Microbiology or host-response markers, or both, for optimal patient management?

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Provenance: This is a Guest Editorial commissioned by Executive Editor Zhi-De Hu (Department of Laboratory Medicine, General Hospital of Ji'nan Military Region, Ji'nan, China).

Comment on: Self WH, Balk RA, Grijalva CG, *et al.* Procalcitonin as a Marker of Etiology in Adults Hospitalized with Community-Acquired Pneumonia. Clin Infect Dis 2017. [Epub ahead of print].

Received: 14 July 2017; Accepted: 30 July 2017; Published: 09 August 2017.

doi: 10.21037/jlpm.2017.07.13

View this article at: http://dx.doi.org/10.21037/jlpm.2017.07.13

In their study entitled "*Procalcitonin as a Marker of Etiology in Adults Hospitalized with Community-Acquired Pneumonia*", Dr. Self and colleagues investigated a relevant daily problem in pulmonary infections, namely the search for better tools to identify the etiology of a community-acquired pneumonia (CAP) (1).

CAP is a common, severe illness leading to a high number of hospitalizations. Despite advances in laboratory techniques, the causative organism cannot be identified in a majority of patients (2-4). As a consequence, patients are often treated with empiric broad antibiotics with the risk for emerging antibacterial resistance. Better identification and characterization of pathogens, as well as the host response by measurement of specific host-response biomarkers, have important implications for more individualized treatment decisions in an individual patient and may help to tackle the problem of diagnostic uncertainty and antibiotic overuse. Several studies evaluated the utility of different inflammatory markers to predict etiology and treatment response as well as clinical outcomes in patients with community acquired pneumonia (5-7). Procalcitonin (PCT) levels predict the severity of a disease and clinical outcomes (6,8-12). Importantly, PCT measurements help to early identify bacterial pneumonia, helps guide antibiotic treatment and stratification of patients (13-15).

Given the ability of PCT to discriminate between viral and bacterial infections (16), Dr. Self and colleagues validated this concept in a well-done, large-size prospective study (1). They performed a multicenter surveillance study with 1,735 patients hospitalized with CAP. The main strength of the study is the high number of patients with systematic, state-of-the-art pathogen detection. Only patients who underwent at least one bacterial and one viral testing were included in the final study population. The pathogen testing included culture; serology and PCR-based techniques. The study team distinguished the PCT levels among different types of pneumonia associated pathogens. The accuracy of PCT for identifying bacterial CAP was highest in the group of typical bacterial pathogen versus viral and atypical pathogens. Therefore, the study showed a strong association of increased PCT levels in typical bacterial pathogen detection. Yet, it was not possible to come up with a single PCT threshold for discriminating viral from bacterial pathogens mainly due to the heterogeneity of patients and types of infections. Therefore, in clinical practice, PCT levels should always be interpreted in the clinical context particularly in regard to antibiotic treatment decisions. Still, the study proved that higher PCT levels are associated with higher likelihood for typical bacterial infections, while PCT levels in atypical pathogens were more similar to the PCT levels in viral pathogens.

Interestingly, despite the use of different highly sophisticated pathogen detection methods, in 62% of patients with a clinical picture of pneumonia, no pathogen was detected. The low sensitivity of these techniques (i.e., 38%) is an important and costly limitation when used for

patient care. This again calls for a broader approach to the patient looking at the pathogens and the host response at the same time.

The done by Self and colleagues is important and validates previous research in the field. Because of the complexity of infections and also the host responses to infection, single biomarkers cannot be expected to capture all useful diagnostic information (17). As a result, the Antibacterial Resistance Leadership Group supports the development of host gene expression signatures as a tool for the differentiation between viral and bacterial infections. With technology progressing rapidly in this area, we can expect better tests soon. Given the low sensitivity of current tests—as demonstrated in the study by Self and colleagues—it is questionable whether focusing only on pathogens will ever give clinicians enough information to adjust their antibiotic management and not use antibiotics in patients with negative tests. PCT protocols to guide antibiotic treatment has been evaluated in more than 30 randomized-controlled trials including different settings and types of infections. These protocols were all similar and recommended for or against initiation or continuation of antibiotic therapy based on initial PCT levels, PCT kinetics, or both, and also included clinical information (18). The PCT cut-offs depend on the clinical setting and the acuity of illness. Research found such PCT protocols to have a strong influence on antibiotic prescription and duration of treatment with lower prescription rates of 60–70% in low risk patients (i.e., bronchitis) and reductions in the duration of antibiotics by 25–40% in higher risk situations. Reductions in antibiotic exposure also resulted in lower side effects and costs.

The converging crisis of increasing resistance and collapse of antibiotic research needs urgent action. Wider spread use of PCT protocols is an evidence-based, first step to slow down this trend while waiting for more sophisticated microbiological techniques for pathogen detection in the long run (19).

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jlpm.2017.07.13). Dr. Mueller reports grants from Thermofisher, grants from Roche Diagnostics, grants from Nestle, from Abbott, outside the submitted work; Dr. Schuetz reports grants from Thermofisher, grants from Roche Diagnostics, grants from Nestle, from Abbott, outside the submitted work; Dr. Neeser has nothing to disclose.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/jlpm.2017.07.13
Cite this article as: Neeser O, Mueller B, Schuetz P. Microbiology or host-response markers, or both, for optimal patient management? J Lab Precis Med 2017;2:56.

