Current Concepts Review

Diagnosis of Periprosthetic Infection

Recent Developments

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- There is no absolute test for the preoperative diagnosis of periprosthetic joint infection (PJI); thus, clinical practice relies on a combination of supportive tests and criteria.
- Novel serum and synovial tests have improved our ability to diagnose PJI. The 2018 evidence-based algorithm for PJI diagnosis provides weighted scores for serum markers, as well as synovial markers, to facilitate diagnosis when major criteria such as positive cultures or a sinus tract are not present.
- Culture-independent technologies such as next-generation sequencing can facilitate pathogen identification, particularly in the setting of culture-negative PJI.
- Despite recent developments, PJI diagnosis remains challenging and warrants further innovation.

Historically, the 2011 Musculoskeletal Infection Society (MSIS) criteria have been the standard for defining periprosthetic joint infection (PJI) after total joint arthroplasty (TJA)[1,2]. These criteria were developed by a workgroup of experts and represent the group's consensus on a "gold standard" definition of PJI based on the literature (Table I). According to the 2011 MSIS criteria, PJI definitely exists if 1 major or 4 minor criteria are met (Table II). PJI may still be present even if <4 minor criteria are present. Although the MSIS definition has been crucial in providing a standard for diagnosing and treating PJI, it has limitations. The criteria represent a consensus rather than an evidence-based algorithm. Three of the minor criteria rely on intraoperative findings, and 4 minor criteria must be met to confirm PJI. In addition, PJI cannot be diagnosed on the basis of the minor criteria preoperatively. The criteria may miss PJI caused by slow-growing organisms or culture-negative infections, and they do not include recently developed diagnostic tests.

New Definition of PJI

Therefore, in 2018, the definition for PJI was updated to reflect new diagnostic tests and recently accrued evidence[3]. The 2018 definition was developed across 3 institutions by comparing 684 patients with proven PJI undergoing revision for infection and 820 patients with aseptic failure undergoing revision for a reason other than infection. Variables investigated were serum C-reactive protein (CRP), D-dimer, erythrocyte sedimentation rate (ESR), synovial white blood-cell (WBC) count, polymorphonuclear (PMN) percentage, leukocyte esterase (LE), alpha-defensin, synovial CRP, intraoperative frozen section, presence of purulence, and pathogen isolation by culture. Regression analyses were used to generate relative weights for each test, as not all tests have the same accuracy, and the new PJI definition (Table III) was then validated against external cohorts. The 2018 definition utilizes a stepwise approach for diagnosis (Table III). If either of the major criteria is present, the patient is infected. If no major criterion is present, the minor criteria are scored. A different score is assigned to each test, on the basis of pretest probability, and a score of ≥6 indicates infection. A score of ≤1 indicates the absence of infection. For patients with a score between 2 and 5 (a possible infection), additional tests and intraoperative findings should be incorporated. By using a stepwise approach, the new criteria take into account the relative weights and pretest probability of multiple tests.

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TABLE I The Evolving Definition of PJI*

	Acute PJI of <90 Days	Chronic PJI of >90 Days	Score	Definition
MSIS 2011 – Definition of PJI adapted from the Workgroup Convened by the MSIS[2]† PJI is present if 1 of the major criteria or 4 of the 6 minor criteria exist: Major criteria 1. There is a sinus tract communicating with the prosthesis; or 2. A pathogen is isolated by culture from 2 or more separate tissue or fluid samples obtained from the affected prosthetic joint; or Minor criteria 1. Elevated serum ESR and serum CRP concentration 2. Elevated SF WBC count 3. Elevated SF PMN% 4. Presence of purulence in the affected joint 5. Isolation of a microorganism in 1 culture of periprosthetic tissue or fluid, or 6. Greater than 5 neutrophils per HPF in 5 HPFs observed from histologic analysis of periprosthetic tissue at ×400 magnification				
IDSA 2013 – Definition modified from Osmon et al.[97]† 1. The presence of a sinus tract that communicates with the prosthesis 2. The presence of acute inflammation as seen on histopathologic examination of periprosthetic tissue at the time of surgical debridement or prosthesis removal 3. The presence of purulence without another known etiology surrounding the prosthesis 4. Two or more intraoperative cultures or combination of preoperative aspiration and intraoperative cultures that yield the same organism. . . . Growth of a virulent microorganism (e.g., *Staphylococcus aureus*) in a single specimen of a tissue biopsy or synovial fluid may also represent PJI 5. The presence of PJI is possible even if the above criteria are not met; the clinician should use his or her clinical judgment to determine if this is the case after reviewing all the available preoperative and intraoperative information				
ICM 2013 – Definition adapted from Parvizi and Gehrke[98]§ PJI is present if 1 of 2 major criteria or 3 of 5 minor criteria exist: Major criteria 1. Two positive periprosthetic cultures with phenotypically identical organisms; or 2. A sinus tract communicating with the joint; or Having 3 of the following minor criteria				

