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QUESTION 2: What metrics should be considered to determine the timing of reimplantation after two-stage exchange arthroplasty of the infected hip or knee?

RECOMMENDATION: There are no definitive metrics to allow determination of optimal timing of reimplantation. Thus, timing of reimplantation should consider resolution of clinical signs of infection, down-trend in the serological markers and results of synovial analysis, if aspiration is performed.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 96%, Disagree: 3%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Because optimal timing for reimplantation is unknown, most surgeons prefer to rely on a combination of clinical evaluations, such as clinical evidence of infection control and normalized laboratory values after a period of antibiotic therapy [1]. There is no gold standard that can guide surgeons to determine the optimal time of reimplantation [2]. Various serum and synovial markers have been studied to identify the most accurate test for screening for persistent periprosthetic joint infection (PJI). A common finding of most of the studies is a high specificity, but low sensitivity.

Serum Analysis

Several serum markers have been evaluated for PJI, but only a few prior to reimplantation. Serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been widely evaluated for diagnosis, monitoring treatment and evaluating their role in identifying the optimal timing of reimplantation [2–9]. Although a decreasing trend in both markers is seen during the interval period, they can still be elevated in patients that are considered to have a treated infection and have also been seen to be normal in persistent infection. In different studies, no cut-off values could be determined and there were no significant differences in average ESR and/or CRP values at time of reimplantation between infected and non-infected cases [3,7].

Interleukin-6 (IL-6) has been recently studied among other biomarkers in PJI. It has been seen that it may have a role in defining persistent infection prior to reimplantation, although stronger evidence is needed [10]. A recent study by Shahi et al. [11], showed promising results in determining the reimplantation time using serum D-dimer test. In their cohort, 29 patients underwent reimplantation surgery for PJI. Five patients had elevated D-dimer levels at the time of reimplantation, two of which had a positive culture from intraoperative specimens (*Staphylococcus epidermidis* in one patient and *Cutibacterium acnes* (*C. acnes*) in the other patient). Both of those patients subsequently experienced failure due to infection. Based on the results of this study, D-dimer outperforms both ESR and CRP for determining the timing of reimplantation. The corresponding CRP and ESR values were falsely negative in both of these patients (a CRP level of 8 mg/L and an ESR of 20 mm/hr in one patient; a CRP level of 1 mg/L and an ESR of 9 mm/hr in the other patient). Ongoing clinical research is currently investigating the utility of D-dimer in determining the timing of reimplantation surgery. D-dimer is an inexpensive and widely available test that can aid in identifying the timing of reimplantation.

Joint Aspiration

Synovial fluid aspiration and analysis for cell count, microbiological culture and biomarkers prior to reimplantation is also widely being used to detect persistent infection. Studies on synovial fluid WBC and differential analysis are contradictory [6–9,12,13]. Kusuma et al. [7], showed that prior to reimplantation, synovial fluid white blood cell (WBC) and differential analysis are poor markers of persistent PJI in the knee. Conversely, Shukla et al. (6) found pre-reimplantation synovial WBC count to be highly diagnostic of persistent infection in the hip. Zmitowski et al. [12], reported elevated synovial WBC count and polymorphonuclear lukocyctes (PMN)% statistically significant in patients with persistent PJI but did not provided useful threshold to identify patients with persistent PJI. Almost all studies evaluating microbiological culture of joint aspirate report a very low sensitivity, which means persistent infections are not detected [8,9,13,14]. In addition, Mühlhofer et al, [8] identified that microbiological synovial fluid analysis can also be misleading due to false positive cultures.

Kheir et al, [15] reported on the use of the leukocyte esterase (LE) as a screening test for persistent infection. This test demonstrated a high specificity (100%), but low sensitivity (25%). A positive LE result had a high predictive value of failure of reimplantation. Frangiamore et al, [16] evaluated synovial fluid cytokines to determine the highest diagnostic accuracy for PJI. IL-6 and IL-1β showed the greatest decrease between first and second stages; these could potentially be used to monitor PJI treatment response. Due to the low sensitivity of these tests, they fail to provide a definite answer as to the infection status.

MusculoSkeletal Infection Society (MSIS) Criteria

The efficacy of MSIS criteria for determining infection resolution in PJI has also been evaluated [15–17]. Despite the clinical importance of these criteria, the lack of sensitivity of these tests do not make them useful in diagnosing persistent infection. Frangiamore et al. reported a specificity of 89% and sensitivity of 0% for MSIS criteria to rule out PJI after the first-stage [16]. Another study by Georges et al. [17], evaluated 97 patients undergoing reimplantation and also demonstrated a high specificity but low sensitivity for MSIS criteria

for diagnosing persistent infection. They concluded that MSIS criteria should be evaluated at the second stage of revision arthroplasty because they discovered that performing reimplantation in a joint that is MSIS-positive for infection significantly increased the risk for subsequent failure.

Intraoperative Tests

Intraoperative frozen sections have also been used as a reliable indicator of infection during revision arthroplasty. These have been well studied for infection eradication in revision surgeries. Although there is still debate about the optimal diagnostic cut-off (number of PMNs per high-power field), authors have recommended that reimplantation should be delayed when frozen sections are positive. However, intraoperative frozen sections are not reliable enough for ruling out persistent infection because of a low sensitivity [17–21]. Della Valle et al. showed a sensitivity of 25% in their study (18). More recently, George et al. reached a 50% sensitivity, despite the fact that these specimens were evaluated by a highly specialized pathologist [17]. Intraoperative microbiology stains are not recommended due to their very low sensitivity [22–24].

We consider that a combination of available diagnostic variables should be evaluated to determine the infection status of a patient prior to reimplantation. A surgeon must rely on this strategy and clinical judgment to proceed with reimplantation.

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QUESTION 3: Is normalization of serological markers necessary prior to reimplantation arthroplasty performed as part of a two-stage exchange?

RECOMMENDATION: No. A trend and decline in C-reactive protein (CRP) and erthyrocyte sedimentation rate (ESR) is expected, but we still recognize that there are certain cases in which reimplantation may be performed despite abnormal levels of ESR and CRP. Surgeons should not wait for complete normalization of the inflammatory markers as this may not occur in some patients and/or take a long period of time.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 95%, Disagree: 4%, Abstain: 1% (Unanimous, Strongest Consensus)