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Editor's Spotlight/Take 5

Editor's Spotlight/Take 5: Diagnosing Periprosthetic Joint Infection: Has the Era of the Biomarker Arrived?

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In 2011, the Musculoskeletal Infection Society (MSIS) published a set of criteria defining the diagnosis of periprosthetic joint infection (PJI) [9]. The definition arose, in part, because there was no widely adopted gold standard for the diagnosis of PJI. This lack of consensus generated varying definitions of infection that yielded broad ranges of sensitivity, specificity, and accuracy [8], as well as confusion, in the many published studies on the topic about what was (and what was not) a PJI.

The MSIS definition [9] was intended to be the gold standard definition for PJI, using both clinical and laboratory criteria to establish the diagnosis. However, even with this defined standard, much uncertainty exists. For instance, the definition comes with the caveat that inflammatory markers may be elevated for up to 2 months after surgery [1, 6]. Additionally, while there is agreement that patients with PJI present with elevated synovial leukocyte count and neutrophil percentage, there is little agreement on a threshold value [4, 5, 10, 11]. By defining a biological problem—infection—using a criterion-based menu, we are acknowledging the presence of an important gap in our knowledge. This large, gray area (and the menu-approach to diagnosis) is reminiscent of our approaches to the diagnosis of classifying rheumatoid arthritis [2] and fibromyalgia [12], two conditions about which many unanswered questions remain.

The idea that we can diagnose PJI from a laboratory test with certainty, regardless of systemic inflammatory status and concurrent antibiotic administration, has eluded us to this point. In this month's issue of *CORR*®, Dr. Carl Deirmengian and his time have opened up a promising avenue of inquiry in pursuit of this goal. By comparing synovial fluid biomarker assays to the MSIS PJI definition in patients with revision arthroplasty, the lab identified several markers with excellent diagnostic performance. The beauty of this study lies in the inclusion of patients with inflammatory diseases as well as individuals taking antibiotics; while systemic inflammation and antibiotic use often confound the clinical picture, synovial fluid biomarkers show diagnostic accuracy even in these complex situations.

With this breakthrough, Dr. Deirmengian and his team bring us into the era of the biomarker, where synovial fluid analyses of certain markers may exceed the MSIS standard definition's

Note from the Editor-In-Chief: In "Editor's Spotlight," *one of our editors provides brief commentary on a paper we believe is especially important and worthy of general interest. Following the explanation of our choice, we present* "Take Five," *in which the editor goes behind the discovery with a one-on-one interview with an author of the article featured in* "Editor's Spotlight."
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utility for diagnosis and rival it in simplicity. I find the results exciting, as the diagnostic accuracies, sensitivities, and specificities of the biomarker approach tested by Dr. Deirmengian's group appear to be as good as they get in medicine.

Take 5 Interview with Carl A. Deirmengian MD Senior Author of "Diagnosing Periprosthetic Joint Infection: Has the Era of the Biomarker Arrived?"

M. Daniel Wongworawat MD: *Congratulations on this important work. With a diagnostic gold standard for PJI already in place, what drove you to look for something better?*

Carl A. Deirmengian MD: Diagnosing patients with a painful arthroplasty is probably one of the most frustrating clinical exercises in orthopaedics. It is this frustration that motivated the MSIS to publish their diagnostic recommendations. This criterion-based definition of PJI was necessary because no individual test for infection was sufficient. Synovial fluid cultures fail to grow an organism in about 30% to 50% of PJIs. The C-reactive protein level, erythrocyte sedimentation rate, and fluid leukocyte count and differential are each insufficient to diagnose PJI. Furthermore, because these tests were never designed to diagnose PJI, there is institutional and publication variation in the performance and interpretation of them.

While the MSIS definition really has empowered institutions to utilize a common method of diagnosing PJI for research, criteria-based diagnostic standards are difficult to use in clinical practice and require constant education. For example, the acquisition of two positive cultures, which is one of the major criteria defining PJI, often provides results only after definitive surgical treatment has been rendered. Diagnosing infection requires the surgeon to know which tests to order, and then understand the literature sufficiently to interpret the tests.

The potential benefit of a simple and accurate test for PJI is clear. When you consider that the synovial compartment is a relatively closed system, I think that it is surprising that dedicated synovial fluid tests for disease have not yet been developed. Given the importance of infection, and our suspicion that the synovial fluid would be a rich source of diagnostic information, we were driven to develop a better test from synovial fluid. If a synovial fluid biomarker test designed to diagnose PJI could provide results similar to the more complex MSIS definition, then diagnosing PJI would be easier to execute, and a final diagnosis could be provided before definitive treatment.