continued

TABLE I (*continued*)

	Acute PJI of <90 Days	Chronic PJI of >90 Days	Score	Definition
1. Elevated ESR and CRP	ESR: no threshold; or CRP of >100 mg/L	ESR of >30 mm/h or CRP of >10 mg/L		
2. Elevated SF WBC count or ++ change on LE test strip	≥10,000 cells/μL; or + or ++	≥3,000 cells/μL; or + or ++		
3. Elevated SF PMN%	≥90%	≥80%		
4. Positive histologic analysis of periprosthetic tissue	>5 neutrophils/HPF in 5 HPFs (×400)	>5 neutrophils/HPF in 5 HPFs (×400)		
5. A single positive culture				
The 2018 definition of PJI—an evidence-based and validated version modified from Parvizi et al.[3]#				
Major criteria (at least one of the following)				Infected
Two positive cultures of the same organism				
Sinus tract with evidence of communication to the joint or visualization of the prosthesis				
Minor criteria				
Preoperative diagnosis				≥6 infected; 2-5 possibly infected**; 0-1 not infected
Serum				
Elevated CRP or D-dimer			2	
Elevated ESR			1	
Synovial fluid				
Elevated synovial WBC or LE (++)			3	
Positive alpha-defensin			3	
Elevated synovial PMN%			2	
Elevated synovial CRP			1	
Intraoperative diagnosis**				≥6 infected; 4-5 inconclusive††; ≤3 not infected
Preoperative score			–	
Positive histological findings			3	
Positive purulence			3	
Positive single culture			2	

*MSIS = Musculoskeletal Infection Society, PJI = periprosthetic joint infection, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, SF WBC = synovial fluid white blood-cell count, SF PMN% = synovial fluid polymorphonuclear percentage, HPF = high-power field, IDSA = Infectious Diseases Society of America, ICM = International Consensus Meeting, and LE = leukocyte esterase. †The MSIS 2011 table is reproduced, with modification, from: Workgroup Convened by the Musculoskeletal Infection Society, New definition for periprosthetic joint infection. J Arthroplasty. 2011;26(8):1136-8. Copyright 2011; with permission from Elsevier. ‡The IDSA 2013 table is reproduced, with modification, from: Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, Rao N, Hanssen A, Wilson WR, Infectious Diseases Society of America. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013;56(1): e1-e25, by permission of the Infectious Diseases Society of America. §The ICM 2013 table is reproduced, with modification, from: Parvizi J, Gehrke T; International Consensus Group on Periprosthetic Joint Infection. Definition of periprosthetic joint infection. J Arthroplasty. 2014 Jul;29(7):1331. Copyright 2014. Reproduced with permission. #The 2018 definition table is reproduced from: Parvizi J, Tan TL, Goswami K, Higuera C, Della Valle C, Chen AF, Shohat N. The 2018 definition of periprosthetic hip and knee infection: an evidence-based and validated criteria. J Arthroplasty. 2018 May;33(5):1309-1314.e2. Copyright 2018, with permission from Elsevier. **For patients with inconclusive preoperative score or dry tap, operative criteria can also be used to fulfill the definition for PJI. ††Consider further molecular diagnostics such as next-generation sequencing.

