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Reply to Schuetz, "The value of a biomarker should be judged on what it adds to the clinical assessment – not the area under the curve"

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Dr. Schuetz argues that the value of procalcitonin (PCT) for predicting bacteremia should be judged on what it adds to the clinical assessment, rather than area-under-the curve metrics alone, and that PCT results should be interpreted in the context of a patient's specific clinical presentation. Indeed, this is true of all laboratory and radiologic investigations. Dr. Schuetz cites an observational study suggesting that combining PCT with clinical scoring systems may increase positive predictive value for positive blood cultures and could in theory reduce blood culture tests with relatively few missed positive culture results [1]. Notwithstanding the challenge of getting clinicians to use and rely upon complex scoring systems, the impact of missed positive blood cultures needs to be considered. A positive blood culture may be the only means through which a bacterial pathogen and its antibiotic susceptibility can be identified. Without these data, patients are at increased risk of misdiagnosis and inappropriate antibiotic therapy, increasing their risk for poor outcomes [2, 3]. Are the potential savings on blood culture sampling that could be made through incorporation of

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PCT into the clinical assessment, as suggested by Dr. Schuetz, worth this risk? Furthermore, the decision to draw blood cultures and administer antibiotics must often be made before PCT results are available, limiting the clinical utility of PCT in guiding blood culturing in many instances where bloodstream infection is suspected and time is of the essence.

Dr. Schuetz has stated that a clinical cutoff for PCT could be used to limit blood culturing, citing the 94% negative predictive value that we found at a cutoff of 0.25 ng/mL. It is well known that the predictive value of a test is dependent upon the prevalence of the disease in the population to which it is being applied. Taking Dr. Schuetz's analogy of the D-dimer, a D-dimer of <1000 ng/mL adequately rules out deep venous thrombosis (DVT) in patients with a low clinical pre-test probability on the Well's score, but this corresponds to a DVT prevalence of 2% [4]. In contrast, patients presenting with suspected serious infection and sepsis tend to have a higher prevalence of BSI, which varies widely by clinical syndrome and global region [5, 6]. In fact, in our study, the prevalence of BSI ranged from 11% for patients without sepsis to 29% for patients with septic shock, considerably higher than that of the DVT study cited. Drawing blood cultures is a very common practice in the emergency room; at a PCT cut-off of >0.25 ng/mL for BSI detection, a negative predictive value of 94% and a corresponding sensitivity of 77% will likely yield an unacceptable number of misses in absolute terms. Baseline prevalence rates of local patient populations and settings would need to be carefully considered before solely relying on a PCT value to rule out BSI, as the operating characteristics of PCT will vary considerably.

Dr. Schuetz also recommends adapting different PCT cut-offs to different clinical scenarios and patient levels of risk. While this would arguably be necessary for PCT to be useful, this approach risks being unwieldy and impractical. Our study shows PCT levels vary widely not only by acute illness severity, but also by presumed source and pathogen (almost always unknown on presentation). As such, 2 or 3 different cut-offs might not cover all relevant clinical scenarios while too many thresholds might be difficult for busy providers to use consistently and reliably.

We wholeheartedly agree with Dr. Schuetz that PCT testing should be closely monitored and clinicians well educated in its applications. Indeed, that was one of the main conclusions of our study. If the intent is to use PCT as a guide for antibiotic discontinuation, then serial testing is critical, something rarely practiced by the clinicians in our study. As our results indicate, PCT results require careful consideration and a nuanced approach to interpretation. While studies on the downstream risks associated with inappropriate interpretation of PCT are lacking, the non-specific nature of elevated PCT levels, low sensitivity for bacteremia, and the marked heterogeneity in PCT performance across infection severities and infecting pathogens creates a high risk for inappropriate interpretation. Training clinicians to appropriately order and interpret PCT levels such that they provide added value to clinical assessments and treatment decisions for suspected BSIs therefore remains an aspirational but elusive goal.

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