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QUESTION 7: What is the diagnostic accuracy of a frozen section (FS) during reimplantation surgery? What thresholds should be used in this context?

RECOMMENDATION: Adequate peer-reviewed literature exists to support either of two diagnostic thresholds for supporting the diagnosis of periprosthetic infections of the hip and knee: 5 neutrophils (PMNs) in each of at least 5 high power (400X) microscopic fields (HPF), or 10 PMNs in each of at least 5 HPFs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 83%, Disagree: 10%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

A common method of treating periprosthetic infection of the hip or knee is two-stage exchange [1], but it can be difficult to determine if and when the infection has been adequately treated and the infected joint is ready to receive a new implant. The tests commonly used to help diagnose infection at revision arthroplasty, such as serologic tests, microbiologic culture, and the cell count with differential of aspirated joint fluid may have been influenced by the previous surgery as well as an antibiotic-containing spacer and may not have the same predictive value as when they are applied at revision arthroplasty [2].

One of the few tests that can be performed during a reimplantation or revision arthroplasty operation is the interpretation of a FS of

TABLE 1. Study results showing similar values as reported for frozen sections obtained at primary arthroplasty

Reference	Cases	Sensitivity	Specificity	PPV	NPV	Accuracy
[10]*	64	25%	98%	50%	95%	94%
[11]**	79	50%	94%	50%	94%	90%
[13] (FS)**	47	56%	95%	73%	97%	87%
[13] (PS)**	47	89%	94%	80%	97%	94%

PPV, Positive Predictive Value; NPV, Negative Predictive Value; FS, Frozen Sections; PS, Permanent Sections

* Threshold: 10 PMN in each of at least 5 HPF

** Threshold: 5 PMN in each of at least 3 HPF

periprosthetic tissue. In that context, the presence of acute inflammation, as characterized by neutrophils (neutrophilic granulocytes, polymorphonuclear leukocytes, (PMNs), suggests ongoing infection [3-6]. The tissue block from which that section was prepared is then formalin fixed and processed, along with additional tissue samples as a "permanent section" to be interpreted a day or two later. As a rule, the higher the tissue concentration of neutrophils, the more likely the joint is infected, but there is controversy about the best threshold to help diagnose or rule out infection. Several systematic reviews have identified adequate high-quality studies support thresholds of either 5 or more neutrophils in each of 5 HPFs or 10 or more neutrophils in each of 5 HPFs to support the diagnosis of infection [3,7] at the time of revision arthroplasty. Several other thresholds have also been suggested [8,9] and the results of FS have also shown good correlation with the modified MusculoSkeletal Infection Society (MSIS) criteria for periprosthetic infection [4]. However, few studies have addressed the accuracy of FSs to diagnose persistent infection at the second stage reimplantation of a two-stage revision arthroplasty for known periprosthetic infection.

In 1999, Della Valle et al. [10] published a retrospective study of 64 patients (33 women and 31 men) who had undergone resection arthroplasty for periprosthetic infections and from whom FSs were obtained. The resection arthroplasties had been obtained a mean 40 months after arthroplasty and reimplantation occurred on average 19 weeks later. The threshold for suggesting infection was 10 PMNs in each of at least 5 HPF. Cases with fewer than 5 PMN in each of 5 HPF were interpreted as negative. None of the cases had more than 5 but less than 10 PMNs per HPF. As is common practice in pathology, microscopic fields represented areas of maximum neutrophil concentration, not the overall average of the entire section. Of the 64 patients, two had positive FSs, but one was negative on review of permanent sections. 61 of the 62 patients with negative FSs were also negative on review of permanent sections. Four patients were considered to be infected; the remaining 60 patients had negative cultures and histology. The results are summarized in Table I and indicate 25% sensitivity (the FS detected one of four persistent infections), 98% specificity, 50% positive predictive value (PPV), 95% negative predictive value (NPV) and 94% accuracy.

George et al. published two retrospective studies testing the use of FSs and permanent histology to diagnose infection at reimplantation. The first [11] sought to compare the diagnostic accuracy of FSs compared with the MSIS criteria of infection [12] and to further test the use of FS and MSIS criteria to predict clinical failure of reimplantation. The study identified 79 patients who had undergone two-stage revision for infected arthroplasty (38 knees and 41 hips) and had adequate records to assess MSIS criteria, had FS results and minimum 1-year follow-up. Patients had undergone the second step of the two-stage procedure after at least six weeks of antibiotics, and intraoperative samples at the time of reimplantation had been obtained for histologic and microbiologic evaluation. There were 48 men and 31 women. The threshold for interpreting a FS as supporting infection included 5 or more PMNs in 3 or more, 400X high power fields (based on fields with maximum PMN concentration). Note that this threshold requires fewer fields than commonly recommended, so might be expected to have greater sensitivity but less specificity than if 5 or more HPF were required. The FS results were compared to the reference standard, which for this part of the study was the based on the MSIS criteria. The results showed sensitivity of 56%, specificity of 94%, PPV of 50%, NPV of 94% and 90% accuracy (Table I).

