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QUESTION 9: How is a periprosthetic joint infection (PJI) diagnosed in the presence of adverse local tissue reaction (ALTR)?

RECOMMENDATION: The diagnosis of PJI in the presence of an ALTR is challenging as many of the commonly used tests for diagnosis (including the appearance of the surgical site) can be falsely positive. An aggressive approach to preoperative evaluation including an aspiration of the hip joint (sending the fluid for a manual synovial fluid white blood cell (WBC) count, differential and culture) is recommended. Testing the synovial fluid for leukocyte esterase (LE) appears as a feasible, inexpensive and reliable test for the diagnosis of PJIs in ALTRs. There is no supporting evidence for other synovial fluid biomarkers in the diagnosis of PJIs in the presence of ATLRs.

LEVEL OF EVIDENCE

Test	Strength
Clinical and radiological findings	Consensus. There is no supporting evidence for PJI diagnosis in ALTR
Serum markers (ESR and CRP)	Strong
Synovial fluid WBC count, manual and PMNs	Strong
Leukocyte esterase in synovial fluid	Moderate
CRP in synovial fluid	Limited
Other fluid biomarkers (i.e., α-defensin, IL-6, and IL-8)	Consensus: There is no supporting evidence for PJI diagnosis in ALTR

DELEGATE VOTE: Agree: 84%, Disagree: 7%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

ALTRs have become increasingly prevalent secondary to failed metal-on-metal (MoM) bearings and corrosion at the head-neck junction associated with metal-on-polyethylene (MoP) bearings [1,2]. Many of the signs and symptoms of ALTRs mimic PJIs including pain, limited range of motion, swelling around the hip and the appearance of purulent fluid seen intraoperatively or at the time of aspiration [3–5]. Furthermore, many of the commonly used markers for the diagnosis of PJI–including the erythryocyte sedimentation rate (ESR), C-reactive protein (CRP), synovial fluid WBC count with polymorphonuclear leukocyte (PMN) differential and synovial fluid alpha-defensin, have all been reported to have higher than expected rates of false positives in the setting of an ALTR. Hence, the diagnosis of PJI is very challenging in this scenario.

Clinical and radiological findings:

There is no supporting evidence for the accuracy of clinical and radiological (i.e., X-ray, CT and MRI) findings for the diagnosis of PJI in presence of ALTR. Nevertheless, by consensus these must be considered essentials for the initial diagnosis suspicion.

The first report to describe the challenges of diagnosing PJI in the setting of a failed MoM bearing was by Mikhael [4]. They reported two patients with failed MoM total hip arthroplasties (THAs). These two patients presented with pain and elevated serum inflammatory markers both of which mimicked an infectious presentation. Similarly, Cooper et al. described several patients eho had comparable presentations–including purulent appearing synovial fluid intraoperatively [2]. This was one of the first reports of symptomatic ALTR secondary to corrosion at the head-neck junction in a MoP bearing. Subsequently, several reports have noted that the synovial fluid WBC count and differential may be falsely positive in this setting. The authors note the false positives may be secondary to cellular debris causing errors in automated synovial WBC counts and differentials [6–8]. Therefore, in the case of an ALTR, a manual synovial fluid WBC count and differential is recommended [4–6,9].

Yi et al. conducted the largest study specifically focusing on the diagnosis of PJIs in hip revision due to an ALTR [7]. In this retrospective study, 150 consecutive failed THAs were reviewed. This study specifically noted the preoperative serum ESR and CRP and the synovial fluid WBC count and differential. A total of 19 of the patients met MusculoSkeletal Infection Society (MSIS) criteria for PJI. Of the 141 attempted synovial WBC counts, 47 of the samples (33%) had a synovial fluid WBC count that was deemed to be inaccurate or unreliable due to the presence of gross cellular debris, metallic debris, clots or some other abnormality in the specimen. They were able to conclude that automated synovial fluid WBC count was prone to false-positive results and should only be relied on if a manual cell count was performed [7]. In a similar study, Wyles et al. reported on 39 patients, of which four were deemed infected [10]. However, synovial fluid WBC count could not be performed in 33% of their samples due to specimen quality [10]. This led Wyles et al. to suggest that the differential was the best diagnostic test [6,10].

