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QUESTION 4: Which patient-specific factors (i.e., inflammatory arthritis, immunocompromised state) influence the thresholds for serum and synovial markers in acute and chronic periprosthetic joint infection (PJI)?

RECOMMENDATION: There are currently no inflammatory arthritis-specific factors known to influence the thresholds for serum and synovial markers in PJIs. The literature on PJIs in inflammatory arthritis (IA) is sparse. While α-defensin is the best studied synovial biomarker, as with synovial white blood cell (WBC) count and C-reactive protein (CRP), there appears to be overlap in values limiting their utility in differentiating septic from aseptic effusions in patients with inflammatory arthritis.

LEVEL OF EVIDENCE: Limited due to small numbers

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

RATIONALE

PJI is a concerning complication of total joint arthroplasty and rapid and accurate diagnosis is critical to determine appropriate treatment [1]. However, differentiating between septic and aseptic failure continues to be a diagnostic challenge and is particularly problematic in patients with IA who, in the setting of PJI, have both systemic and intra-articular sources for increased inflammatory markers.

Synovial fluid biomarkers, like WBC count and percent of polymorphonuclear neutrophils (PMN), CRP, α-defensin, cytokines such as IL-6 and leukocyte esterase may be helpful for detection of PJI [2]. However, as with serum cytokines, synovial fluid cytokines have low specificity and may be abnormal in patients with immunological and inflammatory disease [3]. Synovial WBC count is included in both the International Consensus's and Musculoskeletal Infection Society (MSIS) criteria of PJIs [4,5]. However, counts may be elevated in active disease or flares in IA patients. The α-defensin immunoassay, synovial Il-6 level, and leukocyte esterase have all been proposed for the diagnosis of PJI [6], but the utility in patients with IA is unclear. The aim of our systematic review is to evaluate serum and synovial fluid biomarkers and their efficacy at diagnosing PJI in patients with IA.

Our comprehensive literature search retrieved 20 papers that studied biomarkers in PJI and included patients with IA. Of the 21 studies included, 7 specifically addressed findings in IA patients and 14 included IA patients within a larger cohort. The following ranges of sensitivities and specificities for synovial biomarkers were investigated in three or more studies. These values reflect predictions of PJI versus aseptic failure: CRP elevation had a sensitivity ranging from 87.1 to 100% and a specificity of 28.85 to 97.7% [7–12]. WBC count elevation had a sensitivity of 60 to 91% and specificity of 51.4 to 94.3% [12–16]. IL-6 elevation had a sensitivity of 82 to 97% and specificity of 89 to 100% [8,10,14,17]. IL-8 elevation had a sensitivity of 75 to 95% and specificity of 64.71 to 100% [8,9,11,17]. α-defensin had a sensitivity of 97.3 to 100% and a specificity of 95.5 to 100% [10,11,18].

Of the six studies that specifically addressed IA patients [7,9,15,16,18], Cipriano et al. performed the only one that directly compared results for PJI in IA vs. non-IA patients and showed that values for ESR, CRP and synovial WBC count and PMN percentage in patients with IA have a lower optimal diagnostic threshold and lower specificity (Table 1). Median value for serum CRP from three studies are summarized (Table 2), and demonstrates higher serum CRP in PJI-IA than aseptic-IA patients, although these findings could not be pooled for meta-analysis due to methodological differences. Additional data provided by the authors [7,9] allowed us to further calculate the median value for serum CRP in non-IA patients with PJIs which were lower than those of PJI IA patients but higher than IA patients without infection.

Seven studies included data on α-defensin, [9–11,18–21] and three of these papers specifically provided α-defensin data on IA patients. Bonanzinga et al. reported on a cohort of 156 patients, including 9 patients with inflammatory disease. Of the nine IA patients, one had a PJI and had elevated α-defensin and CRP levels compared to uninfected inflammatory disease patients (Table 3). Overall, the α-defensin test showed one false-positive and four false-negatives. Erdemli et al. provided additional data on seven inflammatory arthritis patients included in their study. Two patients with PJI had rheumatoid arthritis (RA) and of five uninfected patients, one had systemic lupus erythematosus and four had RA. The α-defensin test was negative (< 0.00 ng/mL) for the two patients with PJI and RA [9]. The mean and median value of α-defensin for the aseptic group was 12.4 ng/mL and 15.0 ng/mL respectively. Lastly, Patridge et al. discuss a case report of a patient with acute gout who had a false positive α-defensin lateral assay Synovasure® test [19]. The results of the remaining four studies did not report on IA patients specifically, but included this population in their cohort (the results are summarized in Table 4).

