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CORR Insights®: Does the Alpha-defensin Immunoassay or the Lateral Flow Test Have Better Diagnostic Value for Periprosthetic Joint Infection? A Systematic Review

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Where Are We Now?

Periprosthetic joint infection (PJI) is a devastating complication following THA, and it appears to be becoming more common [5]. In light of the morbidity and costs associated with treating PJI, accurate pre and perioperative tests to either confirm or to rule out infection are badly needed. In recent years, various biomarkers have been implemented into our clinical routine either to confirm or rule out PJI [16] with alpha defensin being one of the most-promising tests now available. The alpha-defensin test is market available as a lateral flow test and a laboratory-based immunoassay. Initial reports have shown outstanding sensitivity and specificity [6] even with prior administration of antibiotics [17]. But recently, we have seen inferior results for alpha-defensin tests concerning sensitivity and specificity [2, 3, 11, 18, 19].

In the current study, Eriksson and colleagues [7] performed a systematic review about alpha-defensin and PJI, and concluded that the alpha-defensin immunoassay (with its high sensitivity and specificity) might be a valuable complement to diagnostics of PJI, while the lateral flow test (which has lower sensitivity and high specificity) might be a useful tool to rule out PJI during surgery. Interestingly, all the studies evaluated in this systematic review used the Musculoskeletal Infection Society (MSIS) criteria for definition of PJI.

Where Do We Need To Go?

In a previous *CORR* Insights®, Eoin Sheehan, MD, MCh, FRCS(Orth) stated that "the perfect test for PJI would have 100% sensitivity and 100% specificity" [19]. But will such a test ever exist? [10]. Before we can create one, we would first need to develop a consensus definition for PJI among the many already published [4, 13-15]. Generally, the MSIS criteria is the most commonly used [13], but this definition poorly diagnoses low-grade infections [13], which remains the most-challenging subgroup of PJI [4]. Indeed, causative bacteria are often low virulent normal skin comensals like *cutibacteria* (formerly *propionibacteria*) or coagulase-negative *staphylococci* and the clinical work-up generally lacks typical clinical features like fistula, reddening, or elevated laboratory parameters [14, 15]. We need studies focusing on this subset of PJIs.

It remains unclear whether sensitivity and specificity for alpha defensin would be the same or worse using different classification systems like the Infectious Diseases Society of America (ISDA) criteria for PJI, for example. Therefore, studies comparing the IDSA criteria [8] or other European classification systems [15] with the MSIS criteria in the same cohort of patients should be a priority. This is important because other definitions generally focus more on

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low-grade infection, and the alpha-defensin test seems to have a weakness, particularly in this subset of PJI.

Studies investigating alpha defensin should not focus solely on hip and knee replacement. We also need studies that can determine whether different cut-off values (comparable to cell count and differential [15]) for ankle or shoulder arthroplasties are needed for alpha-defensin.

How Do We Get There?

We have seen a tremendous effort to bring more evidence to the treatment of PJI [12]. This summer's consensus meeting (http://icm2018.squarespace.com/) will certainly include a discussion on the definition of PJI, and perhaps we will develop a new or more-refined definition that encompasses material from the existing classifications.

Beyond the definition, studies focusing on the performance of alpha defensin in low-grade and culture-negative PJI should examine bacteria like coagulase-negative *staphylococci* or *cutibacteria.* Among patients with shoulder or ankle PJI, there is no evidence of which I am aware that supports the use of alpha-defensin or any other biomarker, but gathering enough patients to perform a robust analysis on these diagnoses is difficult in single-center studies [1, 8], and so multicenter studies might shed light on this in the future. These studies might be coordinated by the international societies focusing on PJI like the European Bone and Joint Infection Society (EBJIS), the MSIS, or like a recent study focusing on *streptococci* by the European Society of Clinical Microbiology and Infectious Diseases Study Group on Implant-Associated Infections [9].