TABLE II 2011 Musculoskeletal Infection Society Criteria for the Diagnosis of PJI*†

Major criteria
There is a sinus tract communicating with the prosthesis; or
A pathogen is isolated by culture from 2 or more separate tissue or fluid samples obtained from the affected prosthetic joint; or
Minor criteria
Elevated serum ESR and serum CRP concentration
Elevated synovial white blood cell count
Elevated synovial polymorphonuclear percentage
Presence of purulence in the affected joint
Isolation of a microorganism in 1 culture of periprosthetic tissue or fluid, or
Greater than 5 neutrophils per high-power field (HPF) in 5 separate HPFs observed from histologic analysis of periprosthetic tissue at ×400 magnification

*Reproduced from: The Workgroup Convened by the Musculoskeletal Infection Society. New definition for periprosthetic joint infection. J Arthroplasty. 2011;26(8):1136-8. Copyright 2011; with permission from Elsevier. †According to these criteria, PJI definitely exists if 1 major criterion or 4 minor criteria are met.

The 2018 system has a 97.7% sensitivity and 99.5% specificity, compared with 86.9% sensitivity and 79.3% specificity of the 2011 MSIS criteria[3]. That said, major criteria were utilized as a gold standard for model development, and further external validation studies outside the institutions developing this definition are needed to determine generalizability.

Serum and Synovial Markers for PJI

A number of serum and synovial markers have been explored to aid in PJI diagnosis. The reported accuracy of these tests has varied among studies on the basis of what was used as the gold standard to define PJI. The studies also utilized different thresholds for some tests, which had an impact on the results presented.

Serum Markers for Diagnosis of PJI

D-Dimer

Early diagnosis of PJI is critical because there is a short window of opportunity to treat acute infection with debridement and implant retention before the development of biofilm. However, the diagnosis of PJI in the postoperative period can be a challenge because ESR and CRP remain elevated for 6 and 2 weeks, respectively[4]. This has prompted a search for a serum marker that may return to baseline levels early after arthroplasty.

D-dimers are fibrin degradation products that form when plasmin dissolves the fibrin clot. The presence of elevated serum D-dimer levels has been associated with numerous inflammatory conditions including venous thromboembolism, cancer, and infection[5,6]. Shahi et al. observed that D-dimer was significantly elevated in patients with PJI compared with those with aseptic failures (1,110 and 299 ng/mL, respectively; $p < 0.0001$), and that 850 ng/mL was the optimal serum D-dimer threshold value for PJI diagnosis[7]. D-dimer was more accurate in predicting the presence of infection than the combination of ESR and CRP.

Lee et al. measured serum ESR, CRP, and D-dimer in 65 TJA patients before and after surgery[4]. D-dimer levels peaked on postoperative day 1 and returned to baseline by postoperative day 2; D-dimers rose again at 2 weeks (Fig. 1). As the level of D-dimer rises and falls more rapidly than ESR and CRP in the acute postoperative period, it is possible that D-dimer may be a useful test in conjunction with ESR and CRP to diagnose

TABLE III 2018 Evidence-Based Stepwise Algorithm for Diagnosis of PJI Adapted from Parvizi et al.*

Criteria	Score *(points)*	Decision
Major criteria (at least 1 of the following)		Infected
Two positive cultures of the same organism		
Sinus tract with evidence of communication to the joint or visualization of the prosthesis		
Minor criteria		
Preoperative diagnosis		≥6 infected; 2-5 possibly infected†; 0-1 not infected
Serum		
Elevated CRP or D-dimer	2	
Elevated ESR	1	
Synovial		
Elevated synovial WBC count or LE	3	
Positive alpha-defensin	3	
Elevated synovial PMN (%)	2	
Elevated synovial CRP	1	
Intraoperative diagnosis†		≥6 infected; 4-5 inconclusive‡; ≤3 not infected
Preoperative score	–	
Positive histology	3	
Positive purulence	3	
Single positive culture	2	

*Reproduced from: Parvizi J, Tan TL, Goswami K, Higuera C, Della Valle C, Chen AF, Shohat N. The 2018 definition of periprosthetic hip and knee infection: an evidence-based and validated criteria. J Arthroplasty. 2018;33(5):1309-1314.e2. Copyright 2018; with permission from Elsevier. †In the case of an inconclusive preoperative score or a dry tap, operative criteria can also be used to fulfill the definition for PJI. ‡Consider further molecular diagnostics such as next-generation sequencing if diagnosis remains inconclusive.

