

Review

Treatment of Prosthetic Joint Infection with Debridement, Antibiotics and Irrigation with Implant Retention – a Narrative Review

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Abstract

Prosthetic joint infection usually requires combined medical and surgical therapy. While revision surgery is widely considered to be the gold standard surgical procedure, debridement, antibiotics and irrigation with implant retention is a very appealing alternative.

There is however great controversy regarding its real worth with success rates ranging from 0% to over 90%. A number of different patient and host related variables as well as specific aspects of surgical and medical management have been described as relevant for the final outcome.

Along this paper, the authors will provide the readers with a critical narrative review of the currently available literature while trying to provide concise and practical treatment recommendations regarding adequate patient selection criteria, proper surgical technique and optimal antibiotic therapy.

Key words: Prosthetic Joint Infection; Irrigation and Debridement; Implant retention; Total Knee Arthroplasty, Total Hip Arthroplasty; Complications

Introduction

Debridement, Antibiotics and Irrigation with implant Retention (DAIR) is an appealing treatment alternative for prosthetic joint infections (PJI). It is less demanding than revision surgery both for the surgeon and the patient. It is less time consuming and technically easier to perform than revision surgery and it represents a reduced physiologic insult making it easier to recover from.

It has been shown that successful DAIR procedures lead to equivalent outcomes to uninfected controls with regards to function and quality of life[1, 2]. However, patients who have undergone DAIR and failed, often undergo multiple subsequent surgical procedures adding morbidity and cost to the process. Moreover, some studies show poor results of

two-stage exchange after failed initial DAIR treatment thus recommending caution in its use[3, 4].

It is not possible to discuss the nuances surrounding DAIR for PJI treatment without a prior acknowledgment of the microbial biofilm paradigm. Ever since the original work by Gristina & Costerton[5], a considerable amount of research has supported this concept[6]. Biofilms are highly structured usually adherent communities of microbial cells (of one or several different species) that express different phenotypes than its planktonic counterparts. They further produce extracellular matrices that surround them allowing for cell-to-cell communication and creating a favorable environment that protects the bacteria against the host immune system

and most antibiotics although the exact mechanisms of such resistance are not fully understood[7, 8].

Currently, there is extensive controversy in the literature regarding the real worth of DAIR procedures with success rates ranging from 0% to over 90%, and averaging at around 50%[9-11]. There are a lot of variables possibly contributing to this wide range of reported success rate. The goal of this review is to make a critical appraisal of currently available knowledge with a special emphasis on conceivable selection criteria and practical treatment recommendations.

Indications and Risk Factors for Failure

Despite the wide variability of recommendations present in the literature, it is indisputable that such an attempt should only be made with a curative intent when facing a well-fixed, well positioned and stable prosthesis (i.e. one worth saving) and when there is a good soft tissue envelope to cover the prosthesis.

Several variables have been implicated in the likelihood of success of this procedure. Some of them such as the actual technique of the procedure and the antibiotic regimen are under the direct control of the medical team, others such as time since presentation, host medical status or even the causative pathogen are not, but may serve as selection criteria to find the best indication for treatment with implant retention.

Duration of Symptoms

Duration of symptoms is a major factor implicated in the prognosis of DAIR. It is important to emphasize the difference between duration of symptoms (i.e. time since infection manifests itself and treatment) and the “joint age” (or time from implant/index surgery to presentation). In fact,

successful outcomes are possible in acute postoperative but also late acute hematogenous infections although some papers seem to point to a less favorable scenario in the latter [12-15]. In other words, it would seem duration of infection and not “joint age” is the decisive factor. The problem in clinical practice is how to be sure that a hematogenous infection is really an acute infection and not an exacerbation of a chronic infection. In fact, not all patients report long lasting symptoms prior to their presentation with a chronic infection and this may be the explanation for less favorable outcomes sometimes found in late acute hematogenous PJI.

Despite the large amount of evidence describing the importance of short duration of symptoms, there are many discrepancies concerning the best threshold for optimal outcomes (see Table 1). Still, the three and four weeks limit for hematogenous and post-operative infections respectively that was proposed by Zimmerli et al.[16] in their original treatment algorithm is widely adopted and finds support in the current literature [17-24].

