Hip and Knee Section, Treatment, Debridement and Retention of Implant

Argenson, Jean Noël; Arndt, Marius; Babis, George; Battenberg, Andrew; Budhiparama, Nicolaas; Catani, Fabio; Chen, Foster; de Beaubien, Brian; Ebied, Ayman; Esposito, Silvano

Published in:
Journal of Arthroplasty

DOI:
10.1016/j.arth.2018.09.025

Publication date:
2019

The Journal of Arthroplasty 34 (2019) S399–S419

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Hip and Knee Section, Treatment, Debridement and Retention of Implant: Proceedings of International Consensus on Orthopedic Infections

Jean Noël Argenson [1], Marius Arndt [12], George Babis [1], Andrew Battenberg [2], Nicolaas Budhiparama [2], Fabio Catani [3], Foster Chen [4], Brian de Beaubien [5], Ayman Ebied [6], Silvano Esposito [7], Christopher Ferry [5], Henry Flores [3], Andrea Giorgini [3], Erik Hansen [8], K.D. Hernugrahanto [2], Choe Hyonmin [6], Tae-Kyun Kim [9], In Jun Koh [9], Georgios Komnos [10], Christian Lausmann [12], Jeremy Loloi [5], Jaime Lora-Tamayo [11,12], I. Lumban-Gaol [2], F. Mahyudin [2], Mikel Mancheno-Losa [11,12], Camelia Marculescu [9], Sameh Marei [6], Kimberly E. Martin [5], Prashant Meshram [9], Wayne G. Paprosky [4], Lazaros Poultsides [3], Arjun Saxena [3], Evan Schwechter [4], Jay Shah [8], Noam Shohat [6], Rafael J. Sierra [1], Alex Soriano [13], Anna Stefánsdóttir [10], Linda I. Suleiman [4], Adrian Taylor [9], Georgios K. Triantafyllopoulos [3], Dwikora Novembri Utomo [2], David Warren [12], Leo Whiteside [5], Marjan Wouthuyzen-Bakker [6,13,14], Jean Yombi [14], Benjamin Zmistowski [11]

ARTICLE INFO

Article history:
Available online 19 October 2018

Keywords:
debridement, antibiotics, implant retention (DAIR)
debridement antibiotics and retention of the prosthesis
irrigation and debridement

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.2018.09.025.

[1] Question 7.
[2] Question 12.
[3] Question 8.
[4] Question 11.
[5] Question 5.
[6] Question 6.
[7] Question 1.
[8] Question 13.
[9] Question 10.
[10] Questoin 4.
[11] Question 2.
[12] Question 3.
[13] Question 9.
[14] Question 14.

indications
contraindications
chronic renal failure (K), liver cirrhosis (L), index surgery (I), cemented prosthesis (C), and C-reactive protein (CRP) >115 mg/L (KLIC) score
chronic obstructive pulmonary disease (COPD)), and C-reactive protein (CRP) >115 mg/L (C), rheumatoid arthritis (R), indication prosthesis (I), male (M), exchange of mobile components (E), age > 80 years (80) (CRIME80) scores
risk stratification
emergency management
patient optimization
acute periprosthetic joint infection (PJI)
pathogen identification
surgical intervention
biofilm
surgical outcome
exchange of modular components
surgical site infection (SSI) recurrence
periprosthetic joint infection (PJI) recurrence
infection recurrence
irrigation
irrigation solution
povidone-iodine
intra-articular antibiotic infusion
unicompartmental knee arthroplasty
debridement, antibiotics, implant retention (DAIR)

https://doi.org/10.1016/j.arth.2018.09.025
0883-5403/

megaprosthesis
treatment success
surgical factors
surgical timing
treatment failure
surgical outcomes
two-stage exchange arthroplasty
failed debridement, antibiotics, implant retention (DAIR) management
antibiotic treatment
antibiotic therapy
length of antibiotics
antibiotic duration
antibiotic combination
rifampicin
methicillin-resistant *Staphylococcus aureus* (MRSA)
gram-negative acute periprosthetic joint infection (PJI)
fluoroquinolone

Question 1: What are the indications and contraindications of using debridement, antibiotics, and implant retention with exchange of modular components for the management of PJI?

Recommendation:

The most significant advantage in performing debridement, antibiotics, irrigation, and retention (DAIR) of the prosthesis is seen in early postoperative PJI and acute hematogenous PJI, defined as symptoms existing for no longer than 4 weeks, and if the implant is stable. The Kidney, Liver, Index surgery, Cemented prosthesis and C-reactive protein value (KLIC) and CRIME80 scores may aid in risk stratification.

Level of Evidence: Moderate

Delegate Vote: Agree: 80%, Disagree: 18%, Abstain: 2% (Super Majority, Strong Consensus)

Rationale:

Open debridement, antibiotics, irrigation, and retention (DAIR) of the prosthesis is considered a less disruptive intervention that seeks to preserve a functional implant and forego the significant morbidity of implant removal and subsequent surgical procedures. Although DAIR remains a viable and a less morbid alternative to resection arthroplasty, recent studies have demonstrated that an unsuccessful procedure is strongly associated with failure of future two-stage revision [1].

Strictly speaking, there are no absolute contraindications to perform a DAIR procedure, but a DAIR should be discouraged when the chance of failure without removing the implant is very high. Therefore, chronic periprosthetic joint infections (PJIs) should be considered an absolute contraindication to performing a DAIR procedure because a fully developed mature biofilm with the presence of "persister cells" excludes the possibility for cure without removal of the implant [2,3]. Indeed, Barberan et al. demonstrated in 60 elderly patients with a staphylococcal infection that when the duration of symptoms exceeds one month, the failure rate increases exponentially when a conservative treatment is chosen without removal of the implant [4]. Although the efficacy of DAIR in chronic infections has been reported to be around 50% in a recent systematic review with a limited number of 29 patients, the average follow-up duration of these patients was only one year [5]. Extending the duration of antibiotic treatment after debridement does not seem to increase the chance for cure. Byren et al. clearly demonstrated that prolonging antibiotic treatment for more than 6 months simply postpones rather than prevents failure [6]. For this reason, when the intention is to cure the PJI and the patient is medically fit for major surgery, chronic infections should undergo revision surgery with removal of hardware.

Failure rates after DAIR for acute PJI vary widely and range from 20% to 70%, with higher failure seen in acute hematogenous (late acute) PJIs. Contraindications to perform a DAIR procedure in acute PJI are controversial. In general, all acute PJIs are candidates for debridement if the implant is well fixed, but several factors have been associated with an increased chance for failure. These factors include host- and implant-related factors, the severity and extensiveness of the infection, the duration of symptoms, the possibility to exchange the modular components during debridement, and the causative microorganism [1,7–40]. To avoid surgery that has a very high risk of failure, selecting a subset of patients who are more likely to benefit from revision surgery instead of DAIR would be helpful. A preoperative risk score has been developed to predict failure after DAIR for early acute (Kidney, Liver, Index surgery, Cemented prosthesis and C-reactive protein value; Fig. 1A) and acute hematogenous PJIs (CRIME80 score; Fig. 1B) [27,30]. These preoperative scoring systems could be used in clinical practice to select those patients who are most eligible for DAIR.

Question 2: Is debridement, antibiotics, and implant retention (DAIR) an emergency procedure for patients with acute PJI or should patient optimization be implemented before surgery to enhance the success of this procedure?

Recommendation:

Debridement, antibiotics, and implant retention (DAIR) is not an emergency procedure but should be performed on an urgent basis when the patient with acute PJI is medically and surgically optimized.

Level of Evidence: Limited

Delegate Vote: Agree: 97%, Disagree: 3%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

At the present time, debridement, antibiotics, and implant retention (DAIR) is reserved for patients with acute periprosthetic joint infections when no loosening of the implants is identified [41,42]. Success rates vary among different studies from 16% to 82% [1,6,13,16,43]. The large majority of studies regarding DAIR focus on reporting the success rates or evaluating the factors that are correlated with success [6,13,14,16,21,37,42,44–49]. However, none of these studies have focused on the urgency of DAIR as a procedure.

DAIR should be considered an urgent, but not emergent, procedure as the time period from the onset of symptoms until the operation has been reported to be an important factor affecting the success of the procedure [13]. Factors that are known to affect the outcome of DAIR include the type of infecting organism [13,17,18,45,50–52], duration of symptoms before intervention [1,6,13,14,16–18,46,47,50], type and duration of antibiotic therapy [6,21,53], age [46], erythrocyte sedimentation rate values at presentation [16,18.47,52], presence of underlying inflammatory conditions [16,52], exchange of modular components [1,10,50], and the presence of preoperative comorbidities such as anemia [54].

An exact cutoff time beyond which DAIR should not be attempted has not been determined. Nevertheless, the duration of symptoms less than 1 week has been correlated to a higher success rate [1,13,14,16,17,50]. Furthermore, age of implant $\leq$15 days has been identified as a prognostic factor for successful DAIR [33].

There are patient-related factors and medical comorbidities, which, if not controlled, may result in severe complications and failure of the procedure. Comorbidities, such as rheumatoid arthritis, are not possible to adjust before debridement. However, correction of malnutrition, coagulopathy, anemia, hyperglycemia, and diabetes should be pursued. Subjecting a patient to irrigation and debridement without addressing an underlying coagulopathy

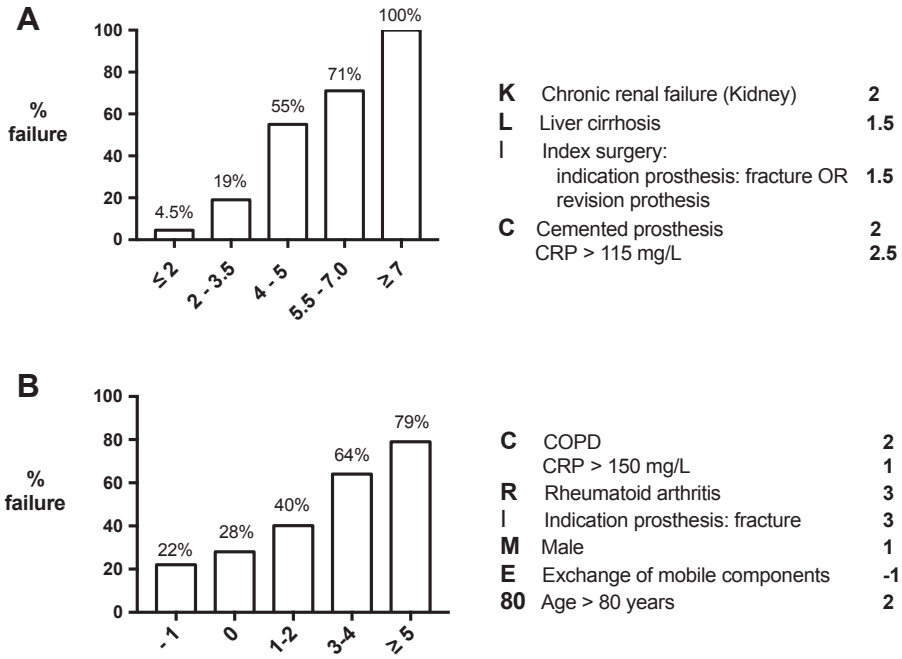

Fig. 1. (A) KLIC preoperative risk score [27,30]. (B) CRIME80 preoperative risk score [27,30]. CRP, C-reactive protein; COPD, chronic obstructive pulmonary disease; KLIC, Kidney, Liver, Index surgery, Cemented prosthesis and C-reactive protein value.

could result in the development of a subsequent hematoma and its adverse effects. Thus, it is critical that conditions such as coagulopathy, nutritional status, uncontrolled hyperglycemia (>200 mg/mL), severe anemia (hemoglobin < 10 mg/dL), and other reversible conditions are addressed before subjecting a patient to DAIR.

In conclusion, we therefore recommend that patients with acute periprosthetic joint infections are evaluated on an urgent basis, and the surgery is performed when patient is optimized from medical and surgical perspectives.

Question 3: Does identification of the pathogen before performing debridement, antibiotics, and implant retention (DAIR) help guide the surgeon's decision-making? If so, should you wait in case of a clinically stable patient until the pathogen has been identified?

Recommendation:

The identification of the responsible microorganism before DAIR is desirable. However, it should not prevent timely surgical intervention if delay in surgery is believed to promote further establishment of biofilm formation and compromise the outcome of surgical intervention.

Level of Evidence: Limited

Delegate Vote: Agree: 94%, Disagree: 4%, Abstain: 2% (Super Majority, Strong Consensus)

Rationale:

In implant-related infections, the need for use of targeted antibiotics with proven action against the infecting pathogen and penetration into the biofilm has been suggested [55]. For instance, experts would likely agree that debridement, antibiotics, and implant retention (DAIR) is appropriate when ciprofloxacin-susceptible *Escherichia coli* is the infecting organism, but they would probably discourage DAIR if the infective organism is a *Candida* spp. Thus, from a general perspective, knowledge of the pathogen before surgical intervention is desired. However, the real debate is whether waiting to determine the infective organism would adversely affect the outcome of DAIR and the timely intervention. The answer to this question requires an understanding of the implications of delaying DAIR and the consequences of performing DAIR without the knowledge of the infecting pathogen.

Regarding the issue of time, Infectious Diseases Societies of America guidelines, in conjunction with other authors, recommend a maximum of 21 days of symptom duration before using DAIR to treat periprosthetic joint infections (PJIs) [41,55]. This time limit, which was not identified in comparative studies, is the same as that used in the pivotal clinical trial by Zimmerli et al on the use of rifampin; none of the patients included in that cohort underwent DAIR beyond 21 days [26]. However, it remains uncertain whether these patients could have benefited from therapy if they had been submitted to DAIR more than 21 days after the beginning of symptoms. To this end, many observational studies have tried to find a precise cutoff of symptom duration, but heterogeneous populations with poorly reproduced results have emerged. Brand et al observed that as little as a two-day delay in performing DAIR would significantly increase the odds of failure in a cohort of patients with staphylococcal PJI mainly managed with β-lactams [56]. Other studies have also observed a poor outcome among patients with longer duration of symptoms without identifying a reliable time limit [4,10,11,17,57–61].

Inability to establish an optimal time threshold for DAIR may be mainly due to two causes. First, a short interval of time for performing DAIR may be a surrogate marker of severity of illness because patients with sepsis or bacteremia are usually operated sooner than more stable cases. Ill patients have a higher likelihood of failure [10,25], causing a short duration of symptoms to be paradoxically associated with a worse prognosis. Second, the duration of symptoms may be difficult to establish, especially in postsurgical cases where the postoperative inflammatory signs and pain may overlap the symptoms of infection. In these postsurgical cases, the prosthesis age before DAIR (i.e., the time from prosthesis placement to debridement) may be a more reliable variable. Yet, there is controversy on the definition of an early postsurgical infection that could be managed by DAIR. Although Infectious Diseases Societies of America guidelines do not recommend DAIR

for patients with PJI that started more than one month from the index arthroplasty [41], other important studies and the First International Consensus extend this period to three months [55,62]. Two large studies including staphylococcal and streptococcal PJI managed with DAIR found no differences in recurrent infection with a prosthesis age of less than one month versus those that were one to three months old [10,11].

Overall, it seems reasonable to assume that the sooner the DAIR is performed, the better the outcome will be, but there is insufficient evidence to recommend a specific time limit of symptoms duration beyond which DAIR should be discouraged.

Bearing these considerations in mind, the question falls back onto the influence of the type of infecting microorganism(s) and its antibiotic susceptibility profile on prognosis. Apart from particular and rare situations such as the fungal infection previously mentioned or other multidrug-resistant bacteria, there is limited consensus on the impact of organism type on the outcomes of DAIR. Wide ranges of clinical success rates have been reported for common pathogens when managed by DAIR: (1) 13% to 90% for *Staphylococcus aureus*, [4,6,25,28,56,63] (2) 27% to 94% for gram-negative bacilli [25,59,63], and (3) 40% to 94% for Streptococci [64–69]. The largest observational studies performed to date set these cure rates in 55% for *S. aureus* [10], 58% for streptococci [11], 51% for enterococci [70], and 68% for gram-negative bacilli (with significant differences between fluoroquinolone-susceptible and fluoroquinolone-resistant strains: 79% vs 40%, respectively) [12].

Whether a 50% risk of failure should discourage the use of DAIR is a matter of controversy. In old patients, Fisman et al. suggested an annual relapse rate of ≈30% after DAIR to be cost-effective when compared with a 2-step exchange procedure [71]. The potential advantages of a successful DAIR (one surgery, bone-stock preservation, less economic costs) [72] should be balanced with the consequences of failure. In this regard, conflicting results have been reported on the consequences of a failed DAIR. Sherrel et al observed a higher likelihood of relapse among patients undergoing a two-stage revision after a nonsuccessful DAIR than that among patients submitted to an elective two-stage exchange procedure [73]. However, these results have been contested by two other observational studies [74,75]. Furthermore, functional outcome has been reported to be identical in patients undergoing two-stage revision after failed DAIR compared with patients undergoing direct two-stage exchange [74].

In summation, the type of infecting pathogen can be valuable information in the treatment algorithm for patients and surgeons considering DAIR. However, a prompt surgery is also of utmost importance. Therefore, the efforts to identify the causative pathogen for PJI should not cause undue delay in timely surgical intervention. Often, the pathogens of concern are virulent in nature and usually identified soon after culture samples are processed and cultured.

Question 4: Does exchange of all modular components during debridement and implant retention (DAIR) reduce the rate of SSI/PJI recurrence?

Recommendation:

Yes. Exchange of all the modular components during debridement and implant retention (DAIR) reduces the risk of PJI recurrence.

Level of Evidence: Moderate

Delegate Vote: Agree: 94%, Disagree: 4%, Abstain: 2% (Super Majority, Strong Consensus)

Rationale:

Prosthetic joint infections in the early stage are commonly treated with debridement, antibiotics, and implant retention (DAIR). If successful, the outcomes of periprosthetic joint infections (PJIs) treated by DAIR show functional outcomes and patient-reported outcomes equivalent to those of primary total joint replacements [7]. During this procedure, the removal of modular components allows for better visualization of the knee, especially in the posterior aspect, thereby facilitating proper debridement and potential bioburden/biofilm elimination. However, it is difficult to judge the necessity of exchanging the modular components during DAIR surgery because of the lack of conclusive evidence.

