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AACC Guidance Document on the Clinical Use of Procalcitonin.
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Guests: Dr. Alison Woodworth is the Clinical Director of Global Laboratory Services for CTI Clinical Trial and Consulting Services in Covington, Kentucky. Dr. Allison Chambliss is an Associate Clinical Professor of Pathology and Laboratory Medicine at the University of California, Los Angeles.

Randye Kaye: Hello and welcome to this edition of *JALM* Talk from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host Randye Kaye.

Procalcitonin is a blood biomarker that becomes elevated in response to systemic inflammation caused by bacterial infection and sepsis. Procalcitonin testing may be useful to assess prognosis in critically ill patients and to make decisions regarding treatment with antibiotic therapy. However, procalcitonin has imperfect specificity and there's a lack of consensus regarding appropriate timing of measurements and interpretation of results, which are highly dependent on clinical context. The May 2023 issue of *JALM* features the AACC Academy's Guidance Document on the Clinical Use of Procalcitonin. The document discusses important clinical and analytical considerations in using procalcitonin tests to manage adult, pediatric, and neonatal patients with suspected sepsis or bacterial infections.

Today, we're joined by two of the guidance document's authors, Dr. Alison Woodworth, Chair of the Writing Committee, and she is the Clinical Director of Global Laboratory Services for CTI Clinical Trial and Consulting Services, based in Covington, Kentucky. We also have Dr. Allison Chambliss, who is an Associate Clinical Professor of Pathology and Laboratory Medicine at the University of California, Los Angeles. Doctors Woodworth and Chambliss, welcome. First, Dr. Chambliss, why did the AACC Academy decide to write a guidance document about procalcitonin?

Allison Chambliss: Well, procalcitonin is a relatively new biomarker to the US clinical lab market, at least relative to the other more traditional biomarkers that we're used to in clinical laboratories, in clinical chemistry laboratories in particular. But like a lot of other newer markers, it has been used in Europe for quite a while now, but it's only been available in the US on common analyzer platforms starting around 2017 or so. It has many potential uses like in evaluating patients with suspected bacterial infections and sepsis, particularly in

critically ill patients. So the stakes are high and there's a lot of complexity involved. And so we felt that since the test is so new and there's a lack of guidance about when to use the test and in what patients, and in what clinical context, how to interpret it, there's really a need for guidance for all of these questions, and there is a growing body of literature out there about procalcitonin, but it's just very complex and some of the studies are inconsistent in their design and in their conclusions. So, we thought that providing a review of these major studies through a laboratory medicine lens in particular, but with appropriate input from clinical stakeholders, would be useful to the clinical lab and clinical communities.

Randye Kaye: All right, thank you. Dr. Woodworth, you chaired the writing group for this guidance document. How did you assemble that writing group and how did the guidance document process work?

Alison Woodworth: Yes. Well, we felt like with a biomarker like procalcitonin, it was really important to gather a variety of perspectives in order to write the guidance document, so we felt like we needed a multidisciplinary team. So we gathered experts in the field of clinical laboratory medicine, clinical infectious disease, as well as in pharmacy, particularly pharmacists with expertise in infectious disease testing. The process of putting together the guidance document involved a comprehensive review of the literature by this multidisciplinary team, expert analysis of the literature to determine whether the papers out there and the guidance out there was worthy of inclusion in the document. We had a writing period where we tackled answering several different questions pertaining to the utilization of procalcitonin as well as some analytical aspects of procalcitonin. We also had an open comment period where members of the AACC Academy and other organizations reviewed the document and provided feedback on that and we incorporated the answers to important comments to this. This was also reviewed by the AACC Board of Directors, the AACC Academy Council, and a number of other experts in the field. So we feel like it's a well-vetted expert review document that provides very valuable information for our community, as well as the clinical community as a whole.

Randye Kaye: Thank you. It sounds like it took quite some time to go through that whole process.

Alison Woodworth: Oh, yes. It was.

Randye Kaye: So what are some of the major topic areas that the guidance document covers?

Allison Chambliss: I'd say that the document is broadly broken up into a clinical section and an analytical section. And so, in the clinical

section, we evaluate how procalcitonin results can be used to inform decisions for either starting or stopping antimicrobial therapy in adult patients with sepsis or respiratory infections. And then we asked the same question but for neonatal and pediatric patients.

We also discuss how effective procalcitonin is as a predictor of outcomes such as mortality, respiratory failure, and shock in each of these populations. And we discuss how the marker can be incorporated into antibiotic stewardship initiatives. On the more analytic side, we discussed pre-analytical considerations like sample type instability and we compiled method comparison studies to provide what are the various FDA approved methods that are out there and how do they compare to each other. And this is particularly important to consider, to determine whether common clinical decision points, or cutoffs, can be used across different methods. And we also discuss things like timing and frequency of serial measurements. And then finally, we touch on some of the clinical specificity limitations of procalcitonin and confounding factors that can affect the interpretation of results.

Randye Kaye: All right. Thank you. So, you mentioned antibiotic stewardship and that seems to be an important topic in the document. Dr. Woodworth, can you expand on the role of procalcitonin in antibiotic stewardship?