An international consensus meeting (ICM) suggested DAIR could be performed in early postoperative infections that occur within 3 months of index primary arthroplasty or in late hematogenous infection that occur within 3 weeks of an inciting event with less than 3 weeks of symptoms in either case[25]. Although such a time-frame is controversial, there is some evidence suggesting it’s merit. Although Grammatopoulos et al. [14] did find significantly greater chances to eradicate PJI if DAIR was undertaken within 6 weeks from the index procedure, good PJI eradication was seen even if DAIR was undertaken after 6 (78%) or even 13 weeks (83%).

Table 1. Summary of selected findings that increase risk of failure after DAIR

	Study details		Success Rate	Factors increasing failure		
	Joint(s)	Country of Origin		Duration of Symptoms	Microorganism(s)	Host Status
Byren et al.[18] 2009	52 THA + 51 TKA + 9 other joints	UK	81%	>14 days from presentation to debridement	<i>S. aureus</i> PJI	Presence of co-morbidity
Azzam et al.[12] 2010	53 THA + 53 TKA	USA	44%	Duration of symptoms failed to predict outcome	Staphylococci PJI; frank purulence	ASA score III/IV
Peel et al.[34] 2012	118 THA + 29 TKA	Australia	71%	Only included PJI within 90 days of implantation	Gram negative PJI	Previous septic exchange; hypotension at presentation;
Buller et al.[17] 2012	62 THA + 247 TKA	USA	52%	>21 days duration of symptoms	Staphylococci PJI; VR Enterococci	Previous joint infection; higher ESR at presentation;
Kuiper et al.[21] 2013	62 THA + 29 TKA	Netherlands	66%	> 7 days before the start of treatment	CoN Staphylococci PJI	Rheumatoid Arthritis; ESR>60mm/h at presentation
Fehring et al.[20] 2013	40 THA + 46 TKA	USA	47%	31-90 days worse than <30 days (joint age)	Type of microorganism failed to predict outcome	Charlson Comorbidity Index failed to predict outcome
Tornero et al.[22] 2015	85 THA + 137 TKA	Spain	77%	Only included PJI with duration of symptoms <21 days	All cultures positive during debridement	Chronic renal failure; liver cirrhosis; revision surgery or cemented prosthesis; CRP >11.5mg/dL; (KLIC score)
Grammatopoulos et al.[14] 2017	122 THA	UK	85%	> 6 weeks after index procedure	Type of microorganism failed to predict outcome	Higher KLIC score

DAIR -Debridement Antibiotics and Irrigation with implant Retention; TKA - Total knee arthroplasty; THA -Total hip arthroplasty; UK - United Kingdom; USA - United States of America; PJI - Prosthetic Joint Infection; VR - Vancomycin-resistant; CoN - coagulase negative; ASA - American Society of Anesthesiologists; ESR - Erythrocyte sedimentation rate; CRP - C-reactive protein

Although time does matter for biofilm formation, DAIR should not be viewed as an emergency procedure except in patients with overt generalized sepsis. Efforts should be made to optimize the patient's comorbidities and whenever possible the procedure should be performed by an experienced septic surgeon.

Type of Microorganism

Although it is of great consequence, specific information about the infecting microorganism(s) and its antibiotic susceptibility is frequently not fully known when choosing to perform surgery.

Indeed, staphylococci infections have been frequently implicated in unfavorable results after DAIR[12, 17, 18, 26, 27]. Methicillin-resistant *S. aureus* (MRSA) specifically, are traditionally considered to be a major risk for failure of debridement with component retention even in acute infections[28-30].

Bradbury et al.[30] have even proposed that if MRSA is encountered, subsequent treatment with exchange arthroplasty should be considered. Joulie et al.[31] analyzed which variables were associated with treatment failure in 93 PJI caused by *S. aureus*. Although they found that exchange arthroplasty offered a better probability of success than debridement alone, they did not find the healing rate to be influenced by methicillin resistance[31]. In a more recent large retrospective, multicenter, observational study of cases of *S. aureus* PJI that were managed with DAIR, the authors found no difference in failure rates in MRSA compared to methicillin sensitive cases[32]. Nevertheless, both these papers showed DAIR was able to save only about 55-57% of *S. aureus* infections[31, 32].