Our literature review identified several studies that support the exchange of modular components to reduce the rate of PJI recurrence [1,7,9–11,76,77]. Among these, six are retrospective and one is a meta-analysis [1] involving 39 retrospective case-control and cohort studies. Notably, all the studies included in this meta-analysis were also retrospective, making its strength of evidence inherently limited. Furthermore, the success rates after modular exchange during DAIR show a wide range of variation from 18% to 83% among different cohorts in various studies. Such wide variations in the impact of modular component exchange suggest that the outcome of DAIR may be associated with multiple factors such as patient selection, thoroughness of debridement, type and virulence of the microorganisms, choice and duration of antibiotic regimen, and the definition of treatment failure rather than the exchange of modular components itself. However, a recent systematic review [1] of DAIR performed for total hip arthroplasty showed that the mean proportion of success rate in studies in which modular components were exchanged was significantly higher (73.9%) than that for studies in which no components were exchanged (60.7%). A multicenter review article [10] of 349 patients with *Staphylococcus aureus* PJI of both hip and knee replacements reported that modular exchange reduced the risk of failure by 33%. In addition, PJI review articles [50,78] and Choi et al [9] study suggest that in total knee arthroplasty, not exchanging the polyethylene was an independent predictor of failure of DAIR (100% failure versus 59% success with modular exchange). Moreover, a recent case-controlled study [76] has shown a ten-year implant survival rate of 86% with modular component exchange in DAIR (as compared to 68% without modular exchange) along with a fourfold increase in eradication rate. In contrast, there are several other studies which suggest that modular component exchange is not related to higher success rate of DAIR [14,27,42,50,78–80].

Owing to the lack of conclusive evidence in the form of well-designed prospective randomized trials and standardized protocols, only a moderate strength of recommendation is provided for exchanging the modular components during DAIR to reduce the PJI recurrence rate.

Question 5: What is the minimum necessary volume of irrigation solution to use in debridement, antibiotics, and implant retention treatment of acute PJI?

Recommendation:

We recommend that 6-9 L of irrigation solution, including saline or antiseptic solution such as sterile dilute povidone-iodine, is used during debridement, antibiotics, and implant retention (DAIR) treatment of acute periprosthetic joint infection (PJI).

Level of Evidence: Consensus

Delegate Vote: Agree: 90%, Disagree: 7%, Abstain: 3% (Super Majority, Strong Consensus)

Rationale:

To date, there are no reported clinical studies relating to the optimal volume of irrigation required during debridement, antibiotics, and implant retention (DAIR) treatment of periprosthetic joint infection (PJI). However, variable outcomes have been reported with different institutions using individual protocols for volumes of irrigation.

Few studies provide limited secondary data with regard to the ideal volume of irrigation to be used during total joint arthroplasty in general and treatment of an infected joint in particular. In one such study, the authors were able to determine that four liters of

sterile saline pulse lavage was sufficient to remove bone and polymethyl methacrylate debris exceeding 1 μm in size from the joint during TJA. The authors extrapolated from their results that bacteria might effectively be removed with the same amount of irrigation given the similarity in size to the particulates assessed [81]. This model did not consider the effect of the developing bacterial biofilm on infected arthroplasty implants. DAIR has traditionally been thought to reduce the bacterial load and be effective in the acute period given that bacteria theoretically had not yet formed a glycocalyx biofilm. In another study, the authors used an *in vitro* model to determine the efficacy of biofilm removal from arthroplasty implants using a high-pressure pulsatile lavage. Three liters of normal saline was used over an area measuring 1 cm^2 recreating a prosthesis covered in *Staphylococcus aureus* biofilm. The authors concluded that pulse lavage is not able to sufficiently debride preexisting biofilm. The volume of irrigation solution required was not investigated as a primary end point, and the authors caution against extrapolating the results to clinical scenarios as their *in vitro* model potentially overestimated the amount of biofilm debrided by three liters of sterile saline pulse lavage [82]. More important than the volume of irrigation, researchers have found that the presence of staphylococcal infection, elevated American Society of Anesthesiologists score, or purulence were more likely to determine failure.

A comprehensive systematic review of the literature relating to open DAIR treatment of acute postoperative and hematogenous periprosthetic hip and/or knee joint infections, with or without modular component exchange, was performed. Databases searched included PubMed, EMBASE, Cochrane Review, and Google Scholar. Initial query generated 664 articles. Review articles and book chapters were excluded, whereas all references from such sources were screened for inclusion (spanning from 1990-2017). We included all level I-IV studies that specified a certain volume of irrigation used per procedure and recorded the type of solution(s) used, mode of lavage administration, use of additive(s), and number of irrigation and debridements performed. We included cases whereby some of the modular components may have been exchanged, but we excluded those with dedicated planned staged exchanges. A total of 14 studies met the aforementioned criteria (Table 1) [14,20,45,78,83–92].

Typically, around 6 to 9 L of solution was used during a single DAIR treatment, with twelve of the fourteen studies using up to 9 L or more of irrigation solution. The evidence base for the specific irrigation volume is poorly defined within all studies, and recommendations for specific volumes in both primary and review articles reference consensus data obtained from previously published guidelines or individual protocols [93–98]. Therefore, this systematic review represents the body of evidence of actual irrigation volumes reportedly used in the literature.

No studies currently exist directly linking the necessary volume of irrigation to use in debridement, antibiotics, and implant retention in acute PJI. Based on several retrospective studies, we extrapolate that the use of 6-9 L of irrigation solution may be required when treating acute PJI. Prospective studies evaluating the volume of irrigation used as a study end point are required to better elucidate the optimal volume of irrigation in DAIR treatment of PJI.

Question 6: Is there a role for direct intraarticular antibiotic infusion after irrigation and debridement for PJI?

Recommendation:

The concept of achieving a minimum biofilm eradication concentration (MBEC) of antibiotics at the site of the infection is compelling. Despite the presence of retrospective studies reporting favorable outcome and because of heterogeneity in terms of adjunctive antibiotics, absence of a control group, and small cohort size, the routine administration of intraarticular antibiotics in treatment of PJI is not justified. Prospective, randomized controlled trials are needed to support the routine use of intraarticular antibiotics as a stand-alone or adjunct treatment of PJI.

Level of Evidence: Consensus

Delegate Vote: Agree: 92%, Disagree: 6%, Abstain: 2% (Super Majority, Strong Consensus)

Rationale:

Current published evidence for intraarticular antibiotic infusion after irrigation and debridement for prosthetic joint infection (PJI) is limited to small case series and retrospective cohort studies. The authors of all studies aimed to achieve higher concentrations of antibiotics at the site of the infection than is possible with systemic therapy. PJI is associated with the presence of biofilms, and sessile bacteria that are encapsulated within a biofilm matrix are more difficult to eradicate than planktonic bacteria [99–105]. Biofilm is the single most important factor causing resistance of bacteria to antibiotics in the treatment of PJI. Although a modest antibiotic concentration can prevent biofilm formation, eliminating established biofilm is a different matter. Bacteria protected by biofilm require concentrations that are orders of magnitude greater than the minimal inhibitory concentration for the planktonic forms of the same bacterium to eliminate resistant organisms that are protected by the glycocalyx.

A systematic review of the literature revealed that biofilm-encapsulated bacteria require minimum biofilm eradication concentrations (MBECs) of antibiotics that are several orders of magnitude (100-1000+) above the minimum inhibitory concentrations sufficient to eradicate planktonic bacteria (Table 2). Currently, MBECs

Table 1
DAIR Studies.

Reference (Author and year)	Study Design	n (Acute PJIs) Irrigation Solution	Additives	Volume per Procedure (L)	Modular Revision Infections Controlled
Mont et al (1997)	Prospective	24 NS	None	10 yes	83%
Azzam et al (2010)	Retrospective	104 NS	Antibiotics	9 some	44%
Estes et at (2010)	Retrospective	20 Castile soap solution	None	6 to 9 yes	90%
Koyonos et al (2011)	Retrospective	102 NS	Antibiotics	9 no	35%
Royo et al (2013)	Retrospective	34 NS	Betadine/peroxide	9 some	74%
Kim et al (2014)	Retrospective	20 NS	Betadine	6 to 9 yes	100%
Moojen et al (2014)	Retrospective	68 NS	None	3 to 6 yes	21%
Koh et al (2015)	Retrospective	52 NS	None	9 some	71%
Sousa et al (2016)	Prospective	23 NS	Chlorhexidine	7 yes	85%
Tornero et al (2016)	Retrospective	143 sterile water	None	6 to 9 no	88%
Bryan et al (2017)	Retrospective	90 NS	None	6 to 9 some	87%
Di Benedetto et al (2017)	Retrospective	20 NS	Betadine	6 to 9 yes	80%
Duque et at (2017)	Retrospective	67 NS	Betadine/Dakin's/Bacitracin	12 yes	69%
Narayanan et al (2017)	Retrospective	55 N/A	None	9 yes	60%

DAIR, debridement, antibiotics, and implant retention; NS, normal saline; N/A, not available; PJI, periprosthetic joint infection.

Table 2
Therapeutic Range, Toxicity, Minimum Biofilm Eradication Concentration (MBEC), and Minimum Inhibitory Concentration (MIC) of Antibiotics Used to Treat Biofilm-Encapsulated Bacteria.

			Staphylococcus aureus		*MRSA*		*Pseudomonas aeruginosa*		*S. epidermidis*		*Escherichia coli*	
Antibiotic	Therapeutic Range	Toxic Plasma Concentration	MIC	MBEC	MIC	MBEC	MIC	MBEC	MIC	MBEC	MIC	MBEC
Azithromycin	0.04-1	-			512	5120		2560				
Ceftazidime	<150	-					1-4	2560-5120				
Ciprofloxacin	2.5-4	11.5			0.06 to >32	256-1280	0.25-2	80-1280				
Clindamycin	<0.5	-			0.015 to 0.06	64 to >1024						
Colistin	1-4	-										
Daptomycin	6-10	-	0.25	600	0.125	1014						
Doxycycline	<10	30			0.064-0.125	64 to 128						
Erythromycin	0.5-6	12-15	1	6400	0.12 to >256	64 to >1024		2560				
Gentamicin	5-10	12	1	6400	0.06-64	1 to >256		512 × MIC				
Linezolid	0.5-4	-	1	6400	1-2	4 to >1024						
Piperacillin	5-20	-					4-128	>5120				
Rifampicin	0.1-10	204	0.16	40								
Tobramycin	5-10	12-15	1	160-4000	1	≥8000	0.2-16	250-2560	32	≥8000	2	62.5-125
Vancomycin	<5-10	30	2	2000-8000	0.25-2	2000-8000			2	1000-8000		

MRSA, methicillin-resistant *Staphylococcus aureus*.

at the site of the joint infection are not achievable with traditional intravenous (IV) antibiotic therapy without systemic toxicity (Table 2). Intravenous antibiotics generally do not achieve these levels of concentration in synovial fluid but instead achieve levels around two to three times the minimum inhibitory concentrations.

Even though extensive work has been carried out to develop adjuvant agents such as antibacterial peptides and chelating agents to reduce the resistance of biofilm bacteria to antibiotics, the only clinically viable method available now is to apply antibiotics directly to the affected joint where the implant resides to achieve concentrations high enough to approach MBEC. The use of antibiotic impregnated polymethylmethacrylate spacers is the most common method used to deliver antibiotics directly into the joint as part of treatment of PJI. Although intraarticular concentration of antibiotics is significantly higher when antibiotic-loaded spacers are used, the level is still an order of magnitude (perhaps thousands of times) lower than what is needed to eradicate the biofilm. Local delivery of antibiotics with antibiotic-laden bone cement does not apply a consistent dose for enough time, with most the elution occurring in the first 48-72 hours and by day 5, the concentrations are often subtherapeutic [106]. Time is an important factor in the management of biofilm, and exposure to high concentrations for long periods enhances the ability to achieve MBEC.

Direct antibiotic infusion through an infusion pump can achieve extremely high local levels of antibiotics for a prolonged period. In addition, when the antibiotic is delivered through an external portal, it can be discontinued if toxicity or sensitivity occurs. Perry et al were the first to describe intraarticular instillation of antibiotics in 1992 [107]. They used an implantable pump with a catheter from the wound surface to deliver 200-350 mg of amikacin in a 50 mg/mL dilution for 8-15 weeks to 72 patients with acute infections. Of these patients, 49 underwent debridement and retained their prostheses, and 23 had their prostheses removed after the initial debridement. They only reported in detail on a subset of twelve patients (10 knees and 2 hips, median age of 59 years) with no prior history of infection, with a 37-month follow-up. Local levels of antibiotics were assessed by assaying wound drainage or synovial fluid and ranged from 150 μg/mL to 1688 μg/mL. Serum levels were 10 μg/mL, except for one patient whose serum concentration rose to 13 μg/mL. Two patients developed recurrent infection, one with the same organism *Staphylococcus aureus*, and the other patient was infected with *Staphylococcus epidermis*, after originally infected with *S. aureus*. In the series of 49 patients who retained their prostheses, 38 patients were infection free; however, follow-up times ranged from 1-58 months.

Fukagawa et al reported on their experience with 15 patients (16 knees) treated for PJI with stable prostheses [108]. A causative microorganism was identified in 8 patients. Patients were treated with open synovectomy, debridement, and exchange of polyethylene insert, and they retained their implant; in five patients with tumor megaprostheses, the anchors were retained. A Hickman catheter was inserted percutaneously, and organism-specific antibiotics (if an organism was cultured) were infused into the joint space twice per day until clinical signs of infection resolved and white blood cell count, C-reactive protein, and erythrocyte sedimentation rate normalized, at which point the catheters were pulled. The mean infusion duration was 20.8 ± 11.7 days. Intraarticular antibiotics used were amikacin (400 mg/d), gentamicin (80 mg/d), and arbekacin (200 mg/d). No serum antibiotic levels were reported. All patients also received IV or oral antibiotic therapy for 1-3 months. All patients were considered infection free and clinically healed during the first follow-up period of 46.7 months (+25.7 months). However, four of the five knees treated with tumor megaprostheses developed recurrent infection after a mean of 28.3 months (+26.1 months). These patients were treated with intraarticular antibiotics again for 13-22 days, and the infection was clear at last the follow-up visit. No local toxicity or infection at the catheter site was reported.

Table 3
Summary of Infected UKA Cases in the Literature.

Author/Year	N (Infected UKA Cases)	Failed DAIR	Treatment	Failures	Follow-up
Labruyere, 2015 [114]	9	5	1-stage conversion to TKA (9)	0	Median 60 mo
Bohm, 2000 [117]	2 (0.7% infection rate)	?	1-stage (1); 2-stage (1)	1 (AKA)	Mean 4 y
Saragaglia, 2013 [118]	8 (2% of failed UKAs)	?	?	?	?
Kim, 2016 [116]	5 (0.3% infection rate)	?	2-stage (5)	?	?

UKA, unicompartmental knee arthroplasty; DAIR, debridement, antibiotics, and implant retention; TKA, total knee arthroplasty.

Tsumura et al [109] reported on the treatment of early knee PJI in ten patients with continuous, concentrated, antibiotic irrigation for 7-29 days. Antibiotics were administered through a Salem double lumen catheter after debridement with implant retention. Eight of the ten patients were infection free and able to retain the original prostheses. The two failures were the only patients with methicillin-resistant *S. aureus*. Antibiotics administered were clindamycin, amikacin, cefotiam, imipenem, arbekacin, piperacillin, cefazolin, ampicillin, and vancomycin. No serum or synovial antibiotic levels were reported.

In two recent publications, Whiteside et al reported on a retrospective cohort of 18 total knee arthroplasty patients with recurrent knee PJIs treated with single-stage (10 patients) or two-stage revision arthroplasty (eight patients), including three patients who required limb lengthening and soft tissue expansion [110,111]. Intraarticular antibiotic infusion using a Hickman catheter was performed as an adjunct to meticulous debridement. The authors administered 100 mg of vancomycin or 20 mg of gentamycin in 3 mL of saline into the joint space and increased the dosage to 500 mg of vancomycin or 80 mg of gentamycin in 8 mL of saline, every 12 or 24 hours as tolerated, once the wound was stable and dry. Patients were also treated postoperatively with 1 g of IV vancomycin and 80 mg of IV gentamicin for 48 hours. The intraarticular antibiotics were continued for 6 weeks, with intraarticular vancomycin levels ranging from 10,233 to 20,167 mg/L. Mean serum vancomycin peak and trough levels were 4.1 ± 1.2 μg/mL and 3.3± μg/mL, respectively. Three patients had to have a reduction in the antibiotic dose due to excessive rise in the level of antibiotics. The follow-up ranged from 2.3 to 12 years, with a mean of 6.1 years. One patient had a recurrent, postoperative infection at 13 months. No other patients had clinical or serological signs of infection, and no patient was placed on chronic suppressive antibiotics. Similarly, Roy et al compared synovial concentrations of antibiotics with IV vs intraarticular administration in a subset of patients in the Whiteside study cohort and found an average, peak intraarticular vancomycin concentration of 9242 ± 7608 mg/L after intraarticular antibiotic infusion compared with an average intraarticular concentration of 6.8 μg/mL after IV administration [112]. These data suggest with reasonable certainty that direct intraarticular infusion of antibiotics offers a significant benefit in treating resistant organisms but certainly does not rise to the same level of evidence as would a randomized controlled trial performed at the same center.

Revision after reinfected two-stage revision total joint arthroplasty is an especially challenging clinical problem and is even more difficult when multiple failures have occurred. The complication rate of using antibiotic spacers is substantial including dislocation, fracture, and migration of the spacer with bone loss that must be considered when contemplating a second two-stage exchange procedure. A revision with intraarticular antibiotic infusion may play a role in this scenario to reduce morbidity. Antony et al described intraarticular antibiotic infusion as an adjunct to single-stage revision for previously failed single- or two-stage revision for knee, hip, or shoulder PJI in 57 patients with a mean age of 65 years [113]. Hickman catheters were used for intraarticular infusion of organism-specific antibiotics for approximately 4-6 weeks, once or twice per day without concomitant systemic antibiotics. The intraarticular antibiotic dose administered was determined to be 50% of the serum dose given in the enclosed space. Infection eradication was defined as negative culture and normal erythrocyte sedimentation rate and C-reactive protein level, and 89.5% of patients were successfully treated at 11 months of follow-up. Synovial levels of antibiotics were not measured.

