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New Sepsis Diagnostics and Their Impacts on Clinical Decision-Making and Treatment Protocols

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Guest: Dr. Allison Chambliss from the Department of Pathology and Laboratory Medicine at the University of California, Los Angeles.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. Sepsis, defined as a disordered immune response to infection, requires prompt and appropriate management to prevent progression to multiple organ failure or death. Despite widespread understanding that early diagnosis and treatment improves outcomes, this has remained an elusive goal because the clinical signs and symptoms of sepsis overlap considerably with other unrelated conditions. Currently available diagnostic tools are similarly nonspecific, but this may be changing with the introduction of new FDA cleared tests. What are the limitations of conventional sepsis markers and how might these new tests improve on those shortcomings? Are these new tests likely to shepherd in a new era of sepsis management or are they destined for a largely peripheral role?

A Q&A article appearing in the February 2024 issue of *Clinical Chemistry* summarizes expert opinion on new tools for the diagnosis of sepsis and their expected impact on clinical laboratory practice. In this podcast, we are pleased to welcome the moderator of the Q&A article. Dr. Allison Chambliss is an associate clinical professor in the Department of Pathology and Laboratory Medicine at the University of California, Los Angeles. She is a clinical chemistry director and also serves as UCLA's director of laboratory stewardship. So, Dr. Chambliss, let's start by giving an overview of how sepsis is defined and what makes it so challenging to diagnose and manage.

Allison Chambliss: Well, there are actually several different definitions of sepsis, which is part of what makes it so challenging. Probably the most widely recognized definition is the one provided by joint guidelines from the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. They last published their consensus guidelines in 2016, called the Third International Consensus Definitions for Sepsis and Septic Shock, which is also known as Sepsis-3. In those guidelines, they define sepsis as life threatening organ dysfunction caused by a dysregulated host response to infection. But what that actually means in clinical practice is not entirely

straightforward. There are several different clinical scores that can be used that incorporate signs and symptoms, such as elevated body temperature, heart rate, respiratory rate, blood pressure, and altered mental status. But all of those clinical signs are nonspecific, so distinguishing sepsis from other diagnoses is often a challenge.

Bob Barrett: So what is the role of the clinical laboratory in the diagnosis and management of sepsis, and how is that role changing with new technologies?

Allison Chambliss: The clinical lab plays a significant role in sepsis diagnosis and management, and that role is becoming even more important and spotlighted with newly available technologies. The status quo, or gold standard sepsis diagnostic, is the blood culture from the microbiology lab, which tests for bloodstream infection but it does not specifically recognize the dysregulated host response to infection that is sepsis. So it's not perfect. Not to mention the fact that blood cultures take days to grow and to have actionable results, while patients need the earliest possible intervention and treatment to improve outcomes.

In the clinical lab, we provide other informative test results for sepsis, such as C-reactive protein, white blood cell count, lactate, procalcitonin, all of which are typically used in various combinations to rule in or rule out patients. But they still lack that ideal specificity that we're really looking for. There have been several new tests that have come to the US market in recent years with possible utility in sepsis. And so, as laboratorians, we have a further significant role to play in working with our clinical partners to evaluate these new tests and technologies and determine how they may or may not fit well into our patient care workflows.

Bob Barrett: Well, let's stop and talk about those new sepsis markers and tests. What are they and how have they become available in recent years?

Allison Chambliss: Yeah, there's been several that have become available or FDA cleared in recent years, and the experts in this Q&A article give a great overview of some of these new tests and their considerations. What's interesting is that these test manufacturers have all taken pretty different approaches, and so we have an interesting mix of new technologies. Some of the new tests measure changes in white blood cell morphology. One specific approach is based off of studies that have demonstrated that acute changes in monocyte size that occur upon the host immune response can discriminate sepsis from other acute illnesses. And what's promising about that specific approach is that those types of test results can be readily available rapidly within a routine complete blood count, or CBC, that's already ordered on essentially all

patients who would be evaluated for sepsis anyways. Another type of new test measures RNA transcripts of multiple genetic markers that are specific to infection and systemic inflammation.

And then a third new technology is a simultaneous panel of host immune proteins measured by immunoassays. So, a common theme here is that we're seeing multianalyte panels, whether they are nucleic acid based or protein based, that use machine learning algorithms to identify optimal ratios of these multiple analytes to distinguish patients who have the highest risk of either bacterial infection or sepsis. And going forward, algorithms might also incorporate preexisting routine data from the medical record, on top of these novel biomarker results to really improve their clinical performance.

Bob Barrett: Did the experts in this article have advice for hospitals and labs who are considering implementing these new sepsis tests?

Allison Chambliss: Yes, the experts provided some great advice. In addition to those typical analytical verification studies that are required for clinical lab accreditation purposes, the experts emphasize the importance of determining how a new test will fit into the clinical workflows, say in the ED and the inpatient areas, as well as how they fit into the laboratory workflows. So we should ask questions such as: Does the blood sample need to be centrifuged? Where will the test be performed and by whom? Do we have the resources to support that and to perform the test with high quality? And then, very importantly, how do we determine which patients will get the test? So, the experts challenge us to really consider whether a new test adds valuable information to the existing tests and screening methods.

So, for example, if a positive test does not actually change the management of the patient, then maybe we should think twice about implementing that test. And finally, a particularly great piece of advice was to consider both diagnostic stewardship and antibiotic stewardship implications. While most new sepsis tests should hypothetically help in better distinguishing patients who need antibiotics, if the test is misordered on the wrong patients, it can cause diagnostic confusion and may actually increase antibiotic use. So hospitals and labs implementing a new test could consider clinical decision support or other order guidance in the electronic health record system, along with provider education to encourage appropriate ordering.

Bob Barrett: While we have these new tests and these new advances, are there still challenges in sepsis diagnosis?

Allison Chambliss: Yes, there's still a lot of work to be done in this area. Firstly, these new tests are just that, they're new and they haven't been well studied in a variety of patient populations. And so we need more trials and evaluations to get a better understanding of their performance. Only one of the tests discussed in the article is approved for pediatric patients, and so we really need more studies in that population. Another major limitation is that these tests generally rely on measuring either the host immune response or white blood cell properties, and this can be challenging in immunocompromised patients who are also patients at particularly high risk of getting these serious infections.

So we need to study test performance in those patient populations and possibly come up with other solutions. And finally, while these tests may aid in sepsis detection or sepsis risk assessment, they still don't necessarily provide specific actionable treatment decisions. So our experts note that we'll need to look to the development of rapid pathogen detection technologies to really better help with those real time antimicrobial therapy decisions.

Bob Barrett: That was Dr. Allison Chambliss from the University of California, Los Angeles. She served as moderator of a Q&A article discussing new tools for a diagnosis of sepsis in the February 2024 issue of *Clinical Chemistry*, and she's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.