Gram negative microorganisms are also a classic concern as they have traditionally been implicated in worse outcomes with implant retention surgery[33, 34]. Nevertheless, it seems that if fundamental principles such as short duration of symptoms and anti-biofilm antibiotic therapy are upheld, success of DAIR procedure can be just as good in this group of patients[35-38]. The key problem in managing Gram negative PJI is the growing antibiotic resistance pattern, especially in the Middle East and Asia as well as in the European Mediterranean region[39, 40]. It has been shown that the prognosis after DAIR is dramatically decreased when fluoroquinolone resistance is found[36]. Furthermore, even more serious problems such as combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides are often encountered, greatly reducing antibiotic treatment alternatives[39]. Carbapenemase-producing *Enterobacteriaceae* are also on the horizon and have already been implicated in

PJI with dire consequences[41].

Enterococcus sp. Infections, although uncommon, are also of special concern as they are implicated in poor outcomes with overall success rates of around 50%[42-44]. This is particularly true when enterococci infection occurs in a polymicrobial setting or exhibits vancomycin resistance[17, 42]. A major European multicenter study including data from 18 hospitals of six different countries focused exclusively on PJI due to *Enterococcus* sp.[44]. They found an overall success rate of 56% (100/178) among patients with at least one year follow-up after surgery. Implant removal showed a higher remission rate than DAIR but this reached statistical significance only in those patients with more than two years from arthroplasty to infection[44]. A recent American multicenter study confirms these findings as their overall success rate was also low at 52% (45/87)[42]. In this study, success rate after DAIR was only 39% (13/33) which was significantly lower than results after two-stage exchange. Despite that finding, it has been shown that a standardized DAIR protocol for treatment of early infections can lead to slightly superior results. Duijf et al.[45] reported on 44 patients with early *Enterococci* infections (35 polymicrobial). Debridement was performed at an average of 15 days after the index implantation and patients were treated with teicoplanin, rifampicin, vancomycin or amoxicillin or a combination of these antibiotics for three months postoperatively. The prosthesis could successfully be retained in 29 patients (66%) which is, nevertheless, worse than with other microorganisms[45].

Streptococcal infections on the other hand have classically shown a more favorable prognosis[14, 26, 46]. Still, a recent retrospective, observational, multicenter, international study that presents the largest series of streptococcal PJI managed by DAIR with 462 cases, showed a worse prognosis than previously reported[47]. However, given the nature of the study design and according to the authors own admission the criteria for ideal case selection were not strictly met by many patients, and the decision to undergo DAIR was taken by individual medical group on a case by case basis[47].

Depending on the specific microorganisms involved, polymicrobial infections potentially accumulate many of the limitations aforementioned and it is natural that they are often implicated in limited success rates after DAIR[48, 49].

Technical Aspects of the Procedure (including Mobile Parts Exchange)

The main goal of surgical debridement is to lower the bacterial load within the joint as much as possible. In that regard, debridement must be

thorough and meticulous and all devitalized tissues must be excised. This is a major variable that is not possible to accurately assess when reviewing the results in the literature.

Despite the wide range of suggestions regarding the best way to perform a DAIR procedure, common ground has been reached as to what constitutes a favorable debridement[25]. After preoperative optimization of the patient has been achieved, good visualization and thorough debridement should be performed, multiple culture samples should be obtained before copious irrigation (6 to 9 L) of the joint. Even when choosing to perform a DAIR, patients should be advised that the prosthesis may still need to be explanted if indicated (e.g. if it is found to be loose).

Mobile parts exchange seems to be an important factor for success. Naturally, removing mobile parts and replacing them by new ones removes associated bacterial biofilm, allows access to parts of the joint that are otherwise inaccessible and it allows for removal of slime from the undersurface of such components, leading to better reduction of bacterial load. Polyethylene exchange is widely recommended and there seems to be enough evidence of its beneficial impact on outcome[13, 16, 17, 19, 21, 23, 25, 36, 50-61]. In a massive retrospective study including over 16,600 PJI, the authors tried to determine risk factors for reinfection after treatment of infected TKA in the United States[52]. They found that patients who underwent DAIR as a first-line treatment had the highest risk of reinfection, compared to one- and two-stage revision surgery or amputation[52]. More interestingly, they found that DAIR with liner exchange had significantly reduced risk of reinfection even after adjusting for all other available variables[52]. Considering all of the above premises, it is natural to assume that arthroscopic debridement will not suffice. Indeed, even when a posterior portal is routinely used to enable debridement of the posterior compartment of the knee, this approach is not as effective as an open debridement[18, 62, 63].

