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CORR Insights®: Measurement of Serum Anti-staphylococcal Antibodies Increases Positive Predictive Value of Preoperative Aspiration for Hip Prosthetic Joint Infection

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Where Are We Now?

Periprosthetic joint infection (PJI) remains a challenging diagnosis. In the current study, Bauer et al. [1] presented a unique serum diagnostic test for PJI, and they highlighted the need for new diagnostic tools to discriminate septic from aseptic failure. A multiplex immunoassay that measures serum anti-staphylococcal antibodies (SASA) was developed to diagnose staphylococcal PJI noninvasively and was validated specifically for detecting host antibodies for three species: *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Staphylococcus lugdunensis* [8]. The test's sensitivity ranges from 72% to 88% and specificity ranges from 81% to 94% [3, 8]. SASA is a relatively inexpensive and accurate tool that aids clinicians in diagnosing staphylococcal infection. It is a serum test, and thus is considered non-invasive compared with other techniques. Any effort to increase its accuracy for diagnosing PJI should be applauded, and the authors' unique approach had not previously been studied.

As seen in this study [1] and others [7, 17], staphylococcal organisms are a frequent cause of PJI, with *S. aureus* and S. epidermidis accounting for most of the genus associated with periprosthetic infections. However, coagulase-negative staphylococci, which include S. epidermidis, are part of normal skin flora and could be cultured as a contaminant, leading to false-positive results. On the other hand, synovial fluid cultures may be falsely negative for these low-virulence staphylococci. This can pose a problem in terms of interpreting culture results for these organisms. Bauer et al.'s study [1] indicates that the SASA assay may help mitigate this problem for these low-virulence species. Thus, the clinician may find the SASA assay most useful in patients with a suspected staphylococcal infection (such as a positive nasal colonization screening result, prior known staphylococcal infections), patients who have had negative culture results or possible contaminants (from either preoperative aspirations or prior PJI treatment) because there may be a slow-growing or low-virulence staphylococcal organism, and patients with concurrent sepsis and bacteremia, because this is a serum test and would likely yield positive results if there is staphylococcal bacteremia.

Diagnosing PJI is constantly evolving as new technologies emerge in the diagnostic arena. The authors [1] used the Infectious Diseases Society of America criteria [9] in their study at the onset of patient recruitment in 2012. However, newer definitions have been adopted since then, concurrent with the development of advanced diagnostic technologies. These advancements include identification of biomarkers such as leukocyte esterase [16], IL-6, alpha-defensin [2], and serum d-dimer [12], among others that provide diagnostic information regarding the presence of an infection, without detecting actual organisms. The most-recent definition of PJI is the multicenter, evidence-based, and validated criteria by Parvizi

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et al. [10], which consider the aforementioned novel, validated biomarkers. This definition was recently adopted in 2018 by the International Consensus Meeting [13], a consortium of experts across the fields of orthopaedic surgery and infectious disease. Other technological innovations currently being studied involve novel molecular methods, such as mass spectrometry, multiplex polymerase chain reaction, and next-generation sequencing. These methods not only determine the presence of infection, but also identify the infecting organisms.

Where Do We Need To Go?

As the authors alluded to in their study [1], the positive predictive value of any diagnostic test is affected by the prevalence of the disease. The authors recruited patients from referral centers with an incredibly high prevalence of PJI of 34%, which is much higher than in most centers in the United States, including tertiary referral practices. Therefore, for external validation, further research in centers with a lower prevalence of disease is needed to produce more-generalizable results.

While SASA is useful, it cannot be used as a single tool for diagnosing infection. As part of each patient's workup, three fundamental questions must be addressed: Is infection present? What organisms are detected? What is the antibiotic susceptibility to guide treatment?

In the most-recent definition of PJI, the criteria sensitivity was 97.7% and specificity was 99.5%, clearly demonstrating that we have made incredible progress in determining the presence of infection [10]. Despite this incredible headway, there is room for improvement in the methods for detecting these novel biomarkers, such as leukocyte esterase and alpha-defensin. More research is needed in order to explore other biomarkers; this is particularly true for serum because it is less-invasive than synovial fluid aspirations. Furthermore, there is a need to develop point-of-care tests for detecting these biomarkers.

While cultures remain the gold standard for identifying organisms and their antibiotic susceptibility, DNA sequencing techniques are being explored as a possible avenue for obtaining this information. Polymerase chain reaction is a molecular diagnostic technique used to identify the genetic material of infecting pathogens by amplifying a single copy of a piece of DNA. The amplified regions of interest are the 16S genes for detecting bacterial and fungal species while avoiding host DNA. However, polymerase chain reaction has not been widely adopted in orthopaedics because of its limited sensitivity and an unacceptably high rate of false-negative results [5]. On the contrary, multiplex polymerase chain reaction uses a series of primers for a specific panel of organisms and demonstrates greater sensitivity [11]. Its main limitation is that one needs to speculate which organisms are likely to be present in order to designate the primer specific to that organism; even then, it can only detect a limited number of organisms at one time.

Shotgun metagenomic sequencing using next-generation sequencing is the most-novel molecular technique being examined. Next-generation sequencing comprehensively explores all genes in all organisms present in a sample and has promising results for detecting organisms in up to 82% of culture-negative PJIs [4, 14, 15]. It might replace time-consuming techniques with a single diagnostic test. Unlike polymerase chain reaction-based sequencing, next-generation sequencing does not rely on a panel of preconceived primer targets and can characterize all microbial DNA in a sample. Next-generation sequencing searches all known microbial databases, including bacteria, viruses, yeast, fungi, and parasites, for a match. Next-generation sequencing can also identify antimicrobial resistance by detecting known resistance genes [6].

How Do We Get There?

Given the substantial patient morbidity, increasing prevalence, and economic burden of PJI, an increasing number of research studies have focused on the diagnosis and treatment of infection. More funding and effort should be channeled into translational research, starting with basic science research, to identify novel biomarkers and bacterial antibodies while testing in serum and synovial fluid and adopting these new discoveries into the development of rapid, inexpensive, and accurate tests for infection. Funding may be obtained via departmental funding or collaboration with musculoskeletal research laboratories. It may also be obtained on a regional or national level through orthopaedic societal grants or federal funding. These biomarkers and tests need to be validated. Internal validity can be achieved by obtaining these biomarkers in patients with PJI and aseptic controls and minimizing confounding variables. External validation can be performed through multi-center studies, which are ideally prospective clinical trials; however, retrospective studies can be more readily accomplished and achieve similar goals. Across institutions, there must

be standardization of inclusion and exclusion criteria including the definition of PJI, similar laboratory equipment to measure biomarkers, and a standardized definition of what constitutes a positive result for biomarkers.

Further study in the form of a multicenter clinical trial is warranted to evaluate and validate the promising results derived from next-generation sequencing-based tests for diagnosing PJI. Barriers to broad-based implementation of next-generation sequencing may be related to its limited availability and overall expenses, which include the cost of instruments, maintenance, sample processing, staff time, data storage, and consumables such as laboratory supplies; however, as genome sequencing becomes more affordable and translates into routine health care, we can expect these costs to decline. Lastly, as we continue to add more validated tests to our diagnostic armamentarium, we should regularly assimilate them into the evolving diagnostic criteria for diagnosing PJI.

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