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Michael K. Mansour
Assistant Professor of Medicine
Harvard Medical School

Assistant in Medicine
Department of Medicine
Division of Infectious Diseases
Massachusetts General Hospital

mkmansour@mgh.harvard.edu

PCT-Guided Antibiotic Stewardship in COVID-19 Patients

Professor Michael Mansour is a physician-scientist with a research concentration in immune responses against invading pathogens. He attends on the Clinical Transplant Infectious Diseases and Immunocompromised Host Service at the Massachusetts General Hospital - Division of Infectious Diseases, where he cares for solid and stem cell transplant recipients and individuals with weakened immunity. He also directs several COVID-19 clinical trials and sits on committees for the development of treatment guidelines for COVID-19 patients. ICU Management & Practice spoke to Prof. Mansour about the role of procalcitonin in guiding antibiotic use in COVID-19 patients.

Can you please discuss the incidence and role of secondary bacterial infections in terms of risk and mortality?

In the COVID-19 patient population, the incidence of secondary infections appears to be significant. We are beginning to appreciate a few key points:

• One, bacterial respiratory infections appear to be the dominant drivers of secondary infection, although there are a significant number of bloodstream infections as well.

• Two, of the bacteria, there is a mix of gram-positive and negative pathogens. We are looking at this more closely, but gram-positive bacteria such as *Staphylococcus* species are likely to be highly represented.

• Three, despite our improved ICU care, many COVID-19 patients still experience protracted recovery periods, often leaving these patients at risk for secondary infections and prolonged empiric courses of antimicrobials.

Do you think there is an association between PCT values and severe COVID-19 disease?

Yes, I do. PCT does appear to rise in the setting of COVID-19 infection. More precisely, PCT seems to rise as a patient is moving from the viremic phase to a more inflammatory one in the setting of SARS-CoV-2 infection. This rise may reflect the mounting host immune response, although further investigations are required to understand the association.

The Surviving Sepsis Guidelines and the NIH treatment guidelines both recommend empiric antibacterial therapy in the management of COVID-19 critically ill adults. What is the frequency of usage of antibiotics in COVID-19 patients?

Let's consider this carefully. Initially, in the pandemic, there was a large gap in our experience and management of COVID-19 patients. Many hospitals, including where I practice, witnessed a large spike in antimicrobial usage. In fact, in my experience, the majority of patients being admitted were placed on empiric antimicrobials.

What we have realised is that this practice habit is really unnecessary. While there are a significant number of secondary infections, almost half of COVID-19 patients can be treated without antibiotics.

It is this portion of patients that we should focus our efforts and safely de-escalate antimicrobial therapy. Moreover, for those patients with bacterial superinfection, we need to parse out COVID-related inflammatory pathology from bacterial infection.

Research suggests that only about 10% of COVID-19 patients have bacterial co-infection but many receive antibiotics. What is your opinion about this?

I think 10% is probably a slight underestimate. A major difficulty in the accurate assessment of secondary bacterial infection stems from clinical judgement of a confusing inflammatory process in CoV-2 pathology. We have significant experience with influenza, for example, where we are more comfortable in judging bacterial superinfection. In the setting of COVID-19, we are still learning and defining the difference in viral versus bacteria pathophysiology. What is progressive COVID-19 versus host response versus bacterial superinfection? These are the clinical struggles that we, as healthcare providers, are faced with daily when managing SARS-CoV-2 infected patients.

What the true superinfection rates are will require careful examination in prospective clinical projects and trials. The careful design of clinical trials must include not only clinical parameters but also the use of additional biomarker tools that will help identify bacterial superinfection and provide insight for the ideal and appropriate usage of antimicrobials.

What could be the consequences of unnecessary antibiotic use use?

This question is incredibly critical and

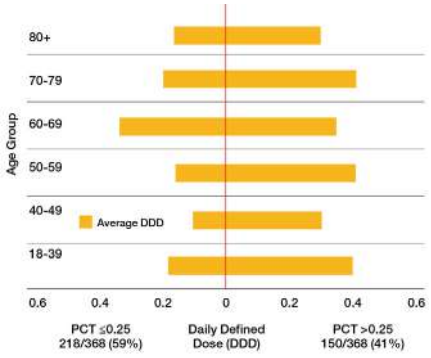

Figure 1. Antibiotic use (DDD) in COVID-19 patients treated in line with a PCT-based guideline recommending to limit antibiotic treatment to patients with PCT >0.25µg/L , if not indicated otherwise by clinical assessment. (Adapted from Williams E.J. et al., 2020; medRxiv preprint doi: https://doi.org/10.1101/2020.06.29.20136572

really the one most central to our discussion. Over the years, we have collected a significant amount of data and experience related to the consequences of antimicrobial overuse. The two most immediate concerns include antibiotic pressure to select resistant pathogens, including MRSA, VRE, multidrug-resistant gram-negative bacteria, and the other is the acquisition of nosocomial infections such as *Clostridioides* (formerly *Clostridium*) difficile.