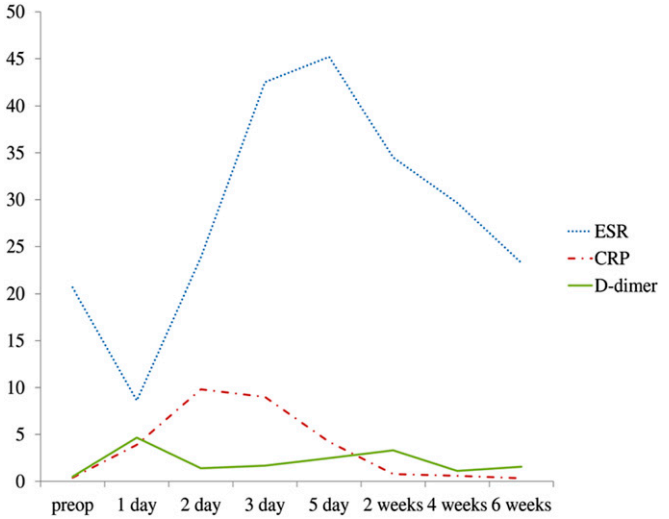

Fig. 1

Trend of serum D-dimer (ng/dL), ESR (mm/hr), and CRP (mg/dL) levels after TJA. (Adapted, under Creative Commons Attribution 4.0 International License, from: Lee YS, Lee Y-K, Han SB, Nam CH, Parvizi J, Koo K-H. Natural progress of D-dimer following total joint arthroplasty: a baseline for the diagnosis of the early postoperative infection. J Orthop Surg Res. 2018 Feb 13;13[1]:36.)

and monitor early acute PJI[4]. A low D-dimer level in the early postoperative period may be helpful in ruling out PJI.

A limitation of D-dimer is that it is nonspecific, and elevated D-dimer could indicate the presence of an inflammatory state unrelated to infection. Skepticism regarding D-dimer was raised by Li et al.[8], who reported a limited diagnostic value with an area under the curve (AUC) of 0.657. The latter report involved a Chinese patient population, with no patient being excluded, and a different threshold for PJI diagnosis was used. The report highlighted the potential issues that may exist with this serum test, and further studies are needed.

Fibrinogen

Fibrinogen is a soluble glycoprotein that is the precursor to fibrin in the clotting cascade, and it assists in activating and mediating the inflammatory cascade[9]. In a study of 84 patients undergoing revision total hip arthroplasty or total knee arthroplasty for septic or aseptic loosening, a serum fibrinogen value of 574 mg/dL had a sensitivity of 81% and a specificity of 25%[10]. This implies that a low fibrinogen level can help rule out PJI. This has been corroborated in a multicenter report that demonstrated an AUC of 0.852, sensitivity of 76%, and specificity of 86%[8]. However, like D-dimer, fibrinogen is nonspecific for PJI.

Interleukin (IL)-6

IL-6 is produced by monocytes and macrophages as part of an activated immune response, and it induces the production of acute phase reactants such as CRP[11]. The serum IL-6 level is approximately 1 pg/mL at baseline and can increase to 430 pg/mL for 3 days after TJA[11]. The peak occurs 2 days after TJA, after which it rapidly returns to normal[12]. Serum IL-6 is significantly elevated in patients with PJI compared with patients with aseptic loosening[13]. At a cutoff value of 2.6 pg/mL, IL-6 was 58% specific and 80% sensitive for PJI detection; when the cutoff was raised to 6.6 pg/mL, specificity increased to 88%, but sensitivity decreased to 48%.

Procalcitonin

Procalcitonin is produced by thyroid parafollicular and lung neuroendocrine cells and has a half-life of 22 to 29 hours. Procalcitonin levels rise rapidly in response to bacterial, but not viral or fungal, infections. A meta-analysis demonstrated that procalcitonin outperformed serum CRP in correctly predicting patients with septic arthritis[14]. However, in a study that screened synovial markers for PJI, procalcitonin had low accuracy[15].

