospective cohort study of 39 patients with PJIs undergoing single-stage exchange, of which 28 had staphylococcal infections, demonstrated that 2 weeks of IV therapy followed by 3 months of oral antimicrobial therapy was sufficient to control the infection [8]. This study was limited by its small cohort size, lack of a control group, and possible confounding variables.

The optimal duration of antimicrobial therapies in 2-stage exchange arthroplasty is unclear. Multiple cohort studies have demonstrated acceptable cure rates in 2-stage exchange arthroplasty, with the use of 6 weeks to 3 months of total antibiotic therapy (IV and oral antibiotics) [60–65].

These retrospective cohort studies included a variety of infecting organisms, including staphylococcal PJIs. These studies did not report any robust evidence that outcomes were worse for any organisms. There are no prospective trials directly comparing the duration of antibiotic therapy for staphylococcal PJIs managed with 2-stage exchange arthroplasty.

A retrospective cohort analysis of 30 patients with streptococcal PJIs demonstrated high failure rates, of 45%, in patients who underwent 2-stage revisions [66]. The patients were managed with 2 weeks of IV antibiotics followed by 10 weeks of oral antibiotics.

Streptococcal infections are generally thought to be very responsive to treatment, due to their broad antimicrobial sensitivity, including penicillins and cephalosporins. However, the high failure rate in this single-center study has not been further studied in other trials.

In the series reported by Eid et al [48], 6 of the 8 patients with rapidly growing mycobacteria PJIs received $\geq$1 active antimicrobial agent for at least 6 months. In this series, the duration of effective therapy was as short as 16 weeks and as long as 55 weeks after resection arthroplasty, but other cases from other series were treated for as short as 3 weeks to as long as 112 weeks [67–73]. However, the optimal duration of antimicrobial therapy for rapidly growing mycobacteria PJIs remains unknown. Shorter courses of 3 months for total knee arthroplasty PJI and 2 months for total hip arthroplasty PJI treated with debridement and retention of the prosthesis have been successful in 87.5% of the patients treated when compared to 89.5% of the patients in the same cohort treated with 6 months and 3 months, respectively [74].

Rare cases of *Mycobacterium tuberculosis* and *Mycobacterium kansasii* PJIs required long courses of antimycobacterial therapies of 12-18 months [75,76]. The optimal medical and surgical therapies for *M tuberculosis* PJIs are unknown. Initial therapy should include isoniazid, rifampin, and pyrazinamide, with the addition of ethambutol or streptomycin in case of suspected isoniazid resistance [77]. Management was successful in patients with unsuspected *M tuberculosis* PJIs incidentally discovered at the time of implantation, or in the early postoperative period with nonrifampin antituberculous combination therapies for 12-18 months [78,79].

Many authors favor a total of 6 months of antifungal therapy (fluconazole) that may start after resection arthroplasty, and continued until after reimplantation, but a definitive duration of therapy has not yet been established [33,34,80].

Question 5: When a patient undergoes aseptic revision and intraoperative culture(s) grow an organism, should patients be treated with antibiotic therapy?

Recommendation:

Antibiotic therapies are recommended if two or more cultures isolate the same organism, as per the Musculoskeletal Infectin Society and the International Consensus Group (ICG) criteria for prosthetic joint infections. Antibiotic therapies may not be required when a single intraoperative culture isolates an organism. However, there may be circumstances when a single positive culture, combined with other tests, may indicate the presence of an infection, and treatment would be indicated.

Level of Evidence: Limited

Delegate Vote: Agree: 90%, Disagree: 8%, Abstain: 2% (Super Majority, Strong Consensus)

Rationale:

It is important to evaluate patients undergoing revision arthroplasty for evidence of infection. Most of these evaluations are performed preoperatively. Revision surgery is then performed, when the patient appears to be clear of an infection. The incidence of positive operative cultures in this setting varies extensively from 0% to 44%, and the significance of these positive cultures is often uncertain [81–83]. Studies of the clinical outcomes of patients with positive cultures at revision surgery have been mainly retrospective, and have limited and inconsistent conclusions [63,85–89].