Question 7: Can debridement, antibiotics, and implant retention (DAIR) be used in patients with an acute or chronic infection of a unicompartmental knee arthroplasty (UKA)?

Recommendation:

In the event of an acute infection after UKA, early irrigation and debridement followed by antibiotic administration with implant retention can be considered. However, if initial treatment effort results in failure or chronic infection is present, the implanted prosthesis should be removed and a one-stage or two-stage conversion to total knee arthroplasty (TKA) should be performed in combination with antibiotic therapy.

Level of Evidence: Limited

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

Rationale:

The main reasons for revision of unicompartmental knee arthroplasty (UKA) are loosening, progression of osteoarthritis to another compartment, and infection [114]. The incidence of infection after UKA at 0.2% to 1% is lower than that reported after total knee arthroplasty (TKA) [114,115]. A distinctive feature of UKA infection is that both the prostheses and the native cartilage are involved [114]. This is in part attributed to the use of minimally invasive exposures, with less damage to the adjacent soft tissue and sparing of bone and ligamentous structures [116].

In the event of immediate or acute infection after UKA, early irrigation and debridement followed by antibiotic administration can be a proper treatment solution. However, if the initial treatment effort ends up in failure or chronic infection is present, the implanted prosthesis should be removed and a one-stage or two-stage revision surgery should be carried out [116]. Labruyere et al reported on failures for 9 infected UKA cases managed with one-stage irrigation, debridement, and conversion to TKA in combination with 3 months of antibiotic therapy [114]. Of note, 5 of these cases first failed debridement, antibiotics, and implant retention (DAIR). Kim et al reported management of 5 infected UKA cases with two-stage conversion to TKA [116]. Bohm et al reported two infected UKAs, one of which was managed with one-stage conversion successfully, and the other was treated with two-stage conversion, ultimately resulting in above the knee amputation [117].

In the setting of UKA, recommendations are weak as only 5 published papers examine the results of failed UKA, including infection, and the rate of infection is very low (Table 3). Two of the infected UKA cases in one study [114] had been posttraumatic infections before implantation of the UKA and thus represent more complex scenarios potentially predisposing to treatment failure. There is no literature directly evaluating the role of DAIR in the setting of UKA. However, subsequent failure due to progression of osteoarthritis occurred in two cases (survival 49%) at an average of 3 years. Therefore, it may be advisable to proceed with one-stage or two-stage conversion to TKA at the time of infection in the setting of UKA to minimize the need for additional revision procedures in the future and prevent associated morbidity.

In general, the surgeon should assess prior UKA function, component position and fixation, and condition of alternate knee compartments to determine whether retention of implants with DAIR is an appropriate initial treatment in the setting of infection.

Question 8: Can debridement, antibiotics, and implant retention (DAIR) be used in the treatment of acute PJI with a megaprosthesis?

Recommendation:

Debridement, antibiotics, and implant retention (DAIR) is a viable treatment option in acute PJI of a megaprosthesis. The effectiveness of DAIR is still unclear due to lack of comparative data among the treatment options and limited evidence to suggest superiority of any one treatment. The treatment decision must be made on a case-by-case basis and account for underlying medical conditions, infection history, organism

characteristics, and surgical history. DAIR is most appropriate for acute PJI without complicating factors, such as extensive and pervasive infection by a high-virulence or high-resistance organism.

Level of Evidence: Limited

Delegate Vote: Agree: 96%, Disagree: 1%, Abstain: 3% (Unanimous, Strongest Consensus)

Rationale:

Acute periprosthetic joint infection (PJI) of megaprostheses is a terrible complication and a difficult situation for treatment [119]. Infection rates in patients with megaprostheses have been reported to range from 3% to greater than 30% [119–121]. In principle, the treatment of acute PJI with a megaprosthesis is similar to treatment of other acute PJIs, except there is significantly more potential space and a greater soft tissue infectious burden requiring more extensive exposure and debridement [122,123]. The surgical options include debridement, antibiotics, and implant retention (DAIR) [12,78,124]; one-stage revision surgery [122]; two-stage revision with an interval cement spacer [76,125,126]; arthrodesis, and amputation [123,124]. Unfortunately, there are limited data on the outcome of these different procedures [119,125]. The lack of comparative data is due to the limited indications for a megaprosthesis as well as the clinical heterogeneity of the affected patients [123]. In addition, treatment details vary greatly, particularly for DAIR. Specific information on the debridement, the type of irrigation solutions, modular component exchange, and local and systemic antibiotic use and duration is generally lacking.

Two-stage revision remains the preferred method for treatment of PJI [124–126]. However, two-stage revision significantly increases surgical and perioperative risks and includes a substantial period of reduced mobility between stages, which has heightened the interest in alternative surgical options such as DAIR. DAIR is an attractive option as it may prevent the unnecessary removal of implants, which could result in further bone loss and fracture [16,76,78]. DAIR is also the simpler and less costly procedure with a demonstrated shorter length of hospital stay [127]. The overall goal of attempting DAIR should be to select the cohort of patients in whom successful treatment is most likely.

Sujith et al summarized the absolute and relative contraindication for DAIR [127]. The absolute contraindications are loose prosthesis, poor soft tissue coverage, and compromised bone cement mantle. The relative contraindications are the presence of sinus tracts, *Staphylococcus aureus* (methicillin-resistant *S. aureus* and methicillin-susceptible *S. aureus*) infection, previously revised joints, immunosuppression, rheumatoid arthritis, polymicrobial involvement, bacteremia, C-reactive protein > 100 mg/L, erythrocyte sedimentation rate > 60 mm/h, two or more previous debridements, and >3 weeks of symptoms.

The decision to perform DAIR can also be based on the classification of the infection. According to Pilge et al, if intraoperative cultures are positive without other signs of infection (Tsukayama Type I), implant retention is attempted, and prolonged systemic antibiotic treatment is recommended. Implant retention should also be attempted with stable arthroplasties in type II or III infections (early postoperative infection or acute hematogenous infection). If there are radiological signs of implant loosening, a one- or two-stage revision must be performed [56,128].

During DAIR, thorough debridement is necessary to improve outcome. All infected and nonviable tissue around a well-fixed prosthesis must be removed. Retained components are irrigated and scrubbed in an effort to remove biofilm [76,127]. Various antibiotic solutions can be used intraoperatively, including dilute betadine and Dakin's solution. Culture-driven systemic antibiotics are also important for successful treatment, and cotreatment with rifampin should be used in staphylococcal PJIs [78]. Prolonged or chronic antibiotic suppression may also be necessary. The use of local antibiotics in addition to the administration of systemic antibiotic agents is an area of consideration. Modular components and the exposed metal of megaprostheses can be covered with antibiotic-eluting cement, though there is no clinical evidence comparing the efficacy of such methods vs more simple modular exchange.

The most important factors contributing to treatment failure are longer duration of symptoms, a longer time after initial arthroplasty, the need for multiple debridements, the retention of exchangeable components, and PJI caused by methicillin-resistant *S. aureus* [16,76,78]. One- or two-stage revision should be performed if DAIR fails [76,127].

In general, DAIR is a treatment option for acute PJI with a megaprosthesis with varying levels of success in selected and noncomplicated patients. The heterogeneity inherent in these cases makes comparisons difficult, and there is always some degree of individualization in the choice of treatment.

Question 9: What are the factors associated with the successful treatment of acute PJI using debridement, antibiotics, and implant retention?

Recommendation:

The following factors have been shown to be associated with treatment success in acute PJIs treated with DAIR:

Exchanging the modular components during debridement.

Performing a debridement within at least 7 days, but preferably as soon as possible, after the onset of symptoms.

Adding rifampin to the antibiotic regimen, particularly when combined with a fluoroquinolone, in cases of susceptible Staphylococci.

Treatment with fluoroquinolones in cases of susceptible gram-negative bacilli.

The following factors have been shown to be associated with treatment failure in acute PJIs treated with DAIR:

Host-related factors: rheumatoid arthritis, old age, male sex, chronic renal failure, liver cirrhosis, and chronic obstructive pulmonary disease.

Prosthesis indication: fracture as indication for the prosthesis, cemented prostheses, and revised prostheses.

Clinical presentation representing the severity of the infection: a high C-reactive protein, a high bacterial inoculum, and the presence of bacteremia.

Causative microorganisms: *Staphylococcus aureus* and Enterococcoci.

Level of Evidence: Moderate

Delegate Vote: Agree: 92%, Disagree: 5%, Abstain: 3% (Super Majority, Strong Consensus)

Rationale:

The success of debridement, antibiotics, and implant retention (DAIR) depends on multiple host- and implant-related factors, clinical presentation, intraoperative variables, causative microorganism(s), and their antibiotic sensitivities and the antibiotic regimen (Table 4). It is of note that the described factors related to treatment outcome in some studies are not always confirmed by others. Most factors associated with success of DAIR are demonstrated in retrospective studies, entailing a high risk of selection bias, especially for those factors involving certain treatment strategies. Therefore, prospective validation is critical for most of the described variables, and differences between cohorts should be taken into consideration in interpreting risk factors. In addition, the success of DAIR depends on the definition of treatment failure and the total duration of follow-up, which also differed among the selected studies.

Factors that are consistently shown in the literature to increase the chance of treatment success are as follows:

Table 4
Literature Review of Factors Associated With Successful Treatment of Acute PJI Using Debridement, Antibiotics, and Implant Retention.

Author, Year	N	PJI	Variables	Failure Rate	Univariate (OR or HR)[g]	Multivariate (OR or (a)HR)[g]
Tsang, 2017 [1], meta-analysis	1296	Early and late	Symptoms ≤7 d vs >7 d	28% vs 48%, $P = .0001$;	-	-
			Exchange of modular components (yes vs no)	26% vs 39%, $P = .0001$		
Grammatopoulos, 2017 [7]	82	Early and late	Symptoms ≤7 d vs >7 d	9% vs 25%, $P = .05$	-	-
			Interval since arthroplasty ≤6 wk vs >6 wk	7.5% vs 27.5%, $P = .01$ 6.6% vs 24.4%, $P = .02$		
			Exchange of modular components (yes vs no)			
Zhang, 2017 [8]	34	Early and late	Exchange of modular components (yes vs no)	39% vs 100%, $P = .008$	-	-
Choi, 2011 [9]	32	Early and late	Exchange of modular components (yes vs no)	47% vs 100%, $P = .001$	-	-
Lora-Tamayo, 2013 [10]	345	Early and late	Immunosuppression (yes vs no)	71% vs 43%, $P = .006$	2.31	2.23
			Bacteremia (yes vs no)	65% vs 41%, $P = .001$	2.29	1.81
			Polymicrobial (yes vs no)	59% vs 41%, $P = .005$	1.76	1.77
			CRP	NP, $P = .001$	1.29	1.22
			Exchange of modular components (yes vs no)	41% vs 56%, $P = .004$ 71% vs 41%, $P = .003$	0.56 1.98	0.65 1.63
			Need of ≥2 debridements (yes vs no)	NP, $P = .008$	0.50	0.42
			Levofloxacin + rifampin[b] Vancomycin + rifampin[c]	NP, $P = .02$	0.34	0.29
Lora-Tamayo, 2017 [11]	462	Early and late	Chronic renal failure (yes vs no)[h]	54.5% vs 40.8%, $P = .05$	1.58	-
			Rheumatoid arthritis (yes vs no)[h]	64.9% vs 40.0%, $P < .01$	2.23	2.36
			Immunesuppression (yes vs no)[h]	60.4% vs 39.9%, $P < .01$	1.86	-
			Revision (yes vs no)[h]	53.6% vs 38.3%, $P < .01$	1.60	1.37
			Late postsurgical infection (yes vs no)[h]	62.9% vs 38.2%, $P < .01$	1.41	2.20
			Bacteremia (yes vs no)[h]	47.7% vs 37.9%, $P = .02$	1.44	1.69
			Exchange of modular components (yes vs no)[h]	33.0% vs 51.6%, $P < .01$	0.59	0.60
Wouthuyzen-Bakker, 2018 (*Pending publication)	340	Late	Gender, male vs female	49.1% vs 40.6%, $P = .11$		2.02
			Age, > 80 y vs ≤ 80 y old	54.8% vs 42.3%, $P = .06$		2.60
			COPD (yes vs no)	55.9% vs 43.8%, $P = .18$		2.90
			Active malignancy (yes vs no)	51.7% vs 44.4%, $P = .04$		-
			RA (yes vs no)	74.1% vs 42.5%, $P = .001$		5.13
			Immunosuppression (yes vs no)	61.5% vs 42.9%, $P = .03$		-
			Fracture (yes vs no)	70.6% vs 41.9%, $P = .02$		5.39
			Revision (yes vs no)	54.2% vs 41.7%, $P = .04$		-
			CRP, >150 vs ≤150 mg/L	47.9% vs 41.7%, $P = .06$		2.00
			Bacteremia (yes vs no)	56% vs 39.8%, $P = .005$		-
			Staphylococcus aureus (yes vs no)	53.9% vs 38.7%, $P = .005$		3.52
			Exchange of modular components (yes vs no)	36.4% vs 52.4%, $P = .004$		0.35
Urish, 2017 [13]	206	Early and late	Symptoms ≤7 d vs >7 d	NP, $P = .004$	1.77	1.68
			S. aureus vs other	NP, $P = .04$	0.63	0.59
Koh, 2015 [14]	52	Early and late	Early vs late PJI	18.7% vs 47.3%, $P = .04$	-	-
Triantafyllopoulos, 2015 [130]	78	NP	Thyroid disease	68.7%, $P = .03$	-	-
			Duration of symptoms	$P = .0001$		
			MR-staphylococci	57%, $P = .004$		
Kuiper, 2013 [16]	91	Early and late	RA (yes vs no)	70% vs 30%, $P = .03$	-	1.2-84[a]
			Symptoms ≤7 d vs >7 d	26.6% vs 48.4%, $P = .02$		1-18[a]
			Early vs late PJI	31% vs 71.4%, $P = .04$		1.1-366[a]
			ESR > 60 mm/h	NP, $P = .001$		2.2-98[a]
			CNS vs others	69% vs 28%, $P = .009$		1.8-309[a]
Marculescu, 2006 [17]	99	Early and late	Sinus tract	61%, $P = .002$	2.85	2.84
			Symptoms > 8 d	51%, $P = .04$	1.79	1.77
Buller, 2012 [18]	309	Early and late	Symptoms <21 d vs ≥21 d	NP, $P = .001$	-	-
			ESR	$P = .02$		
			Previous infection in the same joint (yes vs no)	55% vs 44%, $P = .009$ 65% vs 44%, $P = .005$		
			Resistant GP vs others			
Hsieh, 2009 [19]	154	Early and late	GN vs GP	73% vs 53%, $P = .002$	-	-
Tornero, 2016 [27]	143	Early	Suboptimal vs optimal (rifampin for GP and FQ for GN) antibiotic treatment	31% vs 8%, $P = .004$	-	4.92
Puhto, 2015 [21]	113	Early and late	Early vs late PJI	30.8% vs 54.3%, $P = .002$	-	-
			Leukocytes >10 × 10^9/L vs ≤10 × 10^9/L	50% vs 24.6%, $P < .01$ 60% vs 33%, $P < .006$	R + C vs R + O: 6 R + C vs O: 14	3.7 3.2
			Ineffective empirical antibiotics vs effective	10% vs 40% vs 70%, $P < .01$		-
			Rifampin + ciprofloxacin vs rifampin + other vs other[d]			

(*continued on next page*)

Table 4 (*continued*)

Author, Year	N	PJI	Variables	Failure Rate	Univariate (OR or HR)[g]	Multivariate (OR or (a)HR)[g]
Holmberg, 2015 [22]	145	Early and late	Revision (yes vs no)	63% vs 23%, $P = .02$	-	-
			Rifampin vs no rifampin	19% vs 59%, $P = .01$		
Vilchez, 2011 [23]	65	Early and late	Early vs late PJI	24.5% vs 58.7%, $P = .02$		2.57
			Need of ≥2 debridements	NP, $P = .001$		4.61
El Helou, 2010 [24]	91	Early and late	Rifampin vs no rifampin	4% vs 40%, $P = .03$	-	0.11
Zimmerli, 1998 [26][e]	18	Early	Rifampin + ciprofloxacin vs ciprofloxacin	100% vs 58%, $P = .02$	-	-
Senneville, 2011 [28]	41	Early and late	Rifampin + FQ vs other	6% vs 32%, $P = .001$	-	-
Martínez-Pastor, 2009 [25]	47	Early and late	FQ vs no FQ for GN PJI	7% vs 52%, $P = .005$	-	9.09
			CRP >15 mg/dL vs ≤15 mg/dL	50% vs 17%, $P = .04$		3.57
Tornero, 2015 [27]	222	Early	Chronic renal failure (yes vs no)	60% vs 20%, $P < .001$	-	5.92
			Liver cirrhosis (yes vs no)	48% vs 21%, $P = .004$		4.46
			Femoral neck fracture/revision surgery vs primary	35%/38% vs 16%, $P = .003$ 25% vs 19%, $P = .39$		4.39/4.34 8.71
			Cemented prosthesis (yes vs no)	56% vs 16%, $P < .001$		12.3
			CRP >11.5 mg/dL vs ≤11.5 mg/dL			
Rodriguez-Pardo, 2014 [12]	174	Early and late	Ciprofloxacin (yes vs no)	21% vs 60%, $P < .001$	-	0.23
			Chronic renal failure	NP, $P < .02$		2.56
Grossi, 2016 [29]	35	Early and late	Ciprofloxacin (yes vs no)	21% vs 28%, $P = .65$	-	-
Löwik, 2018 [30]	386	Early	CRP >115 vs ≤115 mg/L	55.2% vs 30.3%, $P < .001$		-
			Gender, male vs female	46.6% vs 33.2%, $P = .08$		2.03
			Left-sided prosthesis (yes vs no)	46.7% vs 31.1%, $P = .002$		1.80
			Sepsis (yes vs no)	52.1% vs 35.1%, $P = .007$		-
			Ischemic heart disease (yes vs no)	50.6% vs 35.3%, $P = .013$		1.84
			Fracture (yes vs no)	52.8% vs 33.3%, $P = .047$		-
			Gentamicin impregnated beads or sponges (yes vs no)	43.0% vs 23.7%, $P = .001$ 50.2% vs 36.6%, $P = .022$		NP NP
			S. aureus (yes vs no)			
Hsieh, 2013 [31]	154	Early and late	RA (yes vs no)	78% vs 48%, $P = .002$	-	-
Son, 2017 [32]	25	Early and late	RA (yes vs no)	50% vs 5%, $P = .04$	-	-
Tornero, 2014 [33]	160	Early	Liver cirrhosis (yes vs no)	67% vs 29%, $P < .001$	-	12.4
			CRP >12 mg/dL vs ≤12 mg/dL	47% vs 29%, $P = .04$		1.06
			GN not treated with a FQ vs treated with a FQ	57% vs 31.5%, $P = .005$		6.5
Bergkvist, 2016 [34]	35	Early	Hip fracture (yes vs no)	64% vs 19%, $P = .01$	-	8.3
Byren, 2009 [6]	112	Early and late	Arthroscopy vs open	53% vs 12%, $P = .008$	5.4	4.2
			S. aureus vs others	30% vs 24%, $P = .05$	2.6	2.9
			Revision vs primary	34.6% vs 12.8%, $P = .008$	2.6	3.1
Vilchez, 2011 [35]	53	Early	CRP >22 mg/dL vs ≤22 mg/dL	54.5% vs 16.6%, $P = .01$	-	20.4
			Need of second debridement (yes vs no)	75% vs 18.4%, $P = .006$		9.8
Rodriguez, 2010 [36]	50	Late	*S. aureus*	62.5%, $P = .01$	3.08	5.3
			GN	0%, $P = .01$	0.46	0.6
Cobo, 2011 [37]	139	Early	MRSA (yes vs no)	66.6% vs 39.6%, $P = .05$	-	None
Tande, 2016 [38]	43	Late		66.6% vs 39.6%, $P = .05$		
Letouvet, 2016 [39]	60	Early and late	Number of prior surgeries	$P = .03$	2.7	6.3
			S. aureus (yes vs no)	50% vs 22%, $P = .02$	3.4	9.4
			Antibiotic treatment <3 mo	46% vs 23.5%, $P = .01$		20
Soriano, 2006 [40]	47	Early	*Enterococcus* spp. or MRSA vs others	87.5% vs 9%, $P = .003$	-	17.6
Kheir, 2017 [130][f]	87	Early and late	VSE	35%	-	-
			VRE	50%		
			Polymicrobial with enterococci	56%		
Tornero, 2014 [70][f]	203	Early and late	VSE	41.8%	-	-
			VRE	72%		
Duijf, 2015 [131]	44	Early	*Enterococcus* spp.	34%	-	-

