Intensive Care Med
https://doi.org/10.1007/s00134-024-07428-1

EDITORIAL

Diagnosing sepsis: where we're at and where we're going

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Diagnosing sepsis remains problematic. Pathogen identification is frequently lacking and the dysregulated host response is non-specific. Blood cultures often take days to deliver a result and, even then, approximately 90% are negative, sometimes despite strong clinical evidence of sepsis. Standard host-response biomarkers such as C-reactive protein (CRP), procalcitonin (PCT) and white cell count are routinely utilised; however, these are insufficiently discriminatory and lack specificity. This is especially challenging in the intensive care unit (ICU) setting where many patients have underlying sterile inflammation that can closely mimic clinical and laboratory features of sepsis [1, 2]. Despite the arrival of multiple new sepsis biomarkers over the years, none has yet achieved widespread adoption by consistently outperforming the standards [1, 3].

Historically, blood cultures could be augmented by faster antigen testing for specific organisms such as Pneumococcus and Legionella. Polymerase chain reaction (PCR) panels are being increasingly utilised to test for a set of common microorganisms in blood, lung fluid, urine, cerebrospinal fluid and other samples. These panels not unreasonably target certain organisms recognised to be pathogenic and the number of testable organisms is progressively expanding. Results can be delivered within a few hours, even direct from blood without the delay needed to sample from a positive culture, alongside a number of resistance genes to assist antibiotic selection.

A binary separation of nasty pathogen from harmless commensal is increasingly recognised as over-simplistic. Many 'intermediate' organisms can also cause infection organisms potentially, sepsis, especially in immunosuppressed patients. Unfortunately, standard culture techniques are not tuned to readily detect such organisms. Other technologies enable many more organisms to be identified. An early forerunner (now alas shelved due to cost and laboratory workload issues) utilised mass spectrometry and PCR to detect approximately 800 organisms direct from whole blood within 6 h. In one multicentre European study of ICU patients with suspected sepsis, pathogen identification was made direct from blood in 28% ($n=173$) of patients compared to only 9% ($n=55$) with positive blood culture [4].

Metagenomic next-generation sequencing (mNGS) is a more recent innovation that can detect all nucleic acid fragments within a sample. These fragments are sequenced simultaneously, analysed and compared to a reference database to identify any organismal DNA present, covering bacteria, fungi, viruses and parasites and independent of taxonomy [5]. Recent studies in respiratory and blood samples indicate the clinical potential of this technique with a significant increase in diagnostic yield [6, 7]. There are, of course, downsides and challenges to this metagenomic approach, including cost issues, laboratory workload, time to access results, and data interpretation, especially in non-sterile samples. DNA from multiple organisms will be frequently found so how do we quantify the relative importance of each and identify which need to be antibiotic-targeted? Transient bacteraemia is recognised after endotracheal intubation, tracheostomy and even toothbrushing; DNAaemia will be more prevalent and may encourage antibiotic overuse. Furthermore, the presence of DNA does not imply viable bacteria.

Also on the horizon are techniques such as chemiluminescence and Raman spectroscopy for rapid (or even ultra-rapid) antimicrobial sensitivity testing that can deliver antimicrobial sensitivity results within a few

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hours [8]. These functional 'phenotypic' tests will be more reliable than identification of antibiotic resistance genes, of which over 2600 have been identified but few are currently measured [9]. Arguably, this information will be more clinically useful than knowing the precise genus or species.

A systematic review recently described how a third of patients admitted to hospital with sepsis had been seen by healthcare practitioners in the week prior but were not considered sufficiently ill to require hospitalisation [10]. Would it not be advantageous to identify these patients early and treat them pre-emptively? Likewise, patients deteriorating from an infectious cause after surgery or chemotherapy could be proactively treated. A recent multicentre study identified a small panel of host-response gene transcripts that could predict post-operative infection and sepsis with good accuracy up to three days before clinical symptoms [11]. This finding needs to be prospectively validated in different patient populations but highlights the fact that infection and sepsis rarely develop within hours but brew over several days, providing the opportunity for presymptomatic diagnosis and early targeted intervention.

An attractive solution is to link organismal detection and simultaneous transcriptomic (or other) analysis of the host response. A recent study identified 99% of culture-positive sepsis cases, and predicted sepsis in 74% of suspected cases and 89% of indeterminate sepsis cases [6]. Conceivably, daily screening could enable presymptomatic detection of impending sepsis with identification of the infecting organism. While certainly an attractive notion, cost reductions and automation (potentially point-of-care) are needed to make such testing financially and logistically plausible. The impact of confounding by