Synovial CRP has been suggested as a simple, cost-effective test for improving the diagnosis of PJI due to several reports finding elevated levels in the synovial fluid [11]. However, the cutoff value of synovial fluid CRP varied in each study: 2.8 mg/L, 3.65 mg/L, 6.6 mg/L, 9.5 mg/L, and 12.2 mg/L [12–14] and further research is needed to determine the utility of this measurement.

Tischler et al. reported on the use of a LE reagent test strip as an adjunct for the rapid diagnosis of PJIs. This study examined 76 patients being revised for a failed MoM bearing or corrosion at a modular junction [15]. Five patients were found to have a deep infection. Unfortunately, 15 of the samples had to be excluded as heavy discoloration of the synovial fluid made interpretation of the reagent strip unreliable, which is a known weakness of this testing modality [15,16]. While the LE strip had reasonable sensitivity (80%) and specificity (93%), the positive predictive value was poor at only

50% [15]. The negative predictive value was found to be 98%, however suggesting the utility of LE as a "rule out" test. Additionally, the LE strip test had the second strongest performance compared to sensitivity of synovial WBC count. Based on these results as well as results from other studies, LE test strips can be a valuable intraoperative test for differentiating PJI from aseptic failures [15,17,18].

Alpha-defensin has been proposed as an accurate test for the diagnosis of PJI due to its high sensitivity and specificity [19–24]. Okroj et al. conducted a multicenter retrospective review of 26 patients who had a diagnosis of ALTR, who had alpha-defensin testing performed [25]. One patient in the study met MSIS criteria for PJI. However, alpha-defensin was positive in 9 of 26 hips, including 8 that were falsely positive (31%). In addition to a positive alpha-defensin, all eight patients were positive on Synovasure. However, five of the eight positive Synovasure results included a warning that they may be falsely positive. Unfortunately, like the synovial fluid WBC count, alpha-defensin is prone to false positive results in the setting of ALTR [25].

Histopathology is often used for the diagnosis of PJI as recommended by the American Academy of Orthopaedic Surgeons (AAOS) Clinical Practice Guideline and as part of the MSIS criteria [26]. Grammatopoulos et al. studied 104 failed MoM THAs. They identified seven of the hips to be infected and suggested a standard criteria for the histopathologic diagnosis of PJI of greater than five PMN per high-powered field (PMN/HPF) [27].

Many studies on PJI diagnosis have recently shifted focus to synovial fluid, for it is the site of primary infection. Furthermore, use of synovial fluid to aid in the diagnosis is theoretically more sensitive than serum measurements. Many antimicrobial peptides and inflammatory cytokines have been proposed as synovial biomarkers indicating infection [21]. Among these are CRP, interleukin-1 (IL-1), IL-6, IL-8, IL-17A, interferon-γ, tumor necrosis factor and cathelicidin LL-37. The synovial fluid biomarkers alpha-defensin, IL-6 and IL-8 all demonstrated high sensitivity for diagnosing PJIs and potentially could be applied in combination for the diagnosis of PJIs [13,14,24]. However, studies are sparse and there is no supporting evidence of these biomarkers as tools for the diagnosis of PJI in cases of ALTR.

Given these findings, a more aggressive approach should be used when evaluating patients for PJI in the setting of an ALTR. Specifically, prior to revision surgery, aspiration of the hip joint is recommended to obtain cultures. These results may be incorporated into the evaluation in combination with a manual synovial fluid WBC count and differential. LE reagent strips can also be used as an adjunct to diagnosis, assuming the sample is not contaminated with excessive metal debris or blood rendering the strip unreliable. This approach gives the surgeon a preview of the appearance of the joint at the time of revision.

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