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From Bench to Bedside

From Bench to Bedside: Alpha-defensin—The Biggest Thing in Joint Replacement Infections Since Prophylactic Antibiotics?

Benjamin K. Potter MD

We have been awaiting the arrival of 21st century biomarker-, gene- or sequence-driven personalized medicine since well before the millennium. Yet the "Golden Age" of personalized medicine has proven elusive. While total joint arthroplasty (TJA) alleviates suffering perhaps better than any other orthopaedic intervention [8], patients whose arthroplasties have been complicated by infection have a very different experience. The condition is painful, the treatments are inconsistent, and most vexingly, our approaches to diagnosing the condition fall well short of what our patients expect from us in the second decade of the 21st century.

Complications and failures outcomes remain. Apart from rare fatal pulmonary emboli, which unfortunately require no treatment, periprosthetic joint infection (PJI) remains among the most dreaded complications that our patients experience. Infection rates have dropped in a range of 300% to 500% since the days of Charnley's pioneering work in the hip, but PJI remains a devastating and feared complication [3, 10]. While most infections can be successfully treated by a variety of approaches that stop short of the last resort, alternatives of fusion, resection arthroplasty, or amputation, PJIs continue to be expensive, profoundly impact patient quality of life, and literally kill people [14].

Often, however, the diagnosis is unclear despite routine inflammatory

A Note from the Editor-In-Chief:
I am pleased to introduce "From Bench to Bedside," *a new quarterly column written by Benjamin K. Potter MD. Dr. Potter is a clinician-scientist in the Department of Orthopaedics at Walter Reed National Military Medical Center and in the Department of Surgery at the Uniformed Services University of Health Sciences. His column will investigate important developments that are making—or are about to make—the transition from the laboratory to clinical practice, as well as technologies and approaches that have recently made that jump.*

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B. K. Potter MD (✉)
Department of Orthopaedics, Walter Reed National Military Medical Center, 8901 Wisconsin Ave, America Building (19), 2nd Floor – Ortho, Bethesda, MD 20889, USA
e-mail: Benjamin.k.potter.mil@mail.mil

B. K. Potter MD
Department of Surgery, Uniformed Services University of Health Sciences, Bethesda, MD, USA

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laboratory values, radiologic studies, and aspirate fluid and culture analysis. There is little doubt that the (at least two-fold) higher infection rate for revision procedures is not simply a result of the increased duration, complexity, and (immunosuppressive) transfusion requirements of these procedures—many "aseptic" revisions, are not. Excellent work has been performed on aspirate cell analysis, but these results require complex interpretation that varies by time from the index procedure, the joint involved, a "clean" versus "bloody" tap, and even the laboratory normative values at your institution [2, 12]. Serum inflammatory markers are generally afflicted by these same limitations, as well as others, and often perform worse. Cut-off values, while helpful, remain imperfect, seemingly moving targets that (needless to say) have not been calibrated to your specific patient and their potential confounding factors.

To help clarify matters, two excellent (and similar) consensus statements from the Musculoskeletal Infection Society and an international panel [11, 13] regarding the diagnosis of periprosthetic joint infections have been produced. While they do not answer all of our questions, these guidelines, at the very least, establish a reference standard we can use to confirm a diagnosis of infection and to measure new diagnostics and therapeutics against.

Ultrasensitive molecular diagnostics have been developed concurrently, but these techniques suffer from expense, lack of widespread adoption outside of clinical investigations, and perhaps from being too sensitive. For example, polymerase chain reaction-based techniques can be limited by both contamination and coincidental findings—a positive finding unfortunately does not necessarily correlate with clinical relevance [9].

Finally, a better answer for the diagnosis of PJI following TJA appears to have arrived in the form of synovial fluid alpha-defensin levels. Measuring synovial fluid levels of this marker, particularly in the context of synovial C-reactive protein, has demonstrated impressive accuracy in the diagnosis of PJI. One series of 26 PJIs and 66 aseptic joints found that α-defensin, as well as a few other candidate biomarkers, demonstrated 100% sensitivity and specificity for the diagnosis of PJI [7]. In a subsequent analysis of 149 synovial aspirates, including 37 with PJI, synovial α-defensin demonstrated 97% sensitivity and 96% specificity for the diagnosis of PJI, improving to 100% specificity with interpreted concurrently with synovial C-reactive protein [6]. Most recently, a separate group of investigators found sensitivity of 100% and specificity of 95% in a prospective cohort of 57 patients [1]. These findings are all the more important given that only around 50% of preoperative synovial cultures are typically positive, even in the setting of PJI.

Two additional factors are important when interpreting these promising results. First, these studies included patients with current antibiotic administration and/or systemic inflammatory arthropathies—two factors that frequently frustrate clinicians and obfuscate routine laboratory result interpretation. Second, rather than being stuck, "on the horizon," this test is commercially available now. We can hope that even if we have not yet solved the problem of PJI, we may at least be on the way to a reliable approach to diagnosis.

In closing, full disclosure: Naturally, much of this progress has been driven by "industry"—no implant or test is free, and no such test or device is likely to reach the market if it were. Much of the work to date on α-defensin has been done by Dr. Carl Deirmengian and colleagues, who have disclosed their financial relationships in their various publications. Dr. Deirmengian began investigating the host response as a means to better diagnose infections when he was a resident, demonstrating critical differences in neutrophil responses between infection and gout in a Mark Coventry Award winning paper [4]. Ultimately, he determined that the gene chips utilized in this analysis were likely to

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impractical for clinical use. However, as a fellow, he revisited the issue of utilizing synovial fluid analysis to diagnose infection. This time focusing on proteins; the resulting manuscript produced promising work that would ultimately spawn his further investigation of α-defensin [5], the eventual formation of a company, and commercial product development. More disclosure: Around a decade ago, Dr. Deirmengian and I both competed in a resident research competition. Carl won.

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