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Biomarkers for sepsis – past, present and future

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ABSTRACT

Sepsis is, in many patients, very difficult to recognise, especially early on and in the elderly and those with multiple comorbidities[1]. This difficulty leads to delayed treatment in some, and over-treatment in others in whom bacterial infection does not exist. One large study of 2579 patients admitted to critical care for presumed sepsis showed that 13% had a post-hoc infection likelihood of "none" and an additional 30% of only "possible"[2].
With increasing recognition of the many detrimental yet usually covert effects of antibiotics, such agents can only cause harm when given unnecessarily. There is a pressing need for reliable, early, sensitive, and specific biomarkers to (i) indicate the presence of infection, (ii) to indicate the likelihood that these infected patients will go on to develop organ dysfunction (sepsis), and (iii) to identify which specific treatments (e.g. immunomodulatory) should be administered to which patient in terms of timing, dosing, and duration.

Infection diagnostics have traditionally relied upon Gram stain and culture; the yield is low and often several days elapse before an organism is identified, speciated, and its antibiotic resistance pattern determined. Newer molecular diagnostics are arriving at an impressive pace and offer the opportunity

for point-of-care testing at the bedside to identify micro-organisms (at least, the commonest pathogens), and some indication of antibiotic sensitivity, within minutes of sampling. Remarkably, bacteria within the lung can also be imaged in real time.
As an example of the power of molecular diagnostics, one study involving 529 patients in nine European ICUs demonstrated that from 616 blood culture samples, polymerase chain reaction/electrospray ionization-mass spectrometry identified a pathogen in 228 cases (37%) whereas traditional blood cultures were positive in just 68 (11%)[3].

For sepsis, current biomarkers such as C-reactive protein and procalcitonin are generally fairly sensitive but are too non-specific to accurately diagnose infection as the cause of inflammation, nor to identify which infected/inflamed patients will proceed to organ failure. Many patients will thus be unnecessarily treated with antibiotics while a smaller number may be inappropriately not treated. It is unlikely that a single biomarker will yield all the necessary information so technologies that can measure multiple markers will probably be more useful. Such devices are being developed, often for point-of-care testing, and include PCR (polymerase chain reaction), lateral flow, microfluidics, and nanotechnology[4,5]. These promise to deliver results in 30-75 minutes at the bedside with no need for involvement of the main hospital laboratory. The challenge now is to find the best biomarkers.

Finally, for treatment selection, it has become clear that sepsis is an umbrella syndrome with many patient subsets within. Inflammatory and hyperinflammatory phenotypes have been described from a combination of clinical and biological markers. At least from retrospective studies, it appears that these subsets respond differently to fluid, PEEP (positive end-expiratory pressure), oxygen, and corticosteroids. So targeted treatment may become a reality in the not-too-distant future though prospective validation is first needed.

Keywords: Biomarkers, sepsis

Disclosures

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