CRP, C-reactive protein; COPD, chronic obstructive pulmonary disease; RA, rheumatoid arthritis; PJI, periprosthetic joint infection; CNS, coagulase-negative staphylococci; ESR, erythrocyte-sedimentation rate; GP, gram-positive cocci; GN, gram-negative bacilli; FQ, fluoroquinolone; RA, rheumatoid arthritis; MRSA, methicillin-resistant *S. aureus*; VSE, vancomycin-susceptible enterococci; VRE, vancomycin-resistant enterococci.

[a] Confidence interval 95%.
[b] Subgroup analysis of patients with a postsurgical PJI due to methicillin-susceptible *S. aureus* (MSSA).
[c] Subgroup analysis of patients with a postsurgical PJI due to methicillin-resistant *S. aureus* (MRSA).
[d] Subgroup analysis of patients with a postsurgical PJI due to Staphylococci.
[e] Randomized, placebo-controlled, double-blind trial.
[f] Including patients treated with DAIR and prosthesis exchange.
[g] Only depicted when *P* value < .05.
[h] Only depicting the results associated with overall failure.

Exchange of Modular Components

The bacterial load detected on polyethylene is higher than that in metal components of prostheses, presumably due to its rough surface that favors the adherence of bacteria [132]. Therefore, exchanging the modular components will reduce the amount of biofilm present on foreign material. Moreover, removing the modular components during DAIR (i.e., femoral head and/or polyethylene component) provides better access to the joint capsule for radical debridement. Tsang et al reviewed all cohort studies published between 1977 and 2015 on the outcome of DAIR in hip periprosthetic joint infection (PJI). The success rate of DAIR in

studies where all patients underwent modular component exchange was 73.9% (471/637 patients; 95% confidence interval [CI], 70 to 77) compared with 60.7% (245/404 patients; 95% CI, 56 to 65) in patients in whom modular components were retained ($P < .0001$) [1]. In addition, Grammatopoulos et al demonstrated in a cohort of 82 acute hip PJIs a treatment success of 93.3% when modular components were exchanged vs 75.7% when modular component were retained ($p = 0.02$) [7]. Smaller studies confirm the same in acute PJIs of the knee [8,9]. The beneficial effect of modular exchange was also demonstrated as independent predictors of treatment success in large multicenter cohort studies evaluating the outcome of DAIR in hip and knee PJIs caused by methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* ($n = 345$; hazard ratio [HR], 0.65; $p < 0.026$) [10], Streptococci ($n = 462$; HR, 0.60; $P < .01$) [11], and solely late acute PJIs ($n = 340$; odd ratio [OR], 0.35; $p = 0.002$).

Performing DAIR Within at Least 7 Days After the Onset of Symptoms

Several studies demonstrated that the duration of symptoms is significantly shorter in patients who were successfully treated with DAIR than that in patients in whom treatment failed [15–19,129]. In most studies, the most prominent difference between success and failure is observed using a symptom duration of one week as optimal cutoff [7,13,14,16,17]. Urish et al demonstrated a treatment success rate of 53.2% in 216 knee PJIs when DAIR was performed within one week after the onset of symptoms. Additional multivariate analysis in this study showed that the chance of failure increased when DAIR was postponed to two weeks after onset of symptoms (HR, 1.68) and further increased after four weeks of symptoms (HR, 2.34) ($p = 0.002$) [13]. Grammatopoulos et al demonstrated a treatment success rate of 90.7% in 82 hip PJIs when DAIR was performed within one week after the onset of symptoms vs 75.0% when DAIR was performed after one week ($p = 0.05$) [7]. As the maximum days of symptom duration was not well described in all studies and chronic PJIs are indeed included in some [7,13,16,18], the beneficial effect of debridement within one week may be overestimated in these studies for solely acute PJIs. However, a study performed in 110 patients who had a maximum of 32 days of symptoms indicates the same conclusion [15,129]. These authors demonstrated that for each additional day of postponing DAIR, the odds of implant retention decreased by 15.7% and 7.5% for hip and knee PJIs, respectively. In the same study, multivariate analysis showed that performing a DAIR within 5 days was an independent predictor for treatment success, with an odds ratio of around 0.05 for both hips and knees (95% CI, 0.01 to 0.24). These data support the concept that a DAIR should be performed within one week to increase the chance of treatment success but should preferably be performed as soon as possible.

The Addition of Rifampin in Staphylococci PJI

In the randomized controlled trial performed by Zimmerli et al in 1998, 24 patients with an infected orthopedic implant caused by staphylococci and treated with surgical debridement were randomized to antimicrobial treatment with a combination of ciprofloxacin and rifampin or with ciprofloxacin monotherapy. Adding rifampin to the antibiotic regimen improved treatment success from 58% to 100% ($p = 0.02$) [26]. Although relatively small in sample size, this study served as the foundation of adding rifampin to the antibiotic regimen in staphylococcal PJI. Thereafter, the benefit of rifampin was primarily demonstrated in observational studies [10,20,22,24]. In a prospective study including 86 monomicrobial staphylococci knee PJIs treated with open debridement, rifampin-based regimens had a 40% higher treatment success than other regimens ($p = 0.01$) [22]. Moreover, the addition of rifampin has shown to be a strong independent predictor for treatment success in multivariate analyses [10,21]. The greatest beneficial effect of rifampin has been shown when combined with a fluoroquinolone, which can be explained by the effectivity of fluoroquinolones against biofilm and by drug interactions of rifampin with several other antibiotics but not with levofloxacin, the most frequently used fluoroquinolone. In a retrospective study of gram-positive infections treated with DAIR, Tornero et al demonstrated that rifampin combined with linezolid, cotrimoxazole, or clindamycin (which are known to have a drug interaction with rifampin) was associated with a higher failure rate (27.8%) than a combination of rifampicin with levofloxacin, ciprofloxacin, or amoxicillin (8.3%) ($P = .026$) [20]. The greater benefit of the fluoroquinolone-rifampin combination therapy compared with other antibiotic regimens was also illustrated by Puhto et al in a study of 113 patients with acute PJI; compared with rifampin-ciprofloxacin, the HR for treatment failure was significantly increased in the rifampin-other antibiotics group (HR, 6.0; 95% CI, 1.5 to 28.8; $p = 0.014$) and even higher in patients treated without rifampin (HR, 14.4; 95% CI, 3.1 to 66.9; $P < .01$) [21]. In addition, Senneville et al observed the same in 41 patients with acute *S. aureus* PJI treated with DAIR; treatment success was 93.8% in the fluoroquinolone-rifampin group, 66.7% in the rifampin-other antibiotics group, and 57.1% in regimens without rifampin ($p = 0.11$) [28]. Altogether, these data indicate that adding rifampin to the antibiotic regimen, particularly when combined with a fluoroquinolone, is associated with an increased chance of treatment success in acute PJI treated with DAIR.

The Use of Fluoroquinolones in Gram-Negative PJI

The protective effect of antibiotic treatment with a fluoroquinolone is demonstrated in 2 prospective and 1 retrospective observational study [12,20,25]. In a prospective cohort of 22 patients with early PJI caused by gram-negative organisms, the use of fluoroquinolones was associated with a lower failure rate (7.1%) than other antibiotic regimens (37.5%) ($P = .04$) [20]. In addition, in a cohort study of 47 cases, treatment with fluoroquinolone in susceptible gram-negative bacilli was associated with a better outcome ($p = 0.0009$) and was an independent predictor of treatment success (OR, 9.09; 95% CI, 1.96 to 50; $p = 0.005$) [25]. Finally, a large retrospective, multicentre study on gram-negative PJI was performed in 16 Spanish hospitals in which DAIR was performed in 72% of the cases (174/242 cases) [12]. The overall success rate of DAIR was 68%, which increased to 79% in gram-negative PJIs treated with ciprofloxacin. In agreement with the previous study, ciprofloxacin treatment exhibited an independent protective effect in the multivariate analysis (HR, 0.23; 95% CI, 0.13 to 0.40; $P < .001$). In all of these studies, no propensity score matching was performed to correct for possible selection bias. In addition, it should be noted that in most of the performed studies, oral therapy with fluoroquinolones was compared with oral beta-lactam antibiotics. Questioning the superiority of fluoroquinolones, Grossi et al demonstrated that treatment with high-dose intravenous beta-lactam antibiotics (alone or with the addition of another antimicrobial agent) was not inferior to treatment with fluoroquinolones [29]. Although this study had a relatively small sample size ($n = 76$) and included both DAIRs and staged revision surgeries, it does provide some evidence for the possibility that alternative intravenous antibiotic regimens and/or combination therapy may be as effective as treatment with fluoroquinolones. More studies are required to confirm this finding.

Factors that are consistently shown in the literature to decrease the chance of treatment success are as follows:

Host-Related Factors

The importance of host factors in the outcome of patients with a PJI was highlighted by McPherson et al, who described the first grading of the medical and immune status of the host to predict outcome [133]. However, this grading system was not validated in large cohorts of patients who underwent DAIR. For patients managed with DAIR, three large cohort studies in streptococci, staphylococci, and late acute PJI identified patients with rheumatoid arthritis (RA) as an important risk factor for failure [10,11]. This high risk for failure in RA patients has been demonstrated in smaller studies as well [16,31,32]. The most pronounced risk was observed for late acute PJIs, demonstrating a failure rate of 74% in patients with RA versus 43% in patients without ($p < 0.001$), and was shown to be an independent predictor for failure in the multivariate analysis, with an OR of 5.1 (95% CI, 1.1 − 24.3; $p = 0.04$). Age has been independently associated with worse outcome in a recent large cohort of late acute PJIs, showing that patients older than 80 years had a significantly higher risk of failure (OR, 2.6). In addition, a clear correlation between treatment failure and age has also been described in a large cohort of early PJIs [30]. Male sex [30], chronic renal failure [11,12,27], and liver cirrhosis [27,33] were also identified as independent predictors of failure in patients treated with DAIR. Patients with chronic obstructive pulmonary disease showed an increased risk for failure in late acute PJIs only. In this study, chronic obstructive pulmonary disease was not a significant predictor for failure in the multivariate analysis (OR, 2.9; 95% CI, 0.99 − 8.68; $p < 0.05$).

Prosthesis Indication

Despite the fact that fracture and revision arthroplasties have a higher predisposition for infection [134–137], these arthroplasties have been associated with a higher risk for treatment failure in acute PJIs as well. Fracture as an indication for the prosthesis has been shown to be associated with DAIR failure in 3 studies of early acute PJIs [27,30,34] and in 1 study of late acute PJIs as well. With an average failure rate that is 20% to 30% higher than that of osteoarthritis, fracture as an indication for prosthesis has been shown to be an independent predictor for treatment failure in 2 studies [27]. The same holds true for revision arthroplasty compared with infected primary arthroplasty, with a failure rate that is 12% to 22% higher [6,27], which is even higher in knees [8]. Revision arthroplasty has been shown to be an independent predictor for failure in early acute PJI [6,27]. Only one study demonstrated an increased risk for failure in cemented prostheses, with an OR of 8.7 in the multivariate analysis [27].

Clinical Presentation

Several factors considered as surrogate parameters for the severity of the infection have been associated with treatment failure: (1) a high C-reactive protein (CRP) at clinical presentation [10,25,27,30,35], (2) the amount/percentage of positive intraoperative cultures representing the bacterial inoculum [27,30], and (3) bacteremia/sepsis [11,23,27,30]. In most of these studies, these factors are closely correlated to one another. In case of CRP value, an average cutoff value of >115 mg/L has been associated with an increased failure rate, depending on the type of infection (late acute or early acute). Notably, late acute/hematogenous infections appear to be associated with worse outcomes compared with early acute/postsurgical infections, especially when the infection is caused by *S. aureus* [10,14,21,23,35–38].

Causative Microorganism

It has been demonstrated in several studies that an infection caused by *S. aureus* is associated with an increased risk of failure [6,30,39,40]. In a large retrospective cohort of 386 early acute PJIs performed by Löwik et al, the percentage of failure was 17% higher when the infection was caused by *S. aureus* than that with other microorganisms (47.5% vs 30.2%; $P < .001$). *S. aureus* infection was also a prominent risk factor for failure in late acute PJIs, illustrated by an OR of 3.52 for *S. aureus* in the multivariate analysis. Methicillin-resistant *S. aureus* infections were associated with an increased risk for failure in a study performed by Cobo et al, but this was not demonstrated as an independent variable in the multivariate analysis [37]. Indeed, Lora-Tamayo et al clearly demonstrated that methicillin-resistant *S. aureus* infections have similar failure rates as methicillin-susceptible *S. aureus*, although the time to failure differs [10]. After *S. aureus*, overall, poor outcomes have been described for enterococcal PJIs [40,70,130,131]. The largest analysis on enterococcal PJI has been performed by Tornero et al, who reported a failure rate of 53% in 94 patients treated with DAIR [70]. Subanalysis demonstrated that infection caused by *E. faecium* has a worse outcome than those caused by *E. faecalis* (72% vs 42% failure, $p < 0.04$). Indeed, two studies identified the presence of enterococci as an independent risk factor for failure in acute PJI treated with DAIR [40].

Ultimately, a clinical risk score including the most potent factors associated with treatment failure and treatment success should be developed to predict the individual chance of treatment success. One of the main objectives of risk scores would be to identify patients with high failure rate using DAIR. To be of most clinical use, these scores should preferably include preoperative variables only. So far, two articles described a risk score for failure in early acute PJIs (Kidney, Liver, Index surgery, Cemented prosthesis and C-reactive protein value; Fig. 2A) [27] and late acute PJIs (CRIME80 score; Fig. 2B) treated with DAIR. These risk scores can aid in the clinical decision-making to choose an alternative surgical approach and/or to intensify the antimicrobial regimen.

Question 10: Does performing a debridement, antibiotics, and implant retention (DAIR) affect the outcome of a subsequent two-stage exchange arthroplasty?

Recommendation:

Unknown. Based on the available evidence, it is not known if prior debridement, antibiotics, and implant retention adversely affects the outcome of a subsequent two-stage exchange arthroplasty.

Level of Evidence: Limited

Delegate Vote: Agree: 93%, Disagree: 6%, Abstain: 1% (Super Majority, Strong Consensus)

Rationale:

There are several surgical treatment options for periprosthetic joint infection (PJI), including irrigation and debridement (I&D) with modular component exchange and one-stage and two-stage exchange arthroplasty, with the ultimate choice depending on a number of variables, including chronicity of infection, organism, and antibiotic sensitivity patterns, host factors, and experience of surgeon. I&D with implant retention has been an attractive strategy in select circumstances as it is less morbid for the patient and less costly to the health-care system overall. However, the failure rate of I&D is not insignificant, averaging 68% in the literature (61-82%). After treatment failure of an I&D, the recommendation for subsequent treatment is often a two-stage exchange arthroplasty. The question remains whether the initial attempt at I&D adversely affects the outcome of the subsequent two-stage exchange arthroplasty.