Adjuvant(s) of Debridement

Although they should not be considered surrogates for adequate surgical debridement, some adjuvant therapies have been advocated as useful during the procedure. By far the most commonly used is to irrigate the joint with copious amounts of normal saline. Although there is the concern that high-pressure pulsatile lavage systems may cause iatrogenic bacterial seeding into deeper tissue layers[64], both low-pressure or high-pressure lavage can be used and no significant difference as been shown to exist in clinical practice[65]. Some authors

argue that adding some kind of chemical to the irrigation liquid could help in reducing bacterial load.

In that regard, detergents, antiseptics or even antibiotics have been proposed but there is very limited evidence of its efficacy in clinical practice and most findings originate from *in vitro* studies. Simply adding antibiotics to the lavage fluid, as appealing as it may appear, has been shown to be no better than saline alone[66, 67]. In light of our current knowledge about the pathogenesis of PJI, it is natural to expect that some kind of "anti-biofilm" agent would perform better. In fact, there is evidence that detergents such as castile soap or benzalkonium chloride are more effective in disrupting biofilm from metal surfaces than saline alone[66, 68]. More recently, chlorhexidine gluconate scrub (antiseptic and detergent) was shown to be the most effective option at decreasing bacterial colony counts when compared to normal saline, povidone iodine scrub or castile soap[69, 70]. An interesting alternative may be acetic acid, commonly known as vinegar. It has been shown *in vitro* to be highly effective against both Gram positive and Gram negative biofilms[71]. There is also limited clinical evidence of the efficacy and safety profile of a 20 minutes' soak of 3% acetic acid solution in the debridement of infected TKA[72].

A different approach is to try and complement surgical debridement by delivering local antibiotics in extremely high concentrations that are able to help eradicate biofilm remnants. Two different ways of achieving this goal have been pursued although there is insufficient evidence to definitively support the use of either until now. Direct continuous intra-articular delivery of antibiotics into the joint was initially promoted by Whiteside as an additional treatment in exchange revision surgery both for knee and hips[73-75]. Fukugawa et al.[58] were the first to apply this concept after DAIR. They reported on a small series of six infected primary TKA, one revision TKA and five tumor mega-prosthesis. There were four recurrences, all of them occurring in the mega-prosthesis group[58]. There are some potential concerns associated with this practice, including drug reactions or possible re-infection through the catheters used to infuse the antibiotic and the need for an additional surgery (to remove the Hickman catheter necessary for the intra-articular infusion) and the available evidence is not enough to state that intra-articular delivery of antibiotics into the joint is an independent success factor.

Another way to deliver local antibiotics that has been explored, is to use some kind of antibiotic-impregnated carrier (PMMA beads, calcium sulphate pellets, collagen fleece, etc.). Antibiotic impregnated PMMA beads have a long tradition in

bone septic surgery and there are some papers exploring its use after DAIR in total joint infections[19, 21, 59, 76]. They do however force a second surgery for its removal and this has moved the focus on to resorbable material such as collagen fleece or calcium sulphate pellets[21, 59, 76]. Although small series have shown encouraging results, there are no randomized, controlled studies to clearly demonstrate that the use of these materials enhances the outcome of a properly performed procedure. Furthermore, resorbable antibiotic carriers are not without problems such as increased cost, local reactions and increased/persistent wound drainage.

Antibiotic Treatment

Following adequate debridement, correct antibiotic therapy is critical in achieving infection eradication. Most of the times, DAIR procedures will take place without previous knowledge of the responsible pathogen and effective empiric antibiotic therapy must be initiated while waiting for intraoperative culture results.

Initial therapy

In the early phase of acute PJI, planktonic bacteria predominate and so treatment usually starts with intravenous (IV) therapy. After the initial debulking of bacterial load caused by surgery and IV antibiotics the switch to regimens with high oral bioavailability and anti-biofilm activity can be made thus avoiding prolonged hospital stay and related complications. Traditionally, 2- 6 weeks of intravenous antimicrobial therapy has been recommended[24] but there is growing evidence that shortening IV therapy before switching to oral therapy is probably not detrimental[77].