Il-6 levels were addressed in six studies, but none of these studies reported outcomes on specifically IA patients [9,10,14,17,22]. Colvin et al. reported on leukocyte esterase test for PJIs but also did not report outcomes for IA patients [23]. Although both these tests show utility for predicting PJI they are untested in IA patients.

The available published studies addressing the diagnosis of PJI in patients with inflammatory arthritis is limited by small numbers. No synovial biomarker demonstrates high sensitivity and specificity for PJI in patients with IA. Diagnostic tests for synovial WBC count, serum CRP, α-defensin appear higher in patients with inflammatory arthritis, but there is overlap between values seen in patients with inflammatory disease who are not infected.

Serum ESR and CRP are known sensitive markers of PJI with poor specificity, however their use in the presence of IA is controversial owing to elevated basal levels that can potentially cause a false-positive result [16,24–26]. The combination of an elevated ESR and CRP with traditional thresholds has been shown to be a more accurate predictor of PJI than isolated elevations of ESR or CRP [24,25,27]. However, optimal threshold levels for these markers may vary for IA. Dizdaveric et al. found significantly higher mean levels of ESR and CRP in patients with IA compared with their non-inflammatory arthritis counterparts [28]. There is sparse literature on the topic and further studies are needed to elucidate whether the cutoff reference values are different in IA patients than in the general population. These thresholds can be affected by multiple factors including time of aspiration, effect of disease-modifying anti-rheumatic drugs (DMARDs) or other treatments, or stage of inflammatory condition (flared versus controlled disease).

It is important to note that adipose tissue can affect IL-6 levels [29], and thus these levels may be elevated in obese patients. Furthermore, metal corrosion can affect serum ESR and CRP levels as well as synovial alpha-defensin levels [18], making it difficult to diagnose PJI.

TABLE 1. Cipriano et al. [16] outcomes summary

Test		Threshold	Sensitivity	Specificity
ESR	Non-IA	32 mm/hr	87.2%	67.1%
IA		30 mm/hr	94.4%	59.4%
CRP	Non-IA	15 mg/L	85.8%	83.4%
IA		17 mg/L	93.8%	70.3%
SFWBC	Non-IA	3,450 cells/μL	91.0%	93.0%
IA		3,444 cells/μL	88.2%	80.0%
SFPMN%	Non-IA	78%	95.5%	87.3%
IA		75%	100%	81.8%

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IA, inflammatory arthritis; SFWBC, synovial fluid white blood cell count; SFPMN%, synovial fluid polymorphonuclear percentage

TABLE 2. Median values for serum CRP (mg/L)

Author	n	CRP PJI IA	n	CRP Aseptic-IA	n	CRP PJI non-IA
Tetreault [7]	5	68.3	8	19.1	27	45.15
Erdemeli [9]	2	26	6	3.56	36	25
Bonanzinga [18]	1	26.5	6	2.35	—	n/a

CRP, C-reactive protein; IA, inflammatory arthritis; PJA, periprosthetic joint infection

TABLE 3. Summary of Bonanzinga et al. [18] inflammatory patients

Inflammatory Disease	Infection Status	CRP (mg/L)	α-defensin (S/CO)
Eczema	Aseptic	0.94	0.2
Irregular antibodies	Aseptic	1.04	< 0.1
Crohn's Disease	Aseptic	0.59	< 0.1
RA	PJI	26.5	7.1
CLL	Aseptic	3.1	< 0.1
Psoriasis	Aseptic	9.77	< 0.1
Psoriasis	Aseptic	5.88	< 0.1
RA	Aseptic	1.67	< 0.1
SLE	Aseptic	3.03	< 0.1

CLL, chronic lymphatic leukemia; CRP, C-reactive protein; PJI, periprosthetic joint infection; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; S/CO, signal cutoff ratio

TABLE 4. Summary of α-defensin results

Study	Population	False Positive	False Negative	Sensitivity	Specificity
Martin [21]	14 cases, no IA distinction	2	1	80%	79%
Frangiamore [20]	116 cases, no IA distinction	2	1	n/a	n/a
Deirmengian [10]	95 cases, 11 IA	n/a	n/a	100	100
Deirmengian [11]	149 cases, 35 IA	5	1	97.3	95.5

IA, inflammatory arthritis

REFERENCES

[1] Patel R, Alijanipour P, Parvizi J. Advancements in diagnosing periprosthetic joint infections after total hip and knee arthroplasty. Open Orthop J. 2016;10:654–661. doi:10.2174/1874325001610010654.

