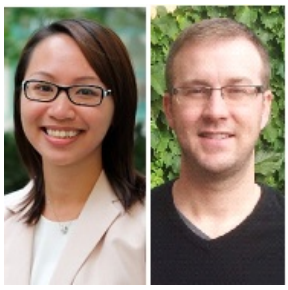
Clinical Chemistry

The Role of Procalcitonin in Diagnosis of Sepsis and Antibiotic Stewardship: Opportunities and Challenges



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Guests: Dr. Daniel Beriault is a clinical biochemist at Saint Michael's Hospital in Toronto. Dr. Angela Fung is a clinical chemist at Saint Paul's hospital of Providence Health Care in Vancouver.

Bob Barrett: This is a podcast from *Clinical Chemistry,* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

Sepsis is a life-threatening condition associated with significant mortality and healthcare cost. Sepsis affects over 26 million people worldwide each year, including more than 1.6 million in the U.S. alone. A timely and accurate diagnosis of sepsis is pivotal for prompt recognition and appropriate intervention. Each hour of delay in administration of antibiotics results in an increase of 7.6% mortality for septic shock. Yet over-diagnosis and inappropriate use of broad spectrum antibiotics contributes to the emergence of antibiotic resistance. Diagnosis of sepsis is a clinical challenge. Early signs of systemic inflammation and associated biomarkers are not specific to sepsis, and traditional infectious disease testing is often not informative in sepsis patients.

There is increasing evidence supporting the use procalcitonin as a biomarker for diagnosis of bacterial sepsis and as a guide to discontinue antibiotic therapy. However, concerns about the efficacy, safety, and availability of procalcitonin exist. A Q&A article in the September 2017 issue of *Clinical Chemistry* asked experts with different roles in this field to share their thoughts on the challenges of procalcitonin-guided diagnosis and antibiotic therapy.

We're joined for this podcast by the moderators of that Q&A, Drs. Angela Fung and Daniel Beriault. Angela Fung is a recent graduate of the clinical chemistry fellowship at the University of Toronto and is currently a clinical chemist at Saint Paul's Hospital of Providence Health Care in Vancouver, Canada. Daniel Beriault is a clinical biochemist at Saint Michael's Hospital in Toronto, Canada, and a researcher in the Department of Laboratory Medicine and Pathobiology at the University of Toronto.

Dr. Fung, let's start with you. The definition of sepsis was updated in 2016. What is sepsis and how does this new definition differ from the previous definition?

Angela Fung: Sepsis is a complex, life-threatening clinical syndrome. The current understanding in this pathophysiology is complicated. It's due to the disregulated host response to infection and this result in organ dysfunction, and the main diagnostic challenge for sepsis is the lack of gold standard in both clinical criteria and laboratory criteria to actually identify sepsis.

In terms of clinical criteria for the past 25 years, the SIRS criteria was used, and this criteria is including very non-specific symptoms such as fever, leukocytosis, tachycardia, and hypotension, and based on this non-specific criteria, a large heterogenous cohort of patient who varies wildly in their ideology and severity are grouped together, and what this resulted is not only in challenges in the definition and diagnosis of sepsis, but also in the interpretation of results from clinical trials. The latest update in sepsis-3 definition aims to provide clear definitions in clinical criteria to help diagnose sepsis, which hopefully also results in greater consistency in the findings from epidemiological studies and clinical trials.

In this new definition the SOFA, and Quick SOFA (qSOFA) score is used, and qSOFA score includes Glasgow Coma score, hypotension, fraction of inspired oxygen, and some laboratory measurements such as platelets, bilirubin, and creatinine. And on the other side, in terms of laboratory criteria, it is identifying this presence of infection and traditionally this is done by blood cultures and used to detect and identify bacterial infection. However, blood cultures take a long time, they typically require 24 hours or more of incubation, before seeing a positive result, and sometimes many septic patients are culturally negative.

So to avoid delays, often broad spectrum antibiotic therapy is initiated and there's a lot of work being done in the microbiology lab to address this.

Bob Barrett: So, it sounds like identifying sepsis is not easy and that a biomarker with high sensitivity and specificity that's rapidly produced and easy to measure, that would be revolutionary to the diagnosis of sepsis. Is procalcitonin that biomarker? What is its role in sepsis and how do you interpret a procalcitonin result?

Angela Fung: There are actually a lot of biomarkers in sepsis, and procalcitonin is one of those that we've started to research around and have results more. In sepsis, procalcitonin serves as the surrogate for infection marker. Procalcitonin is actually the pro-hormone of calcitonin where it is normally synthesizing the C cells of thyroid gland. In response to microbial toxin and certain proinflammatory markers such

as TNF-alspha and interleukin 6, procalcitonin is released systemically from the liver and many different tissue types.

Procalcitonin concentration generally correlates with the severity of infection where it rises within 6 to 12 hours of infection and halves about every 24 hours when the infection is controlled. The harder question, "is procalcitonin that biomarker?", it depends on what you're comparing to and how you're interpreting the results. Comparing to blood cultures and C-reactive protein, procalcitonin has advantages with its kinetics and greater specificity, but procalcitonin doesn't inform you the specific ideology of the infection and still requires the microbiology lab to isolate and identify the microorganism for you to tailor your antimicrobial therapy.

In terms of interpretation of procalcitonin, tissue injury and surgery can release substances called damage-associate molecular patterns, and this may induce procalcitonin expression leading to higher procalcitonin concentrations than other people.