There are larger, theoretical level impacts that remain under careful research scrutiny, but more and more becoming a reality. A good example of such an impact includes the antibiotic influence on microbiome dysfunction, which is gaining significant evidence in the long-lasting impact on overall health. We need to do our utmost best to avoid the net negative effect of antimicrobial overuse.

What role can PCT play in guiding antibiotic use in COVID-19 patients?

In my opinion, there are two large roles for PCT:

• One, procalcitonin serves as a prognostic indicator of COVID-19 pathogenesis; as patients enter the inflammatory phase, there is a rise in PCT, which can potentially identify patients earlier who may require more intensive care or additional hospital resource allocation.

• Two, PCT can play a role in safely de-escalating antimicrobial usage in COVID patients. I believe the majority of these patients in the milder group can avoid antimicrobial use altogether. Our study, as well as other centres, have demonstrated that most patients with a low PCT safely discharge from the hospital.

While there has been significant data to suggest safe de-escalation, further research studies are required for validation. Randomised controlled trials to confirm the safe stewardship in COVID infection are needed, and in fact, for these reasons, we are currently conducting an RCT, ProSAVE (NCT04158804), to investigate the role of PCT-guided antimicrobial stewardship in US-based hospitals that will include COVID-19 infected patients. We look forward to sharing our results in the near future.

Are there any studies that show the benefit of PCT-guided antibiotic stewardship in COVID-19?

Many studies suggest that PCT can be used for de-escalation, including a recent retrospective analysis performed here at the Massachusetts General Hospital, which we hope to share soon with the community.

In our data, there is good evidence that a low PCT correlates with patients who show no evidence of any concerning microbiology results. I think the most important will be to examine this hypothesis in a prospective clinical trial and define the safety and outcome metrics of a PCT-guided strategy. As mentioned, we have launched such an RCT and hope to answer these important questions in the next year.

The recommended PCT threshold is 0.25. Do you think this is a conservative estimate, and a higher threshold could be adopted safely?

In COVID-19, this question has become interesting because of the nature of COVID-related inflammation that may not typically be seen with other respiratory viral infections. In our data, the majority of patients who are eventually discharged safely fall below the 0.25 ng/mL cut-off. In addition, those patients with a milder oxygen requirement on the clinical ordinal scale who do not have evidence of concerning microbiology results (blood or sputum cultures) are also successfully identified using a PCT cut-off of 0.25 ng/mL.

On the other hand, when a COVID-infected patient now requires more invasive ventilation and has a higher oxygen requirement based on the ordinal scale, it appears that the 0.25 ng/mL may not provide the discriminatory performance to separate those individuals without significant secondary superinfection. In this sicker cohort, a higher cut-off, such as 0.5 ng/mL may be more appropriate. This analysis is the subject of ongoing research, and we hope to share these results soon.

Overall, what is your opinion about the use of PCT as an antibiotic stewardship tool?

Procalcitonin has a long track record of safety and good performance in lower respiratory tract infections, especially in the area of antimicrobial de-escalation. We are now faced with rising global antimicrobial resistance. It is imperative that we use all available tools, both biomarker and clinical assessment, to appropriately utilise antibiotics.

The COVID-19 pandemic is teaching us that SARS-CoV-2 appears to be settling in as a long-term member of the respiratory viral microbial ecosystem, making it critical that we develop better approaches to identify and treat superinfections, and, importantly, how to then de-escalate antimicrobial use promptly.

I believe PCT can have a significant role to play in the management of these complex patients. ■

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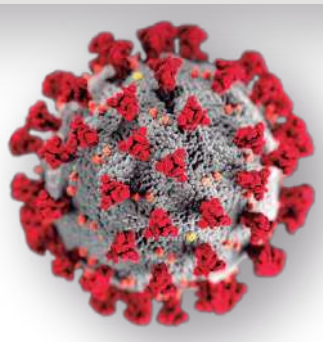
COVID-19 Pneumonia:

Procalcitonin (PCT) for Risk Assessment and Rule-out of Bacterial Coinfection

PCT on admission	PCT during hospital stay
Test PCT as an aid for early risk assessment and prioritization of high risk patients	**Monitor PCT to detect:**
<0.50 µg/L* low risk for bacterial coinfection and adverse outcome	secondary bacterial infections
≥0.50 µg/L high risk patients, bacterial coinfection likely	progression of disease

* Majority of patients with mild disease had PCT values <0.25 µg/L or even <0.1 µg/L. [Ref-1-6]
Likelihood of bacterial infection and recommendation to start antibiotics in patients with LRTI at PCT 0.25 µg/L. [Ref-7]



COVID-19

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Clinical Diagnostics

Thermo Fisher Scientific
B·R·A·H·M·S GmbH
Neuendorfstr. 25
16761 Hennigsdorf
Germany

+49 (0)3302 883 0
+49 (0)3302 883 100 fax
info.pct@thermofisher.com
www.thermoscientific.com/brahms

Find out more at
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