Carl A. Deirmengian MD

Dr. Wongworawat: *What characteristics are you looking for when searching for an ideal diagnostic test?*

Dr. Deirmengian: Obviously, the primary desire is that the diagnostic test for infection is reasonably fast and highly accurate. Ideally, it does not become confounded by systemic inflammation, and is not susceptible to contamination. When we embarked on finding the ideal biomarker for PJI, we made a decision to include patients with systemic inflammatory diseases, and also those patients already on antibiotics. These challenging groups of patients are often excluded by previous studies.

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But there are other important characteristics that are less apparent. For example, the widespread use of any test requires that there is no need for specialty equipment or complex technology. The utility of any test is not only in its accuracy, but also in its ability to be used by everyone; there should be minimal interpretation necessary.

I think that one of the current difficulties in the field of infection is that most emerging diagnostic technologies are complex, difficult to understand, and have barriers to widespread adoption beyond specialized institutions. On the other hand, a biomarker immunoassay, once found to be sufficiently accurate, has no technological barrier to widespread adoption.

Dr. Wongworawat: *In your paper, you performed receiver operator curve analyses. Explain what this type of analysis achieves and why it is something the informed orthopaedic surgeon should understand.*

Dr. Deirmengian: When you change any test's diagnostic threshold, or cutoff, both the sensitivity and specificity of the test can change. Receiver operator curve analysis calculates the sensitivity and specificity of the test at every possible cutoff value. You can then review the analysis to choose a diagnostic cutoff that provides the desired combination of sensitivity and specificity. For many tests that were not explicitly developed for diagnosing infection, such as the synovial fluid leukocyte count and the serum C-reactive protein, choosing a suitable cutoff value is critical for interpreting the laboratory's result. Ideally, for tests that are developed for a specific purpose, the laboratory report not only provides a result, but also an interpretation such as positive or negative. Receiver operator analysis of five of the biomarkers in our study demonstrated an area under the curve of 1.0, which means that the diagnostic cutoff provided complete separation of the diagnostic groups, aseptic and infected.

Dr. Wongworawat: *You found five biomarkers that had perfect sensitivity, specificity, and area under the curve. It does not get much better than that. How do you choose which one or ones to apply to clinical practice?*

Dr. Deirmengian: Performance is a main factor in choosing the right biomarker. Even when comparing biomarkers with apparently perfect diagnostic characteristics, you can see differences in the quantitative separation between diagnostic groups. The wider the separation between diagnostic groups, the more likely it can be developed into a clinically useful assay. A second, but equally important, consideration is the technical difficulty required to develop a reliable laboratory assay for the biomarker. The clinically relevant concentration of the target analyte is critical, since it can direct the potential assay formats that can be utilized. We wanted to select a marker that was amenable to a point-of-care format.

We have chosen to move forward with alpha-defensin for use in clinical practice. In our publication, you can see that alpha-defensin provided a very large separation between the infected and aseptic patients. In fact, 62 of 66 patients who were diagnosed as aseptic in our publication had undetectable levels of alpha-defensin. Furthermore, we have identified antibodies that provide for a quite reliable and rapid immunoassay with negligible background interference. Our unpublished results demonstrated that inflammatory conditions such as gout and rheumatoid arthritis affected alpha-defensin minimally compared to the other top biomarkers.

Additionally, alpha-defensin is stable in synovial fluid at room temperature for at least two days and appears to be stimulated by all clinical bacterial isolates that we have cultured to date. For all these reasons, we have chosen to apply the alpha-defensin test to clinical practice.

Dr. Wongworawat: *The 2011 MSIS diagnostic criteria for PJI is considered a landmark by many. In 2013, the International Consensus Meeting on*

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Periprosthetic Joint Infection, through a Delphi method [3, 7], issued a similar but different definition [13]. Where do you see us heading as we enter this new era?

Dr. Deirmengian: It is only because of the work of the MSIS that all of our research could be performed with rigor. After all, without an accepted definition of infection, there is nothing by which to measure a new test. In the next few years, we will see laboratory-based and point-of-care tests emerge as the standard of care for diagnosing periprosthetic infection. These will really be the first-ever laboratory tests developed and optimized specifically for synovial fluid. In fact, I believe that highly accurate synovial fluid biomarker tests will be soon utilized for a wide array of diseases, such as native septic arthritis, adverse reaction to metals, gout, pseudogout, rheumatoid arthritis, and others.

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