Editor's Spotlight/Take 5

Editor's Spotlight/Take 5: A Diagnostic Serum Antibody Test for Patients With *Staphylococcus aureus* Osteomyelitis

Seth S. Leopold MD

It is astounding that in 2015, physicians cannot diagnose with certainty patients with a limb-threatening condition like bacterial osteomyelitis (or its evil twin, prosthetic joint infection). After all, we have been treating bone infections since the time of Hippocrates [5].

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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Surgeons sometimes fret about the lag time between diagnosis and treatment, but this is more than a lag—we have been waiting nearly 25 centuries to go from treatment to diagnosis.

Perhaps the wait is over, or at least it may be soon. Last year, an article in *Clinical Orthopaedics and Related Research*® asked whether “the era of the biomarker” has arrived [3], and the authors’ answer (seemingly yes, at least for patients with hip and knee prosthesis infections) has been confirmed by other investigators and in other joints [1, 4], at least with respect to alpha-defensin, which is one promising biomarker.

This year’s winner of the *CORR*® ORS Richard A. Brand Award for Outstanding Orthopaedic Research takes us another step closer to the goal of personalized diagnostics in the area of bone infection, by identifying a number of immunologic markers both for the diagnosis of musculoskeletal infections

as well as for prognostic purposes in patients with *Staphylococcus aureus*. I extend my personal congratulations to Stephen L. Kates MD, Edward M. Schwarz PhD, and their team at the University of Rochester, for this creative and exciting project.

This team found a panel of 14 immunoglobulin G antibodies that effectively distinguished patients with infections from those without. The group identified a couple of antibodies (IgG titers against iron-regulated surface determinants B and A) that appear to be associated with the most dangerous infections surgeons treat: Those more likely to cause infection-related death, despite appropriate treatment.

Although this work has not yet made the leap from the bench to the bedside, it represents a promising step in providing patients answers to their two most-serious questions: Do I have the disease, and will I die from it? Efforts along these lines also may lead to approaches that can help surgeons prevent infections, including the development of an *S aureus* vaccine [2], although initial efforts in this direction have not consistently been successful [6].

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What stands between the bench and the bedside here? Join me, Dr. Kates and Dr. Schwarz in the Take-5 interview that follows to find out.

Take Five Interview with Stephen L. Kates MD and Edward M. Schwarz PhD, senior authors of “A Diagnostic Serum Antibody Test for Patients With Staphylococcus aureus Osteomyelitis”

Seth S. Leopold MD: *Congratulations on this very exciting work, and also on winning this year's CORR® ORS Richard A. Brand Award for Outstanding Orthopaedic Research. Well earned! With respect to diagnostic testing in orthopaedics, it seems we may be in a transitional state between the use of nonspecific tests for serious conditions and an era of personalized diagnostics and biomarkers. How do you see the state of this science?*

Stephen L. Kates MD: We see tremendous potential for rapid diagnosis of infections in the future to avoid reliance on obtaining and culturing the pathogen and to help avoid empiric therapy frequently employed by clinicians. Serum diagnostics offer the potential to improve patient care dramatically and reduce costs at the same time.

Dr. Leopold: *You allude in the paper to the possibility that your line of inquiry*

might someday guide us towards ways to improve infection prophylaxis. I note that well-intentioned efforts in this area—in particular anti-Staphylococcal vaccines—sometimes have resulted in serious problems [6]. How might you use an immunologic approach to help prevent infections safely?

Edward M. Schwarz PhD: Some exciting possibilities exist in this area, in particular risk stratification and treatment/prevention. For risk stratification, we are presently studying level of antibody production in patients with

and without infection to understand the effects of BMI, diabetes, and on human immunity against infection. From a treatment/prevention standpoint, we have developed a passive immunization against *S aureus*, which is in animal trials presently. Such a passive immunization would be given at wound closure to high-risk patients, to augment the human immune system's efforts to eliminate the pathogens. By using a passive immunization, safety may be enhanced and the human immune response is less variable.

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Dr. Leopold: *Apart from the immunologic approach you are taking, what do you see as the most promising diagnostic tools being investigated now?*

Dr. Schwarz: Antibody-secreting cells (ASC) hold great diagnostic potential. ASC are activated plasmablasts that are found in the peripheral blood during active infection. These cells are present in the circulation as they migrate from lymph nodes to other lymphoid tissue during the active phase of infection. These cells have been used to monitor efficacy of vaccines for viral pathogens and measure the natural history of tuberculosis. These cells are found within the population of peripheral blood mononuclear cells, which can be easily isolated from plasma.

Our focus is to use the host's immune response to infection to specifically identify the pathogen. We have developed a method to isolate these ASC from the peripheral blood, amplify the number cells and analyze them for specific antibodies against known staphylococcus antigens. This method has the potential for fast and specific pathogen identification without the need for collecting tissue or cells with bacteria or their byproducts present.

Dr. Leopold: *Whenever we evaluate a new diagnostic tool, the issue of the diagnostic gold standard comes into*

play. As you know, cultures can be both falsely positive and falsely negative, and infections can remain quiescent for some time and then reactivate, so establishing the diagnosis and confirming the success of treatments really complicate research in these areas. Your study used patients with obvious clinical infections, but future studies will need to test patients where there is uncertainty about the diagnosis to evaluate the utility of new diagnostic tests; how should these studies be done?

Dr. Kates: Such studies are challenging as you point out because the diagnosis of infection is difficult and the definition of an infection is even controversial. All humans have different baseline anti-Staphylococcal antibody levels. One strategy would be to use large numbers of serum specimens blinded to the lab scientists to predict the presence of infection and then observe the clinical outcomes. Current screening tools including C-reactive protein, erythrocyte sedimentation rate,

Edward M. Schwarz PhD

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and white blood cell count are extremely nonspecific measures. Because there is no “gold standard” for diagnosis, such study design strategies would be required.

Dr. Leopold: *Let us talk about bench-to-bedside stuff. What will it take to commercialize an idea like yours, how expensive are the processes you used, and how much more expensive, time-consuming, or difficult is it to run a battery of 14 antibodies as opposed to one or two?*

Dr. Schwarz: The test would require validation and FDA approval, which would require it to be commercialized as you point out. The methods are already commercially available using the Luminex machine and commercially available antigens, which will expedite this process. The test currently takes us 2.5 hours to run with

the 14 antigens. We hope to reduce it down to about four antigens with similar diagnostic quality and lesser costs. We are looking at a risk adjustment strategy to help sharpen the diagnostic accuracy of the test now—much as creatinine-clearance rates are adjusted for patient descriptors like age and race.

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