If 2 or more operative cultures grow the same microbe, then treatment for prosthetic joint infection (PJI) would be appropriate, as per the Musculoskeletal Infection Society and the Consensus Conference criteria for the diagnosis of PJI [90,91]. However, if only one operative culture has bacterial growth, then the likelihood of a culture contaminant increases. An old but valuable study by Atkins et al [92] in the microbiology literature can be helpful in this analysis. This prospective study found that when 3 or more operative cultures are obtained, a single positive culture reflected PJI due to that organism 13.3% of the time; 2 positive cultures were indicative of PJI in 20.4% of patients and 3 or more cultures positive for the same organism signified a PJI in 94.8% of patients. Based on these data, the risk of treating a patient with a substantial course of antibiotic therapy may well outweigh the benefit if a single positive culture is associated with PJI in only 13.3% of cases. Patients in this category can be observed without antibiotic therapy, with an appropriately timed, postoperative arthroplasty aspirate culture to help determine if the operative bacterial isolate is a contaminant rather than a true pathogen.

Other issues in the present literature which limit us in making solid conclusions include the following:

1. Lack of standardization of operative culture specimens to be submissions of tissues or fluids, but not swabs.
2. Need to analyze operative culture positivity occurrences with knowledge of the duration of the surgery. Revision arthroplasty surgery is usually of longer duration than primary implantation, and intraoperative culture-positivity may only be a surrogate marker for the duration of the surgery, particularly if the operative cultures are obtained toward the end of the surgery.
3. A single operative culture which grows an organism, which was the pathogen treated for a patient's prior PJI, needs to be analyzed separately from those which grow a microbe that is unrelated to any previous infection. Further analysis may find that, although growth of a prior known pathogen represents persistence of true infection, growth of a single, entirely different organism is likely to be a contaminant.
4. Although difficult to perform, prospective, controlled studies are much more likely to result in solid conclusions than retrospective analyses.

Question 6: When should rifampin be added to the regimen of antibiotics for management of patients with periprosthetic joint infections (PJIs) undergoing surgical treatment?

Recommendation:

Rifampin should be considered in the treatment of Staphylococcal PJIs in patients managed surgically with debridement and implant retention (DAIR), or single-stage exchange, where activity against biofilm is required. Rifampin should only be used in combination therapies, with the best reported combination appearing to be with a fluoroquinolone.

Level of Evidence: Moderate

Delegate Vote: Agree: 96%, Disagree: 2%, Abstain: 2% (Unanimous, Strongest Consensus)

Rationale:

The excellent efficacy of rifampin against biofilm produced by staphylococci has been shown in vitro, in animal models, and in patients with orthopedic implant-related infections undergoing debridement, antibiotics, and implant retention [93–100]. Nevertheless, rifampin should be used with care, because of the danger of rapid emergence of resistance and potential unwanted effects, such as severe nausea, hepatotoxicity, interstitial nephritis, and cytopenia [101,102]. Rifampin is a potent inducer of the cytochrome p450 oxidative pathway, and can result in significant drug interactions [102,103]. Monotherapy is known to quickly promote rifampin resistance, and must therefore be avoided [104,105]. The emergence of rifampin resistance in *Staphylococcus aureus* is of particular concern [100,106]. The best documented combination partners for rifampin are fluoroquinolones [107,108].

Clinical data supporting the use of combination rifampin antimicrobial therapy and surgical debridement for the treatment of staphylococcal periprosthetic joint infections (PJIs) are available [106,109]. Widmer et al [110] showed in an open-label study that 9 of 11 patients (82%) with staphylococcal or streptococcal PJIs that could not undergo removal of hardware were successfully treated with rifampin in combination with either a beta-lactam or with ciprofloxacin. A randomized controlled study by Zimmerli et al [107] showed that among 24 patients with methicillin-susceptible *Staphylococcus aureus* (MSSA) or coagulase-negative staphylococcus (CNS) PJI with stable implants and a short duration of infection managed with debridement and implant retention, those able to tolerate long-term (3-6 months) combination therapy with ciprofloxacin-rifampin achieved cure at higher rates than those treated with a ciprofloxacin placebo.

Trebse et al followed 24 patients with PJIs and retained implants prospectively over 4 years showing 83% with a successful outcome. A total of 17 patients had staphylococcal infections and were treated with rifampin combination therapy; 2 of the 4 patients who failed had staphylococcal infections, 1 with methicillin-resistant *Staphylococcus aureus* (MRSA) and 1 with CNS [109].