Two earlier studies and one very recent study on this subject seemed to indicate that failure of an initial I&D, and modular component exchange leads to a higher than expected failure rates of subsequent two-stage exchange arthroplasty. Sherrell et al. performed a multicenter retrospective review of periprosthetic

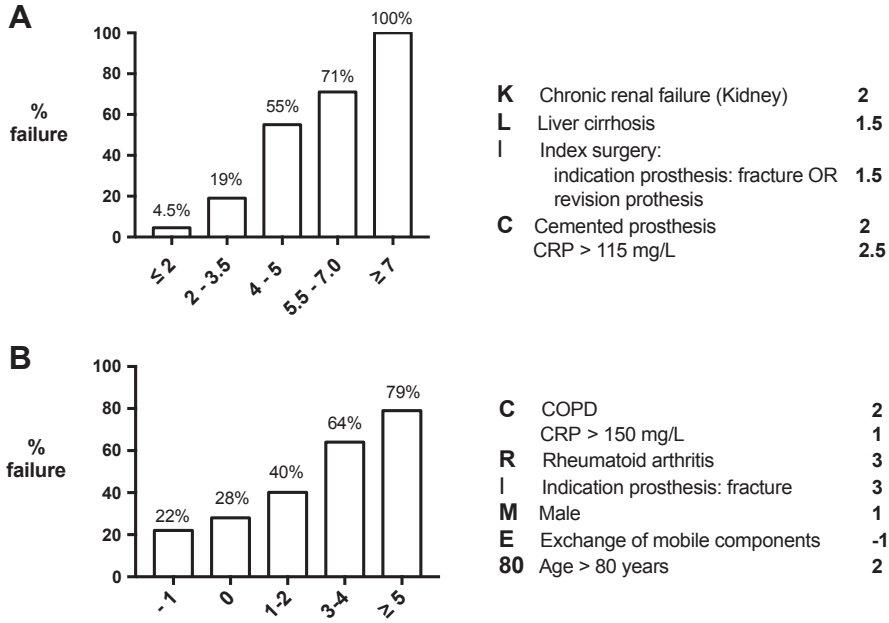

Fig. 2. (A) KLIC preoperative risk score. (B) CRIME80 preoperative risk score. CRP, C-reactive protein; KLIC, Kidney, Liver, Index surgery, Cemented prosthesis and C-reactive protein value.

knee infections treated with a two-stage procedure after an initial treatment with I&D [73]. Of the 83 knees that had undergone prior I&D, 28 (34%) failed subsequent two-stage revision and required reoperation for persistent infection. With the numbers available, there was no difference between success and failure with respect to age, gender, or American Society of Anesthesiologists (ASA) grade. The other earlier study was a retrospective review of 44 patients who had undergone I&D for acute periprosthetic knee infections identified from the St. Paul Health East Joint Registry and the Minneapolis Veterans Affairs Medical Center total knee arthroplasty database [138]. Of the 25 (57%) patients who failed an attempt at I&D, 19 went on to an attempted two-stage revision procedure, and in only 11 of these 19 cases (58%) was the two-stage revision procedure ultimately successful. In a very recent retrospective review of 184 PJIs, Rajgopal et al reported a 23.86% (21/88) failure rate after a two-stage exchange after failed I&D compared with 15.62% (15/96) after direct two-stage exchange [139]. The success rate of the subsequent two-stage exchange arthroplasty procedures in all of these series is lower than historical published results, which the authors conclude may be due to the infection becoming more entrenched in the soft tissues and bone.

Two more recent studies on this topic report the opposite findings, namely that I&D before a two-stage exchange does not increase the risk of failure. Brimmo et al. used the California and New York State Inpatient Databases to identify all two-stage exchange revision total knee arthroplasty patients and compared failure rates, as defined as subsequent surgery due to infection within 4 years, between those with and without prior I&D [75]. Of the 750 patients who underwent two-stage exchange arthroplasty from 2005 to 2011, 57 (7.6%) had undergone a prior I&D. After 4 years, the estimated failure rate was 8.7% (95% CI, 1.9%-16.9%) in the group with prior I&D and 17.5% (95% CI, 14.7%-20.4%) in the group without prior I&D. After adjusting for sex, race, insurance, median household income, and comorbidities, the hazard ratio for the group with a failed I&D was 0.49 ($P = .122$; 95% CI, 0.20-1.20), which the authors indicate revealed a lower risk of failure than the group without prior I&D. Nodzo et al. reviewed their single institutional experience of patients who underwent a two-stage exchange arthroplasty for PJI of total knee replacements, which included 132 who had not had an I&D and 45 patients who had a prior failed I&D [74]. The success rates between groups were similar at 82.5% and 82.2%, respectively, and the only variable they studied which decreased the odds of reoperation was the use of greater than 2 grams of vancomycin in the spacer construct.

As is evident from the current literature, there is no conclusive evidence whether performing a debridement, antibiotics, and implant retention affects the outcome of a subsequent two-stage exchange arthroplasty. All of the articles included, whether single institution, multicenter, or database-derived, reported on a small number of patients who actually had a two-stage exchange arthroplasty after a failed I&D (N = 83, 25, 88, 57, 45), and therefore, small differences in accuracy of coding or interpretation of data could potentially sway the results significantly. For those that support the belief that a failed I&D is associated with a decreased success rate for subsequent two-stage exchange arthroplasty, it may not be due to the infection becoming more established in the periarticular tissue but that it is a patient or organism selection bias/confounding variable, and those individuals that fail an I&D inherently have a higher risk of failing a subsequent 2-stage exchange arthroplasty.

Question 11: How many debridement, antibiotics, and implant retention procedure(s) (DAIR) are acceptable in management of patients with acute periprosthetic joint infection of a primary arthroplasty before removal of components needs to be performed?

Recommendation:

After one failed debridement, antibiotics, and implant retention (DAIR) procedure, strong consideration should be given to removal of components.

Level of Evidence: Limited

Delegate Vote: Agree: 86%, Disagree: 13%, Abstain: 1% (Super Majority, Strong Consensus)

Rationale:

A systematic review of the literature was conducted using the MEDLINE/PubMed (www.ncbi.nlm.nih.gov/pubmed), EMBASE (www.embase.com), and SCOPUS (www.scopus.com) databases. Studies in which there was a standard protocol for a second surgery other than DAIR (i.e. repeat surgery to remove antibiotic beads or planned multiple irrigation and debridement) were not included in this review.

The majority of the studies reviewed are limited by their retrospective nature, small sample sizes, and lack of differentiation between acute postoperative PJI and late-hematogenous PJI. Most researchers viewed failure of DAIR as an indication for a different therapeutic procedure; thus, most studies were limited to a single DAIR. Studies in which multiple DAIRs were performed had given limited insight into their methodology as to why and when a second procedure was performed. Multiple DAIR procedures were only performed in a small portion of the sample size [83,89].

A retrospective review by Triantafyllopoulos et al. attempted to address the appropriate number of DAIR procedures a patient should undergo before resection arthroplasty should be performed. In this retrospective series of 141 patients who underwent DAIR for treatment of a deep periprosthetic infection after primary or revision total knee arthroplasty (TKA) or total hip arthroplasty (THA), 19 patients underwent multiple DAIR procedures [140]. Of the 19 patients who underwent multiple (two or three) DAIR procedures, 10 (52.6%) achieved implant retention with infection control. Of the 122 patients who underwent a single DAIR, 78 (63.9%) achieved implant retention with infection control. All failures underwent prosthesis removal and two-stage reimplantation. The difference in failure rate between those who underwent multiple DAIR and those who underwent a single DAIR was not statistically significant. This study was limited by several factors. The authors included both primary and revision surgeries, as well as a heterogenous mixture of acute postoperative PJI and late-hematogenous PJI. The manuscript also had no clear protocol for which patients underwent repeat DAIR or a different procedure. Furthermore, there was no protocol for patients to undergo additional DAIR or any notation of the timing. Patients who underwent a second DAIR more than 20 days after the first DAIR had 97.4% lower odds of achieving success than patients undergoing the second procedure less than 20 days after the first [140].

A multicenter retrospective analysis by Urish et al. demonstrated that 109 out of 216 patients who underwent DAIR after TKA required an additional procedure [13]. Of the 109 failures, 59 underwent repeat DAIR. Ultimately, of the patients who failed initial DAIR, only 28.4% had DAIR as their final procedure; thus, subsequent irrigation and debridement had a failure rate of over 70%.

Another retrospective study compared 64 patients who underwent DAIR ($n = 39$) versus two-stage revision ($n = 25$) within three months of primary TKA. Of the 39 patients who underwent DAIR, there were 24 failures (61.5%), and all 24 underwent repeat DAIR [5]. All 24 DAIR procedures failed to control the infection [141]. The DAIR patients underwent on average 3.2 additional surgical procedures (range 1-6) to control the infection, whereas the 2-stage exchange patients underwent a mean of 2.2 surgical procedures (range 2-4). A further study by Vilchez et al. of 53 THA and TKA patients with PJI treated with DAIR demonstrated that the need for a secondary DAIR was predictive of failure [36].

The literature demonstrates a second DAIR procedure has, at best, equivalent success as an initial DAIR procedure. To avoid additional surgical procedures, resection arthroplasty should be considered after an initial DAIR procedure.

Question 12: What is the optimal length of antibiotic treatment after debridement, antibiotics, and implant retention (DAIR) for acute periprosthetic joint infections (PJIs)?

Recommendation:

The optimal length of antibiotic treatment after DAIR remains relatively unknown as there is considerable heterogeneity regarding the length, dose, and administration of treatment. A minimum of 6 weeks of antibiotic therapy seems to be sufficient in most cases of PJIs managed by DAIR-provided surgical treatment.

Level of Evidence: Moderate

Delegate Vote: Agree: 91%, Disagree: 8%, Abstain: 1% (Super Majority, Strong Consensus)

Rationale:

Acute periprosthetic joint infections (PJIs) may be treated by debridement, antibiotics, and implant retention (DAIR) [142,143]. In this setting, antimicrobial therapy is administered at high doses during the postoperative period. The median success rate for DAIR for management of acute PJI varies from 34.8% to 100% [8,16,20,28,39,48,51,80,89,144–155]. However, none of the published reports directly compare the outcome of DAIR in relation to the length of antibiotic treatment.

In addition, the details of antibiotic treatment, such as the route of administration, dose, and the duration of therapy, appear to be missing. Two studies, though not providing the route of antimicrobial treatment, stated that patients undergoing DAIR in the cohort received at least six weeks and a median of 7 weeks (range, 3 to 39 weeks) of antimicrobial treatment [16,146]. Majority of the studies reporting the outcome of DAIR [28,39,48,144,145,149–152] used an antibiotic treatment regimen based on the algorithm proposed by Zimmerli et al. [142]. The latter consists of 7 to 14 days of intravenous antibiotics, followed by 3 to 6 months of oral antibiotics with activity against bacteria in biofilm (e.g., ciprofloxacin, adjunct therapy with rifampin).

Four studies report that intravenous antibiotic was used in their cohort, with or without adjunctive oral antibiotics during the course of treatment for a median duration of six weeks [41,51,89,148]. A single study discloses that the patients received oral antibiotics only after the DAIR procedure, with a duration of 6 weeks to lifelong treatment [143]. The remaining 11 studies used a combination of intravenous, followed by oral antibiotic therapy. In these studies, the median duration of intravenous antibiotic therapy was 6 weeks, and among the seven studies which reported the duration of oral antibiotics, the median was 16 weeks (range 9 weeks to lifelong).

There appears to be a wide variation in the length of treatment, route of administration, and the type of antimicrobial therapy that is selected for patients undergoing DAIR. The heterogeneity in the literature and the clinical practice may arise as a result of the fact that there are no reliable clinical or biological parameters that allows clinicians to assess the response to treatment and hence determine the optimal length of antimicrobial therapy [156]. There is a weak signal in the literature to suggest that after a “critical” period of antimicrobial therapy, no further improvement in outcome is encountered by extending the antimicrobial treatment. In fact, some investigators have stated that the length of antimicrobial therapy does not influence the outcome of treatment of PJI patients by DAIR [6]. To the contrary, some investigators believe that prolonged antimicrobial therapy is more likely to lead to masking of the infection and a delay in identifying treatment failure [6,94].

There is little literature regarding the optimal route of administration of antimicrobial therapy. Majority of treating clinicians would recommend that patients undergoing DAIR should receive intravenous antimicrobials, at least initially. One observational nonrandomized comparative study concludes that the only factor associated with failure was the selection of oral antibiotics and not the duration of treatment [20]. The majority of studies that advocate the use of a 6- to 8-week course of antibiotic therapy state that intravenous antibiotics for two weeks followed by 4 to 6 weeks of oral antibiotics is optimal [14,87,94,157–161].

Table 5
Comparative Studies Addressing the Length of Antimicrobial Therapy in the Setting of Prosthetic Joint Infection Managed by Debridement, Antibiotics, and Implant Retention.

Reference	Design	N	Etiology	Antimicrobials	Observations
[6]	Observational, retrospective, one center	112	Various	6 wk of β-lactams/glycopeptides, followed by oral treatment	Length of therapy did not predict the likelihood of failure
[162]	Observational, retrospective, comparative, nonrandomized, one center	60	Various (mostly Staphylococci)	Common use of rifampin and ciprofloxacin	A 6-wk treatment was noninferior than a 12-wk treatment
[163]	Observational, retrospective, comparative, pre–post design, one center	50	Various (mostly Staphylococci)	Common use of rifampin and fluoroquinolones	An 8-wk treatment was noninferior than long standard treatments (3-6 mo)
[53]	Observational, retrospective, comparative, nonrandomized, multicenter	87	Various (mostly Staphylococci)	Rifampin-based combinations	Same outcomes for 6- and 12-wk treatments
[164]	Multicenter randomized clinical trial	63	Staphylococci	Levofloxacin + Rifampin	ITT analysis: 8-wk treatment was noninferior than 3-6 mo. PP analysis: a trend toward noninferiority was observed.

All studies included hip and knee prostheses.
ITT, intention-to-treat; N, number of patients included (referring to those managed by debridement, antibiotics, and implant retention); PP, per protocol.

There are three observational nonrandomized comparative studies showing no differences in success of DAIR when long or short course of antimicrobials were used (Table 5). In a study by Bernard et al., which included a cohort of 60 patients managed by DAIR, the success rate among patients treated for 6 weeks of antimicrobials was not lower than that among those treated for 12 weeks [162]. In 2012, Puhto et al. published a pre-post comparison of 50 patients with PJI treated for 8 weeks vs 72 patients who received either 3 (hips) or 6 (knees) months of treatment, showing similar success rates (63% vs 67% in the intention-to-treat analysis, and 89% vs 87% in the per-protocol analysis) [163]. More recently, Chaussade et al. analyzed 87 episodes of PJI managed by DAIR, with similar success rates when patients were treated for 6 or 12 weeks [53]. All three studies included knee and hip cases, all types of organisms with a predominance of Staphylococci, and varying antibiotic regimen.

One randomized multicenter study compared an 8-week course of levofloxacin plus rifampin vs a long course, 3 of oral therapy for hip PJI and 6 months of therapy for knee PJI in the setting of Staphylococcal PJI managed by DAIR [164]. Although the number of patients included was low, the noninferiority hypothesis of the 8-week course was proven in the intention-to-treat analysis (success rate of 73% vs 58% for the short-course and long-course groups, respectively; n = 66), and a trend toward noninferiority was observed in the per protocol analysis (cure rate of 92 and 95%; n = 44) [164]. The results of Treatment of the Infections on Osteoarticular Prostheses by 6 Versus 12 Weeks of Antibiotherapy (DATIPO) study, an ongoing French multicenter randomized clinical trial comparing 6 weeks vs 12 weeks of antimicrobial therapy for patients with PJI undergoing surgical management, including DAIR, is eagerly awaited.

Although the results of high-level studies are awaited and based on the evaluation of the available literature, it appears that six to eight weeks of antimicrobial therapy is the ongoing standard for patients undergoing DAIR. There is less evidence regarding the optimal route of administration, with majority of the studies advocating the initial treatment should include intravenous route. The type of antimicrobials is also based on the organisms isolated with studies proposing that antibiotics targeting biofilm, such as rifampin, should also be part of the treatment algorithm.

Question 13: What is the most effective combination of antibiotics in the treatment of acute periprosthetic joint infections (PJIs) caused by methicillin-resistant *Staphylococcus aureus* (MRSA) that has undergone surgical management with debridement, antibiotics, and implant retention (DAIR)?

Recommendation:

We recommend a combination of a parenteral antibiotic plus oral rifampin for one to six weeks, followed by rifampin and a companion highly bioavailable oral drug for additional 3 months, depending on the susceptibility profile of MRSA, patient tolerability, and side effect profile.

Level of Evidence: Limited

Delegate Vote: Agree: 88%, Disagree: 10%, Abstain: 2% (Super Majority, Strong Consensus)

Rationale:

Treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) periprosthetic joint infections (PJIs) that have undergone debridement and retention 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 guidelines recommend a quinolone–rifampin combination for susceptible *S. aureus* strains, and cure rates of 70% to 100% have been reported [41,55,165]. The duration of antimicrobial therapy for PJI managed with debridement and retention has not been well established. We recommend 2 to 6 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 [41,80,144]. Certain highly bioavailable drugs such as fluoroquinolones, rifampin, linezolid, and trimethoprim-sulfamethoxazole reach levels in bone that exceed the minimal inhibitory concentration for most organisms [166].

Zimmerli et al. have suggested a duration of therapy of three months for THA PJIs and six months for total knee arthroplasty PJIs [41,55]. Shorter courses of therapy (6 vs 12 weeks) were studied in PJIs treated with debridement and retention. 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) [53]. 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.

Although the current Infectious Diseases Society of America guidelines recommend vancomycin as the primary parenteral agent for treatment of MRSA infections, its use has been questioned due to increasing reports of heterogeneous resistance, treatment failure, and nephrotoxicity. Vancomycin is not bactericidal against small

Table 6
Overview Treatment Duration and Outcome in Gram-Negative Periprosthetic Joint Infections (PJIs) Solely Treated With Surgical Debridement and Implant Retention DAIR.

Author, y	Patients (n)	IV (d)	Oral (d)	Total (d)	Failure (%)
Tornero et al, 2016 [20]	21	8 (IQR, 5-12)[b]	69 (IQR 45-95)[b]	ND	14
Grossi et al, 2016 [29]	35	36 (IQR, 14-90)[a]	ND	90 (IQR 89-92)[a]	23
Jaén et al, 2012 [174]	47	14 (IQR, 8-24)	64 (IQR 28-102)	ND	26
Rodriguez-Pardo et al, 2014 [12]	174	14 (IQR, 6-23)	58 (IQR 27-90).	ND	32
Zmistowski et al, 2011 [173]	10	ND	ND	ND	30
Aboltins et al, 2011 [172]	17	40 (range, 9-79)	365 (range, 30-1678).	ND	6
Hsieh et al, 2009 [19]	27	38 (range, 24-52)	49 (range, 28-92)	ND	27

ND, no data; DAIR, debridement, antibiotics, and implant retention; IQR, interquartile range.
[a] Duration of treatment included cases treated with revision surgery.
[b] Duration of treatment included gram-positive PJIs.

colony variants (SCVs) of MRSA. Moreover, Lenhard et al. showed recently in mixed-population experiments that vancomycin favorably selects for the growth of the SCV subpopulation [166]. 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, which may offer a new option for combating SCVs [167–169]. Although 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 [170].

