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QUESTION 2: What are the indications for interim cement spacer exchange or repeat irrigation and debridement (I&D) instead of reimplantation?

RECOMMENDATION: Interim cement spacer exchange and/or repeat I&D may be performed, instead of reimplantation, in the presence of persistent infection and/or mechanical complications.

LEVEL OF RECOMMENDATION: Limited

DELEGATE VOTE: Agree: 97%, Disagree: 0%, Abstain: 3% (Unanimous, Strongest Consensus)

RATIONALE

Two-stage exchange arthroplasty remains the most utilized surgical treatment for the treatment of chronic periprosthetic joint infections (PJIs). However, there are occasions when the antibiotic cement spacer may be exchanged, or an I&D performed, and the reimplantation delayed [1]. The reason for these additional surgical procedures may include the inability to control infection or when potential infection is encountered during an intended reimplantation.

The rationale behind this spacer exchange practice is to deliver a further "new load" of local antibiotics as a strategy to treat the persistent infection [2,3]. Alternatively, an I&D at this stage is hypothesized to reduce the microbial bioburden. Although these practices seem intuitively rational, there is little to no published literature on the outcomes of interim spacer exchanges or additional irrigation and debridement. These additional procedures also carry marked morbidity and affect the patient journey, with Gomez et al. reporting that 17.3% of these patients never undergo reimplantation and 11.9% require more than one spacer [1]. It therefore remains unknown whether interim spacer exchange confers any benefit versus conventional two-stage exchange or in comparison to altered inter-stage antibiotic treatment.

George et al. recently presented a series of 416 two-stage exchanges for PJIs, of which 59 (17%) had an interim spacer exchange performed [4]. On assessment of Delphi treatment success, two-year and five-year success rates were 77% and 66% in the exchange group versus 86% and 77% in the non-exchange group. Their spacer exchange group had a lower infection-free survival adjusted hazard ratio (aHR) 10.69, 95% confidence interval (CI) 1.02-2.81; p = 0.039. Similar findings were presented by Goswami et al. in a retrospective study of 75 interim spacer exchanges and 352 matched controls undergoing conventional two-stage exchange at mean 3.5-year follow-up [5]. They found 31.1% of the interim exchange cohort failed treatment after eventual reimplantation, with a significantly lower treatment success compared to matched patients who underwent conventional two-stage exchange (p = 0.045).

Current indications for an additional spacer exchange or I&D include persistent infection, wound-related problems, draining sinus or mechanical complications such as spacer dislocation or fracture. However, there is also no gold standard diagnostic method demonstrating eradication of joint infection or for optimal timing of reimplantation. Several studies have identified metrics that are useful in determining if there is a persistent infectious state prior to reimplantation. Histological analysis, synovial fluid cell counts, serum D-dimer, leukocyte esterase (LE), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have all been investigated [6–12].

Feldman et al. evaluated the ability of frozen section histology to identify ongoing infection [13]. They concluded that >5 polymorphonuclear (PMN) cells per high power field (HPF) had 100% sensitivity and 96% specificity for the detection of infection. On the contrary, in a cohort of 54 patients, Cho et al. evaluated the role of PMN cell count in frozen sections at reimplantation in total knee arthroplasties (TKAs) [12]. They identified 15 patients with 5 to 20 PMNs per HPF during reimplantation. At a minimum follow-up of two years, they reported 100% eradication of infection, casting doubt on the role of frozen sections. Furthermore, George et al. demonstrated limited utility of this method for ruling out infection, given a sensitivity of only 50% (CI, 13 - 88%) [14]. False-positive frozen section results can potentially arise in patients with the use of dynamic spacers in hips, which may result in debris that accentuates inflammation seen in frozen sections, thereby making conclusions from frozen section, unreliable in such scenarios.

ESR, CRP and joint aspiration have also been evaluated in this context [8,15]. However, there is no convincing evidence to establish their roles in diagnosing persistent infection or in determining if reimplantation is indicated. Ghanem et al. attempted to define cut-off values for ESR and CRP that improve clinical differentiation between aseptic failure and periprosthetic infection prior to revision total hip arthroplasty [16]. They published that an ESR threshold of 30 mm/h has a sensitivity of 94.3% and a CRP threshold of 10 mg/L had a sensitivity of 91.1% for infection. When combining ESR and CRP cut-offs for a positive diagnosis, this increased the sensitivity to 97.6%. However, when calculated by receiver operating curve (ROC) analysis, the predictive cut-offs equated to 31 mm/h for ESR and 20.5 mg/L for CRP.