Exact empirical antibiotic regimens must be nation or institution specific in accordance with local microbial flora antibiotic susceptibility patterns. As soon as definitive microbiology results are available, antibiotic therapy is deescalated according to isolated pathogen(s) and antibiotic susceptibility pattern.

Continuation therapy

The heterogeneous nature of PJI concerning both the microorganisms and the host, results in a huge diversity of clinical scenarios that make it impossible to offer universal solutions. Every case must be considered on an individual basis and multidisciplinary consultation including infectious diseases specialists is critical. There are however some helpful guidelines available for consultation[16, 24].

Notwithstanding, antibiotic therapy after DAIR procedures holds some peculiarities that must be observed. Unlike revision surgery where the implant

is removed, it is natural to expect the presence of biofilm remnants in the prosthesis after surgical debridement. As such, selected antibiotics should ideally have anti-biofilm activity. In this regard, ever since the pioneer work by Zimmerli[78] et al., rifampicin has gained an indisputable role in biofilm-related staphylococci infections[13, 16, 51, 60, 61, 77, 79-81]. Interestingly, it has also been suggested that rifampicin in combination with other antibiotics may also lead to lower rate of failure in early *Enterococcus* sp. infections treated with DAIR[44]. It is important to stress that, because bacteria rapidly develop antimicrobial resistance, rifampicin should never be administered alone but rather in combination therapy[16]. Plus, it should only be used after the bulk of bacterial load has been eliminated and never in persistently draining wounds[82]. Acherman et al.[82] have found that rifampicin therapy with inadequate surgical debridement or less than two weeks of intravenous treatment was independently associated with emergence of rifampicin resistance.

An analogous declaration of importance can be made regarding the use of quinolones in Gram negative (GN) infections. There is good evidence to recommend the use of quinolones when facing adequately sensitive GN microorganisms[35, 36, 77, 83]. In a recent large multicenter study including 242 Gram negative PJI, ciprofloxacin therapy exhibited an independent protective effect[36]. In patients with ciprofloxacin-susceptible GN-PJI treated with ciprofloxacin, success was 79% (98/124). In ciprofloxacin-resistant cases, the efficacy of DAIR management was at 41% (14/34). In those with susceptible isolates not treated with ciprofloxacin success rate was similar at 40% (6/15), suggesting lack of ciprofloxacin use and not resistance pattern is responsible for the negative impact. The effectiveness of ciprofloxacin in these patients is probably attributable to its acceptable oral bioavailability, optimal diffusion into synovial fluid and bone, and activity against biofilm[84].

Correct antibiotic regimen is a critical part of therapy. A very recent paper by Tornero et al.[77] confirms that incorrect antibiotic selection is the most important predictor of late failure after DAIR. In their study of 143 patients, antibiotic treatment was categorized as optimal if it included a combination of rifampicin plus rifampicin-independent antibiotic (levofloxacin, ciprofloxacin or amoxicillin) or monotherapy without rifampicin for Gram positives and when it included a fluoroquinolone for Gram negatives. It was found to be suboptimal if it included a combination of rifampicin plus rifampicin-dependent antibiotic (linezolid, co-trimoxazole or

clindamycin) for Gram positive or a regimen without fluoroquinolone for Gram negative. Receiving suboptimal antibiotic treatment proved to be the only independent predictor of failure in this study[77].

Duration of therapy

The duration of antibiotic treatment after DAIR is also matter of intense controversy. Traditionally, guidelines have recommended 3 months for infections in total hip and 6 months for total knee prosthesis[24]. There are however several papers questioning this axiom.

Tornero et al.[77] found no relationship between failure and duration of treatment after a median duration of intravenous and oral antibiotic treatment of 8 days and 69 days respectively. A similar finding was reported by Lora-Tamayo[85] et al. in a randomized clinical trial including over 60 patients with acute staphylococcal PJI managed with DAIR. Patients were randomized to receive 8 weeks of treatment (short schedule) versus a long schedule (3 months or 6 months for hip or knee prostheses, respectively) of levofloxacin plus rifampicin. They suggest that the short schedule could be just as effective as a longer standard treatment for THA but some doubt persisted over its value for TKA[85]. Despite some conflicting evidence, extending therapy for 3 months seems to be sufficient for the majority of

cases[60, 61, 77, 81, 83]. Although many physicians rely on C-reactive protein serial measurements to guide antibiotic discontinuation, this practice has been found to be unreliable and not predictive of failure and should therefore be discouraged[85-87].