References

1. Achermann Y, Sahin F, Schwyzer HK, Kolling C, Wüst J, Vogt M. Characteristics and outcome of 16 periprosthetic shoulder joint infections. *Infection*. 2013; 41:613–620.
2. Adams J, Schwartz RAJ. False-negative synovial alpha-defensin. *Arthroplast Today*. 2017;3:239–241.
3. Berger P, Van Cauter M, Driesen R, Neyt J, Cornu O, Bellemans J. Diagnosis of prosthetic joint infection with alpha-defensin using a lateral flow device: A multicentre study. *Bone Joint J*. 2017; 99B:1176–1182.
4. Clauss M. CORR insights(R). Sonication of arthroplasty implants improves accuracy of periprosthetic joint infection cultures. *Clin Orthop Relat Res.* 2017;475: 1837–1839.
5. Dale H, Fenstad AM, Hallan G, Havelin LI, Furnes O, Overgaard S, Pedersen AB, Karrholm J, Garellick G, Pulkkinen P, Eskelinen A, Makela K, Engesaeter LB. Increasing risk of prosthetic joint infection after total hip arthroplasty. *Acta Orthop*. 2012;83: 449–458.
6. Deirmengian C, Kardos K, Kilmartin P, Cameron A, Schiller K, Booth RE Jr, Parvizi J. The alpha-defensin test for periprosthetic joint infection outperforms the leukocyte esterase test strip. *Clin Orthop Relat Res.* 2015;473: 198–203.
7. Eriksson H, Nordström J, Gabrysch K, Hailer NP, Lazarinis S. Does the Alpha-defensin Immunoassay or the Lateral Flow Test Have Better Diagnostic Value for Periprosthetic Joint Infection? A Systematic Review. *Clin Orthop Relat Res*. [Published online ahead of print]. DOI: 10.1007/s11999.0000000000000244.
8. Kessler B, Knupp M, Graber P, Zwicky L, Hintermann B, Zimmerli W, Sendi P. The treatment and outcome of periprosthetic infection of the ankle: A single cohort-centre experience of 34 cases. *Bone Joint J.* 2014;96B: 772–777.
9. Lora-Tamayo J, Senneville É, Ribera A, Bernard L, Dupon M, Zeller V, Li HK, Arvieux C, Clauss M, Uçkay I, Vigante D, Ferry T, Iribarren JA, Peel TN, Sendi P, Miksic NG, Rodríguez-Pardo D, Del Toro MD, Fernández-Sampedro M, Dapunt U, Huotari K, Davis JS, Palomino J, Neut D, Clark BM, Gottlieb T, Trebše R, Soriano A, Bahamonde A, Guío L, Rico A, Salles MJC, Pais MJG, Benito N, Riera M, Gómez L, Aboltins CA, Esteban J, Horcajada JP, O'Connell K, Ferrari M, Skaliczki G, Juan RS, Cobo J, Sánchez-Somolinos M, Ramos A, Giannitsioti E, Jover-Sáenz A, Baraia-Etxaburu JM, Barbero JM, Choong PFM, Asseray N, Ansart S, Moal GL, Zimmerli W, Ariza J; Group of Investigators for Streptococcal Prosthetic Joint Infection. The not-so-good prognosis of streptococcal periprosthetic joint infection managed by implant retention: The results of a large multicenter study. *Clin Infect Dis*. 2017;64:1742–1752.
10. Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, Rao N, Hanssen A, Wilson WR. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2013;56: e1–e25.
11. 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.
12. Parvizi J, Gehrke T. International consensus on periprosthetic joint infection: let cumulative wisdom be a guide. *J Bone Joint Surg Am.* 2014; 96:441.
13. Parvizi J, Zmistowski B, Berbari EF, Bauer TW, Springer BD, Della Valle CJ, Garvin KL, Mont MA, Wongworawat MD, Zalavras CG. New definition for periprosthetic joint infection: From the Workgroup of the Musculoskeletal Infection Society. *Clin Orthop Relat Res.* 2011;469:2992–2994.
14. Perez-Prieto D, Portillo ME, Puig-Verdie L, Alier A, Martinez S, Sorli L, Horcajada JP, Monllau JC. C-reactive protein may misdiagnose prosthetic joint infections, particularly chronic and low-grade infections. *Int Orthop*. 2017;41: 1315–1319.
15. Sendi P, Zimmerli W. Diagnosis of periprosthetic joint infections in clinical practice. *Int J Artif Organs*. 2012;35: 913–922.

16. Shahi A, Parvizi J. The role of biomarkers in the diagnosis of periprosthetic joint infection. *EFORT Open Rev.* 2016;1: 275–278.
17. Shahi A, Parvizi J, Kazarian GS, Higuera C, Frangiamore S, Bingham J, Beauchamp C, Valle CD, Deirmengian C. The Alpha-defensin test for periprosthetic joint infections is not affected by prior antibiotic administration. *Clin Orthop Relat Res.* 2016; 474:1610–1615.
18. Suda AJ, Tinelli M, Beisemann ND, Weil Y, Khoury A, Bischel OE. Diagnosis of periprosthetic joint infection using alpha-defensin test or multiplex-PCR: Ideal diagnostic test still not found. *Int Orthop*. 2017;41:1307–1313.
19. Suen K, Keeka M, Ailabouni R, Tran P. Synovasure 'quick test' is not as accurate as the laboratory-based alpha-defensin immunoassay: A systematic review and meta-analysis. *Bone Joint J*. 2018;100: 66–72.