The types of infection can also affect how procalcitonins express. For example, gram negative infections typically result in a higher value than gram positive or fungal infections, while viral mediated infections suppresses procalcitonin expression. So knowing the etiology is important. Additionally, there's also a host response differences from each patient with the similar infection. So, it makes interpretation very difficult. Therefore, sometimes serial measurements of procalcitonin have added value indicating the presence of infection.

Bob Barrett: Okay. Dr. Beriault let's get you in here. What is the clinical utility for procalcitonin and does this also apply to pediatric populations?

Daniel Beriault: Well, as Dr. Fung mentioned, procalcitonin has been shown to correlate well with severity of bacterial infection, and in February of 2017, the FDA approved the first procalcitonin assay, the VIDAS assay, for diagnosis and management of lower respiratory tract infections and in guiding earlier discontinuation of antibiotics in sepsis patients. From a clinical utility perspective, I think procalcitonin is still controversial and it's something we need to iron out. In my own experience there is a wide opinion on whether procalcitonin is useful or not, depending on who you talk to. Issues that are often cited include the heterogeneity in critically ill patients. For example patients with traumas, burns, immunocompromised, post surgery, whether or not these different conditions will confound the procalcitonin results.

There are issues with the fact that different threshold values have been used in different studies. The lack of a gold standard reference method, and that the efficacy of procalcitonin as a diagnostic tool is questionable. However, all that being said, the most recent multicenter landmark trial that was completed in the Netherlands, published in *Lancet*, of last year, demonstrate a significant reduction in antibiotic use and mortality in sepsis patients with the daily procalcitonin measurements.

So that is very promising in the management of septic patients in guiding earlier just continuation of antibiotic therapy, and this is very important as there is an emerging need to control antibacterial resistance to antibiotics which is a rapidly evolving public health threat. As for use in the pediatric population, there are handful of randomized control trials were procalcitonin was used to diagnose lower respiratory tract infections and it's used in antibiotic discontinuation. However, the data so far has been limited and generally inclusive in the pediatric population and this is partly because it is especially difficult to get a large number of pediatric participants for a study, and additionally the children in response to inflammatory stimuli may develop higher levels of procalcitonin when compared to adults, thus, the treatment threshold remains to be confirmed in this population.

Bob Barrett: Well Dr. Fung, can you comment about the currently available procalcitonin assays and their analytical performance?

Angela Fung: Sure. Initial procalcitonin studies used BRAHMS procalcitonin immunoassay. Over the years, more sensitive procalcitonin assays with lower detection limits are becoming available. There are now several automated commercial BRAHMS procalcitonin assays available on common analytical platforms including Siemens, Abbott, Roche, and DiaSorin, and there are also recently novel rapid procalcitonin point-of-care devices that are available. One thing to keep in mind is that most of these point-of-care procalcitonin assays are not based on the BRAHMS antibodies, and require more independent evaluations on their quality and performance.

For the intended use of early detection of sepsis and antibiotic stewardship, the functional sensitivity of the assay is important. It needs to detect concentrations below 0.1 micrograms per liter for a useful differentiation of sepsis and local infection. And also accurately at 0.25 and 0.5 micro grams per liter for discontinuation of antibiotic, and those are your common decision cut points in the studies.

Other performance parameters including reproducibility and linearity and method comparison and more practical things like assay time, sample volume, and matrix should meet the needs of the individual sites, and one thing that Dr. Beriault mentioned is that due to the overlapping pathophysiologic stimuli and the expression of procalcitonin-specific threshold ranges, tailored settings to the intended patient population such as surgery and trauma should also be evaluated.

Bob Barrett: Well, finally doctor, if a physician approaches the laboratory about implementation of procalcitonin assays for antibiotic de-escalation, in addition to the analytical performance and diagnosis accuracy, what are some factors and utilization strategies that one should consider?

Daniel Beriault: Great. So, it's a, it's an important question. First thing you should do when bringing in any test is to determine the clinical need, physician interest, necessary turnaround time, and what value this test may add. So, in terms of procalcitonin-guided antibiotic discontinuation, it would be important to collaborate with key stakeholders in critical care antimicrobial stewardship to determine their interest.

Working with the physicians, you should consider restricting orders to in-patients in the ICU, and limit the frequency to once per day in this setting. A specific protocol should be designed to include these restrictions as well as indicate a lower threshold value where antibiotic discontinuation is recommended. How you alert the physicians to this recommendation is important. Examples of this could include building a triggered pop up message in your hospital information system or getting your antimicrobial stewardship team to check the procalcitonin levels during their daily rounds, and they can then make recommendations to the staff.

Keep in mind that this recommendation to discontinue antibiotics is only a recommendation, and ordering physicians should be educated that the procalcitonin level should never replace good clinical judgment. If the patient is doing poorly, you need to keep them on the antibiotic. I would suggest also tracking a number of metrics, both pre and post implementation, including antibiotic usage, antibiotic cost, resistance rates, length of stay in the ICU, and 30-day mortality of sepsis patients. This is important because it will allow you to determine if procalcitonin is having a positive impact at your institution. It's often said that different countries have very different antibiotic prescribing habits and so the onus is on us, the laboratorians and physicians, to prove that procalcitonin is a useful tool and one that we should continue to use.

Bob Barrett: That was Dr. Daniel Beriault, a clinical biochemist at Saint Michael's Hospital in Toronto and a researcher in the Department of Laboratory Medicine and Pathobiology at the University in Toronto. He was joined by Dr. Angela Fung, a recent graduate of the clinical chemistry fellowship at the University of Toronto and currently a clinical chemist at Saint Paul's hospital of Providence Health Care in Vancouver. They have both been our guests in this podcast on sepsis from *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.