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QUESTION 5: Are point-of-care (POC) rapid tests for diagnosing periprosthetic joint infections (PJIs) validated and useful?

RECOMMENDATION: Yes, there are several useful POC tests which can be added to the diagnostic workup of PJIs. A number of studies support the usefulness and reliability of the leukocyte esterase (LE) test strip and the alpha-defensin lateral flow test kit. Diagnostic criteria for PJIs should be updated and consider inclusion of these tests.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 73%, Disagree: 21%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

A POC test is defined as a medical diagnostic tool which is used at the time of evaluation of a patient with an immediate result. These are rapid and simple medical tests that can be performed at the bedside. The idea behind a POC test is to provide real-time information upon which the treating physician can act.

After our systematic review, 11 original papers [1–11] and 4 review articles [12–15] assessing the diagnostic value of the LE test strip were included. The pooled data of 2,061 patients extracted from the original papers revealed a sensitivity of 85.7% (95% confidence interval (CI), 65.9 to 90.7%), a specificity of 94.4% (95% CI, 85.3 to 97.7%), a positive predictive value (PPV) of 84.3% (95% CI, 71.5 to 91.7%) and a negative predictive value (NPV) of 94.0% (95% CI, 85.8 to 97.1%).

The first prospective study investigating the utility of the LE strip test in diagnosing PJIs was conducted by Parvizi et al. A total of 108 patients who had painful total knee arthroplasties (TKAs) were investigated and the LE test (with a positive result being ++) had a sensitivity of 80.6% (95% CI, 61.9 to 91.9%), specificity of 100% (95% CI, 94.5 to 100.0%), and PPV of 100% (95% CI, 83.4 to 100.0%). The authors concluded that the LE strip test could be used effectively, by itself or in conjunction with other tests, either as a rapid screening mechanism or for confirmation of a suspected PJI [6].

In a systematic review of Wyatt et al. involving nearly 2,000 patients from five studies, the pooled diagnostic sensitivity and specificity of LE for PJI was 81% (95% CI, 49 to 95%) and 97% (95% CI, 82 to 99%), respectively [15]. Another meta-analysis of eight qualified studies with a total of 1,011 participants showed a higher pooled sensitivity of 90% (95% CI, 76 to 96%) and a similar specificity of 97% (95% CI, 95 to 98%) [14].

The limitation of the LE test is blood contamination interfering with readability of the test result. A recent study confirmed the reliability of the LE strip test by reporting an excellent sensitivity (92.0%) and specificity (93.1%). Furthermore, the latter study confirmed that synovial fluid centrifugation is an effective means of overcoming interference from erythrocytes [5].

After our systematic review, six original papers [16–21] and one review article [22] assessing the diagnostic value of the alpha-defensin lateral-flow test were included. The pooled data of 486 patients showed a sensitivity of 78.5% (95% CI, 64.7 to 94.5%), a specificity of 93.3% (95% CI, 87.0 to 99.6%), a PPV of 87.2% (95% CI, 74.6 to 98.1%) and a NPV of 90.2% (95% CI, 83.7 to 98.2%).

Deirmengian et al. introduced alpha-defensin as a robust synovial biomarker; however, the first studies were published about the laboratory-based enzyme-linked immunosorbent assay (ELISA) test (immuno-assay) [2]. Recent studies showed validated good results of the lateral-flow version of the alpha defensin test being a POC test [16–21]. A level II diagnostic study based on the results of 121 patients revealed a sensitivity and specificity of 97.1 and 96.6%, respectively [17]. The largest series was published by Gehrke et al. as a level I diagnostic study with 195 joints of 191 patients. The overall sensitivity of the alpha-defensin PJI test was 92.1% (95% CI, 83.6 to 97.1%), the specificity was 100% (95% CI, 97.0 to 100%), the PPV was 100% (95% CI, 94.9 to 100%), and the NPV was 95.2% (95% CI, 89.9 to 98.2%). The overall accuracy was 96.9% (95% CI, 93.4 to 98.9%) [18].

In the meta-analysis performed by Suen et al., the pooled sensitivity and specificity of the alpha-defensin lateral flow test was somewhat less appealing, being 77.4% (95% CI, 63.7 to 87.0%) and 91.3% (95% CI, 82.8 to 95.8%), respectively [22]. There is clear evidence that the lateral-flow test has a lower accuracy than the lab-based ELISA immuno-assay [18,22]. The test results may be influenced by metallosis [19] or crystal arthropathy, such as gout [23]. In addition, the

test is somewhat difficult to perform as it involves multiple steps for preparation of the sample.

In a recent meta-analysis about synovial fluid biomarkers alpha-defensin and LE demonstrated high sensitivity for diagnosing PJIs, with alpha-defensin being the best synovial marker. However, other synovial fluid tests like synovial fluid leukocyte count, polymorphonuclear (PMN) %, C-reactive protein (CRP), Interleukein-6 (IL-6) and Interleukin-8 (IL-8) that demonstrate good diagnostic performance can also be used in combination for the diagnosis of PJIs [12]. Molecular diagnostic studies, such as synovial alpha-defensin and LE, may provide rapid, accurate identification of PJIs, even in the setting of concurrent antibiotic administration or systemic inflammatory disease [13].

Additionally, there are a few studies exploring potential technologies which were developed as bed-side tests detecting calprotectin [24,25] or bacterial DNA sequences [26,27] as possible diagnostic tools of the future.

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QUESTION 6: What is the prevalence of culture-negative periprosthetic join infections (CN-PJIs) and what are the diagnostic protocols for further investigating these cases?

RECOMMENDATION: The reported prevalence of CN-PJIs in the hip or knee has ranged from 5-42%. Diagnostic protocols for further investigating these cases include repeat sampling, longer incubation of culture samples, sonication of implants, the use of dithiothreitol (DTT) technology, polymerase chain reaction (PCR) and next generation sequencing (NGS).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 91%, Disagree: 8%, Abstain: 1% (Super Majority, Strong Consensus)