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QUESTION 3: Does identification of the pathogen prior to performing debridement, antibiotics and implant retention (DAIR) help guide the surgeon's decision making? If so, should you wait, in 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 [1]. For instance, experts would likely agree DAIR is appropriate when ciprofloxacin-susceptible *Escherichia coli* is the infecting organism but, would probably discourage DAIR if the infective organism is a *Candida* spp. Thus, from a general perspective, knowledge of the pathogen prior to 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 knowledge of the infecting pathogen.

Regarding the issue of time, Infectious Diseases Society of America (IDSA) guidelines, in conjunction with other authors, recommend a maximum of 21 days of symptom duration before utilizing DAIR to treat periprosthetic joint infection (PJI) [1,2]. This time limit, which has not been 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 [3]. 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 cut-off 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 [4]. Other studies have also observed a poor outcome among patients with longer duration of symptoms without identifying a reliable time limit [5–13].

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, since patients with sepsis or bacteremia are usually operated on sooner than more stable cases. Ill patients have a higher likelihood of failure [12,14], 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 post-surgical cases where the postoperative inflammatory signs and pain may overlap the symptoms of infection. In these post-surgical 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 post-surgical infection that could be managed by DAIR. While IDSA guidelines do not recommend DAIR for patients with PJI that started greater than one month from the index arthroplasty [2], other important studies and the First International Consensus extend this period to three months [1,15]. 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 [12,13]. 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 multi-drug 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: 13% - 90% for *Staphylococcus aureus* [4,6,14,16–18], 27% - 94% for gram-negative bacilli (GNB) [8,14,17] and 40% - 94% for streptococci [19–24]. The largest observational studies performed to date set these cure rates in 55% for *S. aureus* [12], 58% for streptococci [13], 51% for enterococci [25] and 68% for GNB (with significant differences between fluoroquinolone-susceptible and -resistant strains: 79% vs.40%. respectively) [26].

Whether a 50% risk of failure should discourage use of DAIR is a matter of controversy. In older patients, Fisman et al. suggested an annual relapse rate ≈ 30% after DAIR to be cost-effective when compared with a two-step exchange procedure [27]. The potential advantages of a successful DAIR (one surgery, bone-stock preservation and less economic costs) [28] 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 non-successful DAIR, as compared with patients submitted to an elective two-stage exchange procedure [29]. However, these results have been contested by two other observational studies [30,31]. Furthermore, functional outcome has been reported to be identical in patients undergoing two-stage after failed DAIR compared to patients undergoing direct two-stage exchange [30, 31].

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.

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QUESTION 4: Does exchange of all modular components during debridement, antibiotic and implant retention (DAIR) reduce the rate of surgical site infection (SSI)/periprosthetic joint infection (PJI) recurrence?

RECOMMENDATION: Yes. Exchange of all the modular components during 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 DAIR. If successful, the outcomes of PJI treated by DAIR show functional outcomes and patient reported outcomes equivalent to those of primary total joint replacements [1]. 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 bio-burden/bio-film elimination. However, it is difficult to judge the necessity of exchanging the modular components during DAIR surgery due to 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]. Amongst these, six are retrospective and one is a meta-analysis [7] 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 shows a wide range of variation from 18-83% among different cohorts in various studies. Such wide variations in the impact of modular component exchange suggests 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 [7] of DAIR performed for total hip arthroplasty showed that the mean proportion of success rate in studies where modular components were exchanged was significantly higher (73.9%) than studies in which no components were exchanged (60.7%). A multicenter review article [5] 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 [8,9] and Choi et al. [2] 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 [3] has shown the 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 [8,10–15].

Due 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.

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