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CORR Insights®: How Reliable Is the Alpha-Defensin Immunoassay Test for Diagnosing Periprosthetic Joint Infection? A Prospective Study

Thomas W. Bauer MD, PhD

Where Are We Now?

Periprosthetic joint infection (PJI) is difficult to diagnose and treat [11]. Although we are continually seeking more sensitive and specific tests to diagnose PJI prior to surgical intervention, there remains no diagnostic “gold standard.”

This CORR Insights® is a commentary on the article “How Reliable Is the Alpha-defensin Immunoassay Test for Diagnosing Periprosthetic Joint Infection? A Prospective Study” by Bonanzinga and colleagues available at: DOI: 10.1007/s11999-016-4906-0.

The author certifies that he, or a member of his immediate family, has no funding or commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

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In 1985, Ganz and colleagues isolated three small cysteine-rich peptides (CRPs) from human neutrophilic granules that demonstrated strong antimicrobial properties, and coined the term “defensins” [8]. It is now recognized that in response to bacterial pathogen-associated molecular patterns, neutrophils, macrophages, T-lymphocytes, and some epithelial cells can release a family of cationic molecules, the alpha defensins, which disrupt bacterial cell membranes [4]. Previous studies [5, 6] have suggested

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This CORR Insights® comment refers to the article available at DOI: 10.1007/s11999-016-4906-0.

T. W. Bauer MD, PhD (✉)
Departments of Anatomic Pathology and Orthopaedic Surgery L25,
The Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195-5138, USA
e-mail: osteoclast@aol.com
URL: <http://www.bauert@ccf.org>

that an immunoassay of aspirated joint fluid for one or more of these alpha-defensin molecules has high sensitivity and specificity for diagnosing periprosthetic infection [5, 6]. The relatively few false-positive test results were associated with metallosis, and could be recognized if a simultaneous assay for CRP yielded a low result [5]. A commercially available, Laboratory Developed Test, Synovasure, (CD Diagnostics, Claymont, DE, USA) has not yet been evaluated by FDA, but reports synovial fluid alpha-defensin along with simultaneously measured CRP [3].

In their study, Bonanzinga and colleagues designed a prospective study to test the sensitivity, specificity, and predictive value of the alpha-defensin assay for diagnosing periprosthetic infection. The authors concluded that if the alpha-defensin test is negative, then “it is quite likely that the pain in the joint after THA or TKA is not caused by PJI.” Previous studies [5–7, 12] have made similar conclusions. If the test result is positive, then the

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likelihood of infection is high, but other reasons for positive test results (for example, metallosis), should be considered.

Where Do We Need To Go?

This publication confirms the high sensitivity and specificity of the alpha-defensin assay to diagnose or rule out periprosthetic infection in selected patient populations. The test is rarely associated with false-negative values, and most false-positives appear to be associated with metallosis. However, it is not obvious how much additional information this test provides beyond commonly available tests. For example, when tested individually, the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and synovial fluid cell count do not perform as well as the alpha-defensin assay [1], but a combination of those tests, does yield high sensitivity and specificity [9, 10]. The alpha-defensin threshold level for diagnosing an acute periprosthetic infection (within three months of arthroplasty) has not yet been established, nor has the test been validated for other types of orthopaedic infections. Charges and costs of these tests vary, but will also need to be taken into consideration [3].

On the other hand, one of the strengths of this test is its apparently

high sensitivity and specificity when used in patients with an underlying inflammatory arthropathy. The test also has a low number of false-negative results. In that respect, it may be of most value when used in combination with tests that have high-positive predictive value, especially in cases for which other tests are inconclusive.

How about the big picture? The alpha-defensin test appears to have good sensitivity and specificity, but still requires aspirated joint fluid. It is currently considered a “send out” test so the results are not immediately available, although that may change if point-of-care kits are developed. We are still seeking a preoperative test that does not require aspirated joint fluid (perhaps a blood test or an imaging study). We also need a test (besides frozen section histology) with a turnaround time short enough to be of use during a revision arthroplasty operation. A rapid molecular test that would provide the species of bacteria and drug sensitivity would be even better. Finally, the cell biology of alpha-defensin release, most likely from macrophages in some cases of metallosis, and the modulation of macrophage proinflammatory cytokine release by alpha defensins [12] are of interest with respect to the basic science of inflammation and the various adverse

local tissue reactions associated with failed arthroplasty.

How Do We Get There?

Current evidence suggests that the alpha-defensin assay, especially in combination with synovial fluid CRP level, is a good test to diagnose or rule out a chronic periprosthetic infection in the hip or knee. Prospective clinical studies that evaluate test efficacy in the first 3 months after arthroplasty, that measure sensitivity and specificity at the second stage of a two-stage revision for known infection, and that determine the extent to which this test provides independently significant additional value beyond currently available, inexpensive tests are needed. Modification of the test to a point-of-care kit that uses joint fluid aspirated during a revision arthroplasty operation should make this test of even more value in patients with equivocal preoperative evaluations.

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