Question 14: Which 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?

Response/recommendation:

After 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-negative bacilli (GN), has increased [171]. Several studies have been published on antibiotic treatment of these infections in patients treated with surgical debridement and implant retention (DAIR) [12,19,20,25,172–174]. 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 Gram-Negative PJIs Treated with DAIR

Rodriguez-Pardo et al. performed a retrospective analysis on 242 GN PJIs, including 174 cases (72%) treated with debridement and implant retention [23]. The study demonstrated that the use of fluoroquinolones (in this study ciprofloxacin) was associated with the highest success rate of 79% (98 of 124), whereas 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; $P < .001$). 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 regimen showed a trend toward better outcome (aHR, 0.42; $p < 0.07$). The cohort of patients included in the study was 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. [172] studied the outcome of 17 consecutive patients with an early gram-negative PJI, mostly polymicrobial in origin (76%), and mainly involving *Enterobacteriaceae* spp. (94%). All of these patients were initially treated with β-lactam

Table 7
Proposed Antibiotic Regimen for Gram-Negative PJIs Treated With DAIR.

Microorganisms[a]	IV Regimen	Oral Regimen
Enterobacteriacae, ciprofloxacin susceptible	Ceftriaxone 2 g QD ± ciprofloxacin 400 mg TID	Ciprofloxacin 750 mg BID
Pseudomonas spp., ciprofloxacin susceptible	Cefepime 2 g TID or meropenem 2 g TID or ceftazidime 2 g TID or Piperacillin-tazobactam 4.5 g QID ± Ciprofloxacin 400 mg TID or tobramycin 7 mg/kg QD	Ciprofloxacine 750 mg BID
Enterobacteriaceae, ciprofloxacin-resistant	Ceftriaxone 2 g QD ± tobramycin 7 mg/kg QD	IV β-lactam antibiotics during the whole treatment period; possible alternative cotrimoxazole 960 mg TID
Pseudomonas spp., ciprofloxacin resistant	Cefepime 2 g TID or meropenem 2 g TID or ceftazidime 2 g TID or piperacillin-tazobactam 4.5 g QID ± Tobramycin 7 mg/kg QD or Colistin 3 million IU TID or fosfomycin 2-4 g 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.
[a] In case of multidrug-resistant or extremely drug-resistant gram-negative infectant, the antibiotic treatment should be guided by the antibiogram and preferentially by combining 2 antibiotics with a different mechanism of action.

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 the treatment success in the univariate analysis [20,25,174].

Recently, Grossi et al. [29] 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 3 months) was similar compared with the use of an oral fluoroquinolone (failure rate 16.7 vs 22.4%, $P = .75$). 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 the treatment with fluoroquinolones.

The use of alternative oral regimens other than β-lactam, such as cotrimoxazole, has been poorly studied in the field of PJI and requires further investigation.

Only 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, using the efficacy of carbapenems, combined with tigecycline, colistin, or fosfomycin when the microorganism is susceptible [175–178]. 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 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 has been reported as well, demonstrating a higher cure rate for combination therapy [179,180].

Treatment Duration, Route, and Dosage for Gram-Negative PJIs Treated with DAIR

Table 6 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 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 [174]. Although studies have demonstrated an equal success rate with 6 to 8 weeks compared with the standard 12 weeks of antibiotic treatment [53,160,162,163,181], these studies have been mainly performed in rifampin-susceptible staphylococci and cannot be extrapolated to gram-negative 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 case where β–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 7.

References

[1] Tsang S-TJ, Ting J, Simpson AHRW, Gaston P. Outcomes following debridement, antibiotics and implant retention in the management of periprosthetic infections of the hip: a review of cohort studies. Bone Joint J 2017;99-B:1458–66. https://doi.org/10.1302/0301-620X.99B11.BJJ-2017-0088.R1.

[2] Lebeaux D, Ghigo J-M, Beloin C. Biofilm-related infections: bridging the gap between clinical management and fundamental aspects of recalcitrance toward antibiotics. Microbiol Mol Biol Rev 2014;78:510–43. https://doi.org/10.1128/MMBR.00013-14.

[3] Davies D. Understanding biofilm resistance to antibacterial agents. Nat Rev Drug Discov 2003;2:114–22. https://doi.org/10.1038/nrd1008.

[4] Barberán J, Aguilar L, Carroquino G, Giménez M-J, Sánchez B, Martínez D, et al. Conservative treatment of staphylococcal prosthetic joint infections in elderly patients. Am J Med 2006;119:993.e7-10. https://doi.org/10.1016/j.amjmed.2006.03.036.

[5] Maillet M, Pavese P, Bruley D, Seigneurin A, François P. Is prosthesis retention effective for chronic infections in hip arthroplasties? A systematic literature review. Eur J Clin Microbiol Infect Dis 2015;34:1495–502. https://doi.org/10.1007/s10096-015-2388-8.

[6] Byren I, Bejon P, Atkins BL, Angus B, Masters S, McLardy-Smith P, et al. One hundred and twelve infected arthroplasties treated with "DAIR" (debridement, antibiotics and implant retention): antibiotic duration and outcome. J Antimicrob Chemother 2009;63:1264–71. https://doi.org/10.1093/jac/dkp107.

[7] Grammatopoulos G, Bolduc M-E, Atkins BL, Kendrick BJL, McLardy-Smith P, Murray DW, et al. Functional outcome of debridement, antibiotics and implant retention in periprosthetic joint infection involving the hip: a case-control study. Bone Joint J 2017;99-B:614–22. https://doi.org/10.1302/0301-620X.99B5.BJJ-2016-0562.R2.

[8] Zhang C, Yan CH, Chan PK, Ng FY, Chiu KY. Polyethylene insert exchange is crucial in debridement for acute periprosthetic infections following total knee arthroplasty. J Knee Surg 2017;30:36–41. https://doi.org/10.1055/s-0036-1579667.

[9] Choi H-R, von Knoch F, Zurakowski D, Nelson SB, Malchau H. Can implant retention be recommended for treatment of infected TKA? Clin Orthop Relat Res 2011;469:961–9. https://doi.org/10.1007/s11999-010-1679-8.

[10] Lora-Tamayo J, Murillo O, Iribarren JA, Soriano A, Sánchez-Somolinos M, Baraia-Etxaburu JM, et al. A large multicenter study of methicillin-susceptible and methicillin-resistant Staphylococcus aureus prosthetic joint infections managed with implant retention. Clin Infect Dis 2013;56:182–94. https://doi.org/10.1093/cid/cis746.

[11] Lora-Tamayo J, Senneville É, Ribera A, Bernard L, Dupon M, Zeller V, et al. The not-so-good prognosis of streptococcal periprosthetic joint infection managed by implant retention: the results of a large multicenter study. Clin Infect Dis 2017;64:1742–52. https://doi.org/10.1093/cid/cix227.

[12] Rodríguez-Pardo D, Pigrau C, Lora-Tamayo J, Soriano A, del Toro MD, Cobo J, et al. Gram-negative prosthetic joint infection: outcome of a debridement, antibiotics and implant retention approach. A large multicentre study. Clin Microbiol Infect 2014;20:O911–9. https://doi.org/10.1111/1469-0691.12649.

[13] Urish KL, Bullock AG, Kreger AM, Shah NB, Jeong K, Rothenberger SD, et al. A multicenter study of irrigation and debridement in total knee arthroplasty periprosthetic joint infection: treatment failure is high. J Arthroplasty 2018;33:1154–9. https://doi.org/10.1016/j.arth.2017.11.029.

[14] Koh IJ, Han S-B, In Y, Oh K-J, Lee D-H, Kim TK, et al. Open debridement and prosthesis retention is a viable treatment option for acute periprosthetic joint infection after total knee arthroplasty. Arch Orthop Trauma Surg 2015;135:847–55. https://doi.org/10.1007/s00402-015-2237-3.

[15] Triantafyllopoulos GK, Poultsides LA, Sakellariou VI, Zhang W, Sculco PK, Ma Y, et al. Irrigation and debridement for periprosthetic infections of the hip and factors determining outcome. Int Orthop 2015;39:1203–9. https://doi.org/10.1007/s00264-015-2753-3.

[16] Kuiper JWP, Vos SJC, Saouti R, Vergroesen DA, Graat HCA, Debets-Ossenkopp YJ, et al. Prosthetic joint-associated infections treated with DAIR (debridement, antibiotics, irrigation, and retention): analysis of risk factors and local antibiotic carriers in 91 patients. Acta Orthop 2013;84:380–6. https://doi.org/10.3109/17453674.2013.823589.

[17] Marculescu CE, Berbari EF, Hanssen AD, Steckelberg JM, Harmsen SW, Mandrekar JN, et al. Outcome of prosthetic joint infections treated with debridement and retention of components. Clin Infect Dis 2006;42:471–8. https://doi.org/10.1086/499234.

[18] Buller LT, Sabry FY, Easton RW, Klika AK, Barsoum WK. The preoperative prediction of success following irrigation and debridement with polyethylene exchange for hip and knee prosthetic joint infections. J Arthroplasty 2012;27:857–864.e1-4. https://doi.org/10.1016/j.arth.2012.01.003.

[19] Hsieh P-H, Lee MS, Hsu K-Y, Chang Y-H, Shih H-N, Ueng SW. Gram-negative prosthetic joint infections: risk factors and outcome of treatment. Clin Infect Dis 2009;49:1036–43. https://doi.org/10.1086/605593.

[20] Tornero E, Morata L, Martínez-Pastor JC, Angulo S, Combalia A, Bori G, et al. Importance of selection and duration of antibiotic regimen in prosthetic joint infections treated with debridement and implant retention. J Antimicrob Chemother 2016;71:1395–401. https://doi.org/10.1093/jac/dkv481.

[21] Puhto A-P, Puhto T, Niinimäki T, Ohtonen P, Leppilahti J, Syrjälä H. Predictors of treatment outcome in prosthetic joint infections treated with prosthesis

retention. Int Orthop 2015;39:1785–91. https://doi.org/10.1007/s00264-015-2819-2.
[22] Holmberg A, Thórhallsdóttir VG, Robertsson O, W-Dahl A, Stefánsdóttir A. 75% success rate after open debridement, exchange of tibial insert, and antibiotics in knee prosthetic joint infections. Acta Orthop 2015;86:457–62. https://doi.org/10.3109/17453674.2015.1026756.
[23] Vilchez F, Martínez-Pastor JC, García-Ramiro S, Bori G, Tornero E, García E, et al. Efficacy of debridement in hematogenous and early post-surgical prosthetic joint infections. Int J Artif Organs 2011;34:863–9. https://doi.org/10.5301/ijao.5000029.
[24] El Helou OC, Berbari EF, Lahr BD, Eckel-Passow JE, Razonable RR, Sia IG, et al. Efficacy and safety of rifampin containing regimen for staphylococcal prosthetic joint infections treated with debridement and retention. Eur J Clin Microbiol Infect Dis 2010;29:961–7. https://doi.org/10.1007/s10096-010-0952-9.
[25] Martínez-Pastor JC, Muñoz-Mahamud E, Vilchez F, García-Ramiro S, Bori G, Sierra J, et al. Outcome of acute prosthetic joint infections due to gram-negative bacilli treated with open debridement and retention of the prosthesis. Antimicrob Agents Chemother 2009;53:4772–7. https://doi.org/10.1128/AAC.00188-09.
[26] Zimmerli W, Widmer AF, Blatter M, Frei R, Ochsner PE. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. Foreign-Body Infection (FBI) Study Group. JAMA 1998;279:1537–41.
[27] Tornero E, Morata L, Martínez-Pastor JC, Bori G, Climent C, García-Velez DM, et al. KLIC-score for predicting early failure in prosthetic joint infections treated with debridement, implant retention and antibiotics. Clin Microbiol Infect 2015;21. https://doi.org/10.1016/j.cmi.2015.04.012. 786.e9-786.e17.
[28] Senneville E, Joulie D, Legout L, Valette M, Dezèque H, Beltrand E, et al. Outcome and predictors of treatment failure in total hip/knee prosthetic joint infections due to Staphylococcus aureus. Clin Infect Dis 2011;53:334–40. https://doi.org/10.1093/cid/cir402.
[29] Grossi O, Asseray N, Bourigault C, Corvec S, Valette M, Navas D, et al. Gram-negative prosthetic joint infections managed according to a multidisciplinary standardized approach: risk factors for failure and outcome with and without fluoroquinolones. J Antimicrob Chemother 2016;71:2593–7. https://doi.org/10.1093/jac/dkw202.
[30] Löwik CAM, Jutte PC, Tornero E, Ploegmakers JJW, Knobben BAS, de Vries AJ, et al. Predicting failure in early acute prosthetic joint infection treated with debridement, antibiotics, and implant retention: external validation of the KLIC score. J Arthroplasty 2018;33:2582–7. https://doi.org/10.1016/j.arth.2018.03.041.
[31] Hsieh P-H, Huang K-C, Shih H-N. Prosthetic joint infection in patients with rheumatoid arthritis: an outcome analysis compared with controls. PLoS One 2013;8:e71666. https://doi.org/10.1371/journal.pone.0071666.
[32] Son WS, Shon O-J, Lee D-C, Park S-J, Yang HS. Efficacy of open debridement and polyethylene exchange in strictly selected patients with infection after total knee arthroplasty. Knee Surg Relat Res 2017;29:172–9. https://doi.org/10.5792/ksrr.16.040.
[33] Tornero E, Martínez-Pastor JC, Bori G, García-Ramiro S, Morata L, Bosch J, et al. Risk factors for failure in early prosthetic joint infection treated with debridement. Influence of etiology and antibiotic treatment. J Appl Biomater Funct Mater 2014;12:129–34. https://doi.org/10.5301/jabfm.5000209.
[34] Bergkvist M, Mukka SS, Johansson L, Ahl TE, Sayed-Noor AS, Sköldenberg OG, et al. Debridement, antibiotics and implant retention in early periprosthetic joint infection. Hip Int 2016;26:138–43. https://doi.org/10.5301/hipint.5000328.
[35] Vilchez F, Martínez-Pastor JC, García-Ramiro S, Bori G, Maculé F, Sierra J, et al. Outcome and predictors of treatment failure in early post-surgical prosthetic joint infections due to Staphylococcus aureus treated with debridement. Clin Microbiol Infect 2011;17:439–44. https://doi.org/10.1111/j.1469-0691.2010.03244.x.
[36] Rodríguez D, Pigrau C, Euba G, Cobo J, García-Lechuz J, Palomino J, et al. Acute haematogenous prosthetic joint infection: prospective evaluation of medical and surgical management. Clin Microbiol Infect 2010;16:1789–95. https://doi.org/10.1111/j.1469-0691.2010.03157.x.
[37] Cobo J, Miguel LGS, Euba G, Rodríguez D, García-Lechuz JM, Riera M, et al. Early prosthetic joint infection: outcomes with debridement and implant retention followed by antibiotic therapy. Clin Microbiol Infect 2011;17:1632–7. https://doi.org/10.1111/j.1469-0691.2010.03333.x.
[38] Tande AJ, Palraj BR, Osmon DR, Berbari EF, Baddour LM, Lohse CM, et al. Clinical presentation, risk factors, and outcomes of hematogenous prosthetic joint infection in patients with staphylococcus aureus bacteremia. Am J Med 2016;129:221.e11-20. https://doi.org/10.1016/j.amjmed.2015.09.006.
[39] Letouvet B, Arvieux C, Leroy H, Polard J-L, Chapplain J-M, Common H, et al. Predictors of failure for prosthetic joint infections treated with debridement. Med Mal Infect 2016;46:39–43. https://doi.org/10.1016/j.medmal.2015.11.007.
[40] Soriano A, García S, Bori G, Almela M, Gallart X, Macule F, et al. Treatment of acute post-surgical infection of joint arthroplasty. Clin Microbiol Infect 2006;12:930–3. https://doi.org/10.1111/j.1469-0691.2006.01463.x.
[41] Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the infectious diseases Society of America. Clin Infect Dis 2013;56:e1–25. https://doi.org/10.1093/cid/cis803.
[42] Achermann Y, Stasch P, Preiss S, Lucke K, Vogt M. Characteristics and treatment outcomes of 69 cases with early prosthetic joint infections of the hip and knee. Infection 2014;42:511–9. https://doi.org/10.1007/s15010-014-0584-6.
[43] Bradbury T, Fehring TK, Taunton M, Hanssen A, Azzam K, Parvizi J, et al. The fate of acute methicillin-resistant staphylococcus aureus periprosthetic knee infections treated by open debridement and retention of components. J Arthroplasty 2009;24:101–4. https://doi.org/10.1016/j.arth.2009.04.028.
[44] Matthews PC, Berendt AR, McNally MA, Byren I. Diagnosis and management of prosthetic joint infection. BMJ 2009;338:b1773. https://doi.org/10.1136/bmj.b1773.
[45] Duque AF, Post ZD, Lutz RW, Orozco FR, Pulido SH, Ong AC. Is there still a role for irrigation and debridement with liner exchange in acute periprosthetic total knee infection? J Arthroplasty 2017;32:1280–4. https://doi.org/10.1016/j.arth.2016.10.029.
[46] de Vries L, van der Weegen W, Neve W, Das H, Ridwan B, Steens J. The effectiveness of debridement, antibiotics and irrigation for periprosthetic joint infections after primary hip and knee arthroplasty. A 15 years retrospective study in two community hospitals in The Netherlands. J Bone Joint Infect 2016;1:20–4. https://doi.org/10.7150/jbji.14075.
[47] Klare CM, Fortney TA, Kahng PW, Cox AP, Keeney BJ, Moschetti WE. Prognostic factors for success after irrigation and debridement with modular component exchange for infected total knee arthroplasty. J Arthroplasty 2018;33:2240–5. https://doi.org/10.1016/j.arth.2018.02.004.
[48] Sendi P, Lötscher PO, Kessler B, Graber P, Zimmerli W, Clauss M. Debridement and implant retention in the management of hip periprosthetic joint infection. Bone Joint J 2017;99B:330–6. https://doi.org/10.1302/0301-620X.99B3.BJJ-2016-0609.R1.
[49] Anagnostakos K. Can periprosthetic hip joint infections be successfully managed by debridement and prosthesis retention? World J Orthop 2014;5:218–24. https://doi.org/10.5312/wjo.v5.i3.218.
[50] Qasim SN, Swann A, Ashford R. The DAIR (debridement, antibiotics and implant retention) procedure for infected total knee replacement – a literature review. SICOT-J 2017;3:2. https://doi.org/10.1051/sicotj/2016038.
[51] Choi HR, Von Knoch F, Kandil AO, Zurakowski D, Moore S, Malchau H. Retention treatment after periprosthetic total hip arthroplasty infection. Int Orthop 2012;36:723–9. https://doi.org/10.1007/s00264-011-1324-5.
[52] Kuiper JW, Willink RT, Moojen DJF, van den Bekerom MP, Colen S. Treatment of acute periprosthetic infections with prosthesis retention: review of current concepts. World J Orthop 2014;5:667–76. https://doi.org/10.5312/wjo.v5.i5.667.
[53] Chaussade H, Uçkay I, Vuagnat A, Druon J, Gras G, Rosset P, et al. Antibiotic therapy duration for prosthetic joint infections treated by debridement and implant retention (DAIR): similar long-term remission for 6 weeks as compared to 12 weeks. Int J Infect Dis 2017;63:37–42. https://doi.org/10.1016/j.ijid.2017.08.002.
[54] Swenson RD, Butterfield JA, Irwin TJ, Zurlo JJ, Davis CM. Preoperative anemia is associated with failure of open debridement polyethylene exchange in acute and acute hematogenous prosthetic joint infection. J Arthroplasty 2018;33:1855–60. https://doi.org/10.1016/j.arth.2018.01.042.
[55] Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med 2004;351:1645–54. https://doi.org/10.1056/NEJMra040181.
[56] Brandt CM, Duffy MC, Berbari EF, Hanssen AD, Steckelberg JM, Osmon DR. Staphylococcus aureus prosthetic joint infection treated with prosthesis removal and delayed reimplantation arthroplasty. Mayo Clin Proc 1999;74:553–8. https://doi.org/10.4065/74.6.553.
[57] Burger RR, Basch T, Hopson CN. Implant salvage in infected total knee arthroplasty. Clin Orthop Relat Res 1991;273:105–12.
[58] Geurts JAP, Janssen DMC, Kessels AGH, Walenkamp GHIM. Good results in postoperative and hematogenous deep infections of 89 stable total hip and knee replacements with retention of prosthesis and local antibiotics. Acta Orthop 2013;84:509–16. https://doi.org/10.3109/17453674.2013.858288.
[59] Hsieh P-H, Huang K-C, Lee P-C, Lee MS. Two-stage revision of infected hip arthroplasty using an antibiotic-loaded spacer: retrospective comparison between short-term and prolonged antibiotic therapy. J Antimicrob Chemother 2009;64:392–7. https://doi.org/10.1093/jac/dkp177.
[60] Schoifet SD, Morrey BF. Treatment of infection after total knee arthroplasty by débridement with retention of the components. J Bone Joint Surg Am 1990;72:1383–90.
[61] Tattevin P, Crémieux AC, Pottier P, Huten D, Carbon C. Prosthetic joint infection: when can prosthesis salvage be considered? Clin Infect Dis 1999;29:292–5. https://doi.org/10.1086/520202.
[62] Parvizi J, Gehrke T, Chen AF. Proceedings of the international consensus on periprosthetic joint infection. Bone Joint J 2013;95-B:1450–2. https://doi.org/10.1302/0301-620X.95B11.33135.
[63] Aboltins CA, Page MA, Buising KL, Jenney AWJ, Daffy JR, Choong PFM, et al. Treatment of staphylococcal prosthetic joint infections with debridement, prosthesis retention and oral rifampicin and fusidic acid. Clin Microbiol Infect 2007;13:586–91. https://doi.org/10.1111/j.1469-0691.2007.01691.x.
[64] Duggan JM, Georgiadis G, VanGorp C, Kleshinski J. Group B streptococcal prosthetic joint infections. J South Orthop Assoc 2001;10:209–14. discussion 214.
[65] Meehan AM, Osmon DR, Duffy MCT, Hanssen AD, Keating MR. Outcome of penicillin-susceptible streptococcal prosthetic joint infection treated with debridement and retention of the prosthesis. Clin Infect Dis 2003;36:845–9. https://doi.org/10.1086/368182.