Retrospective case series have described the success of rifampin combination therapy [10,102]. Successful treatments with rifampin-fluoroquinolone therapy were shown by Berdal et al and Barberán et al [111,112]. Rifampin, in combination with other antibiotics, including fusidic acid, vancomycin, or daptomycin, has also been reported to be effective [113–115]. Many of the reported case series primarily address the successful treatments of MSSA and CNS infections. Barberán et al observed a nonsignificantly ($P = .08$) higher failure rate in 7 MRSA-infected patients, compared to 14 MSSA-infected patients. More important, in patients with a duration of infection $\leq$1 month treated with levofloxacin plus rifampin, the outcome was significantly better than that for patients with a longer duration of infection [116]. A cohort study by Peel et al included 43 methicillin-resistant staphylococcal infections (24 MRSA), and found that 86% of patients were treated successfully, most with rifampin-fusidic acid. The found that 8 of 9 failures were in MRSA cases [117]. A retrospective multicenter study by Lora-Tamayo et al reported on 345 *S aureus* PJIs managed with joint retention including 81 MRSA cases. A total of 88% of patients received rifampin combination therapy and failure rates were similar in MRSA (46%) and MSSA (44%) cases [118].

The Infectious Diseases Society of America PJI and MRSA management guidelines recommend the use of rifampin combination therapy (2-6 weeks of pathogen-specific intravenous antimicrobial therapy plus rifampin followed by 3-6 months of rifampin plus an oral companion drug) in the treatment of staphylococcal PJIs/hardware infections in patients managed with debridement or single-stage exchange [46,119]. European guidelines include similar recommendations [120].

Unanswered questions regarding the role of rifampin remain; however, many clinical studies have focused on rifampin-quinolone combinations, with little information available for beta-lactam-rifampin therapy. Of note, fluoroquinolone-resistant staphylococci are found in many settings, especially in MRSA strains [121]. The emergence of rifampin resistance can occur even when using combination therapies [100,117,118,122]. Drug interactions lowering the serum concentrations of companion antimicrobials, including fusidic acid and clindamycin, have been reported [123,124]. The clinical significances of these interactions, however, are still unknown. Additionally, the optimal duration of combination antimicrobial therapies, including rifampin, for the treatment of prosthetic joint infections with retained hardware are not yet known. Although extended treatment (3-6 months) is recommended and often used, shorter treatment courses may be as effective in some settings [125].

Question 7: What is the optimal antibiotic therapy in cases of culture-negative periprosthetic joint infections (PJIs)?

Recommendation:

In patients with true culture-negative (CN) PJIs, the antibiotics should be selected to have broad spectrum activity against both Gram-positive and Gram-negative organisms. In addition, the exact choice should relate to the known modern epidemiology in that country.

Level of Evidence: Limited

Delegate Vote: Agree: 87%, Disagree: 6%, Abstain: 7% (Super Majority, Strong Consensus)

Rationale:

In the literature, rates of culture-negative (CN) periprosthetic joint infections (PJIs) vary from 0% to 42% but reports suggest that the outcomes are not necessarily worse than for culture-positive cases if rigorous and robust pathways for diagnosis and management are followed [63,126–131]. Factors associated with increased risk of culture negativity include prior antibiotic use, delay in transportation of the samples to the laboratory, and variations in culture techniques including short duration of culture [126,132–135]. It is important to note that several studies demonstrate that administration of antibiotic prophylaxis prior to obtaining culture samples did not interfere with isolation of the infecting organism [136].

A recent systematic review by Yoon et al evaluated clinical studies related to CN PJI. After exclusions, 7 studies were included in the analysis, with all studies being retrospective [63,126,130–132,136–139]. Of these, 4 studies defined PJI using Musculoskeletal Infection Society criteria [130,137–139]. In the majority of these studies, glycopeptides, such as vancomycin, were used followed by cephalosporins, beta-lactams, quinolones, or combination therapy. The duration of intravenous antibiotics for CN PJI was usually 6 weeks. The investigators also noted that the use of antibiotics for CN PJI was accompanied with appropriate surgery, stating that the choice of surgical strategy greatly affects the treatment results of PJI. Most of the included studies reported that 2-stage arthroplasty followed by 4-6 weeks of antibiotic therapy was effective with a success rate of 70%-100%. Six of the 7 studies in this review demonstrated similar success rates between culture-

positive and CN PJI, with one reporting greater success for CN PJI [63,126,130–132,137–139]. The authors of the systematic review recommended that further studies are required to determine optimal therapy for patients with CN PJI. The latter systematic review did not include studies that have demonstrated a suboptimal outcome for patients with CN PJI [140–142].

