HK47: Do the thresholds for serum and synovial tests used for the diagnosis of periprosthetic joint infection also apply to reimplantation?

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Response/Recommendation: No. Based on limited data, the thresholds for serum and synovial tests used to diagnose periprosthetic joint infection (PJI) should not be used to determine the presence/absence of infection for reimplantation in patients undergoing two-stage exchange arthroplasty.

Level of Evidence: Weak

Delegate Vote:

Rationale:

A two-stage exchange procedure is widely regarded as the preferred surgical strategy for management of patients who have chronic periprosthetic joint infection (PJI), with reported success rates of up to 90% [1]. However, significant heterogeneity exists in how studies evaluate persistent PJI at reimplantation.

There were four studies retrospectively assessed the established serum **C-reactive protein (CRP)** threshold of 1 mg/dl at reimplantation via comparison against intraoperative microbiology, recurrence of PJI, and Delphi Criteria [2–5], with sensitivity from 17 to 67% and specificity from 40 to 82%. A wide variety of studies investigated optimal thresholds for serum CRP. They identified optimal cutoffs from 0.33 to 5.2 mg/dL. However, those that employed a threshold > one mg/dL demonstrated a trend towards increased specificity, rendering it potentially useful as a rule-in test [6–21].

When evaluating the standard **erythrocyte sedimentation rate (ESR)** threshold of 30 mm/hour at reimplantation, Lindsay et al. observed a sensitivity of 75% and a specificity of 100% in 21 cases, using recurrent infection after reimplantation as the outcome. However, Pannu et al. identified a sensitivity of 30% and specificity of 67% through retrospective analysis of 44 cases and comparison against Delph Criteria [4], while Ghanem et al. found a sensitivity of 65% and specificity of 32.4% when retrospectively applying the established threshold in 109 knees [2]. Ten other studies [6,9–15,21,22] identified optimal cutoffs based on varying outcome measures ranging from 29 mm/h (sensitivity: 64%, specificity: 88%) [14] to 102 mm/hour (sensitivity: 29%, specificity: 89%) [15], indicating an overall trend towards higher cutoffs at reimplantation.

None of the identified studies directly assessed the **standard d-dimer** threshold of 860 ng/mL, with optimal thresholds ranging from 600 to 3,070 ng/mL and no clear trend in sensitivity or specificity, leaving its value at reimplantation unclear [4,10,13,14,23–26].

Regarding synovial **white blood cells (WBCs**), no study directly assessed the established cutoff, but six of them identified thresholds below the standard of 3,000 cells/μL, most of which used intraoperative cultures as an outcome measure for failure [8,9,11,12,15,27–31]. Seven out of the ten studies report cutoff values below the current standard for initial diagnosis, ranging from 640 [12] to 2,733 cells/μL [29] with variable diagnostic performance. Further, Boelch et al. found noteworthy differences in synovial WBC cutoff when comparing against histology for

polymorphonuclear (PMN) cells (3,250 cells/μL) or intraoperative tissue culture (4,450 cells/μl) in 94 revision knees [30].

Similar to WBCs, optimal **PMN%** thresholds in literature all range below the established >80% limit when compared against a variety of outcome measures. These results indicate a possible need for lowering limits at reimplantation[9,11,12,15,25,27,29,31]. Thresholds ranged from 52% (sensitivity 82%, specificity 78%) in a study from Ascione et al. [31] to 79% (sensitivity 78%, specificity 82%) identified by Kusuma et al. [9], with consistently good diagnostic performance. However, due to the heterogeneity of outcome measures, no definitive recommendation or cutoff could be established.

When assessing **cultures of aspirated synovial fluid**, a single positive culture sample was generally considered a positive test result, and in most studies compared against intraoperative microbiology and/or histology or MSIS criteria. Throughout all identified studies, specificity was consistently much higher than sensitivity with values ranging from 85 to 100%, indicating its potential as a rule in tests with at least one positive sample as the threshold [8,27,28,30,32–35].

Recently, a study by Li et al. was the first one to prospectively assess **synovial CRP** at reimplantation. They identified a reasonably high sensitivity of 78% and specificity of 89% at a threshold of 0.89 mg/dL when comparing it against the emergence of a new sinus tract infection or positive cultures as an outcome [19]. However, further evidence is needed to fully support this threshold as opposed to the established 0.68 mg/dL [36].

