RATIONALE

Treatment of MRSA PJI that has undergone DAIR remains challenging. An ideal combination of antimicrobial therapy has not been established. Treatment should take into account antimicrobial susceptibilities of MRSA and tailored accordingly. Whenever possible, rifampin-based combinations should be used, but rifampin alone should never be used due to the rapid development of resistance. Rifampin-based combination therapy regimens have been shown to be effective in eradication of staphylococcal organisms and cure PJIs. A widely used algorithm by Zimmerli and the Infectious Diseases Society of America (IDSA) guidelines recommend a quinolone–rifampin combination for susceptible *Staphylococcus aureus* strains and cure rates of 70 - 100% have been reported [1–3]. The duration of antimicrobial therapy for PJI managed with DAIR has not been well established. We recommend two to six weeks of parenteral antimicrobial therapy in combination with rifampin 300 to 450 mg orally twice a day, followed by rifampin plus a susceptible companion oral drug (such as trimethoprim-sulfamethoxazole, ciprofloxacin or levofloxacin, a tetracycline, fusidic acid) depending on the individual tolerance, side effect profile and antimicrobial susceptibility testing [1,4,5]. Certain highly bioavailable drugs such as fluoroquinolones, rifampin, linezolid and trimethoprim-sulfamethoxazole, reach levels in bone that exceed the minimal inhibitory concentration (MICs) for most organisms [6].

Zimmerli et al. have suggested a duration of therapy of three months for total hip arthroplasties (THAs) PJIs and six months for total knee arthroplasties (TKAs) PJIs [1,3]. Shorter courses of therapy (6 vs. 12 weeks) were studied in PJIs treated with DAIR. However, in this study by Chaussade et al. the presence of MRSA, which comprised only 13.8% of infections, was associated with a poorer outcome (remission in 41.7 vs. 73.3% for other pathogens [7]. Chronic oral suppression with trimethoprim-sulfamethoxazole, minocycline or doxycycline based on in vitro-susceptibilities and individual side effect profile and tolerance may be considered following the above regimens and should be reserved for patients who are unsuitable or refuse further surgical therapy. The duration of chronic oral suppression remains unknown.

While the current IDSA guidelines recommend vancomycin as the primary parenteral agent for treatment of MRSA infections, its utility has been questioned due to increasing reports of heterogeneous resistance, treatment failure, and nephrotoxicity. Vancomycin is not bactericidal against small colony variants (SCV) of MRSA. Moreover, Lenhard et al. showed recently in mixed-population experiments that vancomycin favorably selects for the growth of the SCV subpopulation [6]. Therefore, clinicians should consider glycopeptide combination regimens or alternative antimicrobials in patients with severe persistent MRSA infections in which the SCV phenotype may play a role.

In vitro analyses have identified fluoroquinolones and oritavancin as retaining high levels of vancomycin in vitro against SCVs and β-lactam combinations with daptomycin may offer a new option for combating SCVs [8,9,10]. While optimal treatment for infections caused by staphylococcal SCVs is not known, combination therapy including either rifampin or oritavancin appears to be particularly effective at eradicating intracellular SCVs [11].

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QUESTION 14: What antibiotic therapy (agent, route, dose and duration) is recommended for gram-negative acute periprosthetic joint infections (PJIs) being treated with debridement, antibiotics and implant retention (DAIR)?

RECOMMENDATION: Following surgical intervention (DAIR), gram-negative acute PJI patients should also receive antibiotic treatment for 6 to 12 weeks based on the type of organism. In fluoroquinolone-susceptible cases, the recommended antibiotic agent is a fluoroquinolone.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 83%, Disagree: 11%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

In recent decades, the number of PJIs caused by gram-negative organisms, including multidrug-resistant gram-negatives (GNs), has increased [1]. Several studies have been published on antibiotic treatment of these infections in patients treated with surgical debridement and implant retention (DAIR) [2–8]. Studies have been performed demonstrating the preferred antibiotic agent for treating these infections, but few relate to the preferred route, dose and duration of antibiotic treatment.