Synovial Markers for Diagnosis of PJI

Numerous synovial biomarkers have been analyzed for possible utility for PJI diagnosis. Those with sufficient data from pooled analyses are summarized in Table IV. The synovial markers with greatest diagnostic promise appear to be alpha-defensin, LE, IL-6, and IL-8.

Alpha-Defensin

Alpha-defensin is an antimicrobial peptide released by activated neutrophils, which then integrates into and destroys the bacterial cell membrane[15,16]. A cutoff for synovial alpha-defensin of 4.8 ug/mL was 100% specific and 100% sensitive for diagnosing PJI in 1 study[15]. A meta-analysis demonstrated that elevation of alpha-defensin beyond the threshold was 100% sensitive and 96% specific for PJI, with an AUC of 0.99[17]. Combining alpha-defensin with synovial CRP increased the specificity of the test to 100%[18].

Alpha-defensin performs well in challenging situations like culture-negative PJI, systemic inflammatory conditions, and concurrent antibiotic use[18,19]. Alpha-defensin also appears to be triggered by a wide array of pathogens, with no difference in the magnitude of the alpha-defensin level[20]. However, alpha-defensin has limitations, with low positive predictive value (PPV) and specificity in the setting of metallosis or adverse local tissue reactions (ALTR)[21,22]. On review of the available literature by the 2019 American Academy of Orthopaedic Surgeons Diagnosis and Prevention of Periprosthetic Joint Infections Clinical Practice Guideline, alpha-defensin testing was noted to be useful for ruling in PJI (positive likelihood ratio [LR] range = 4.36 to 32.33) and ruling out PJI (positive LR = 0.03 to 0.36)[23]. However, the test's rule-out ability as a screening tool for infection has been questioned because of the limited sensitivity reported elsewhere in the literature[24-26].

At the time of writing, there were 2 commercially available tests that measure alpha-defensin in combination with other biomarkers (synovial CRP and human neutrophil elastase): (1) a laboratory-based enzyme-linked immunosorbent assay (ELISA) test, which produces a numerical value within a

TABLE IV Sensitivity and Specificity of Synovial Biomarkers*

Test	Sensitivity†	Specificity†	Log DOR†	AUC‡
Leukocyte count	0.89 (0.86-0.91)	0.86 (0.80-0.90)	4.17 (3.69-4.65)	0.91
PMN%	0.89 (0.82-0.93)	0.86 (0.77-0.92)	4.05 (3.02-5.08)	0.93
CRP	0.85 (0.78-0.90)	0.88 (0.78-0.94)	4.15 (2.89-5.41)	0.90
α-defensin	0.97 (0.93-0.99)	0.96 (0.94-0.98)	6.70 (5.65-7.75)	0.99
LE	0.77 (0.63-0.87)	0.95 (0.86-0.98)	4.57 (3.46-5.67)	0.92
IL-6	0.81 (0.70-0.89)	0.94 (0.88-0.97)	4.38 (2.86-5.89)	0.95
IL-8	0.87 (0.67-0.96)	0.94 (0.88-0.97)	4.92 (2.84-7.00)	0.96
Culture	0.62 (0.50-0.74)	0.94 (0.91-0.96)	3.27 (2.64-3.90)	0.94

*Reproduced from: Lee YS, Koo KH, Kim HJ, Tian S, Kim TY, Maltenfort MG, Chen AF. Synovial fluid biomarkers for the diagnosis of periprosthetic joint infection: a systematic review and meta-analysis. J Bone Joint Surg Am. 2017 Dec 20;99(24):2077-84. †The 95% confidence interval is given in parentheses. DOR = diagnostic odds ratio. ‡AUC = area under the curve.

few days, and (2) a point-of-care lateral flow test (Synovasure; Zimmer Biomet), which produces a binary positive or negative result within minutes. The majority of the reported results regarding the utility of alpha-defensin have assessed the laboratory-based ELISA assay and not the point-of-care test. A meta-analysis of 42 articles suggested that the ELISA assay performs better than the lateral flow test[27]. Specifically, the lateral flow test has lower overall accuracy (AUC of 0.75 versus 0.98 for the ELISA assay), but it remains relatively specific (90% versus 96%)[28]. Therefore, the lateral flow test may still be a useful rapid test to "rule in" infection. The lateral flow test was recently approved in the U.S., and further work assessing the accuracy is needed.

