CHEST

To Procalcitonin, or Not to Procalcitonin?

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PODCAST

Procalcitonin (PCT) has been one of the most studied biomarkers in current times (a cursory PubMed search on "procalcitonin" shows 4,749 references); with so much available data, the reader must be asking…why *CHEST* decided to publish it…or why bother reading another PCT meta-analysis. The reasons will become clear in the course of this editorial.

We will not discuss the use of PCT for diagnosis or antibiotic initiation; we will only discuss the serial PCT measurement for antibiotic de-escalation and discontinuation. Here are the highlights of the new meta-analysis by Pepper et al[1] in this issue of *CHEST*: the authors selected the randomized trials that used PCT to guide antibiotic de-escalation in critically ill patients and evaluated four outcomes: mortality, antibiotic duration/exposure, hospital, and ICU length of stay. Separate analyses were done for two populations: all critically ill patients and sepsis-only patients. The results were significantly in favor of the use of PCT regarding reducing mortality and antibiotic duration/exposure in critical illness; however, in the sepsis subanalysis, the mortality was not reduced, but antibiotic duration/exposure remained significantly beneficial with PCT. Hospital and ICU length of stay were not reduced with PCT in both study populations.

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At first glance, similar to most previous meta-analyses, PCT remains associated with positive outcomes; however, particular features addressing neglected aspects in previous meta-analyses were assessed by Pepper et al. They dissected the trials into several clinically meaningful variables that could also be associated (ie, potential confounders) with their primary outcome: use of an antibiotic stewardship program, concomitant use of other biomarkers such as C-reactive protein, adherence with the original study protocol, and Grading of Recommendations Assessment, Development and Evaluation evaluation of risk of bias. What they found was highly relevant to better understand why the PCT controversy persists: low-certainty evidence resulting from the high risk of bias and indirectness of effect in the randomized trials (consistent with a previous study[2]); unknown or no application of antibiotic stewardship programs in control arms; and the absence of mortality reduction in the following analyses: sepsis; only $>$ 80% protocol adherence; no industry sponsorship; and if PCT was used without other biomarkers.

Following are possible explanations for their findings: (1) sepsis: the total number of patients included in this subanalysis was about one-half of the entire sample size, and the 95% CI was barely $>$ 1, so it is possible that the sepsis subanalysis lacked statistical power; also, the use of aggregate data, in contrast to the use of individual patient data in two other studies[3,4] may have prevented the detection of mortality differences; (2) Protocol adherence: high protocol adherence may be a surrogate marker for the Hawthorne effect, which may have improved the care of all patients in both PCT and non-PCT arms, and then nullified the detection of PCT beneficial effects; (3) The absence of industry sponsoring suggests that the funding from PCT assays' manufacturing companies may have biased the studies in favor of PCT; (4) Use of other concomitant biomarkers such as C-reactive protein may have provided extra information to the clinician, which in turn could have reduced the detection of PCT benefits because several biomarkers produce broader clinical information for decision-making than a single one.

Similar to the findings from Pepper et al, at least four other meta-analyses on PCT were published in 2018[3-6]; all of them consistently showed that the use of

antibiotics was statistically significantly reduced with PCT in patients with sepsis or lower respiratory infections. The absence of best available care regarding antibiotic duration based on stewardship programs in control groups of individual studies was not properly assessed, however. One could ask another question: if PCT consistently reduces antibiotic duration/exposure in randomized trials and meta-analyses, then it is reasonable to expect that patients will have a lower rate of antibiotic side effects, fewer allergic reactions, lower risk of acquiring *Clostridium difficile* colitis, and less development of bacterial resistance; therefore, why even assume that PCT alone would reduce mortality? Will any biomarker by itself ever directly reduce mortality in severe infections?

Regarding antibiotic utilization, three other studies[7-9] have just been published after Pepper et al. Huang et al[7] and van der Does et al[8] were randomized trials performed in the ED to evaluate antibiotic use; both failed to demonstrate antibiotic reduction with PCT. Both trials included a small number of patients with confirmed bacterial infection (30%-35%), low proportion of patients with pneumonia (20%-30%), low adherence with study protocol (60%-65%), a few patients who needed ICU admission (4%-5%), and very low mortality (2%-3%). This means that the pretest probability for serious bacterial infection was low in both studies, which led to a low chance to detect any effects from PCT, or any other biomarker for that matter. In addition, the numerous PCT studies done over more than a decade for acute bronchitis and COPD exacerbation have demonstrated the efficacy and safety of short course of antibiotics, which has already changed the standard of care to just a few days of antibiotics now.[9] In more recent studies in COPD patients adjusting antibiotic duration according to standard of care recommendations in the control group, PCT algorithms failed to demonstrate reduction on antibiotic exposure.[10] Further, the case mix and the absence of critically ill patients indicate that neither of these two trials[7,8] would meet the inclusion criteria by Pepper et al. The third study, by Towsend et al[9] had a quasi-experimental design that showed a significant reduction in antibiotic use in lower respiratory tract infections; however, this study's design would also not meet Pepper et al criteria.

Curiously, the two authors of this editorial have shown different views on the use of PCT.[11,12] This has made our joint writing more challenging and gratifying at the same time. A large number of randomized trials have been conducted on PCT, and this evidence has altered the clinical standard of care for antibiotic duration. Antibiotic stewardship programs have already taken advantage of this literature and are applying the learned lessons to avoid the unnecessary prolongation of antibiotics. At this time, we already know that we can use a short course of antibiotics for the majority of critically ill patients, including patients with hospital-acquired pneumonia or sepsis[13,14]; thus, the current standard of care will make challenging for new PCT studies to be able to provide further evidence on antibiotic exposure reduction.

In conclusion, a large body of evidence supports PCT-guided antibiotic de-escalation and discontinuation in critically ill patients, but weak evidence to support direct survival benefits. Considering the unrelenting growing rate of multidrug-resistant infections and *C difficile* colitis worldwide, as well as the currently scarce antibiotic pipeline, all caused by the excessive use of unnecessary antibiotics, the application of stewardship strategies, including PCT, tailored to individual patient and hospital's needs to reduce antibiotic overuse, can help curbing this progressive antibiotic loss.

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