[66] Everts RJ, Chambers ST, Murdoch DR, Rothwell AG, McKie J. Successful antimicrobial therapy and implant retention for streptococcal infection of prosthetic joints. ANZ J Surg 2004;74:210–4. https://doi.org/10.1111/j.1445-2197.2004.02942.x.
[67] Zeller V, Lavigne M, Biau D, Leclerc P, Ziza JM, Mamoudy P, et al. Outcome of group B streptococcal prosthetic hip infections compared to that of other bacterial infections. Joint Bone Spine 2009;76:491–6. https://doi.org/10.1016/j.jbspin.2008.11.010.
[68] Sendi P, Christensson B, Uçkay I, Trampuz A, Achermann Y, Boggian K, et al. Group B streptococcus in prosthetic hip and knee joint-associated infections. J Hosp Infect 2011;79:64–9. https://doi.org/10.1016/j.jhin.2011.04.022.
[69] Corvec S, Illiaquer M, Touchais S, Boutoille D, van der Mee-Marquet N, Quentin R, et al. Clinical features of group B streptococcus prosthetic joint infections and molecular characterization of isolates. J Clin Microbiol 2011;49:380–2. https://doi.org/10.1128/JCM.00581-10.
[70] Tornero E, Senneville E, Euba G, Petersdorf S, Rodriguez-Pardo D, Lakatos B, et al. Characteristics of prosthetic joint infections due to Enterococcus sp. and predictors of failure: a multi-national study. Clin Microbiol Infect 2014;20:1219–24. https://doi.org/10.1111/1469-0691.12721.
[71] Fisman DN, Reilly DT, Karchmer AW, Goldie SJ. Clinical effectiveness and cost-effectiveness of 2 management strategies for infected total hip arthroplasty in the elderly. Clin Infect Dis 2001;32:419–30. https://doi.org/10.1086/318502.
[72] Dzaja I, Howard J, Somerville L, Lanting B. Functional outcomes of acutely infected knee arthroplasty: a comparison of different surgical treatment options. Can J Surg 2015;58:402–7. https://doi.org/10.1503/cjs.017614.
[73] Sherrell JC, Fehring TK, Odum S, Hansen E, Zmistowski B, Dennos A, et al. The Chitranjan Ranawat Award: fate of two-stage reimplantation after failed irrigation and débridement for periprosthetic knee infection. Clin Orthop Relat Res 2011;469:18–25. https://doi.org/10.1007/s11999-010-1434-1.
[74] Nodzo SR, Boyle KK, Nocon AA, Henry MW, Mayman DJ, Westrich GH. The influence of a failed irrigation and debridement on the outcomes of a subsequent 2-stage revision knee arthroplasty. J Arthroplasty 2017;32:2508–12. https://doi.org/10.1016/j.arth.2017.03.026.
[75] Brimmo O, Ramanathan D, Schiltz NK, Pillai ALPC, Klika AK, Barsoum WK. Irrigation and debridement before a 2-stage revision total knee arthroplasty does not increase risk of failure. J Arthroplasty 2016;31:461–4. https://doi.org/10.1016/j.arth.2015.08.044.
[76] Grammatopoulos G, Kendrick B, McNally M, Athanasou NA, Atkins B, McLardy-Smith P, et al. Outcome following debridement, antibiotics, and implant retention in hip periprosthetic joint infection-an 18-year experience. J Arthroplasty 2017;32:2248–55. https://doi.org/10.1016/j.arth.2017.02.066.
[77] Kim JG, Bae JH, Lee SY, Cho WT, Lim HC. The parameters affecting the success of irrigation and debridement with component retention in the treatment of acutely infected total knee arthroplasty. Clin Orthop Surg 2015;7:69–76. https://doi.org/10.4055/cios.2015.7.1.69.
[78] Bryan AJ, Abdel MP, Sanders TL, Fitzgerald SF, Hanssen AD, Berry DJ. Irrigation and debridement with component retention for acute infection after hip arthroplasty: improved results with contemporary management. J Bone Joint Surg Am 2017;99:2011–8. https://doi.org/10.2106/JBJS.16.01103.
[79] Deirmengian C, Greenbaum J, Lotke PA, Booth RE, Lonner JH. Limited success with open debridement and retention of components in the treatment of acute Staphylococcus aureus infections after total knee arthroplasty. J Arthroplasty 2003;18:22–6.
[80] Peel TN, Buising KL, Dowsey MM, Aboltins CA, Daffy JR, Stanley PA, et al. Outcome of debridement and retention in prosthetic joint infections by methicillin-resistant staphylococci, with special reference to rifampin and fusidic acid combination therapy. Antimicrob Agents Chemother 2013;57:350–5. https://doi.org/10.1128/AAC.02061-12.
[81] Niki Y, Matsumoto H, Otani T, Tomatsu T, Toyama Y. How much sterile saline should be used for efficient lavage during total knee arthroplasty? Effects of pulse lavage irrigation on removal of bone and cement debris. J Arthroplasty 2007;22:95–9. https://doi.org/10.1016/j.arth.2006.02.078.
[82] Urish KL, DeMuth PW, Craft DW, Haider H, Davis 3rd CM. Pulse lavage is inadequate at removal of biofilm from the surface of total knee arthroplasty materials. J Arthroplasty 2014;29:1128–32. https://doi.org/10.1016/j.arth.2013.12.012.
[83] Azzam KA, Seeley M, Ghanem E, Austin MS, Purtill JJ, Parvizi J. Irrigation and debridement in the management of prosthetic joint infection: traditional indications revisited. J Arthroplasty 2010;25:1022–7. https://doi.org/10.1016/j.arth.2010.01.104.
[84] Di Benedetto P, Di Benedetto ED, Salviato D, Beltrame A, Gisonni R, Cainero V, et al. Acute periprosthetic knee infection: is there still a role for DAIR? Acta Biomedica 2017;88:84–91. https://doi.org/10.23750/abm.v88i2-S.6518.
[85] Estes CS, Beauchamp CP, Clarke HD, Spangehl MJ. A two-stage retention debridement protocol for acute periprosthetic joint infections. Clin Orthop Relat Res 2010;468:2029–38. https://doi.org/10.1007/s11999-010-1293-9.
[86] Kim JH, Chun SK, Yoon YC, Lakhotia D, Shon WY. Efficacy of debridement for early periprosthetic joint infection after hip arthroplasty. Hip Pelvis 2014;26:227–34. https://doi.org/10.5371/hp.2014.26.4.227.
[87] Koyonos L, Zmistowski B, Della Valle CJ, Parvizi J. Infection control rate of irrigation and debridement for periprosthetic joint infection. Clin Orthop Relat Res 2011;469:3043–8. https://doi.org/10.1007/s11999-011-1910-2.
[88] Moojen DJF, Zwiers JH, Scholtes VA, Verheyen CC, Poolman RW. Similar success rates for single and multiple debridement surgery for acute hip arthroplasty infection. Acta Orthop 2014;85:383–8. https://doi.org/10.3109/17453674.2014.927729.
[89] Mont MA, Waldman B, Banerjee C, Pacheco IH, Hungerford DS. Multiple irrigation, debridement, and retention of components in infected total knee arthroplasty. J Arthroplasty 1997;12:426–33. https://doi.org/10.1016/S0883-5403(97)90199-6.
[90] Narayanan R, Anoushiravani AA, Elbuluk AM, Chen KK, Adler EM, Schwarzkopf R. Irrigation and debridement for early periprosthetic knee infection: is it effective? J Arthroplasty 2018;33:1872–8. https://doi.org/10.1016/j.arth.2017.12.039.
[91] Royo A, Bertrand ML, Ramos L, Fernandez-Gordillo F, Guerado E. Is there still a place for continuous closed irrigation in the management of periprosthetic total knee infection? Open Orthop J 2013;7:205–10. https://doi.org/10.2174/1874325001307010205.
[92] Laffer RR, Ruef C. Diagnosis and treatment of prosthetic joint infections. Z Rheumatol 2006;65:12–7. https://doi.org/10.1007/s00393-005-0016-1.
[93] Jiranek WA, Waligora AC, Hess SR, Golladay GL. Surgical treatment of prosthetic joint infections of the hip and knee: changing paradigms? J Arthroplasty 2015;30:912–8. https://doi.org/10.1016/j.arth.2015.03.014.
[94] Fink B, Schuster P, Schwenninger C, Frommelt L, Oremek D. A standardized regimen for the treatment of acute postoperative infections and acute hematogenous infections associated with hip and knee arthroplasties. J Arthroplasty 2017;32:1255–61. https://doi.org/10.1016/j.arth.2016.10.011.
[95] Martínez-Pastor JC, Maculé-Beneyto F, Suso-Vergara S. Acute infection in total knee arthroplasty: diagnosis and treatment. Open Orthop J 2013;7:197–204. https://doi.org/10.2174/1874325001307010197.
[96] Volpin A, Sukeik M, Alazzawi S, Haddad FS. Aggressive early debridement in treatment of acute periprosthetic joint infections after hip and knee replacements. Open Orthop J 2016;10:669–78. https://doi.org/10.2174/1874325001610010669.
[97] Parvizi J, Cavanaugh PK, Diaz-Ledezma C. Periprosthetic knee infection: ten strategies that work. Knee Surg Relat Res 2013;25:155–64. https://doi.org/10.5792/ksrr.2013.25.4.155.
[98] Gehrke T, Alijanipour P, Parvizi J. The management of an infected total knee arthroplasty. Bone Joint J 2015;97-B:20–9. https://doi.org/10.1302/0301-620X.97B10.36475.
[99] Abdi-Ali A, Mohammadi-Mehr M, Agha Alaei Y. Bactericidal activity of various antibiotics against biofilm-producing Pseudomonas aeruginosa. Int J Antimicrob Agents 2006;27:196–200. https://doi.org/10.1016/j.ijantimicag.2005.10.007.
[100] Castaneda P, McLaren A, Tavaziva G, Overstreet D. Biofilm antimicrobial susceptibility increases with antimicrobial exposure time. Clin Orthop Relat Res 2016;474:1659–64. https://doi.org/10.1007/s11999-016-4700-z.
[101] Dosler S, Karaaslan E. Inhibition and destruction of Pseudomonas aeruginosa biofilms by antibiotics and antimicrobial peptides. Peptides 2014;62:32–7. https://doi.org/10.1016/j.peptides.2014.09.021.
[102] Goel S, Mishra P. Thymoquinone inhibits biofilm formation and has selective antibacterial activity due to ROS generation. Appl Microbiol Biotechnol 2018;102:1955–67. https://doi.org/10.1007/s00253-018-8736-8.
[103] Regenthal R, Krueger M, Koeppel C, Preiss R. Drug levels: therapeutic and toxic serum/plasma concentrations of common drugs. J Clin Monit Comput 1999;15:529–44.
[104] Schulz M, Iwersen-Bergmann S, Andresen H, Schmoldt A. Therapeutic and toxic blood concentrations of nearly 1,000 drugs and other xenobiotics. Crit Care 2012;16:R136. https://doi.org/10.1186/cc11441.
[105] Marquès C, Tasse J, Pracros A, Collin V, Franceschi C, Laurent F, et al. Effects of antibiotics on biofilm and unattached cells of a clinical Staphylococcus aureus isolate from bone and joint infection. J Med Microbiol 2015;64:1021–6. https://doi.org/10.1099/jmm.0.000125.
[106] Kuechle DK, Landon GC, Musher DM, Noble PC. Elution of vancomycin, daptomycin, and amikacin from acrylic bone cement. Clin Orthop Relat Res 1991;264:302–8.
[107] Perry CR, Hulsey RE, Mann FA, Miller GA, Pearson RL. Treatment of acutely infected arthroplasties with incision, drainage, and local antibiotics delivered via an implantable pump. Clin Orthop Relat Res 1992;281:216–23.
[108] Fukagawa S, Matsuda S, Miura H, Okazaki K, Tashiro Y, Iwamoto Y. High-dose antibiotic infusion for infected knee prosthesis without implant removal. J Orthop Sci 2010;15:470–6. https://doi.org/10.1007/s00776-010-1487-8.
[109] Tsumura H, Ikeda S, Ono T, Itonaga I, Taira H, Torisu T. Synovectomy, debridement, and continuous irrigation for infected total knee arthroplasty. Int Orthop 2005;29:113–6. https://doi.org/10.1007/s00264-004-0626-2.
[110] Whiteside LA, Peppers M, Nayfeh TA, Roy ME. Methicillin-resistant Staphylococcus aureus in TKA treated with revision and direct intra-articular antibiotic infusion. Clin Orthop Relat Res 2011;469:26–33. https://doi.org/10.1007/s11999-010-1313-9.
[111] Whiteside LA, Nayfeh TA, LaZear R, Roy ME. Reinfected revised TKA resolves with an aggressive protocol and antibiotic infusion. Clin Orthop Relat Res 2012;470:236–43. https://doi.org/10.1007/s11999-011-2087-4.
[112] Roy ME, Peppers MP, Whiteside LA, Lazear RM. Vancomycin concentration in synovial fluid: direct injection into the knee vs. intravenous infusion. J Arthroplasty 2014;29:564–8. https://doi.org/10.1016/j.arth.2013.08.017.
[113] Antony SJ, Westbrook RS, Jackson JS, Heydemann JS, Nelson JL. Efficacy of single-stage revision with aggressive debridement using intra-articular