Alison Woodworth: Yes, absolutely. That's actually one of the reasons why we decided that the timing to put together this document was so important. Antibiotic stewardship is one of the new FDA claims that has been utilized by a number of these new assays that are out on the market. In particular, the claim suggests that procalcitonin can be used to monitor patients with infectious diseases, to monitor the response to antibiotic therapy over time. And so procalcitonin is measured regularly to determine whether a patient is responding to the therapy that they're receiving or if they're getting sicker. This is a really important aspect of antibiotic stewardship but I think it's important for folks to understand that procalcitonin alone cannot be used for this. Its clinical indication is really to be used in combination with many other clinical factors, including signs and symptoms and the opinions of a multidisciplinary clinical team.

And for that reason, it's really important for us to incorporate procalcitonin use in the context of interpretive algorithms, specific clinical decision support, and provider education. Again, this really requires a multidisciplinary team of folks: pharmacists, infectious disease specialist, clinical laboratorians to put together those clinical decision support documents and to determine just how we utilize specifically, and how we roll out educational programs and how we roll out interpretive comments and alerts about changes in

procalcitonin, and how we should respond with changes in treatment of patients. And so, it's actually quite a complex sort of network of testing and clinical response that's important for appropriate rollout of procalcitonin as a part of an antibiotic stewardship program.

Randye Kaye: Thank you. So for clinical laboratorians who are looking to maybe implement procalcitonin testing, what are some of the key take-home messages of this new guidance?

Allison Chambliss: From the clinical utility perspective, I'd say the biggest take-home message is probably that the data we reviewed is supportive of procalcitonin as a marker for prognosis, and for reducing antibiotic exposure or duration in critically ill patients in particular, and particularly those with respiratory tract infections. That is a condition that is most studied and the power really lies in trending serial measurements over time to detect rises or falls.

Unfortunately, we found that there's less data to support the use of procalcitonin in pediatric patients. Certainly, more studies are needed there, or at least, as Dr. Woodworth mentioned procalcitonin should not be used alone in these patients to make management decisions. And then another major take-home message is that it is very important to implement this test in a holistic antibiotic stewardship program approach, which Dr. Woodworth nicely touched on in the previous question. So I just really echo all that she said there and reiterate that we recommended that labs not simply verify this test and open it up for ordering without providing these essential education and provider team efforts around the test result interpretation.

And then finally, we'd say that labs should think carefully about their reference ranges and the interpretive information that's appropriate for their own method that they're using because we found the assays are not completely harmonized across platforms.

Also, if the institution will be using the test for neonates, everyone should be aware that there is a natural elevation of procalcitonin in healthy neonates over their first few days of life. And so, in this age group, interpretive ranges need to be stratified by hours after birth.

Randye Kaye: So, finally looking to the future, do you think there'll be a need for more novel biomarkers in the diagnosis and management of sepsis, Dr. Woodworth?

Alison Woodworth: So that's a really great question, Randye. I think, after our review, even though we've reviewed thousands and thousands of documents because there is quite a bit of

literature out there on this topic, we still felt that the research in the area was somewhat wanting for procalcitonin.

There were not very large, randomized control trials looking specifically at timing of measurements, at which cutoffs are appropriate, and as Allison mentioned, the assays are not harmonized across different platforms. So for that reason, I still think that time should be spent looking at procalcitonin. Its specificity though is in question, particularly when looking at patients with sepsis and respiratory tract infections. Procalcitonin is elevated due to a number of inflammatory conditions including trauma, post-surgery, and other just generalized inflammatory situations that may not be related to an infection. And so for that reason, it's really important to understand how to use procalcitonin in the presence of those sorts of confounding inflammatory situations.

Another issue that I think that is really important for us to consider is that because procalcitonin is an inflammatory marker, we're not totally sure about how it behaves in patients that are immunocompromised, or in pediatric patients, which speaks a little bit to what Dr. Chambliss mentioned about its limited use in the pediatric population. And so, for these reasons, I think we really need to take a two-fold approach. One, we need to do more carefully designed randomized control trials looking at procalcitonin with specific timepoints, specific assays across specific responses and concentrations, but we also need to begin looking at novel biomarkers. And perhaps the solution isn't one biomarker to monitor infectious disease over time, but maybe a panel of biomarkers that represents the full composite of what's going on in patients.

Now, there are more and more really interesting machine learning approaches that involve multiple biomarkers, that may be an option in the case of patients with sepsis and infection disease monitoring. More work is definitely needed, both in the area of new biomarkers and in looking at procalcitonin. And so, what we really hope is that in this document we bring to light the importance of what is out there and what still needs to be done, with an eye on the future of new biomarkers.

Randye Kaye: So a lot of work still to be done. Thank you so much for joining us today.

Allison Chambliss: Thank you, Randye.

Alison Woodworth: Thank you, Randye.

Randye Kaye: That was Doctors Alison Woodworth and Allison Chambliss discussing the *JALM* article, "AACC Guidance Document on the Clinical Use of Procalcitonin." Thanks for tuning in to this

episode of *JALM* Talk. See you next time and don't forget to submit something for us to talk about.