Failure and treatment options

In an effort to accurately predict the probability of success thus helping decide on the best course of treatment, some authors have tried to come out with prognostic preoperative scores such as the KLIC-score [22]. This score based on patient and index surgery specific variables has been shown to be highly predictive especially in the lower and upper ends of the spectrum [14, 22, 88, 89]. While, data on prospectively applying these tools for decision-making before DAIR is undertaken is still missing, it seems natural to rely on it for reconsideration after initial treatment failure.

Failures can be broadly divided into early failures where DAIR fails to achieve infection control and late failures where infection relapses after apparent good initial response. In both cases, recurrent PJI after DAIR procedures is most often due to identical microorganisms suggesting treatment failed to eradicate infection effectively [12, 17, 18, 21, 22, 27].

Table 2. Summary of selected recent findings regarding antibiotic regimen after DAIR

	Joint(s)	Country of Origin	Overall Success Rate	Major finding(s)
Aboltins et al.[35] 2011	15 THA + 2 TKA	Australia	94% at the 2-years follow-up	Exclusively GN PJI - oral ciprofloxacin in 14 cases and amoxicillin/clavulanic acid in three cases Median duration of oral antibiotic treatment was 12 months
Vilchez et al.[81] 2011	18 THA + 35 TKA	Spain	75% minimum two-year follow-up	Exclusively <i>S. aureus</i> PJI - rifampin combination therapy in 91% of the patients. Only 4 MRSA. Duration of antibiotic therapy >90days did not improve outcome
Puhto et al.[61] 2012	55 THA + 77 TKA	Finland	65% at the 2-years follow-up	Rifampin combination(s) preferred for staphylococci and quinolones preferred for GN Reducing duration of treatment to 3 months (vs. 6) for TKA and 2 months (vs. 3) for THA did not influence outcome
Peel et al.[60] 2013	28 THA + 15 TKA	Australia	77% at the 2-years follow-up	Exclusively MR staphylococci PJI - rifampin combination therapy in 93% of the patients MRSA infections and <90 days antibiotic therapy were more likely to fail
Rodríguez-Pardo et al.[36] 2014	115 THA + 57 TKA + 2 other joints	Spain	68% median 25-months follow-up	Exclusively GN PJI - 79% (98/124) success rate in ciprofloxacin-susceptible treated with it 41% (14/34) success rate in ciprofloxacin-resistant and 40% (6/15) success rate in ciprofloxacin-susceptible not treated with it 79% (33/42) success rate in <i>Pseudomonas</i> PJI increased to 88% (29/33) when treated with ciprofloxacin 53% (8/15) success rate in ESBL-producing <i>Enterobacteriaceae</i> PJI Median antibiotic treatment duration was 70 days
Holmberg et al.[13] 2015	145 TKA	Sweden	75% minimum one-year follow-up	Risk of failure was 4 times higher if no rifampin used in staphylococci infections (59% vs 19%) Failure rate was higher in polymicrobial (9/30) and Gram negative cases (2/5) - albeit not statistically significant Large variation in duration of antibiotic treatment
Lora-Tamayo et al.[85]2016	29 THA + 24 TKA	Spain	93% minimum one-year follow-up	Randomized and open trial. Exclusively staphylococci acutePJI receiving rifampin-levofloxacin combination. Cure rate in the patients who completed antibiotic treatment was 22/24 (92%) in the short (8 weeks) protocol vs. 19/20 (95%) in the long (3 and 6 months for THA and TKA respectively)
Grossi et al.[83] 2016	35 THA + 18 TKA + 23 Hemi hips	France	79% minimum one-year follow-up	Exclusively GN PJI: 35 DAIR procedures -8 (22%) failed Failure rate was similar whether fluoroquinolones or three month IV β-lactams were used Median antibiotic treatment duration was 90 days