A few recent studies have attempted to further explore the issue of CN PJI. Kang et al [142] reported on the challenges of selecting the appropriate antibiotics, the treatment of CN PJI was commenced with cefazolin and changed to glycopeptides if infection did not respond to the initial treatment. Wang et al [141] also reported on the challenges of treatment for CN PJI. They utilized intravenous vancomycin and/or an aminoglycoside for 2 weeks followed by an oral antibiotic such as levofloxacin and rifampicin for additional 4 weeks. A cement spacer containing vancomycin/meropenem was used in their cohort. In another study, Peel et al [133] reported the use of vancomycin and cephalosporin followed by a broad-spectrum oral combination comprising fusidic acid, rifampicin ± ciprofloxacin for a median of 7 months (3-20 months interquartile range) in the majority of the patients but choice of regimen varied by presentation.

In 2013, Marschall et al published a survey in which members of the Emerging Infections Network were asked about the current treatment of PJI. Regarding CN PJI, the vast majority of the responders choose a 2-drug regimen in hip and knee infections most commonly using vancomycin with ceftriaxone or vancomycin with oral fluoroquinolone as upfront antibiotic treatment [143].

In summary, it appears that the rate of CN PJI varies vastly from one study to another perhaps reflecting the variability in definition of PJI, differences in culture techniques, and the local epidemiology. Despite the presence of some studies demonstrating acceptable outcomes for CN PJI, the selection of optimal antibiotics for these cases remains challenging. The majority of reported series utilize a combination of antibiotics in the CN PJI. In an effort to reduce financial and psychological costs associated with optimal management of CN PJI, all efforts should be made to isolate the infecting organism. Similar to CN endocarditis, zoonotic agents such as *Coxiella*, *Brucella*, *Bartonella*, and *Tropheryma whipplei* are not easily detectable by the usual means and are not treated by common empirical agents such as glycopeptides [144]. A recent study has demonstrated that next-generation sequencing has a promising role in isolation of infecting organism in up to 90% of CN PJI cases [145]. Based on the emerging data, consideration should be given to the use of next-generation sequencing or other molecular techniques in isolation of the infecting organism in patients with CN PJI. Serologies or serologic markers for certain zoonotic and endemic fungal infections should also be considered as the appropriate context.

If all attempts to isolate the infecting organism fails, then strategies employed in choosing an antibiotic regimen for CN PJI must be individualized, based on risk factors, previous history, and knowledge of the local epidemiology. The antibiotic treatment of CN PJI usually includes broad-spectrum antibiotics with a prolonged intravenous phase. Glycopeptides play a pivotal role but consideration should be given to the use of multiple drug regimens.

Question 8: What antibiotic therapy and duration of treatment should be used in Enterococcal PJIs?

Recommendation:

Based on the limited available evidence, combination antimicrobial therapy should be considered for the treatment of Enterococcal PJIs, at least during the first weeks of treatment. Antibiotics should be tailored according to the susceptibility of the infective microorganism.

Level of Evidence: Limited

Delegate Vote: Agree: 85%, Disagree: 9%, Abstain: 6% (Super Majority, Strong Consensus)

Rationale:

Enterococci are often part of polymicrobial infections [146,147], have the ability to form biofilms [148,149], and thus can be difficult to manage [150]. *Enterococcus faecium* is listed as one of the ESKAPE (an acronym for *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) organisms, which are resistant to a majority of antibiotics available in our arsenal [151,152].

There is a lack of high quality randomized, controlled, prospective comparative treatment studies. However, based on the high failure rate of enterococcal periprosthetic joint infections (PJIs) and the known limited bactericidal activity of beta-lactams on enterococci, some authors have suggested the use of combination antibiotic therapy for management of patients with enterococcal PJIs [153]. Another study demonstrated that patients who received monotherapy had the same outcome as those treated using combination therapy regimen [154]. El Helou et al [154] described an 80% success rate using debridement, retention of the implant, and intravenous ampicillin with or without gentamicin. The success rate was similar in the monotherapy and combination groups, but nephrotoxicity was significantly higher among those receiving aminoglycosides. The results of the multi-institutional study by Kheir et al [146] support the former recommendation of combination systemic therapy. Although the authors did not find statistical significance, there was a trend toward higher treatment success with combination antibiotic therapy. In addition, there is a high risk of selection bias in retrospective studies evaluating the efficacy of antibiotic therapy, as dual therapy is often applied in more severe infectious cases. The efficacy of dual therapy in enterococcal infections in clinical studies is primarily demonstrated for enterococcal endocarditis. For monomicrobial nonresistant *Enterococcus faecalis* and *E faecium* PJI, we recommend a combination of an intravenous cell wall synthesis inhibiting agent (ampicillin or vancomycin, respectively) and to add gentamicin as a synergistic antibiotic, at least during the first 2 weeks of treatment, which is concordant with previous literature [146,150,155,156]. It is important to note that administration of a systemic aminoglycoside can increase the risk of nephrotoxicity and ototoxicity [154]. Other alternatives suggested in the literature to include as synergistic antibiotic (instead of gentamicin) is ceftriaxone [157] or daptomycin [158–160].