Calprotectin

Like many of the other synovial biomarkers, calprotectin is an antimicrobial molecule that is released by activated neutrophils and is therefore a marker of infection. With a cutoff value of 50 mg/L, synovial calprotectin is 87% sensitive and 92% specific for PJI, with an AUC of 0.94[29,30]. Calprotectin is less sensitive and specific than other synovial markers, including alpha-defensin, IL-6, and IL-8. However, it can be measured quantitatively by an inexpensive lateral flow assay that is already commonly used for other purposes in hospitals, so it may offer a relatively simple way to add information to the clinical picture.

Synovial Fluid CRP (SF-CRP)

Measurement of serum CRP has been a mainstay for PJI diagnosis, but slow-growing organisms and those that form a biofilm may not elevate serum CRP beyond the threshold for PJI diagnosis[31]. SF-CRP levels may be more accurate than serum CRP for diagnosing PJI[32,33]. A multiplex ELISA assay set to a diagnostic threshold of 3.7 mg/L had 84% sensitivity, 97% specificity, and an AUC of 0.91[32]. This SF-CRP assay slightly outperformed the serum CRP assay, with 76% sensitivity, 93% specificity, and an AUC of 0.88. When the study was repeated using the hospital laboratory assay for both serum and SF-CRP, a threshold of 9.5 mg/L was 85% sensitive and 95% specific and had an AUC of 0.92[33]. Another study observed that SF-CRP had an AUC of 0.96 for detecting chronic PJI of the hip, and that the addition of SF-CRP aided in making the diagnosis for 80% of the patients who had not met the criteria based on elevated serum markers[34].

Although these studies demonstrated that SF-CRP may outperform serum CRP, SF-CRP continues to lag behind synovial alpha-defensin, synovial IL-6, and synovial IL-8 in diagnostic accuracy. Moreover, one of the purposes of measuring serum CRP is to act as a screening test to determine which patients require SF aspiration for further testing; synovial CRP obviously cannot play a similar role.

SF-IL-6 and SF-IL-8

SF-IL-6 may be an accurate and helpful marker of PJI[13,15,35]. SF-IL-6 of >2.1 ng/mL is 86% specific and 59% sensitive for diagnosing PJI[13]. Deirmengian et al. showed that SF-IL-6 of >2.3 ng/mL is 97% specific for PJI, with an AUC of 0.95[15]. At SF-IL-6 values of >9.0 ng/mL, specificity approaches 100%[13]. When serum IL-6 is >2.6 pg/mL and SF-IL-6 is >2.1 ng/mL in the same patient, the PPV was 89%[13]. Since SF-IL-6 alone at a cutoff of 2.3 ng/mL is already fairly specific for PJI, we do not believe that the combination of serum and SF-IL-6 adds meaningful value to the diagnostic algorithm.

SF-IL-8 may be nearly as accurate for the diagnosis of PJI as alpha-defensin. In an analysis of SF from 95 patients, 29 of whom met MSIS criteria for PJI, a cutoff for SF-IL-8 of 6.5 ng/mL was 95% specific and 100% sensitive for diagnosing PJI[15]. A meta-analysis that included 3 studies examining SF-IL-8 showed slightly lower pooled specificity (94%) and sensitivity (87%)[36]. The inability of some laboratories to perform these tests, the relative expense involved, and a lack of a clear threshold has prevented these tests from entering clinical practice on a broader scale. With further studies focused on determining the appropriate threshold and overcoming some of the aforementioned limitations, these tests may gain future widespread use.

Leukocyte Esterase (LE)

LE is produced by activated neutrophils at the site of infection and therefore can be a marker of synovial leukocytosis and PJI. Synovial LE levels can be easily and quickly assessed using a urinalysis dipstick; results are categorized as negative, trace, +, or ++[37]. It is important to mention that a version of the LE strip that also provides a +++ read is available in Asia and other countries. Test strips producing a ++ result were 84% sensitive and 100% specific for knee PJI, with a PPV of 100% and negative predictive value (NPV) of 79%[38]. A meta-analysis demonstrated a pooled sensitivity of 81% and specificity of 97%, with ++ as the threshold[17]. The AUC was 0.97, indicating high accuracy[17].