There were three studies that evaluated the diagnostic value of **leukocyte esterase strips** at reimplantation, all interpreting grades >+ as positive per the current MSIS criteria [36]. Through prospective comparison against treatment failure after one year, as defined by the Delphi Consensus, Bielefeld et al. found a negative leukocyte esterase result in all 18 patients, yielding a sensitivity of 0% and a specificity of 100% [17]. Kheir et al. retrospectively applied the same threshold and endpoint and found a sensitivity of 26% and specificity of 100% at a mean follow-up of just under two years in 77 patients [22]. A third study by Logoluso et al. showed an outstanding sensitivity of 82% and specificity of 99% through comparison against MSIS criteria at reimplantation or PJI recurrence at a minimum follow-up of 16 months [18]. Although these studies suggest that the previously established threshold for leukocyte esterase strips may be reasonable for reimplantation, further research is needed to confirm its reliability and optimize diagnostic accuracy.

In terms of **synovial alpha-defensin**, divergent evidence exists when compared against (modified) 2018 MSIS criteria at reimplantation, with Stone et al. reporting a 71% sensitivity [37], while Owens et al. found 0% sensitivity [38], both showing near-perfect specificity. When assessed for failure after at least one year, three studies comparing synovial alpha-defensin to the Delphi Consensus showed extremely low sensitivity but almost absolute specificity [17,39,40]. Thus, its clinical utility at reimplantation cannot be supported based on current evidence.

A recent systematic review and meta-analysis by Sabater-Martos et al. [41] assessed 24 studies regarding positive **intraoperative cultures** at reimplantation and subsequent failure. The number of reported samples ranged from one to eight, and one positive culture was considered a positive result at reimplantation in the vast majority of studies as defined in the postoperative section of the 2018 MSIS criteria [36]. The overall risk of failure with positive cultures was significantly higher in the antibiotic holiday group (i.e., group pausing antibiotics before reimplantation, odds ratio (OR) of 4.8) as well as the non-holiday group (OR 2.2). However, studies directly assessing the optimal number of samples needed are still required to fully support this evidence.

The Feldman criterion (≥ five PMN in ≥ five high-power fields) is currently used by both the MSIS and EBJIS criteria as the standard for **intraoperative histology** [36,42]. Using it, Bori et al. demonstrated a sensitivity of 29% and specificity of 100% when compared to positive intraoperative microbiology as the gold standard. Alternatively, the application of the Athanasou criterion (≥ one PMN per high-power field, on average, in 10 fields) showed a shift towards increased sensitivity (71%) and lowered specificity (64%) in the same cohort [43]. Two other studies also found low sensitivity (0 to 38%) and high specificity (83 to 91%) with the Feldman criterion compared to infection recurrence [44,45]. George et al. considered intraoperative frozen sections as positive if ≥ five PMN were seen in ≥ three high-power fields, resulting in a sensitivity of 59% and specificity of 94% in comparison to the MSIS criteria at reimplantation [46]. Further, Straub et al. found a sensitivity of 29% and specificity of 76% with a cutoff of ≥ 23 PMN per ten high-power fields and treatment failure defined as tier 3B or 3D according to the MSIS reporting tool [47]. In total, no cutoff can be fully supported, with the previous ones primarily useful for ruling in infection.

In a study by Nelson et al., **sonication cultures** were performed on 36 patients who had a sensitivity of 82% and specificity of 50% with an average antibiotic-free duration before reimplantation of seven weeks. When considering only sonication results with more than 20 colony-forming units as positive, the sensitivity decreased to 63% and the specificity increased to 78%, respectively [48]. Another study by Sorli et al. applied a threshold of at least five colony-forming units in 55 patients, but did not report sensitivities or specificities [49]. Similarly, a study by Bereza et al. [32] assessed sonication results, but neither reported colony-forming unit cutoffs nor sensitivity and specificity.

Therefore, thresholds established at explantation cannot be fully supported at reimplantation due to variability in diagnostic performance and lack of standardization across studies [50]. The established serum and synovial test thresholds for the diagnosis of PJI showed lower overall performance at reimplantation in 2-stage revision. While some thresholds, such as those for CRP, ESR, or synovial WBC may provide insights, they show inconsistent sensitivity and specificity across studies. Although some established thresholds seem beneficial for ruling in infection, their clinical relevance is highly diminished by the lack of standardization in study protocols, antibiotic management, and outcome measures, making it difficult to recommend specific cutoffs.

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