Interestingly, it has also been suggested that rifampin in combination with other antibiotics may also lead to a lower rate of failure in early enterococcal PJIs. Tornero et al [161] found that the administration of rifampin combined with other antibiotics was associated with a lower rate of failure than alternative antibiotics. In addition, recent in vitro data showed that linezolid or ciprofloxacin combined with rifampin had better activity against enterococcal biofilms than ampicillin or ampicillin plus rifampin; therefore, these combinations are potential alternatives [162].

Emerging antibiotic resistance, specifically to vancomycin, is a challenging problem for the management of enterococcal PJI [150,163]. Plasmid-mediated resistance to vancomycin was first described in 1986, and shortly thereafter numerous reports of the vancomycin-resistant *Enterococcus* (VRE) species appeared in the literature [164]. VRE species are phenotypically and genotypically heterogeneous, and among all of these phenotypes and genotypes, VancA resistance phenotype has been most commonly investigated [164]. For VRE, the literature suggests the use of either linezolid (with or without rifampin) [162] or daptomycin [146,165]. Although linezolid resistance has been reported, fortunately at present there is no report of emerging daptomycin-resistant *Enterococcus* [166–169].

Polymicrobial infections are challenging to treat, as administration of multiple antibiotics is often needed [170]. For polymicrobial infections, broad-spectrum coverage should be performed. Literature is sparse on the use of oral antibiotics for patients with polymicrobial enterococcal PJI, and it is not known if oral antimicrobial can be used for successful treatment of these patients.

The review of the available literature revealed that there was a high variability of antibiotic treatment duration for enterococcal infections and lack of analysis regarding treatment duration in the above studies. In the study by Kheir et al [146], each patient's antibiotic duration was listed, and the majority of patients had 6 weeks of antibiotic treatment (although the range was broad from 4 to 36 weeks of duration). Duijf et al [171] reported 3 months of antibiotic treatment resulting in 66% of patients retaining their implants. This may suggest that longer antibiotic treatment may be beneficial in enterococcal PJIs; however, further study is warranted in this domain.

Based on the available literature, and our experience, we recommend that patients with enterococcal PJI should be treated with 6-12 weeks of antimicrobial agents, preferably in combination.

Question 9: What are the indications for utilizing Fosfomycin, Tigecycline, and Daptomycin, either instead of other antibiotics or in conjunction with other antibiotics for the management of periprosthetic joint infections (PJIs)?

Recommendation for Daptomycin:

Daptomycin is an alternative treatment for patients with prosthetic joint infections (PJIs) caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

Level of Evidence: Moderate

Recommendation for Fosfomycin:

Although there is no clinical experience using fosfomycin in PJIs, it could be considered in infections due to multi drug resistant Gram-positive (MDR-GP) or Gram-Negative Bacteria (GNB) as a part of a combination regimen with daptomycin, rifampicin, or tigecycline when the microorganism is susceptible.

Level of Evidence: Limited

Recommendation for Tigecycline:

Tigecycline could be considered for the treatment of MDR-GP or MDR-GNB as a part of a combination regimen when the microorganism is susceptible.

Level of Evidence: Limited

Delegate Vote: Agree: 86%, Disagree: 4%, Abstain: 10% (Super Majority, Strong Consensus)

Rationale:

Daptomycin

Daptomycin is a cyclic lipopeptide with concentration-dependent bactericidal activity against Gram-positive microorganisms. It is highly active against *Staphylococcus aureus*, coagulase-negative Staphylococci, *Enterococcus faecalis*, and *Enterococcus faecium*, including both planktonic and biofilm-embedded bacteria [172]. Daptomycin combined with gentamicin has been shown to have synergistic activity on intracellular *S aureus*. Additionally, daptomycin seems to exhibit activity against the stationary-phase bacteria inside a biofilm [173–175]. Several animal models of foreign body infection demonstrated a high success rate with daptomycin but always in combination with rifampin [98,176].

