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On the Threshold of a Dream

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Standard work for sepsis employing a bundled treatment approach emphasizes the need to keep an eye on the clock (1). Like trauma, there also exists a 'golden hour' for sepsis resuscitation (2). Accordingly time to initial fluid administration (3, 4) and time to administration of appropriate antimicrobials (5, 6) represent key elements of early sepsis resuscitation that are associated with improved patient outcomes. However, before sepsis can be treated, it must be recognized. Sepsis recognition and verification must occur in order to initiate implementation of the sepsis bundle. However, this process may be complicated. As one example, it has been reported that emergency physicians may underestimated likelihood of serious bacterial infection among young children with fever, resulting in under treatment with antibiotics. Conversely 20% of such children without bacterial infection were prescribed antibiotics. There is a real need for sensitive and specific, real time diagnosis of bacterial infection (7). Existing culture-based microbe identification is slow and unreliable. Particularly in the intensive care unit, false negative cultures are problematic, and are often likely associated with concurrent antibiotic treatment. Mean while, missed or delayed sepsis diagnosis is a quality issue. In this regard the article by Vincent and colleagues is intriguing to both researchers and clinicians alike (8).

The RADICAL research team compared microbe identification using a novel, polymerase chain reaction/electrospray ionization-mass spectrometry (PCR/ESI-MS) technology with standard culture-base microbiological testing. Bloodstream, pneumonia, body fluid, and tissue infections were all examined. The authors point out that PCR/ESI-MS can detect more than 800 relevant pathogens. The current work represents a logical follow-up of previously published research examining this technology (article references 9-13). In addition to pathogen identification, the technology can also identify three classes of antibiotic resistance (methicillin, vancomycin, and carbapenems). Coagulase negative staphylococcus and other common skin microbes were excluded from the overall analysis—this may be appropriate for validation of the test, but not for clinical diagnosis of sepsis particularly among immunosuppressed individuals or infants and small children.

Employing culture as the ‘gold standard’, PCR/ESI-MS demonstrated a sensitivity of 81% and negative predictive value of 97% for blood stream infections. Interestingly PCR/ESI-MS reported a relevant organism in 173 specimens that were culture negative, resulting in a calculated assay specificity of 69%—one could argue about the appropriate ‘gold standard’ relative to this sensitivity result. The PCR/ESI-MS test also appeared to perform well with bronchoalveolar lavage and endotracheal tube aspirate samples, as well as body fluid and tissue samples. Perhaps more important, results from PCR/ESI-MS were available within 6 hours from sample acquisition, permitting near real time decisions about starting, continuing or discontinuing antimicrobials. In addition, utilizing a panel of independent clinical adjudicators, the authors determined that the PCR/ESI-MS technology results might have altered sepsis treatment in nearly 60% of patients. Ability of PCR/ESI-MS to rule out infection within 6 hours has important antimicrobial stewardship implications that relate to antimicrobial resistance, occurrence of adverse reactions to antimicrobials, and a variety of costs associated with administration of antimicrobials.

Systematic review and meta-analysis (examining 41 phase III diagnostic accuracy studies for SeptiFast) of another real-time PCR technology (albeit limited microbe repertoire) for microbe identification, reported a summary sensitivity and specificity of 0.68 (95% CI 0.63–0.73) and 0.86 (95% CI 0.84–0.89) respectively when compared to blood culture (9). Because of deficiencies in study quality, no firm recommendations regarding the likely clinical utility of this test were provided. Similar results have been reported for PCR-based sepsis diagnostic testing among premature infants (10). Authors of the systematic review emphasized the importance of utilizing (Standards for Reporting of Diagnostic Accuracy) STARD criteria for evaluating such technology when there is no ‘gold standard’ (11, 12).

Although the RADICAL study focused on microbe identification at onset of infection, this technology will likely also be valuable in terms of defining when it is safe to discontinue antimicrobials. This has certainly been an area of interest for other sepsis biomarkers, particularly C reactive protein and procalcitonin (13, 14). As the RADICAL authors discuss, this application will need to address the findings of sterile culture versus detection of the last vestiges of microbial structural elements. Advantages of the RADICAL 6 hour turn around time include tailoring of antimicrobials after the first dose (discontinuation, adding, deleting, substitution); institution of appropriate isolation as needed; and final discontinuation of antimicrobials.

To maximize value a new diagnostic test must not only be quality-improving, but also cost-lowering (15, 16). Facilitating antimicrobial stewardship in all of its facets is one way to improve value for sepsis treatment (17). Investigators have examined a mathematical prediction model describing the impact of PCR-based rapid tailoring of antimicrobial treatment (18). Such testing enables earlier, adequate treatment and is expected to reduce mortality. The authors estimate that cost for such testing (~300 €/test) could be fully recovered for patients with daily treatment costs exceeding 717 €.

Sepsis is initiated by a microbial pathogen eliciting a host response that usually neutralizes the invading microorganism, but frequently at the expense of considerable collateral damage termed sepsis-mediated multiple organ dysfunction syndrome. Both the microbe e.g. (8) and

host response characteristic of sepsis e.g.(19, 20) can now be accurately and precisely characterized with clinically relevant turn around times. Hopefully clinicians stand at the threshold of a new diagnostic era that will include optimized sensitivity and specificity for sepsis detection and hence accelerated appropriate sepsis treatment ultimately reflecting improved sepsis outcomes.

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