Zmitowski et al. evaluated 129 patients undergoing two-stage arthroplasty who had an aspiration before their second-stage procedure [6]. Persistent infection was defined as a positive aspirate culture. In 33 cases (25.6%) that were classified as persistent PJIs, patients had significantly elevated PMN % (62.2 vs. 48.9%; p = 0.03) and white blood cell (WBC) counts (1,804 vs. 954 cells/μL; p = 0.04). Although statistically significant differences were noted, diagnostic accuracy for persistent PJIs was <60% for all variables, except synovial WBC counts.

In another retrospective study of 76 infected TKAs treated with two-stage exchange, Kusuma et al. evaluated the role of serological tests for determining eradication of infection during two-stage exchanges [8]. They concluded that while the ESR, CRP and synovial fluid WBC count decreased in cases where infection control was achieved, these values frequently remained elevated. The ESR remained persistently elevated in 54% of knees and the CRP remained elevated in 21% of knees where the infection had been controlled. Despite their inability to identify any patterns in these tests indicative of persistent infection, they proposed that synovial fluid WBC counts as the best test for confirmation of infection control.

Furthermore, Janz et al. investigated the effectiveness of synovial aspiration in resection arthroplasty hips for detecting persistent infection in patients undergoing two-stage revision total hip arthroplasty (THA) [10]. Diagnostic performance of the synovial aspiration

of these hips achieved a sensitivity of only 13% and a specificity of 98%. They concluded that aspiration is of limited diagnostic validity and cannot reliably detect or rule out infection. However, they highlighted the fact that a positive aspiration culture had a high diagnostic performance.

Recently, serum D-dimer tests have been proposed as promising tests for diagnosing PJIs [7]. The study evaluated the role of D-dimer in detecting the presence of infection at the time of reimplantation. Out of five patients with raised D-dimer levels at the time of reimplantation, two had a positive culture from samples taken during reimplantation and subsequently failed. It is worth mentioning that both ESR and CRP values were normal in these two patients.

As previously mentioned, there is no gold standard test for PJIs. After spacer insertion and a period of antibiotic treatment, infection control is expected and laboratory and clinical signs are expected to improve.

In the setting of a failure to improve or if there is ongoing active infection at the time of planned reimplantation, a repeated irrigation, debridement and spacer exchange may be considered. Further research is essential to establish effective tests that prove eradication of PJIs and therefore determine if reimplantation should be performed. The role of several tests, such as elevated ESR and CRP, synovial WBC, and PMN % as well as serum D-dimer are helpful in determining whether reimplantation can be carried out but are not absolute determinants. A combination of these tests, clinical suspicion, completion of antibiotic therapy and careful evaluation of MusculoSkeletal Infection Society (MSIS) criteria [17] should be used to determine if a repeated cement spacer exchange may be indicated. Repeated I&D of an implanted spacer, without antibiotic spacer exchange, does not seem to have any evidence and is generally considered a suboptimal approach in this setting.

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QUESTION 3: Should the antibiotics placed in a cement spacer be tailored to the sensitivity of the infective organism?

RECOMMENDATION: Antibiotics added to cement spacer during resection arthroplasty should be tailored towards the causative organism and its susceptibility. In case of culture negative periprosthetic joint infections (PJIs), consideration should be given to the addition of a broad-spectrum antibiotic to the cement spacer to cover the most potential pathogens causing PJI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 94%, Disagree: 3%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

The literature was reviewed to identify all publications related to the above question. The systemic review revealed 12 publications with clear information about tailored local antibiotics in bone cement spacers. The majority of the papers were retrospective studies with a relatively low number of patients in each report. One study by Hsieh et al. contained 99 patients, which was the largest cohort [1]. There were two review articles from the same group [2,3]. Kiniet al. reviewed the available literature that consisted of 17 publications related to hip infections and 18 studies related to PJIs of the knee. They did not find clear evidence related to the issue of antibiotics