DAIR -Debridement Antibiotics and Irrigation with implant Retention; TKA -Total knee arthroplasty; THA -Total hip arthroplasty; MRSA -methicillin-resistant *S. aureus*; GN -Gram negative

In the first clinical scenario, a repeated surgical debridement may be attempted although this strategy is highly controversial. On one hand, Vilchez et al.[81] found the need for a second debridement to be associated with failure. These results were confirmed in a large, retrospective multicenter study of *S. aureus* PJI (n=345) where the need of a second debridement was an independent variable associated with failure[32]. On the other hand, there are a number of papers that do not find the need for more than one unplanned debridement to be associated with worse outcomes[18, 21, 59]. This controversy is even more intricate by the fact that some centers advocate for standard repeated debridements every 48-72h in order to reduce the bacterial load regardless of clinical evolution. Peel et al.[60] performed protocolized multiple debridements and found the optimal number to be two or three as there was significantly higher risk of failure in patients with either a single or at least four surgical debridements.

Recently, Moojen et al.[90] compared these two different strategies in the treatment of acute THA infection. Although it was not statistically significant, they did find an increased failure rate in the group of patients that always received multiple surgical debridements (10/35) as compared to the group of patients that received a single surgical debridement and only additional surgery if infectious symptoms persisted (4/33)[90]. Additionally, in the former group, new and more resistant microorganisms were found in subsequent debridements suggesting every time the wound is opened there is a risk of further contamination[90].

Another treatment alternative is to proceed to implant removal. Although the real impact of previous failed DAIR on the likelihood of success after exchange surgery is not yet fully understood, most surgeons would agree that exchange surgery is the natural choice when facing a late infection relapse[3, 4, 91]. The same might be true in some cases of early failure, especially if significant risk factors for DAIR failure are present (e.g. high KLIC score, unfavorable microbial pathogen, etc.) as previously discussed.

Future Perspectives

Presently, duration of infection before DAIR is indisputably a major variable to consider as it correlates directly to the microbial biofilm paradigm. It is known that the development of a biofilm onto an orthopedic implant starts within the first few minutes and hours after exposure. There is a progressive maturation process and younger biofilms do seem to be more susceptible to (a limited number of) antibiotics than more mature biofilms and this is a

major premise behind adequate case selection for DAIR[8]. What constitutes the difference and where the exact frontier is between a young susceptible biofilm and a more mature resistant infection is still undetermined. Naturally some way to differentiate chronic mature biofilm infections from acute cases where biofilm is still susceptible would be of great benefit. A promising research path based on serological detection of elevated levels of antibody to microbial antigens, specifically "anti-biofilm" antigens is underway[92, 93].

Another potential target would be to increase our ability to cause biofilm disruption *in vivo*. Chlorhexidine and acetic acid are examples of such strategies that are already being used but they offer limited efficacy. Presently, rifampicin and ciprofloxacin to some degree are the only effective antibiotic therapy and alternative drug(s) are desperately needed. Antimicrobial peptides (ex. chitosan) are a new class of antibiotics with very interesting features. They are highly active against a broad spectrum of microorganisms, highly selective towards microorganisms and not mammalian cells, present fast killing even at low concentrations and most importantly, they have a much lower tendency to induce resistance[94]. If *in vivo* biofilm disruption therapy becomes real, the need for revision surgery would greatly diminish.

Conclusion

For the time being accurate case selection and attention to detail in every aspect of treatment such as rigorous surgical procedure technique and adequate postoperative anti-biofilm antibiotic therapy is critical if DAIR is to be performed.

However, in some extreme clinical conditions, usually old and frail patients, DAIR may be indicated as a means to temporarily alleviate symptoms caused by planktonic bacteria leaving the biofilm during acute exacerbations of a chronically infected implant. It will not be able to eradicate biofilm and ensuing chronic suppressive antibiotic therapy is often required but sometimes this may be the lesser of two evils in situations where the patient is not fit to undergo major revision surgery.

It is the authors belief that if appropriate minimal conditions are met (short duration of symptoms in a stable and well-fixed prosthesis with sound soft tissues and no sinus tract), DAIR should be regarded as first-line treatment choice in the vast majority of cases. This approach has resulted in successful infection eradication in 85% of cases at two-years minimum follow-up[95].

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Competing Interests

The authors have declared that no competing interest exists.

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