antibiotics in the treatment of infected joint prosthesis. Infect Dis (Auckl) 2015;8:17–23. https://doi.org/10.4137/IDRT.S26824.
[114] Labruyère C, Zeller V, Lhotellier L, Desplaces N, Léonard P, Mamoudy P, et al. Chronic infection of unicompartmental knee arthroplasty: one-stage conversion to total knee arthroplasty. Orthop Traumatol Surg Res 2015;101:553–7. https://doi.org/10.1016/j.otsr.2015.04.006.
[115] Vasso M, Corona K, D'Apolito R, Mazzitelli G, Panni AS. Unicompartmental knee arthroplasty: modes of failure and conversion to total knee arthroplasty. Joints 2017;5:44–50. https://doi.org/10.1055/s-0037-1601414.
[116] Kim KT, Lee S, Lee JI, Kim JW. Analysis and treatment of complications after unicompartmental knee arthroplasty. Knee Surg Relat Res 2016;28:46–54. https://doi.org/10.5792/ksrr.2016.28.1.46.
[117] Böhm I, Landsiedl F. Revision surgery after failed unicompartmental knee arthroplasty: a study of 35 cases. J Arthroplasty 2000;15:982–9.
[118] Saragaglia D, Bonnin M, Dejour D, Deschamps G, Chol C, Chabert B, et al. Results of a French multicentre retrospective experience with four hundred and eighteen failed unicondylar knee arthroplasties. Int Orthop 2013;37:1273–8. https://doi.org/10.1007/s00264-013-1915-4.
[119] Ercolano LB, Christensen T, McGough R, Weiss K. Treatment solutions are unclear for perimegaprosthetic infections. Clin Orthop Relat Res 2013;471:3204–13. https://doi.org/10.1007/s11999-013-2852-7.
[120] Hardes J, Gebert C, Schwappach A, Ahrens H, Streitburger A, Winkelmann W, et al. Characteristics and outcome of infections associated with tumor endoprostheses. Arch Orthop Trauma Surg 2006;126:289–96. https://doi.org/10.1007/s00402-005-0009-1.
[121] Henderson ER, Groundland JS, Pala E, Dennis JA, Wooten R, Cheong D, et al. Failure mode classification for tumor endoprostheses: retrospective review of five institutions and a literature review. J Bone Joint Surg Am 2011;93:418–29. https://doi.org/10.2106/JBJS.J.00834.
[122] Holzer G, Windhager R, Kotz R. One-stage revision surgery for infected megaprostheses. J Bone Joint Surg Br 1997;79:31–5.
[123] Kapoor SK, Thiyam R. Management of infection following reconstruction in bone tumors. J Clin Orthop Trauma 2015;6:244–51. https://doi.org/10.1016/j.jcot.2015.04.005.
[124] McDonald DJ, Fitzgerald RH, Ilstrup DM. Two-stage reconstruction of a total hip arthroplasty because of infection. J Bone Joint Surg Am 1989;71:828–34.
[125] Eralp L, Ozger H, Kocaoglu M. Treatment strategies for infected megaprosthesis. Orthop Proc 2009;91-B:301. https://doi.org/10.1302/0301-620X.91BSUPP_II.0910301a.
[126] Hardes J, Ahrens H, Gosheger G, Nottrott M, Dieckmann R, Henrichs M-P, et al. [Management of complications in megaprostheses]. Unfallchirurg 2014;117:607–13. https://doi.org/10.1007/s00113-013-2477-z.
[127] Kendoff D, Morgan-Jones R, Haddad FS, editors. Periprosthetic joint infections: changing paradigms. Switzerland: Springer International Publishing; 2016.
[128] Pilge H, Gradl G, von Eisenhart-Rothe R, Gollwitzer H. Incidence and outcome after infection of megaprostheses. Hip Int 2012;22(Suppl 8):S83–90. https://doi.org/10.5301/HIP.2012.9576.
[129] Triantafyllopoulos GK, Poultsides LA, Zhang W, Sculco PK, Ma Y, Sculco TP. Periprosthetic knee infections treated with irrigation and debridement: outcomes and preoperative predictive factors. J Arthroplasty 2015;30:649–57. https://doi.org/10.1016/j.arth.2014.10.026.
[130] Kheir MM, Tan TL, Higuera C, George J, Della Valle CJ, Shen M, et al. Periprosthetic joint infections caused by enterococci have poor outcomes. J Arthroplasty 2017;32:933–47. https://doi.org/10.1016/j.arth.2016.09.017.
[131] Duijf SV, Vos FJ, Meis JF, Goosen JH. Debridement, antibiotics and implant retention in early postoperative infection with Enterococcus sp. Clin Microbiol Infect 2015;21:e41–2. https://doi.org/10.1016/j.cmi.2015.01.006.
[132] Lass R, Giurea A, Kubista B, Hirschl AM, Graninger W, Presterl E, et al. Bacterial adherence to different components of total hip prosthesis in patients with prosthetic joint infection. Int Orthop 2014;38:1597–602. https://doi.org/10.1007/s00264-014-2358-2.
[133] McPherson EJ, Woodson C, Holtom P, Roidis N, Shufelt C, Patzakis M. Periprosthetic total hip infection: outcomes using a staging system. Clin Orthop Relat Res 2002;403:8–15. https://doi.org/10.5301/jabfm.5000209.
[134] Guren E, Figved W, Frihagen F, Watne LO, Westberg M. Prosthetic joint infection-a devastating complication of hemiarthroplasty for hip fracture. Acta Orthop 2017;88:383–9. https://doi.org/10.1080/17453674.2017.1301009.
[135] Kurtz SM, Lau E, Schmier J, Ong KL, Zhao K, Parvizi J. Infection burden for hip and knee arthroplasty in the United States. J Arthroplasty 2008;23:984–91. https://doi.org/10.1016/j.arth.2007.10.017.
[136] Mortazavi SMJ, Molligan J, Austin MS, Purtill JJ, Hozack WJ, Parvizi J. Failure following revision total knee arthroplasty: infection is the major cause. Int Orthop 2011;35:1157–64. https://doi.org/10.1007/s00264-010-1134-1.
[137] Mortazavi SMJ, Schwartzenberger J, Austin MS, Purtill JJ, Parvizi J. Revision total knee arthroplasty infection: incidence and predictors. Clin Orthop Relat Res 2010;468:2052. https://doi.org/10.1007/s11999-010-1308-6.
[138] Gardner J, Gioe TJ, Tatman P. Can this prosthesis be saved?: implant salvage attempts in infected primary TKA. Clin Orthop Relat Res 2011;469:970–6.
[139] Rajgopal A, Panda I, Rao A, Dahiya V, Gupta H, et al. Does prior failed debridement compromise the outcome of subsequent two-stage revision done for periprosthetic joint infection following total knee arthroplasty? J Arthroplasty 2018;33:2588–94.
[140] Triantafyllopoulos G, Poultsides LA, Zhang W, Sculco PK, Ma Y, Sculco TP. Multiple irrigation and debridements for periprosthetic joint infections: facing a necessity or just prolonging the inevitable? J Arthroplasty 2016;31:219–24. https://doi.org/10.1016/j.arth.2015.06.051.
[141] Lizaur-Utrilla A, Gonzalez-Parreño S, Gil-Guillen V, Lopez-Prats FA. Debridement with prosthesis retention and antibiotherapy vs. two-stage revision for periprosthetic knee infection within 3 months after arthroplasty: a case-control study. Clin Microbiol Infect 2015;21:851.e11-17. https://doi.org/10.1016/j.cmi.2015.05.028.
[142] Zimmerli W, Ochsner PE. Management of infection associated with prosthetic joints. Infection 2003;31:99–108. https://doi.org/10.1007/s15010-002-3079-9.
[143] Kösters K, van Crevel R, Sturm PDJ, Willem Schreurs B, de Waal Malefijt MC, van Kampen A, et al. Treatment of knee prosthesis infections: evaluation of 15 patients over a 5-year period. Int Orthop 2009;33:1249–54. https://doi.org/10.1007/s00264-008-0638-4.
[144] Leijtens B, Elbers JBW, Sturm PD, Kullberg BJ, Schreurs BW. Clindamycin-rifampin combination therapy for staphylococcal periprosthetic joint infections: a retrospective observational study. BMC Infect Dis 2017;17:321. https://doi.org/10.1186/s12879-017-2429-2.
[145] Berdal J-E, Skråmm I, Mowinckel P, Gulbrandsen P, Bjørnholt JV. Use of rifampicin and ciprofloxacin combination therapy after surgical debridement in the treatment of early manifestation prosthetic joint infections. Clin Microbiol Infect 2005;11:843–5. https://doi.org/10.1111/j.1469-0691.2005.01230.x.
[146] Westberg M, Grøgaard B, Snorrason F. Early prosthetic joint infections treated with debridement and implant retention: 38 primary hip arthroplasties prospectively recorded and followed for median 4 years. Acta Orthop 2012;83:227–32. https://doi.org/10.3109/17453674.2012.678801.
[147] Matsumoto T, Ishida K, Tsumura N, Nagai K, Muratsu H, Hida Y, et al. Treatment of 50 deep infections after total knee arthroplasty. Orthopedics 2015;38:e529–35. https://doi.org/10.3928/01477447-20150603-63.
[148] Tsukayama DT, Estrada R, Gustilo RB. Infection after total hip arthroplasty. A study of the treatment of one hundred and six infections. J Bone Joint Surg Am 1996;78:512–23.
[149] Giulieri SG, Graber P, Ochsner PE, Zimmerli W. Management of infection associated with total hip arthroplasty according to a treatment algorithm. Infection 2004;32:222–8. https://doi.org/10.1007/s15010-004-4020-1.
[150] Kessler B, Knupp M, Graber P, Zwicky L, Hintermann B, Zimmerli W, et al. The treatment and outcome of peri-prosthetic infection of the ankle: a single cohort-centre experience of 34 cases. Bone Joint J 2014;96-B:772–7. https://doi.org/10.1302/0301-620X.96B6.33298.
[151] Spormann C, Achermann Y, Simmen BR, Schwyzer H-K, Vogt M, Goldhahn J, et al. Treatment strategies for periprosthetic infections after primary elbow arthroplasty. J Shoulder Elbow Surg 2012;21:992–1000. https://doi.org/10.1016/j.jse.2011.10.007.
[152] Weenders SGM, Nijhof MW, Schimmel JJP, Goosen JHM. Debridement, antibiotics and implant retention in early periprosthetic joint infection after primary total hip arthroplasty : 88 percent survival after two years follow-up. Acta Orthop Belg 2016;82:530–8.
[153] Corona Pérez-Cardona PS, Barro Ojeda V, Rodriguez Pardo D, Pigrau Serrallach C, Guerra Farfán E, Amat Mateu C, et al. Clinical experience with daptomycin for the treatment of patients with knee and hip periprosthetic joint infections. J Antimicrob Chemother 2012;67:1749–54. https://doi.org/10.1093/jac/dks119.
[154] Dennison T, Alentorn-Geli E, Assenmacher AT, Sperling JW, Sánchez-Sotelo J, Cofield RH. Management of acute or late hematogenous infection after shoulder arthroplasty with irrigation, débridement, and component retention. J Shoulder Elbow Surg 2017;26:73–8. https://doi.org/10.1016/j.jse.2016.05.018.
[155] Hyman JL, Salvati EA, Laurencin CT, Rogers DE, Maynard M, Brause DB. The arthroscopic drainage, irrigation, and débridement of late, acute total hip arthroplasty infections: average 6-year follow-up. J Arthroplasty 1999;14:903–10.
[156] Piso RJ, Elke R. Antibiotic treatment can be safely stopped in asymptomatic patients with prosthetic joint infections despite persistent elevated C-reactive protein values. Infection 2010;38:293–6. https://doi.org/10.1007/s15010-010-0019-y.
[157] Triantafyllopoulos GK, Soranoglou V, Memtsoudis SG, Poultsides LA. Implant retention after acute and hematogenous periprosthetic hip and knee infections: whom, when and how? World J Orthop 2016;7:546–52. https://doi.org/10.5312/wjo.v7.i9.546.
[158] Lee HD, Prashant K, Shon WY. Management of periprosthetic hip joint infection. Hip Pelvis 2015;27:63–71. https://doi.org/10.5371/hp.2015.27.2.63.
[159] Van Kleunen JP, Knox D, Garino JP, Lee G-C. Irrigation and débridement and prosthesis retention for treating acute periprosthetic infections. Clin Orthop 2010;468:2024–8. https://doi.org/10.1007/s11999-010-1291-y.
[160] Farhad R, Roger P-M, Albert C, Pélligri C, Touati C, Dellamonica P, et al. Six weeks antibiotic therapy for all bone infections: results of a cohort study. Eur J Clin Microbiol Infect Dis 2010;29:217–22. https://doi.org/10.1007/s10096-009-0842-1.
[161] Armstrong MD, Carli AV, Abdelbary H, Poitras S, Lapner P, Beaulé PE. Tertiary care centre adherence to unified guidelines for management of periprosthetic joint infections: a gap analysis. Can J Surg 2018;61:34–41.
[162] Bernard L, Legout L, Zürcher-Pfund L, Stern R, Rohner P, Peter R, et al. Six weeks of antibiotic treatment is sufficient following surgery for septic arthroplasty. J Infect 2010;61:125–32. https://doi.org/10.1016/j.jinf.2010.05.005.

[163] Puhto A-P, Puhto T, Syrjala H. Short-course antibiotics for prosthetic joint infections treated with prosthesis retention. Clin Microbiol Infect 2012;18:1143–8. https://doi.org/10.1111/j.1469-0691.2011.03693.x.
[164] Lora-Tamayo J, Euba G, Cobo J, Horcajada JP, Soriano A, Sandoval E, et al. Short- versus long-duration levofloxacin plus rifampicin for acute staphylococcal prosthetic joint infection managed with implant retention: a randomised clinical trial. Int J Antimicrob Agents 2016;48:310–6. https://doi.org/10.1016/j.ijantimicag.2016.05.021.
[165] Trampuz A, Zimmerli W. Antimicrobial agents in orthopaedic surgery: prophylaxis and treatment. Drugs 2006;66:1089–105.
[166] Lenhard JR, von Eiff C, Hong IS, Holden PN, Bear MD, Suen A, et al. Evolution of staphylococcus aureus under vancomycin selective pressure: the role of the small-colony variant phenotype. Antimicrob Agents Chemother 2015;59:1347–51. https://doi.org/10.1128/AAC.04508-14.
[167] Begic D, von Eiff C, Tsuji BT. Daptomycin pharmacodynamics against Staphylococcus aureus hemB mutants displaying the small colony variant phenotype. J Antimicrob Chemother 2009;63:977–81. https://doi.org/10.1093/jac/dkp069.
[168] Mehta S, Singh C, Plata KB, Chanda PK, Paul A, Riosa S, et al. β-Lactams increase the antibacterial activity of daptomycin against clinical methicillin-resistant Staphylococcus aureus strains and prevent selection of daptomycin-resistant derivatives. Antimicrob Agents Chemother 2012;56:6192–200. https://doi.org/10.1128/AAC.01525-12.
[169] Ortwine JK, Werth BJ, Sakoulas G, Rybak MJ. Reduced glycopeptide and lipopeptide susceptibility in Staphylococcus aureus and the "seesaw effect": taking advantage of the back door left open? Drug Resist Updat 2013;16:73–9. https://doi.org/10.1016/j.drup.2013.10.002.
[170] Massey RC, Peacock SJ. Antibiotic-resistant sub-populations of the pathogenic bacterium Staphylococcus aureus confer population-wide resistance. Curr Biol 2002;12:R686–7.
[171] Benito N, Franco M, Ribera A, Soriano A, Rodriguez-Pardo D, Sorlí L, et al. Time trends in the aetiology of prosthetic joint infections: a multicentre cohort study. Clin Microbiol Infect 2016;22:732.e1-8. https://doi.org/10.1016/j.cmi.2016.05.004.
[172] Aboltins CA, Dowsey MM, Buising KL, Peel TN, Daffy JR, Choong PFM, et al. Gram-negative prosthetic joint infection treated with debridement, prosthesis retention and antibiotic regimens including a fluoroquinolone. Clin Microbiol Infect 2011;17:862–7. https://doi.org/10.1111/j.1469-0691.2010.03361.x.
[173] Zmistowski B, Fedorka CJ, Sheehan E, Deirmengian G, Austin MS, Parvizi J. Prosthetic joint infection caused by gram-negative organisms. J Arthroplasty 2011;26:104–8. https://doi.org/10.1016/j.arth.2011.03.044.
[174] Jaén N, Martínez-Pastor JC, Muñoz-Mahamud E, García-Ramiro S, Bosch J, Mensa J, et al. Long-term outcome of acute prosthetic joint infections due to gram-negative bacilli treated with retention of prosthesis. Rev Esp Quimioter 2012;25:194–8.
[175] Perez-Jorge C, Gomez-Barrena E, Horcajada J-P, Puig-Verdie L, Esteban J. Drug treatments for prosthetic joint infections in the era of multidrug resistance. Expert Opin Pharmacother 2016;17:1233–46. https://doi.org/10.1080/14656566.2016.1176142.
[176] de Sanctis J, Teixeira L, van Duin D, Odio C, Hall G, Tomford JW, et al. Complex prosthetic joint infections due to carbapenemase-producing Klebsiella pneumoniae: a unique challenge in the era of untreatable infections. Int J Infect Dis 2014;25:73–8. https://doi.org/10.1016/j.ijid.2014.01.028.
[177] Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Machuca I, Pascual A. Treatment of infections caused by extended-spectrum-beta-lactamase-, AmpC-, and carbapenemase-producing enterobacteriaceae. Clin Microbiol Rev 2018;31. https://doi.org/10.1128/CMR.00079-17.
[178] Tumbarello M, Viale P, Bassetti M, De Rosa FG, Spanu T, Viscoli C. Infections caused by KPC-producing Klebsiella pneumoniae: differences in therapy and mortality in a multicentre study–authors' response. J Antimicrob Chemother 2015;70:2922. https://doi.org/10.1093/jac/dkv200.
[179] Ribera A, Benavent E, Lora-Tamayo J, Tubau F, Pedrero S, Cabo X, et al. Osteoarticular infection caused by MDR Pseudomonas aeruginosa: the benefits of combination therapy with colistin plus β-lactams. J Antimicrob Chemother 2015;70:3357–65. https://doi.org/10.1093/jac/dkv281.
[180] Lora-Tamayo J, Murillo O, Bergen PJ, Nation RL, Poudyal A, Luo X, et al. Activity of colistin combined with doripenem at clinically relevant concentrations against multidrug-resistant Pseudomonas aeruginosa in an in vitro dynamic biofilm model. J Antimicrob Chemother 2014;69:2434–42. https://doi.org/10.1093/jac/dku151.
[181] Cunningham DJ, Kavolus JJ, Bolognesi MP, Wellman SS, Seyler TM. Specific infectious organisms associated with poor outcomes in treatment for hip periprosthetic infection. J Arthroplasty 2017;32:1984–1990.e5. https://doi.org/10.1016/j.arth.2017.01.027.