Treatment

5.1. TREATMENT: ALGORITHM

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QUESTION 1: Should early postoperative infection and acute hematogenous infection be treated and managed differently?

RECOMMENDATION: There is no evidence to support the notion that early postoperative infection and acute hematogenous infection should be treated differently as long as the onset of symptoms is <4 weeks (favorable <7 days), implants are well-fixed, no sinus tract exists and the isolated infecting organism is sensitive to an antimicrobial agent.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 94%, Disagree: 5%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

Early postoperative infection is usually defined as infection occurring within three weeks of index arthroplasty, although some authorities state that any infection within three months (90 days) of the index arthroplasty should be considered acute [1]. Hematogenous infections associated with a remote source are often classified as late infections, which can occur one to two years after arthroplasty [2]. Acute hematogenous infection is defined as infections with no more than three weeks of symptoms [3]. According to the Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), patients who have a well-fixed, functioning prosthesis without a sinus tract, infection occurring within 30 days of index arthroplasty or <3 weeks of onset of infectious symptoms and having an organism susceptible to oral antimicrobial agents, should be candidates for debridement antibiotcs and implant retention (DAIR) [4]. The International Consensus Meeting (ICM) 2013 also proposed that DAIR should be considered in patients with infection occurring within three months of the index arthroplasty, with less than three weeks of symptoms in early postoperative infections and those with symptoms less than three weeks in late hematogenous infection [3]. When these criteria are met, DAIR is a reasonable option for early postoperative or acute hematogenous infection. However, because of the relatively high failure rate of DAIR in some reports and the fact that mature biofilm on an implant surface forms within a few days, some studies have suggested that DAIR should be restricted to patients with less than five days of infection symptoms [5].

One prospective study demonstrated that 52% of acute hematogenous infections failed at two-year follow-up following DAIR [6]. Treatment failure rates were 57.8% in staphylococcal infection, 14.3% in streptococcal infections and no failures were seen in gram-negative PJI [6]. A second comparative study reported that the success rates after DAIR in hip and knee PJI may be significantly increased if treatment was initiated within two days of symptoms [7]. In the latter study, DAIR showed overall success rate of 82.1% for early infections and 57.1% for acute hematogenous infections. Patients with acute hematogenous infections had an eight-fold higher chance of failure. Given the higher failure rate in the acute hematogenous group, the authors suggested that treatment parameters for these infections required additional studies with higher patient numbers [7]. A recent study evaluating the outcome of DAIR showed no statistically significantly different treatment outcome between early postoperative infection (15%) versus acute hematogenous infection (21%) [8]. Modular components were exchanged in only 70% of the included patients in the latter study. Systemic host grade A (McPherson classification) was a strong predictor of treatment success [8].

Several systematic reviews suggest that interventions in both early postoperative and acute hematogenous infections should be timely and aggressive (with exchange of modular parts), as each additional day of waiting lowers the odds for a successful outcome [9–12]. A recent meta-analysis reported the significant determinants of successful outcome following DAIR [12]. Time from onset of symptoms or index arthroplasty (< 7 days) and the exchange of modular components were the most significant factors influencing outcome. In the latter meta-analysis, the authors detected that the reported success of DAIR has increased since 2004 [12]. The exact reason for this improvement in outcome is not known but may relate to a publication in 2004 by Zimmerli et al. which established an algorithm for DAIR [10]. The algorithm may have encouraged the orthopaedic community to change their indications for DAIR, attempt to optimize patients prior to DAIR by modifying risk factors for failure and possibly altering the administration of antimicrobial regimen.

Virulent organisms causing PJI are also predictors for treatment failure following DAIR, according to some studies. *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA) have been reported to result in a higher failure rate following DAIR when compared to gram-negative pathogens [9,13]. In addition, infections with methicillin-resistant *Staphylococcus epidermidis* (MRSE) and vancomycin-resistant enterococci (VRE) have been associated with inferior outcome following DAIR [9,10]. In contrast, in a study on early postoperative and acute hematogenous infections caused by *S. aureus*, this difference could not be shown [14].

Acute hematogenous infection might be a marker of poor general health as almost half of the patients in one study had some critical medical comorbidity that may have predisposed them to developing infection in the first instance [15]. Relative high mortality rates around 20% after 2 years has been reported for patients with acute hematogenous infections, which could be attributed to higher rates of systemic sepsis at presentation in this patient population [14,15].

In conclusion, DAIR is a viable option and a reasonable first therapeutic approach for patients with early postoperative and acute hematogenous infections. However, some studies have reported a high failure rate of this surgical treatment and a relatively high early mortality rates after DAIR for acute hematogenous infections compared to acute postoperative infections. These differences might be related to differences in the pathoetiology of these infections and the influence of the intrinsic host factors on the outcome. Therefore, studies focusing on improving treatment outcomes after acute hematogenous infections are desperately needed.

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QUESTION 2: Should operative treatment differ in patients with systemic sepsis in the setting of periprosthetic joint infection (PJI)?

RECOMMENDATION: Yes. Patients with systemic sepsis in the setting of PJI should have surgical bioburden reduction, either with implant retention or resection of components (if indicated and safe), along with concurrent anti-microbial therapy. Reimplantation should be delayed until sepsis is resolved.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 79%, Disagree: 19%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Infection of total joint arthroplasty is a known and devastating complication all surgeons seek to avoid. Despite best efforts, prosthetic joints can be seeded from local and systemic sources [1–9]. Although PJI usually presents without systemic signs of pyrexia, chills and other symptoms, occasional PJI may result in systemic sepsis when the blood culture may also be positive for infection. In the context of systemic sepsis, hematogenous spread is the definitive mechanism by which PJI develops in previously well patients. Orthopaedic infections appear to be caused by the same common group of bacterial pathogens. In this group, the majority are gram-positive cocci, namely, *Staphylococcus aureus* and *Staphylococcus epidermidis*. There is the ever-present threat of methicillin-resistant *Staphylococcus aureus* (MRSA) as a difficult PJI infection to remove. Moreover, the growing number of vancomycin-resistant enterococcus and other serious gram-negative bacteria are also a concern. Gram-negative bacteria are associated with more severe episodes of sepsis due to the production and release of lipopolysaccharides (endotoxin).

Highlighted across several studies is the concept of the arthroplasty surface acting as a unique microbial substratum [10]. Gallo et al. reported the affinity of *S. epidermidis* to attach to polyethylene surfaces as opposed to *S. aureus* preference for bare metal. In each of the papers examined by Gallo et al. the presence of biofilm on the wearing or corroded surfaces of the implants was a key factor in the bacterial resistance to host and antimicrobial attack. A paper referenced in the Gallo et al. review by Gristina [11], characterised the colonization of the prosthesis as a "race for the surface" [10]. This concept is apt at highlighting the need for pathogens to colonize, undeterred by local and host factors.

These concepts are of pivotal importance when examining the published material reviewed here in the context of the original question, "to evaluate whether operative treatment should differ in patients with systemic sepsis in the setting of prosthetic joint infection." As demonstrated in this review and supported by the significant cohort size, PJI can occur as a consequence of local or hematogenous colonization. Overall, severity of infection is higher with hematogenous spread [12–14], as is the difficulty in clearing the infection for subsequent implant revision. Osteomyelitis prior to implantation of prosthetic joints indicates increased risk as