Diagnosing Sepsis –
where we're at and where we're going

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

Given the complexity of the immune response to pathogen contact and the recognition that various biological 'subphenotype' signatures exist within the sepsis syndrome umbrella, [4,5] 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.[6] A multi-marker approach will better characterize 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.[4] Far too many putative treatments have failed, though should we blame the intervention or the unwittingly undesirable enrolment of non- or even negative responders?[7]

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 hospitalization.[8] Would it not be advantageous to identify these patients early and treat them pre-emptively? A recent multicentre study identified a small panel of host-response gene transcripts that could predict postoperative infection and sepsis with good accuracy up to three days before clinical symptoms.[9] 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.

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 utilized to test for a set of common microorganisms in blood, chest fluid, urine, cerebrospinal fluid and other samples. These panels not unreasonably target certain organisms recognized to be pathogenic. Results can be delivered within hours, alongside a number of resistance genes to assist antibiotic selection.

A binary separation of nasty pathogen from harmless commensal is increasingly recognized as over-simplistic. Many organisms are 'intermediate', and can also cause infection and, 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) utilized mass spectrometry and PCR to detect approximately 800 organisms direct from whole blood within 6 hours. 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.[10] 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, analyzed and compared to a reference database to identify any organismal DNA present, covering bacteria, fungi, viruses and parasites, and is independent of taxonomy.[11] Recent studies in respiratory and blood samples indicate the clinical potential of this technique with a significant increase in diagnostic yield.[12,13]

There are, of course, downsides and challenges to this metagenomic approach, in particular interpretation of results, and especially so in non-sterile samples. What significance should be placed on *Pseudomonas* DNA detected in the sputum of a patient with known COPD, or *E. coli* DNA found in the blood sample of a patient with colitis and probable gut translocation? DNA from multiple organisms will be frequently found but 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; DNA-aemia will likely be more apparent so coincident blood sampling may encourage antibiotic overuse. Furthermore, the presence of DNA does not imply viable bacteria. A potential solution is to link organismal detection with clinical deterioration 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.[12] 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 concurrent non-infectious causes of inflammation such as recent surgery or trauma must be assessed.

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 minutes to a few hours.[14] These functional tests will be more reliable than identification of antibiotic resistance

genes, of which over 2600 have been identified.[15] Arguably, this information will be more clinically useful than knowing the precise genus or species.

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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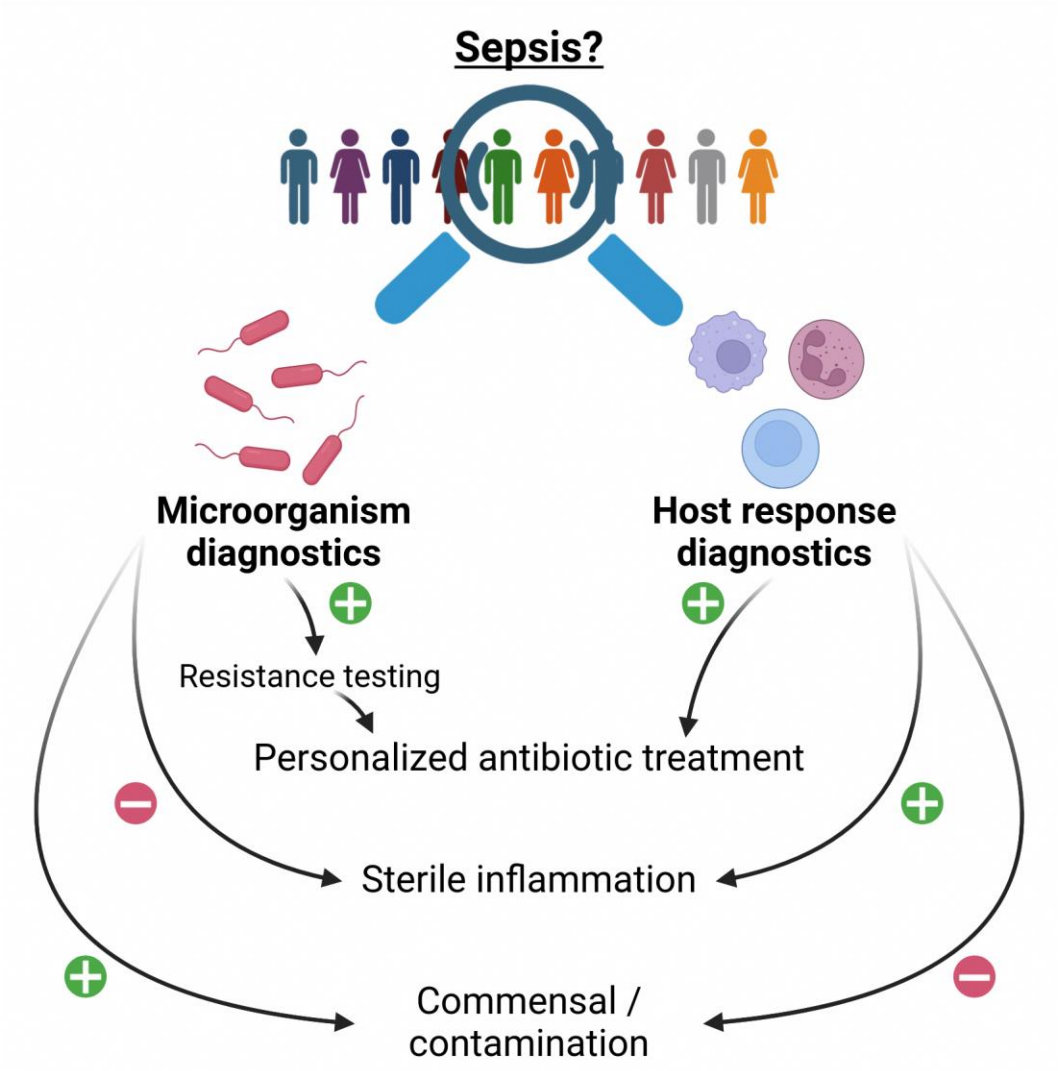
Figure Legends:

Figure 1: Proposed future diagnostic pathway for sepsis



* Assuming perfect test characteristics