Since its commercialization, several case series and 1 clinical trial have evaluated the efficacy of daptomycin in PJIs (Table 1). The first description [177] included 12 patients who received 4 mg/kg of daptomycin in monotherapy with a success rate of 45.5%. In addition, of the 5 patients considered as success, only 1 retained the implant with oral suppressive therapy. Byren et al [178] performed a prospective, randomized controlled trial in periprosthetic joint infections (PJIs) treated with 2-stage exchange to evaluate the safety and efficacy of 6 or 8 mg/kg of daptomycin in monotherapy for 6 weeks compared with the standard-of-care (vancomycin, teicoplanin, or semisynthetic penicillin). A total of 75 patients were included and the clinical success rates were higher in daptomycin groups than in control group (58.3% for 6 mg/kg daptomycin vs 60.9% for 8 mg/kg daptomycin vs 38.1% for the comparators). The frequency of adverse events was similar in both groups; however, 16% and 22% of the patients in the 6 mg/kg and 8 mg/kg of daptomycin had increased creatine phosphokinase levels (>500 U/L) vs 8% in the control group.

In a retrospective study, Corona et al [159] described 20 patients with PJI who received an average daptomycin dose of 6 mg/kg/d for a mean duration of 44.9 days. Fourteen patients were evaluated and 4 received rifampin (28.6%). The remission rate was higher than in previous studies (78.6%), and all patients treated with rifampin (including 3 acute PJIs treated with debridement, antibiotics, and implant retention [DAIR]) were in remission. Noteworthy, severe side effects occurred in 2 patients (10%) receiving daptomycin without rifampin and both required admission in the intensive care unit. One developed a daptomycin-induced eosinophilic pneumonia and the other a massive rhabdomyolysis with acute renal failure. For this reason, the authors recommended close monitoring for symptoms of myopathy with weekly serial follow-up of serum creatinine. In addition, Jugun et al [179] evaluated prospectively 16 patients with an osteoarticular infection treated with 8 mg/kg/d of daptomycin plus 600 mg of rifampin for a median duration of 3 weeks. Only 6 had a PJI but no clinically or laboratory-documented adverse events occurred that required adjustment or discontinuation of daptomycin therapy. All patients were in remission after an average of 15.8 (range 12.4-30) months of follow-up. Lora-Tamayo et al [180] performed a retrospective, multicentric study to evaluate the efficacy and safety of a 6-week course of daptomycin at 10 mg/kg plus rifampin in 20 patients with acute staphylococcal PJI managed with DAIR. Results were compared with 44 matched historical controls with PJI caused by fluoroquinolone-resistant staphylococci. The clinical failure rate was 50% in the daptomycin group vs 34% in historical controls ($P = .265$) and 29% and 30% had microbiological failure, respectively.

Malizos et al [182] evaluated all patients with osteoarticular infection retrospectively collected from the European Cubicin Outcomes Registry and Experience study that registered real-world outcome data from patients receiving daptomycin. Of 638 patients, 432 (67.7%) had osteomyelitis and 206 (32.3%) had an orthopedic device infection. More than 75% of the patients received ≥6 mg/kg of daptomycin during a median of 16 days (range 1-176) for orthopedic device infections. The remission rate was 81.8% overall and 85% in patients with PJI. Unfortunately, data about the type of infection (acute or chronic), methicillin-resistant *Staphylococcus aureus* (MRSA) rate, and the surgical management were not reported. Overall, adverse events were reported in 78 (12.2%) patients, being severe in 39 (6.1%) and requiring discontinuation in 35 (5.5%). The most recent report is a retrospective description of 16 patients treated with high doses of daptomycin (8.3 mg/kg/d) in monotherapy during a median of 14 days [183]. After this, all patients received oral antibiotics during a median of 35 days. The oral antibiotic combinations included were sulfamethoxazole/trimethoprim plus rifampin or fusidic acid plus rifampin. The study included 5 patients with an acute PJI treated with DAIR and 11 with a chronic PJI treated with 2-stage exchange. It is important to highlight the high percentage of MRSA (62.5%) and the high remission rate

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Table 1
Summary of the Clinical Experience With Daptomycin in PJIs Including Case Series With More Than 5 Cases.