Advantages of the LE test strip include ease of use, immediate results, and low cost[17]. A limitation is that a bloody aspirate affects test strip color and makes it difficult to interpret. This issue is resolved by centrifuging the sample prior to testing; however, this equipment may not be available or feasible for clinicians in the office setting. Furthermore, the sensitivity of the test is reduced, after samples are centrifuged, from 98% to 93%[39]. Thus, there is a need for a point-of-care test that can overcome the issue of blood-stained SF.

The Clinical Need for a Diagnostic Alternative to ESR and CRP

ESR and CRP are often not elevated in PJI cases caused by slow-growing organisms, such as *Cutibacterium acnes,* that do not produce a suppurative host response[40]. This is of particular clinical concern in the setting of shoulder arthroplasty[41,42]. A review of 1,200 hip and knee revision arthroplasties demonstrated that ESR and CRP had higher false-negative rates than previously reported, particularly for slow-growing and culture-negative organisms[43]. Another group reported that 4% of confirmed PJI cases were seronegative, without ESR and CRP elevation[44].

ESR and CRP demonstrate temporal variations, complicating diagnosis of PJI and impacting the ability to use these tests to determine optimal timing of reimplantation. CRP levels peak at 2 to 3 days postoperatively, with normalization in one-third of patients after 3 weeks[45,46], but they can take approximately 3 months to return to baseline[47,48]. Serum ESR levels usually peak at postoperative day 5, and then gradually return to baseline over 90 days[48]. Surprisingly, 43% of patients do not follow the typical patterns described above, further illustrating the challenges with using ESR and CRP to diagnose and monitor PJI in the early perioperative period[48].

Challenging Situations

Diagnosing PJI in the presence of ALTR[49-51], crystalline deposition arthropathy[52], systemic inflammatory disease[53], or steroid treatment[54] poses an even greater challenge[3,55]. These conditions often mimic PJI, and serum markers may be elevated.

To help distinguish aseptic failure from PJI in patients with ALTR, higher diagnostic thresholds have been proposed[56-59]. Since metallic debris can lead to errors in automated readings of SF-WBC and PMN differential, manual cell counts should be performed in cases of metallosis[50,60]. Alpha-defensin also has lower specificity and PPV in this setting[21,22]. LE test strips can be a valuable, inexpensive, and reliable intraoperative test for discerning PJI in the presence of ALTR[61,62], notwithstanding the limitations of this test when the specimen is blood-tinged after ALTR. Ultimately, a systematic and thorough preoperative evaluation for PJI is recommended in these patients—with possibly manual evaluation of the synovial WBC, PMN differential, and prolonged incubation of the SF for culture[60].

Inflammatory arthritis raises both systemic and intra-articular inflammatory markers, complicating PJI diagnosis using serum and synovial markers for infection[63]. In this setting, threshold values of 30 mm/hr for ESR and 17 mg/L for CRP had an AUC of 0.850 and 0.851, respectively[64]. Using thresholds of 29.5 mm/hr for ESR and 28 mg/L for CRP to diagnose persistent infection during 2-stage revision, the sensitivity and specificity was 64% and 77% for ESR, and 64% and 90% for CRP[65]. That said, a recent multicenter study of 1,220 patients suggested that the thresholds associated with PJI in patients with and without inflammatory arthritis were similar and resembled conventional cutoffs[53]. This contrast in the impact of rheumatologic disease on CRP and ESR thresholds seen in the historical compared with the more recent literature is likely a representation of modern management of inflammatory arthritis. Rheumatologists utilize CRP and ESR as measures of efficacy of biologic and disease-modifying treatments; thus, when one is evaluating a patient with well-controlled inflammatory arthritis for suspected PJI, the CRP and ESR thresholds become reliable. However, when inflammatory arthritis is not under control, caution is needed as these serum tests may be less reliable at the standard PJI cutoffs. The diagnostic utility of alpha-defensin may also be similarly affected by inflammatory arthritis[66-71].