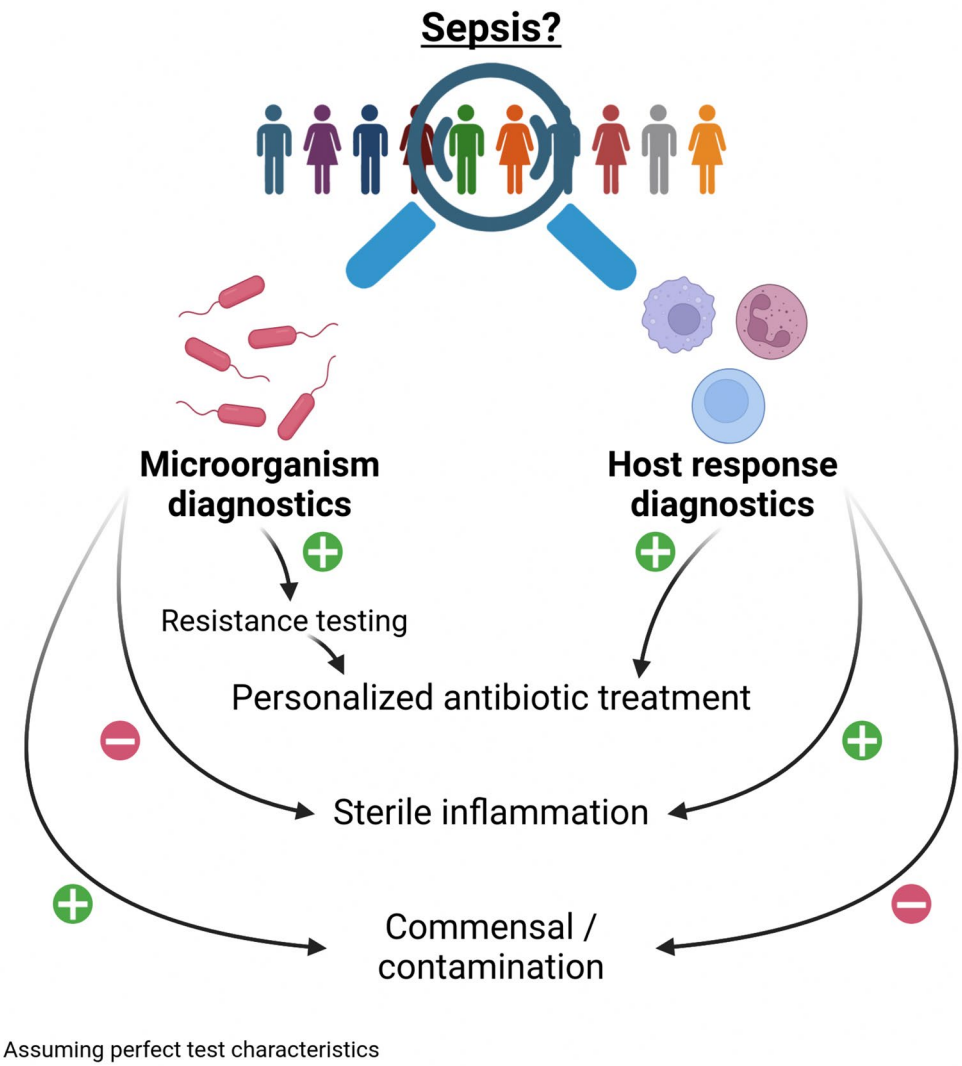

Fig. 1 Proposed future diagnostic pathway for sepsis

concurrent non-infectious causes of inflammation such as recent surgery or trauma must be assessed (Fig. 1).

Given the complexity of the immune response (both regulated and dysregulated) to pathogen contact, and the recognition that various biological 'subphenotype' signatures exist within the sepsis syndrome umbrella [12, 13], a single-target biomarker will be unlikely to substantially surpass the diagnostic capabilities of our old friends. These may, however, offer utility as a theranostic to identify patients suitable for specific host-response modulatory therapies [14]. A multi-marker approach will better characterise the highly individualised (and changing) dysregulated host response to infection. These can be based on laboratory or, preferably, point-of-care-based assays, and possibly enhanced by complementary physiological findings. Such panels may also play an important role in identifying patients likely to respond positively to an intervention, which can then be titrated to optimal effect [12]. Far too many putative treatments have failed, though should we blame the intervention or the unwittingly undesirable enrolment of non- or even negative responders?

In conclusion, the future is very bright with some impressive technologies in development. These will be increasingly more competitive over the coming years in terms of affordability, accessibility and ease of use, including point-of-care offering a rapid turnaround. However, successful adoption of any such new technology must demonstrate both clinical- and cost-effectiveness and, crucially, must change clinician behaviour. Distrust or litigation anxieties will diminish or even prevent application into mainstream clinical practice.

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Data availability
This is an editorial so we have no data - so non-applicable.

Declarations

Conflicts of interest
Outside the submitted work but relevant to its content, MS reports research grants and/or personal fees and/or donations to University Research Fund for advisory board/consultancy/educational videos/lecturing from Safeguard-Biosystems, DSTL, Roche Diagnostics, deePull, Gentian and Biomerieux. DB reports research grants and/or personal fees for lecturing from DSTL, Gentian, Biomerieux and Innovate UK. TZ has no conflicts to report.

Publisher's Note

Received: 2 February 2024 Accepted: 2 April 2024
Published online: 02 May 2024

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