performance of D-dimer in this specific cohort. Larger cohorts are needed to not only further validate D-dimer as a serological marker of PJI, but also to develop a D-dimer threshold that can be used universally. Given its superior diagnostic performance and universal availability in hospitals, we recommend the routine use of D-dimer as part of the battery of serological markers used in evaluating a patient with suspected PJI.

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QUESTION 4: How does the level of leukocyte count and neutrophil percentage in the synovial fluid change with time following total joint arthroplasty?

RECOMMENDATION: The levels of leukocyte count and neutrophil percentage in the synovial fluid drop as one moves further away from the index arthroplasty. The latter is the rationale behind using different thresholds for these parameters in the diagnosis of acute versus chronic periprosthetic joint infections (PJIs).

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 4%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

We have recognized that the synovial composition changes as postoperative time increases, which is the reason for separate optimal cut-off values in the diagnosis of acute and chronic PJIs. During the last consensus meeting, the recommended cut-off value for the diagnosis of acute PJI (< 6 weeks from surgery) for synovial white blood cell (WBC) count was > 10,000 cells/μL and > 90% polymorphonuclear cells (PMNs) [1]. Likewise, the synovial fluid cut-off values for a chronic PJI were a WBC count > 3,000 cells/μL and > 80% PMNs [1]. When the optimal cut-off values are adjusted for the span of time after a procedure to differentiate an acute and chronic PJIs, synovial analysis remains a highly reliable diagnostic tool with similar diagnostic accuracy between acute and chronic PJIs.

Although adjustments in the WBC count and percentage of PMNs have improved the diagnostic accuracy for acute and chronic PJI, we have a limited understanding of the change in reliability of synovial analysis on a week-by-week basis. For instance, we do not have a strong understanding whether application of the same threshold two-weeks and six-weeks postoperatively has the same diagnostic reliability. Because we do not have literature to compare the proposed situation specifically, we must qualitatively compare two studies utilizing similar threshold cut-off values at different times postoperatively.

Kim et al. and Bedair et al. each investigated the diagnostic accuracy with similar optimal cut-off values from synovial analysis in the early postoperative period following primary total knee arthroplasty (TKA); however, each utilized differing patient inclusion criteria of three- and six-weeks, respectively [4, 6]. Applying a WBC count threshold of >11,200 cells/μL, Kim et al. had a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 100, 98.9, 65.4, and 100%, respectively [6]. Similarly, a percentage PMN threshold of >88% had a sensitivity, specificity, PPV, and NPV of 100, 65.6, 5.7, and 100%, respectively [6].

When compared to the diagnostic characteristics published by Bedair et al. (Table 1), the two studies demonstrate similar diagnostic accuracy for synovial WBC count and percentage PMNs. Therefore, increasing postoperative timespans appears to have limited influence on the diagnostic accuracy between three- and six-weeks from surgery. However, the same might not hold true for the diagnosis of chronic PJI.

Christensen et al. investigated the effect of increasing time intervals on synovial analysis in TKA patients who underwent aspiration as part of an evaluation for PJI and ultimately were determined not to have a PJI [7]. The authors investigated synovial analysis at ≤45 days, 45 to 90 days, 3 months to 1 year, and 1 to 2 years after surgery. Their data demonstrated synovial WBC count and percentage PMNs normalized between three months and one year after surgery [7]. As a result, it is possible increasing postoperative time intervals could alter the interpretation of synovial analysis in the setting of diagnosing a chronic PJI.

TABLE 1. Synovial cut-off values and associated test characteristics

Variable/Statistical Test	Acute Hip PJI [2]	Chronic Hip PJI [3]	Acute Knee PJI [4]	Chronic Knee PJI [5]
Cut-off Values WBC count (cells/μL); %PMNs	>12,800; >89%	>3,966; >80%	>10,700; >89%	>3000; >80%
Sensitivity (WBC count; %PMNs)	89%; 81%	89.5%; 92.1%	95%; 84%	80.6%; 83.9%
Specificity (WBC count; %PMNs)	100%; 90%	91.2%; 85.8%	91%; 69%	91.2%; 94.9%
Positive Predictive Value (WBC count; %PMNs)	100%; 91%	76.4%; 59.3%	62%; 29%	67.5%; 78.8%
Negative Predictive Value (WBC count; %PMNs)	88%; 79%	97.5%; 98.0%	99%; 97%	95.4%; 96.3%

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QUESTION 5: What is the role of alpha-defensin in the diagnosis of periprosthetic joint infections (PJIs)?

RECOMMENDATION: Measurement of alpha-defensin in synovial fluid is a complement to existing diagnostic tests for PJIs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 82%, Disagree: 14%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Alpha-defensins are antimicrobial peptides released by neutrophils in response to pathogens. They can be measured in synovial fluid and have been proposed as an indicator for PJI. Alpha-defensin use as a PJI diagnostic marker was introduced first by Deirmengian et al. in 2014 [1].

There are two commercially available methods for measuring alpha-defensin in synovial fluid: (1) the enzyme-linked immunosorbent assay-based alpha-defensin immunoassay (Zimmer Biomet, Warsaw, IN, USA), which gives a numeric readout within 24 hours and (2) the alpha-defensin lateral flow test (Zimmer Biomet, Warsaw, IN, USA), which gives a binary readout within minutes. Both assays were developed with the intention of matching the MusculoSkeletal Infection Society (MSIS) criteria as the gold standard for diagnosis of PJI.

The Alpha-defensin Laboratory Test

The alpha-defensin laboratory-based immunoassay measures the alpha-defensin concentration in synovial fluid, providing results relative to a signal/cutoff ratio of one. This form of the assay has been studied at numerous institutions, including The Rothman Institute [1], The Mayo Clinic in Arizona [2], The Cleveland Clinic (Cleveland) [3], the Cleveland Clinic (Florida) [4] and the HELIOS ENDO-Klinik [5]. The following table demonstrates the results of these studies. Both the sensitivity and specificity of the alpha-defensin laboratory test exceed 95% when using the MSIS consensus criteria for PJI as a gold standard.

In addition to individual studies, there have been meta-analyses of the alpha-defensin laboratory test. Lee et al. [6] performed a meta-analysis of the performance of the synovial fluid leukocyte count, polymorphonuclear (PMN) %, C-reactive protein (CRP), alpha-defensin, leukocyte esterase, Interleukin-6 (IL-6), IL-8 and culture in diagnosing PJI. They found the alpha-defensin laboratory test to demonstrate the highest sensitivity (97%) of any individual test for PJI. No other test in this meta-analysis had a sensitivity >90%. In this same study, the alpha-defensin test was found to demonstrate the highest specificity (96%) of any individual test for PJI. A meta-