Test results and clinical findings may be similarly confounded in crystalline deposition disease. Turbid, yellowish-white fluid suggestive of an inflammatory reaction in response to infection[72] may also be seen in noninfectious crystalline deposition diseases[73,74]. Alpha-defensin results can be influenced by crystal arthropathy, reducing its utility in this setting[75]. False-positive alpha-defensin lateral flow assays have been cited in the setting of acute gout[69].

Culture-Negative PJI and Molecular Diagnostic Methods

Culture-negative infections are associated with increased diagnostic uncertainty. Several measures can be implemented to improve culture yield[76], including obtaining multiple samples, using separate sterile instruments for collection, expeditiously transferring samples to the laboratory, transporting SF in blood culture bottles, and prolonging culture incubation duration[76-79]. Despite these measures, culture-negative PJI rates have been reported to range between 5% and 42%[80-86]. Consequently, culture-independent molecular technologies have garnered interest for pathogen identification. Conventional and multiplex polymerase chain reaction (PCR)-based modalities have shown improved sensitivity for detecting

infective organisms in culture-negative cases; however, they are prone to false-positives and are limited by initial primer choice[87-89].

More recently, next-generation sequencing (NGS) has shown promise for detecting infective organisms in the research setting after orthopaedic infections. NGS refers to non-Sanger-based high-throughput DNA sequencing methods that produce massive amounts of genomic data, at reduced cost, in a shorter time, and with less manual intervention than prior methods[89]. Unlike PCR, NGS can be used in so-called open mode, which does not rely on a set of parameters or a panel of PCR primer targets. It is thus capable of characterizing all microbial DNA present within a sample by searching curated microbial databases that include bacteria, viruses, fungi, and parasites. Tarabichi et al. first demonstrated the utility of NGS by detecting *Streptococcus canis* in a patient with culture-negative PJI[90]. NGS has been useful for detecting organisms in 82% of culture-negative PJIs[91]. Furthermore, high concordance was found between SF NGS and culture[92].

Metagenomic shotgun sequencing can identify a wide range of PJI pathogens and may be particularly helpful in culture-negative PJI[93]. When metagenomic sequencing was used, "known pathogens" (confirmed by culture) were identified in 95% of culture-positive PJIs, and new "potential pathogens" (not identified by culture) were detected in 44% of culture-negative PJIs. Sequencing sonicated fluid from PJIs was 88% sensitive and 88% specific at the species level compared with pathogens identified on fluid culture[94].

While the clinical importance of microbial DNA detected by NGS is not yet certain, emerging data from prospective multicenter studies have suggested that PJI is polymicrobial at the DNA level in a majority of cases[95]. Data presented at the annual meeting of the American Association of Hip and Knee Surgeons in 2019 suggested that patients with PJI who eventually had treatment failure because of a new organism had that same infective organism isolated by NGS during the initial resection arthroplasty in 89% of failures[95].

However, the cost-effectiveness of molecular testing is undetermined. Current recommendations from the Infectious Diseases Society of America (IDSA) have suggested that NGS testing is justified when there is ongoing suspicion of infection, but conventional culture fails to confirm a diagnosis. Torchia et al. showed that NGS cost-effectiveness was dependent on a pretest probability of >70.0% and specificity of >94.1% in a Markov model projecting lifetime costs and quality-adjusted life years[96]. Further work in the form of multicenter randomized trials examining patient treatment outcomes will be necessary to validate the clinical diagnostic and therapeutic benefits of NGS and other molecular techniques in the setting of PJI.

Overview

The nature of implant-related infections is complex. The infective organisms exist in the form of biofilm and may take refuge inside osteoblasts and bone canaliculi. Thus, reliance on culture to diagnose these infections is often inadequate. There currently is no absolute test for PJI diagnosis (Table I). Therefore, we recommend using the combination of tests described in the evidence-based and validated 2018 definition for PJI (Table III). While the new criteria and development of novel tests have helped to improve diagnostic accuracy, PJI diagnosis remains challenging and is in need of cost-effective innovations. ■

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