Antibiotic Agent for GN PJIs Treated with DAIR

Rodriguez-Pardo et al. performed a retrospective analysis on 242 GN PJIs, including 174 cases (72%) treated with DAIR [2]. The study demonstrated that the use of fluoroquinolones (in this study ciprofloxacin) was associated with the highest success rate of 79% (98 of 124), while the success in the remainder of the patients treated with other antibiotic regimen (e.g., β-lactam or cotrimoxazole) was only 40% (20 of 49). In addition, ciprofloxacin treatment exhibited an independent protective effect in the prevention of subsequent failure in the multivariate analysis (adjusted hazard ratio (aHR) 0.23; $p < 0.001$). In addition to endorsing the use of fluoroquinolones, the latter study also favored the use of combination therapy, as a β-lactam antibiotic combined with a fluoroquinolone or an aminoglycoside as this regiment showed a trend towards better outcome (aHR 0.42, $p < 0.07$). The cohort of patients included in the study were mostly infected with *Enterobacteriaceae* spp. (78%) and some with *Pseudomonas* spp. (20%). The study was not able to glean which of the PJI cases benefited from the combination therapy. Several other smaller studies have been performed, supporting the beneficial effect of fluoroquinolones. Aboltins et al. [3] studied the outcome of 17 consecutive patients with an early GN PJI, mostly polymicrobial in origin (76%), and mainly involving *Enterobacteriaceae* spp (94%). All of these patients were initially treated with β-lactam antibiotics intravenously, and 14 patients were subsequently treated with oral ciprofloxacin. Treatment failure occurred in two patients not treated with ciprofloxacin (median period of follow-up of 28 months). Only one of these failures was caused by a relapse with the same GN, suggesting a cure rate of 100% (14/14) when using ciprofloxacin versus 66% (2/3) when using another oral antibiotic regimen (in these particular cases amoxicillin/clavulanic acid). In addition, a study performed by Jaén et al. (n = 47) and Tornero et al. (n = 21) on GN PJIs treated with DAIR, which were partly based on the same cohort of patients, also demonstrated that the use of fluoroquinolones in susceptible GN was the only factor associated with treatment success in the univariate analysis [4,7,8].

Recently, Grossi et al. [9] demonstrated in 76 GN PJIs that the outcome of treatment with IV β-lactam antibiotics (alone or in combination with another antimicrobial agent) during the whole treatment period (median three months) was similar compared to the use of an oral fluoroquinolone (failure rate 16.7 vs. 22.4%, $p = 0.75$). Although the study of Grossi et al. included both DAIRs and revisions as surgical strategy, outcome remained the same after stratification according to the surgical procedure, suggesting that intravenously antibiotic regimens and/or combination therapy may be as effective as treatment with fluoroquinolones.

The use of alternative oral regimens other than β-lactam, like cotrimoxazole, have been poorly studied in the field of PJI and require further investigation.

Only a few data are available on how to treat multidrug-resistant (MDR) GN in the field of PJIs, but extensive reviews and expert opinions have been published, utilizing the efficacy of carbapenems, combined with tigecycline, colistin or fosfomycin when the microorganism is susceptible [10–13]. Another question in the consensus document elaborates on the efficacy of tigecycline and fosfomycin alone or in conjunction with β-lactam in the treatment of PJI, suggesting that tigecycline or fosfomycin could be considered for the treatment of MDR GN PJI of as a part of a combination regimen when the microorganism is susceptible.In addition, the benefit of adding colistin to a β-lactam for osteoarticular infections caused by MDR, have been reported as well, demonstrating a higher cure rate for combination therapy [14,15].

Treatment Suration, Route and Dosage for GN PJIs Treated with DAIR

Table 1 shows the treatment duration and subsequent failure rate of the above-mentioned studies. Whether a short or long treatment duration was associated with a respectively lower or higher cure rate was not described in most studies. Only Jaén et al. evaluated the difference in outcome between patients treated with more or less

TABLE 1. Overview treatment duration and outcome in GN PJIs solely treated with DAIR

Author, Year	Patients (n)	IV (days)	Oral (days)	Total (days)	Failure %
Tornero et al. 2016 [4]	21	8 (IQR 5-12)#	69 (IQR 45-95)#	ND	14
Grossi et al. 2016 [9]	35	36 (IQR 14-90)*	ND	90 (IQR 89-92)*	23
Jaén et al. 2012 [8]	47	14 (IQR 8-24)	64 (IQR 28-102)	ND	26
Rodriguez-Pardo et al. 2011 [2]	174	14 (IQR 6-23)	58 (IQR 27-90).	ND	32
Zmistowski et al. 2011 [5]	10	ND	ND	ND	30
Aboltins et al. 2011 [3]	17	40 (range, 9 - 79)	365 (range, 30 - 1678).	ND	6
Hsieh et al. 2009 [6]	27	38 (range, 24-52)	49 (range, 28-92)	ND	27

*, duration of treatment included cases treated with revision surgery; #, duration of treatment included gram-positive PJIs; IQR, interquartile range; ND, no data.

than 14 days of IV treatment and treated with more or less than 64 days of oral antibiotic treatment and demonstrated no differences in outcome [8]. Although studies have demonstrated an equal success rate with 6 to 8 weeks compared to the standard 12 weeks of antibiotic treatment [16–20], these studies have been mainly performed in rifampin susceptible staphylococci and cannot be extrapolated to GN PJIs. For this reason, we would still recommend a 6 to 12-week treatment duration (including 1 to 2 weeks of IV treatment), especially in ciprofloxacin-resistant GN. In caseβ –lactam is indicated, it should be administered intravenously throughout the entire treatment period.

No studies evaluated the dosage of antibiotic treatment and its relation to outcome. We propose the recommendations depicted in Table 2.