[2] Lee YS, Koo KH, Kim HJ, Tian S, Kim TY, Maltenfort MG, et al. Synovial fluid biomarkers for the diagnosis of periprosthetic joint infection: a systematic review and meta–analysis. J Bone Joint Surg Am. 2017;99:2077–2084. doi:10.2106/JBJS.17.00123.

[3] Shahi A, Parvizi J. The role of biomarkers in the diagnosis of periprosthetic joint infection. EFORT Open Rev. 2016;1:275–278. doi:10.1302/2058–5241.1.160019.

[4] Parvizi J, Zmistowski B, Berbari EF, Bauer TW, Springer BD, Della Valle CJ, et al. New definition for periprosthetic joint infection: from the Workgroup of the Musculoskeletal Infection Society. Clin Orthop Relat Res. 2011;469:2992–2994. doi:10.1007/s11999–011–2102–9.

[5] Parvizi J, Gehrke T, International consensus group on periprosthetic joint infection. definition of periprosthetic joint infection. J Arthroplasty. 2014;29:1331. doi:10.1016/j.arth.2014.03.009.

[6] Wyatt MC, Beswick AD, Kunutsor SK, Wilson MJ, Whitehouse MR, Blom AW. The alpha–defensin immunoassay and leukocyte esterase colorimetric strip test for the diagnosis of periprosthetic infection: a systematic review and meta–analysis. J Bone Joint Surg Am. 2016;98:992–1000. doi:10.2106/JBJS.15.01142.

[7] Tetreault MW, Wetters NG, Moric M, Gross CE, Della Valle CJ. Is synovial C–reactive protein a useful marker for periprosthetic joint infection? Clin Orthop Relat Res. 2014;472:3997–4003. doi:10.1007/s11999–014–3828–y.

[8] Jacovides CL, Parvizi J, Adeli B, Jung KA. Molecular markers for diagnosis of periprosthetic joint infection. J Arthroplasty. 2011;26:99–103.e1. doi:10.1016/j.arth.2011.03.025.

[9] Erdemli B, Özbek EA, Başarir K, Karahan ZC, Öcal D, Biriken D. Proinflammatory biomarkers' level and functional genetic polymorphisms in periprosthetic joint infection. Acta Orthop Traumatol Turc. 2018;52:143–147. doi:10.1016/j.aott.2017.11.002.

[10] Deirmengian C, Kardos K, Kilmartin P, Cameron A, Schiller K, Parvizi J. Diagnosing periprosthetic joint infection: has the era of the biomarker arrived? Clin Orthop Relat Res. 2014;472:3254–3262. doi:10.1007/s11999–014–3543–8.

[11] Deirmengian C, Kardos K, Kilmartin P, Cameron A, Schiller K, Parvizi J. Combined measurement of synovial fluid α–defensin and C–reactive protein levels: highly accurate for diagnosing periprosthetic joint infection. J Bone Joint Surg Am. 2014;96:1439–445. doi:10.2106/JBJS.M.01316.

[12] Kawamura M, Kobayashi N, Inaba Y, Tomoyama A, Choe H, Tezuka T, et al. The usefulness of synovial fluid C–reactive protein for periprosthetic hip joint infection. http://www.ors.org/Transactions/63/2178.pdf 2017.

[13] Mühlhofer HML, Knebel C, Pohlig F, Feihl S, Harrasser N, Schauwecker J, et al. Synovial aspiration and serological testing in two–stage revision arthroplasty for prosthetic joint infection: evaluation before reconstruction with a mean follow–up of twenty seven months. Int Orthop. 2018;42:265–271. doi:10.1007/s00264–017–3700–2.

[14] Lenski M, Scherer MA. Synovial IL–6 as inflammatory marker in periprosthetic joint infections. J Arthroplasty. 2014;29:1105–1109. doi:10.1016/j.arth.2014.01.014.

[15] Lenski M, Scherer MA. Diagnostic potential of inflammatory markers in septic arthritis and periprosthetic joint infections: a clinical study with 719 patients. Infect Dis (Lond). 2015;47:399–409. doi:10.3109/00365548.2015.1006674.