Author (y)	Type of Study	Number of Patients/Type of PJI/Surgical Treatment	Dose, Duration	Rifampin (%)	Adverse Events Related to Daptomycin (%)	Follow-Up Months (Range)	MRSA n/Total (%)	Remission n/Total Evaluated (%)
Rao and Regalla (2006) [177]	P	12/5 early acute/DAIR 7 chronic 2S	4 mg/kg, 6 wk	0	0	9 (range 7-13)	7/12 (58.3)	5/11 (45.5)
Byren et al (2012) [178]	RCT	75/chronic/2S	6 mg/kg vs 8 mg/kg vs control, 6 wk	0	CPK >500 µ/L 6 mg/kg: 16% 8 mg/kg: 21.7% Control: 8%	5-7	3/25 (12) 7/24 (30.4) 3/25 (12)	6 mg/kg: 14/24 (58) 8 mg/kg: 14/23 (61) Control: 8/21 (38)
Corona et al (2012) [159]	R	20/8 early acute/5 DAIRs/3 2S and 12 chronic/9 2S and 3 1S	6.6 mg/kg (median), 6.4 wk	Yes:8 (40) No:12 (60)	↑ CPK: 1 (12.5) ↑ CPK: 1 (8.3) Eosinophilic pneumonia: 1 (8.3)	20 (range 12-41)	1/14 (7.1)	Acute infection: 5/6 (83.3) Chronic infection: 5/7 (71.4)
Jugun et al (2013) [179]	P	16 osteoarticular infection (6 with PJI)	8.15 mg/kg (median) + rifampin 600 mg/d, 7.3 wk (range 2-17)	16 (100)	0	15.8 (range 12.4-30)	3/6 (50)	Totally or partially removed: 3/3 (100) DAIR: 3/3 (100)
Lora-Tamayo et al (2014) [180]	R	20/early acute/DAIR	10 mg/kg + rifampin 600 mg/d, 6 wk	20 (100)	Rhabdomyolysis: 1 (5)	25 (range 24.4-32.3)	10/18 (55.5)	Daptomycin + rifampin: 9/18 (50) Control group: 15/44 (34)
Chang et al (2017) [181]	R	16/5 early acute/DAIR 11 chronic 2S	8.3 mg/kg, 2 wk	0	0	27	10/16 (62.5)	2S: 10/11 (91) DAIR: 4/5 (80)

1S, 1-stage exchange; 2S, 2-stage exchange; DAIR, debridement, antibiotic, and implant retention; MRSA, methicillin-resistant *Staphylococcus aureus*; P, prospective cohort; PJI, prosthetic joint infection; RCT, randomized control trial; R, retrospective cohort; CPK, creatine phosphokinase.

(87.5%). Specifically, there was 1 failure in acute PJIs (20%) and 1 among chronic ones (9%), both due to MRSA. No serious adverse events were reported.

In conclusion, a clinical trial showed that daptomycin at 6 or 8 mg/kg for 6 weeks had a higher cure rate than monotherapy with teicoplanin, vancomycin, or a semisynthetic penicillin. However, the clinical data suggest that ≥14 days of daptomycin in monotherapy is associated with adverse events (mainly creatine phosphokinase elevation). In contrast, other clinical studies combining daptomycin with rifampin did not observe problems with adverse events even after >14 days of treatment and doses up to 10 mg/kg. These data suggest that rifampin could reduce the serum concentration of daptomycin (substrate of P-glycoprotein) but more data are necessary to support this hypothesis [183]. On the other hand, a short course of high-dose (≥8 mg/kg) daptomycin without rifampin for the first 2 weeks of treatment followed by an oral rifampin combination seems to be well tolerated and associated with good outcome. Recent data show that the addition of daptomycin to cloxacillin or cefazolin may provide synergy, as shown by in vitro studies and animal experimental models [176,184]. This combination is promising to avoid the use of rifampin during the first 1-2 weeks of antibiotic treatment and to reduce the risk of selecting daptomycin-resistant mutants [185].

Fosfomycin

Fosfomycin has a broad spectrum including multidrug-resistant (MDR) Gram-positive (GP) and Gram-negative (GN) microorganisms, it has a time-dependent bactericidal activity, and it is maintained in a low pH and in anaerobiosis [186–188]. Fosfomycin has a high bone penetration (bone:serum ratio of 43%) achieving concentrations above the minimum inhibitory concentration for most susceptible bacteria [189]. There are 3 presentations, sodium fosfomycin for intravenous administration and trometamol and calcium salt for oral administration. Unfortunately, the oral bioavailability is <20% for calcium salt and <40% for trometamol; therefore, only intravenous antibiotic is recommended for the treatment of bone infections [190].

