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QUESTION 6: What is the diagnostic accuracy of histologic tests and thresholds used in the diagnosis of periprosthetic joint infections (PJIs)?

RECOMMENDATION: There is a variability of the histologic examination of intraoperative frozen sections as well as the thresholds used for the presence of neutrophils. The preparation and interpretation of frozen sections can be highly operator-dependent.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 88%, Disagree: 5%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

A recently published meta-analysis of longitudinal studies that compared histologic results with simultaneously obtained microbiologic cultures by Tsaras et al. 2012 [2] included 26 studies, published between 1982 and 2009 and included 3,269 patients who had undergone hip or knee arthroplasty. Of those patients, 796 (24.3%) had a culture-positive PJI. Using the diagnostic criteria chosen by the investigating pathologist, the pooled data showed that a positive result from a frozen section by histopathology predicted a 75% (95% confidence interval (CI), 67-82) probability of a positive culture infection and a negative frozen section result predicted a 5% (95% CI, 4-8) probability of a culture-positive infection. In 15 studies, the threshold of 5 polymorphonuclear leukocytes (PMN) per high power fields (HPF) in each of at least 5 HPF to define a positive frozen section had a diagnostic odds ratio (OR) of 52.6 (95% CI, 23.7 – 116.2), while 6 studied the threshold of 10 PMNs per HPF and had a diagnostic OR of 69.8 (95% CI, 33.6-145). No statistically significant difference between the two thresholds was found. The authors concluded that intraoperative frozen section histologic evaluation was very good at predicting a diagnosis of culture-positive PJI and had a moderate accuracy in ruling out the diagnosis of PJI.

Corresponding results of a meta-analysis of the accuracy10 vs. 5 PMNs as a threshold in frozen sections to diagnose PJIs was published by Zhao et al. in 2013 [3]. The meta-analysis includes 12 studies, published between 1972 and 2012, involving 1,011 patients undergoing hip arthroplasty of which 194 (19.2%) patients had a PJI. In 7 studies, the threshold of 5 PMNs per HPF was used, in 2 studies, the threshold of 10 PMNs per high-power field was used, while in 3 studies, both thresholds were used. The diagnostic OR was 23.5 (95% CI, 10.5 – 52.7) when 5 PMNs per HPF was used and 35 (95% CI, 7.7– 159.3), when 10 PMNs per HPF was used. Equally, they found no statistically significant difference between the two thresholds. The authors concluded that their results indicates that though both thresholds are stable and effective, a threshold of 10 PMNs per HPF is better for diagnosing PJI.

Since the meta-analysis included studies until 2009 [2], 17 studies [4–20] have been published from 2010 to 2017 and considered as relevant to the question about the accuracy of the method. These studies show a variability of the accuracy between 65.6 and 99%, a sensitivity between 38.8 and 96.6% and a specificity between 77 and 100% [4–20]. The studies were performed at single centers, and the majority of the studies included less than 100 patients of which less than 25 patients were infected.

The accuracy value of thresholds in the meta-analysis by Zhao et al. in 2013 [3] was 85.2% (95% C,I 79.3-91.1) when 5 PMNs per HPF was used and 89.1 (95% CI, 80.5– 97.7), when 10 PMNs per HPF was used. The true positive rate (sensitivity) was 0.67 (95% CI, 0.49-0.86) and 0.6 (95% CI, 0.27-0.93) for 5 PMNs per HPF and 10 PMNs HPF, respectively. The corresponding figures for the true negative rate (specificity) was 0.9 (95% CI, 0.85-0.96) and 0.93 (95% CI, 0.85-1.0).

The results of the meta-analysis [2,3] of the thresholds show wide 95% CI in the diagnostic OR for the 5 and 10 PMNs per HPF, respectively. This may indicate small sample sizes that may not be able to show a difference that exists.