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TABLE 2. Proposed antibiotic regimen for GN PJIs treated with DAIR

Microorganisms1	IV Regimen	Oral Regimen
Enterobacteriacae, ciprofloxacin susceptible	Ceftriaxon 2 gm QD ± Ciprofloxacin 400 mg TID	Ciprofloxacin 750 mg BID
Pseudomonas spp, ciprofloxacin susceptible	Cefepime 2 gm TID *or* Meropenem 2gm TID *or* Ceftazidime 2gm TID *or* Piperacillin-tazobactam 4.5gr QID ± Ciprofloxacin 400 mg TID *or* Tobramycin 7mg/kg QD	Ciprofloxacine 750 mg BID
Enterobacteriaceae, ciprofloxacin-resistant	Ceftriaxone 2 gm QD ± Tobramycin 7mg/kg QD	IV β-lactam antibiotics during the whole treatment period *Possible alternative* Cotrimoxazole 960 mg TID
Pseudomonas spp, ciprofloxacin resistant	Cefepime 2 gm TID *or* Meropenem 2gm TID *or* Ceftazidime 2gm TID *or* Piperacillin-tazobactam 4.5gr QID ± Tobramycin 7mg/kg QD *or* Colistin 3 million IU TID *or* Fosfomycin 2-4g QID	IV antibiotics during the whole treatment period

DAIR, debridement, antibiotics and implant retention; PJIs, periprosthetic joint infections; QD, four times daily; TID, three times daily; BID, twice daily

± Duotherapy can be considered in patients who have a high risk for treatment failure.

1 In case of multidrug-resistant or extremely drug-resistant gram-negative, the antibiotic treatment should be guided by the antibiogram and preferentially by combining two antibiotics with a different mechanism of action.

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5.3. TREATMENT: ONE-STAGE EXCHANGE

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QUESTION 1: What are the potential advantages of a one-stage exchange arthroplasty?

RECOMMENDATION: The potential advantages of a one-stage exchange arthroplasty are multiple, including a decrease in surgical morbidity and mortality, earlier functional return, decrease in healthcare and global economic costs as well as an increase in health-related quality adjusted life years.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 89%, Disagree: 8%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

While multiple studies have been performed evaluating the efficacy of a one-stage or two-stage exchange arthroplasty for periprosthetic joint infection (PJI) [1–13], the majority demonstrated a reduced rate of recurrent infection after a two-stage exchange in comparison to a one-stage exchange, although the comparative value of these results is difficult to interpret given discrepancies in patient comorbidities, bacterial profiles, treatment protocols as well as variances in the definitions of PJIs, clinical success, and failure.

In North America, treatment of PJIs using a two-stage revision procedure remains the most widely utilized and reported method in the literature [14–16]. However, there is no clear evidence that shows superiority of two-stage over one-stage revision in terms of success, eradication of infection or patient satisfaction [1–11,13,16–18]. In addition, one-stage revision has demonstrated multiple advantages in several prognostic and observational studies, particularly within the European literature [1–13].

Depending on the study and follow-up time, one-stage revision procedures have demonstrated a success rate ranging between 75 to 95% [1–5,7–13,17–19]. This is comparable to the reported reinfection rates after two-stage revisions between 9 and 20% of cases [20]. Furthermore, when appropriately performed, one-stage revision can avoid the morbidity associated with multiple surgeries while providing the advantages of reduced total length of stay, overall cost and earlier functional rehabilitation [19,20]. Other advantages include the reduced duration of postoperative systemic antibiotic therapy and systemic antibiotic side effects [19,20].

Despite this demonstrated success of one-stage revisions, it is critical to recognize that this procedure is contingent on strict patient selection criteria and specific operative planning protocols. For example, preoperative identification of the responsible bacterial organism in the synovial fluid is a prerequisite to determine the specific local and systemic antibiotic therapy regimen [3,6,10,11,19]. Also, patients who fail prior one-stage revision, those with an unclear causative pathogen or lack of susceptibility to available antibiotics and those with more extensive infections, may not be candidates for one-stage exchange [20].

In addition to strict selection criteria, several meticulous intraoperative steps, including aggressive soft tissue debridement, meticulous removal of the prior cement material and all hardware, as well as the use of antibiotic-loaded cement for reimplantation, along with specific postoperative antibiotic regimens, are important for success [19]. In a systematic review comparing one- to two-stage exchange, superior outcomes for one-stage revision were reported when performed in this selective patient population [21].

Two recent meta-analyses comparing outcomes for one-stage versus two-stage exchange for patients who have PJIs after both total hip [22] and total knee [23] arthroplasties demonstrated statistically equivalent reinfection rates for both protocols. These findings, were, however limited by the quality of the studies included in the meta-analyses, as well as a relative paucity of studies evaluating one-stage protocols in comparison to two-stage exchange.

Wolf el al. utilized Markov modeling in a decision-tree analysis to suggest a possible superiority of treatment of a one-stage exchange in comparison to a two-stage protocol as it pertains to health-related quality of life years, despite an objective decrease in recurrent infection with a two-stage protocol [24]. Although