[16] Cipriano CA, Brown NM, Michael AM, Moric M, Sporer SM, Della Valle CJ. Serum and synovial fluid analysis for diagnosing chronic periprosthetic infection in patients with inflammatory arthritis. J Bone Joint Surg Am. 2012;94:594–600. doi:10.2106/JBJS.J.01318.

[17] Frangiamore SJ, Saleh A, Grosso MJ, Farias Kovac M, Zhang X, Daly TM, et al. Neer Award 2015: Analysis of cytokine profiles in the diagnosis of periprosthetic joint infections of the shoulder. J Shoulder Elbow Surg. 2017;26:186–196. doi:10.1016/j.jse.2016.07.017.

[18] Bonanzinga T, Zahar A, Dütsch M, Lausmann C, Kendoff D, Gehrke T. How reliable is the alpha–defensin immunoassay test for diagnosing periprosthetic joint infection? A prospective study. Clin Orthop Relat Res. 2017;475:408–415. doi:10.1007/s11999–016–4906–0.

[19] Partridge DG, Gordon A, Townsend R. False–positive synovial fluid alpha–defensin test in a patient with acute gout affecting a prosthetic knee. Eur J Orthop Surg Traumatol. 2017;27:549–551. doi:10.1007/s00590–017–1942–8.

[20] Frangiamore SJ, Gajewski ND, Saleh A, Farias–Kovac M, Barsoum WK, Higuera CA. α–Defensin accuracy to diagnose periprosthetic joint infection–best available test? J Arthroplasty. 2016;31:456–460. doi:10.1016/j.arth.2015.09.035.

[21] Martin E, Qamar F, Ng A, Koch L, Shetty A. Synovasure are we really sure? (Presentation). Br Hip Soc Annual Mtg. 2015. https://www.britishhipsociety.com/uploaded/Joint_Hip_2015_Final_Program_x_web.pdf (accessed July 18, 2018).

[22] Randau TM, Friedrich MJ, Wimmer MD, Reichert B, Kuberra D, Stoffel–Wagner B, et al. Interleukin–6 in serum and in synovial fluid enhances the differentiation between periprosthetic joint infection and aseptic loosening. PLoS One. 2014;9:e89045. doi:10.1371/journal.pone.0089045.

[23] Colvin OC, Kransdorf MJ, Roberts CC, Chivers FS, Lorans R, Beauchamp CP, et al. Leukocyte esterase analysis in the diagnosis of joint infection: can we make a diagnosis using a simple urine dipstick? Skeletal Radiol. 2015;44:673–677. doi:10.1007/s00256–015–2097–5.

[24] Ghanem E, Antoci V, Pulido L, Joshi A, Hozack W, Parvizi J. The use of receiver operating characteristics analysis in determining erythrocyte sedimentation rate and C–reactive protein levels in diagnosing periprosthetic infection prior to revision total hip arthroplasty. Int J Infect Dis. 2009;13:e444–e449. doi:10.1016/j.ijid.2009.02.017.

[25] Greidanus NV, Masri BA, Garbuz DS, Wilson SD, McAlinden MG, Xu M, et al. Use of erythrocyte sedimentation rate and C–reactive protein level to diagnose infection before revision total knee arthroplasty. A prospective evaluation. J Bone Joint Surg Am. 2007;89:1409–1416. doi:10.2106/JBJS.D.02602.

[26] Berbari E, Mabry T, Tsaras G, Spangehl M, Erwin PJ, Murad MH, et al. Inflammatory blood laboratory levels as markers of prosthetic joint infection: a systematic review and meta–analysis. J Bone Joint Surg Am. 2010;92:2102–2109. doi:10.2106/JBJS.I.01199.

[27] Schinsky MF, Della Valle CJ, Sporer SM, Paprosky WG. Perioperative testing for joint infection in patients undergoing revision total hip arthroplasty. J Bone Joint Surg Am. 2008;90:1869–1875. doi:10.2106/JBJS.G.01255.

[28] Dizdaveric IA, Cashman B, Parvizi J. ESR and CRP serology in inflammatory and non–inflammatory arthritis patients undergoing joint revision surgery. (Presentation). Williamsburg, VA: EOA 42nd Annual Mtg. 2011.

[29] Galic S, Oakhill JS, Steinberg GR. Adipose tissue as an endocrine organ. Mol Cell Endocrinol. 2010;316:129–139. doi:10.1016/j.mce.2009.08.018.