Against GP, fosfomycin has demonstrated a potent in vitro synergistic activity against MRSA in combination with beta-lactams, daptomycin, and linezolid. In addition, in an experimental foreign body infection, fosfomycin combined with daptomycin or rifampin was the second and third regimens with the highest cure rate (defined as the percentage of eradication from the implant) only behind daptomycin plus rifampin, and this was corroborated by other authors [191–195]. However, there are no clinical data supporting the efficacy of fosfomycin in PJI due to GP.

Fosfomycin has bactericidal activity in combination with carbapenems and colistin against carbapenemase-producing *Klebsiella pneumoniae* [196,197]. Corvec et al [198] evaluated the activity of fosfomycin and tigecycline alone or in combination with other drugs against extended-spectrum beta-lactamase producing *Escherichia coli* strains in a foreign body infection model. Fosfomycin was the only single agent for which the eradication of *E coli* from cages was achieved and the combination that showed the highest antibiofilm activity was fosfomycin plus colistin, suggesting that fosfomycin should be considered in the treatment of MDR-GNB (GN bacteria) susceptible to fosfomycin strains. It is of note that fosfomycin could decrease the nephrotoxicity of aminoglycosides that in some occasions are the only one active drug [199]. Although there is no clinical experience using fosfomycin in PJI due to GNB, it should be considered in infections due to MDR-GNB as a part of a combination regimen when the microorganism is susceptible.

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Tigecycline

Tigecycline is active against GP and GN (except *Pseudomonas*), including vancomycin-resistant enterococci, MR-staphylococci, extended-spectrum beta-lactamase, carbapemen-producing *Enterobacteriaceae*, and *Acinetobacter* spp. Tigecycline has demonstrated synergistic activity against *Enterococcus* spp. combined with rifampicin, and with amikacin or colistin against some MDR-*Enterobacteriaceae* spp., *Acinetobacter baumannii*, or *Stenotrophomonas maltophilia* [200]. Data from foreign body infection model due to MRSA showed that tigecycline in monotherapy was similar to vancomycin and in combination with rifampin was as effective as vancomycin with rifampin and both options avoid the selection of rifampin-resistant mutants [201,202]. A recent study in healthy volunteers undergoing elective orthopedic surgery demonstrated a good bone penetration after multiple doses of tigecycline (bone:serum ratio of 4) [203].

Clinical experience in osteomyelitis with tigecycline was documented in 13 cases with success in 85% but only 1 case was associated with an orthopedic implant. In PJI, the level of evidence is limited to few case reports [204]. Vila et al [205] described 3 patients with early PJI of total hip arthroplasty due to MDR *A baumannii* treated with debridement, implant retention, and a high dose of tigecycline (100 mg every 12 hours). All patients received colistin concomitantly during a mean of 8.7 days and required at least 1 additional debridement, but all were asymptomatic after a median of 2.5 years. The major limitation for the prolonged use of tigecycline is the high frequency of nausea and vomiting. Vila et al diluted tigecycline in 400 mL of dextrose and administered at a slow infusion rate in order to reduce the adverse events and the therapy was well tolerated.

In contrast, de Sanctis et al [206] evaluated 3 patients with a PJI due to carbapenem-resistant *K pneumoniae* with poor outcome. All were polymicrobial infections, and required multiple surgeries and complex antibiotic courses including tigecycline (2 cases in monotherapy and 1 combined with amikacin first and with colistin later on). Prostheses were removed in 2 cases, but patients finally died and the only one who survived required salvage limb amputation. In addition, resistant mutants to colistin and amikacin were selected while on antibiotic treatment; however, the dose of tigecycline was not reported. Furthermore, Asseray et al [207] described 4 patients with PJI due to MDR GP managed with implant removal and tigecycline during a median of 105 days (range 90-150). In addition, 2 patients received concomitant treatment with fosfomycin and 1 with linezolid. All patients but one (75%) was in remission after an average of 20.2 (range 14-32) months of follow-up. Only 1 patient treated with tigecycline plus fosfomycin experienced a moderate adverse event with anemia and thrombocytopenia, which was not attributed with certainty to tigecycline; however, the dose of tigecycline was not specific. The rationale for increasing the dose (100 mg/12 h) is based on its pharmacodynamic properties (area under the receiver operating characteristic curve/minimum inhibitory concentration ratio is the most predictive parameter related to clinical and microbiological efficacy), the presence of biofilms, and the multidrug-resistant profile of the involved organism [208]. Further experience and clinical studies are necessary but tigecycline should be considered for the treatment of MDR-GP or GNB as a part of a combination regimen when the microorganism is susceptible.

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