Nevertheless, adequate published evidence exists to support diagnostic thresholds of either 5 PMN in each of 5, 40X HPF (maximum tissue concentration) or 10 PMN in each of 5 HPF to help diagnose or rule-out periprosthetic infection at revision arthroplasty. Exceptions exist, but in general, increasing the concentration of PMN required for diagnosing infection from 5 to 10 PMN per HPF may slightly increase specificity but have little effect on sensitivity. A few studies have advocated using lower PMN concentrations to maximize sensitivity [13,19]. The studies reviewed apply only to tissue obtained at revision arthroplasty of the hip or knee; different optimum thresholds may exist for the shoulder or other sites.

Kashima and his co-workers [21] found that all cases of aseptic loosening contained fewer than 2 PMNs per HPF and that in some cases of septic loosening, fewer than, on average, 5 PMNs per HPF are present in periprosthetic tissues. The study included 76 patients of which 22 were infected. The histological criterion of more than 2 PMNs per HPF showed increased sensitivity and accuracy for the diagnosis of septic loosening. The sensitivity, specificity, and accuracy for +++ neutrophil polymorph infiltration was 83, 96 and 91 %, respectively, and for >++ neutrophil polymorphs 94, 96 and 97 %, respectively. In their conclusion, they suggest that the MusculoSkeletal Infection Society (MSIS) histological criterion of more than 5 PMNs per HPF is too high an index figure for the diagnosis of all cases of hip and knee arthroplasty infection.

Limitations

It is likely that the method of tissue sampling by the surgeon and the experience of the pathologist influence the value of frozen sections obtained at revision arthroplasty. For example, it has been suggested that PMNs entrapped in superficial fibrin or migrating from capillaries in granulation tissue should not be included in the PMN quantification. Pathologists should also avoid misinterpreting granulocyte precursors in the hematopoietic bone marrow that often accompanies these biopsies as suggestive of infection and it can be difficult to distinguish eosinophils from neutrophils in some frozen sections. The microscopic fields selected for PMN quantification should represent the maximum neutrophil concentration, not the overall average on the microscope slide, and tissue obtained from near a recent periprosthetic fracture may contain neutrophils unrelated to infection. Many of the reports in this review fail to specify the above limitations, so subtle differences in the routine practice of pathologists in different centers may contribute to the variable quality of frozen section (FS) interpretation [22]. In addition, the reference standard against which FS interpretation has been meas-

ured has not been consistent. Some authors have considered one positive culture as indicating infection, others have required additional factors or have used the MSIS criteria [7] Other studies have recognized that long-term clinical follow-up may be needed to define clinically relevant periprosthetic infections, especially those involving organisms of low-virulence [23].

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QUESTION 7: What is the role of specific granulocyte counting methods and new immunohistologic staining techniques in diagnosing periprosthetic joint infection (PJI)?

RECOMMENDATION: The role of specific granulocyte counting methods and new immunohistologic staining techniques is to support the diagnosis of infection when diagnosis is uncertain. The recommended threshold is 5 or more polymorphonuclear leukocytes (PMNs) per field in each of 5 high power (400x objective) magnification fields. The stains reported-to-date can only be performed on sections of formalin-fixed, paraffin embedded tissue. Therefore, they are not available for use on frozen sections obtained during an operation.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 85%, Disagree: 4%, Abstain: 11% (Super Majority, Strong Consensus)

RATIONALE

Currently, histology has been considered as one of the variables for PJI diagnosis [1]. Literature has reported on tissue reaction associated with implant failure and its relationship with infection [2]. It has been seen that an increase of PMNs correlates with the presence of an active infection [3,4]. New methods have been introduced to increase diagnostic performance. A literature search of PubMed, Ovid, Embase and the Cochrane Library was performed to include studies that evaluated the role of granulocyte counting methods and/or evaluating new immunohistologic staining techniques. The following types of studies were excluded:

1. Studies with histology metrics were used as the gold standard to test the results of other tests.
2. Studies involving primarily sites other than hip or knee (for example, shoulder operations are excluded).
3. Reviewed articles and case reports.
4. Articles published in languages other than English.