Recognizing that rheumatoid arthritis might complicate the interpretation of serologic and other tests for infection at reimplantation, George and co-authors also reviewed the utility of Fss and permanent histology to diagnose infection at reimplantation in patients with an underlying inflammatory arthropathy [13]. They identified 47 revisions (39 patients) with confirmed inflammatory arthropathy, and compared the results of FS interpretation, and interpretation of corresponding permanent sections with the presence or absence of persistent infection as defined by the MSIS criteria at the planned second stage re-implantation. The threshold for positive histology was the same as in their previous study: 5 or more PMN in at least 3 HPF. The results of FS showed sensitivity of 56%, specificity of 95%, PPV of 73%, NPV of 97% and 87% accuracy. Of the 120 specimens analyzed by frozen and permanent sections, there were only four discrepancies. In each, the permanent section was interpreted as positive (infected) while the FS had been interpreted as negative, although not all of these were clinically relevant because some cases had other positive Fss. Ultimately the permanent sections had two false positive results and one false negative, while the FSs had two false positives and four false negatives. Therefore, the results of permanent sections were sensitivity of 89%, specificity of 94%, PPV of 80%, NPV of 97% and accuracy of 94% (Table I).

Although reported results are variable, most studies have indicated that the interpretation of a FS at revision arthroplasty has good NPV (i.e., absent neutrophils supports the absence of infection) [10], but that observation is dependent in part on sampling. In 2010, a Practice Guidelines Committee of the American Academy of Orthopaedic Surgeons (AAOS) found adequate high-quality published literature to support either of two diagnostic thresholds: 5 neutrophils in each of 5 HPFs (of maximum tissue concentration), or 10 neutrophils in each of 5HPFs [14]. A lower threshold for neutrophil concentration would be expected to be associated with increased sensitivity and lower specificity (increased false positive diagnoses [15]. Although most studies have shown the sensitivity of the two thresholds to be equivalent, some studies have reported slightly higher specificity if 10 neutrophils are required rather than 5 [16]. Recognizing that no test has perfect specificity and sensitivity, the

clinical importance of recognizing periprosthetic infection is high enough that some surgeons prefer maximizing sensitivity even at a slight cost of specificity. For example, Kwiecen et al. [4] recently reported sensitivity of 73.7% and specificity of 98.8% for a FS obtained at hip and knee arthroplasty using a threshold of 5 neutrophils in only 3 or more HRFs (the same threshold used in both studies by George et al. described above).

As noted above, the thresholds used to support the presence or absence of periprosthetic infection have been reported mostly from specimens obtained at intended primary revision arthroplasty. Patients with known periprosthetic infection are often treated with the two-stage procedure and it is thought that the surgery and presence of an antibiotic-containing spacer may alter the results of tests commonly used to diagnose infection, including serologic markers, joint aspiration with cell count, microbiologic cultures and possibly histology [2,17,18]. Although few published studies have included enough information to document sensitivity and specificity of different diagnostic thresholds for recognizing persistent infection at the second-stage of a two-stage operation for known infection, the results summarized here show similar values as those reported for FSs obtained at primary arthroplasty. Additional studies, including the use of special stains and rapid molecular tests are needed to help document either persistent infection or adequate resolution of the infection at the time of reimplantation.

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QUESTION 8: Should patients with periprosthetic joint infections (PJIs) caused by Mycobacterium tuberculosis (TB) undergo the typical two-week antimicrobial holiday prior to reimplantation?

RECOMMENDATION: There is no evidence supporting the two-week antimicrobial holiday before reimplantation. Patients with PJIs caused by TB do not need to have the two-week drug holiday.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 88%, Disagree: 6%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

TB is a rare cause of PJIs for which management is not clearly standardized [1,2]. This may be due to the little clinical suspicion and the difficulty in diagnosing this entity [3]. Literature reflects this infrequency with very few publications, the majority being case reports [2,4–14]. McCullough et al. [14] were the first to describe a prosthetic joint involvement due to TB. They hypothesized that this occurred during a bacteremic state following reactivation of latent tuberculosis. This and other reports have shown infection control can be achieved after surgical and pharmacological treatment although no conclusions can be made as to formal and standardization of treatment.