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)

RATIONALE

Among the efforts to improve the effectiveness of the two-stage exchange for periprosthetic joint infection (PJI) are the attempts to identify persistent infection, by the use of primary and secondary inflammatory markers, before reimplantation.

A decline in ESR and CRP levels in conjunction with the absence of clinical signs of infection are often believed to be an indication that it is safe to proceed with reimplantation. Ghanem et al. [1] demonstrated that in patients with recurrent infection, ESR and CRP mean levels, before the second stage, were similar to those in patients whose infection had been successfully treated. Similarly, Kusuma et al. [2] found no significant difference in test results between the persistently infected and non-infected groups before second-stage surgery. In both studies, the authors constructed a retrospective review with the intent of determining a specific value of ESR, CRP, or both that could be used to detect continued infection prior to reimplantation. They found that no such value could be determined and that the ESR and CRP of those with and without infection were similar.

The persistently elevated ESR and CRP levels, at the time of reimplantation, were found in 54% and 21% of the patients, respectively. Also, Shukla et al. [3] reported that the mean ESR and CRP levels significantly decreased between stages, but remained elevated in 62.5 and 27.5% of the patients in whom the infection had been eradicated.

Kubista et al. [4] found no statistically significant differences in mean values for CRP or ESR before resection or reimplantation when comparing the treatment failure group to the control group.

One study did note that there was a weak trend between the level of inflammatory markers prior to reimplantation and the subsequent outcome in total knee arthroplasty (TKA) patients undergoing two-stage exchange arthroplasty [5]. In a similar study for total hip arthroplasty (THA), no association between successful second stage reimplantation and pre-reimplantation levels of ESR and CRP could be detected [6]. Likewise, the values did not differ between failure and success groups in a series reported by Mortazavi et al. [7]. Therefore, the available evidence suggests that serologic markers cannot be the only factor in guiding the surgeon for the appropriate timing of reimplantation.

While some authors advocate for waiting until normalization of inflammatory markers ESR and CRP [8–11], many others [12–16] rely upon a downward trend of the markers before proceeding with reimplantation. In those cases, in which no constant decrease of the values is observed, some prefer to promote spacer exchange instead of reimplantation [17,18].

The level of inflammatory markers may remain elevated in patients with inflammatory conditions which can cloud the picture [19,20]. The inflammatory markers should still be measured in patients with inflammatory conditions both for the purpose of diagnosis of PJI and also determining the timing of reimplantation. George et al. [21] analyzed the diagnostic utility of ESR and CRP to detect, at the time of the second stage, persistent infection in patients with inflammatory arthritis. At the time of reimplantation, ESR and CRP remained elevated above the MusculoSkeletal Infection Society (MSIS) threshold in many patients with inflammatory arthritis. The authors, however, did conclude that persistently elevated serological markers should not always be presumed to be the result of underlying inflammatory arthritis, and could suggest an ongoing infection [21].

Previous studies have examined the role of other serum markers for infection. One such marker is Interleukin-6 (IL-6) that has been shown to be highly predictive of PJI in patients undergoing revision surgery in one study [22]. A cut-off serum value of 8 pg/ml is a sign of an absence of infection and perhaps an indication for reimplantation. Other studies have not been able to prove value for serum cytokines but have suggested that if such markers are measured a downtrend between the two stages may provide an important guide for clinicians to monitor the treatment response [23]. Recently the serum D-dimer was reported to have a great potential for diagnosis of PJI [24]. The utility of this test for optimal timing of reimplantation is being evaluated and the preliminary results presented in the American Academy of Orthopaedic Surgeons (AAOS) annual meeting, by the same authors, appeared to be encouraging.

Regarding the analysis of synovial fluid, Zmistowski et al. [25] postulated that synovial fluid analysis, even though of unclear utility, may detect persistent PJI before reimplantation. Shukla et al. [3] observed that white blood cell (WBC) count could identify persistent infection with a cut-off value of 3,000 cells/μL. To the contrary, Muhlhofer et al. [26] could not establish cutoff values for CRP, leucocytes, WBC count and polymorphonuclear (PMN) percentage, thereby observing that no reliable markers were indicative of persistence of infection. CRP and leucocytes were often found to be elevated, even when the infection had been controlled.

A synovial biomarker with great promise is leucocyte esterase (LE). A study by Kheir et al. found that a positive LE test (defined as ++) at the time of reimplantation was indicative of persistent infection and predicted a later failure with great accuracy [27]. Another recent study from the same institution by Tarabichi et al. [28] posited that analysis of LE, when used in conjunction with serologic screening, is a powerful point of-care test for diagnosis of PJI and timing of reimplantation. Based on the available evidence it is worthwhile to consider the use of LE strips at the time of reimplantation that can provide the surgeons with additional and definitive analytical information.

Based on the current evidence, serum inflammatory markers, ESR and CRP, are not believed to be reliable on their own in determining the presence of infection. It is our understanding and recommendation that these markers should still be monitored between the two stages and a decline in their value sought before proceeding with reimplantation. The value of the serum ESR and CRP in timing the reimplantation may be improved if the result of synovial fluid analysis, in particular using the LE strip test, and possibly other serum markers, such as D-dimer, are combined. There is a need for future studies to identify the most appropriate marker that may be indicative of persistent infection.

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QUESTION 4: What is the importance of two-week antibiotic holiday prior to reimplantation?

RECOMMENDATION: Unknown. There is no conclusive evidence to support the need or the ideal length of an antibiotic holiday prior to reimplantation.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 7%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

Two-stage exchange arthroplasty continues to be the preferred method of treatment for chronic periprosthetic joint infections (PJIs) in the United States and Europe. Traditionally, the procedure involves removal of all foreign material and a six-week period of ensuing antibiotic treatment. Prior to reimplantation it is customary to implement a 14-day antibiotic-free interval, known as a drug holiday, intended to allow for "emergence" of residual infection [1]. During this period serological testing and synovial aspiration are usually performed to ensure that infection is under control prior to proceeding with reimplantation. However, this widely implemented therapeutic option has remained controversial [2] because of the paucity of the systemic antibiotic treatment after six weeks, which can lead to the persistence of an infection and the development of multiple drug-resistant bacterial strains.

In addition, the accuracy of serological tests and synovial aspiration under ongoing systemic antibiotic therapy is debatable. Ghanem et al. [3] and Spangehl et al. [4] have reported that data regarding the value of serological markers and synovial aspiration between the stages have been published using heterogeneous cohorts, short follow-up periods and inconsistent antibiotic-free intervals. Meanwhile, some studies have suggested the abandonment of the systemic antibiotic pause after six weeks in favor of a continuous antibiotic administration [5,6].

Bejon [7] et al. (2010) retrospectively reported on 152 patients with periprosthetic joint infection (PJI) who were treated with two-stage revision with a success rate of 83% over a median follow-up duration of 5.7 years; this is within the reported range of success rates [7]. The reimplantation was preceded by a two-week antibiotic-free period in 88% of the cases. However, the microbiology was positive in 3 of 18 patients (16%) without a two-week antibiotic-free period compared with 18 of the 134 patients (13%) with a two-week antibiotic-free period. At reimplantation, more knee joints were culture positive than hip joints, despite being less frequently culture positive at the first-stage excision. Spacers were used in all knee joint revisions; however, they were rarely used for the hips (13%). They did not use aspiration but waited during the two-week antibiotic-free period and decided whether to perform reimplantation based on the clinical appearance. Most unexpected debridements following the first