

## Commentary

# Diagnosing sepsis: does the microbiology matter?

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See related review by Gao *et al.*, <http://ccforum.com/content/12/3/212>

### Abstract

Sepsis is caused by infection, and knowing what type of organism is causing the infection certainly matters in terms of both epidemiology and selecting antibiotic therapy. Although there is considerable laboratory evidence that micro-organisms initiate sepsis in different ways, the clinical consequences are usually indistinguishable. New drugs that target specific points in the activation pathway are starting to emerge, and these will require us to be much more accurate in how we diagnose sepsis.

Given the time and attention devoted to sepsis in most intensive care units and the amount of antibiotics that are prescribed for what is by common consent a disease caused by micro-organisms, the title of the paper by Gao and coworkers [1] in this issue of *Critical Care* might seem a little curious. Knowing whether the infecting organism is *Streptococcus pneumoniae* or *Escherichia coli* quite clearly matters when it comes to prescribing antibiotics. It is intuitively the case that patients who are treated with antibiotics that are effective against the causative organism are more likely to do well than if they are treated with an ineffective agent - an impression confirmed by a number of observational studies [2,3]. Indeed, a recent paper [4] went further and demonstrated that it was not only the choice of antibiotics but also the speed with which they were given that was crucial; delaying the start of treatment, even by as little as 1 hour, increases the chance of a poor outcome. Identifying the organism is also important for epidemiological reasons [5]. For instance, it clearly matters whether the patient's wound abscess is caused by a fully sensitive *Staphylococcus aureus* or a methicillin-resistant *S. aureus*, not just because antibiotic therapy (if indicated) would be different, but also because we might wish to isolate the patient with methicillin-resistant *S. aureus* or at least use enhanced infection control practices. However, the real question posed by Gao and coworkers is whether knowing the micro-organism 'matters' in terms of either the clinical course of the illness or response to treatment, and this is considerably less clear.

There is no doubt that different micro-organisms initiate what we call 'sepsis' in different ways. Bacteria have a wide range of components that can injure the host, and these components vary fundamentally. For instance, Gram-negative bacteria have lipopolysaccharide (endotoxin) in their cell wall but Gram-positive bacteria do not; instead, many of them produce soluble exotoxins. Certain bacteria have rather specific virulence mechanisms; for example, the O157 strains of *E. coli* produce the verocytotoxin that is associated with haemolytic-uraemic syndrome, and certain strains of *S. aureus* produce toxic shock syndrome toxin-1, which is indelibly associated with the tampon-associated syndrome (although it is now known to cause disease in other settings too). These different virulence mechanisms engage with the host in different ways, and indeed the past 10 years has seen a quite remarkable dissection of the innate immune response to severe infection [6]. Most striking has been the opportunity afforded by advances in gene profiling to demonstrate that exposing human cells and tissues to different types of bacteria elicits different patterns of gene activation [7], which is perhaps the clearest evidence yet that the infecting organism does indeed 'matter'.

However, the uncomfortable reality is that with few exceptions we cannot tell from the end of the bed whether the patient's nosocomial pneumonia is due to *S. aureus* or *E. coli*, and we certainly cannot tell whether it is caused by *Klebsiella pneumoniae* or *Pseudomonas aeruginosa*. Furthermore, apart from ensuring that we choose the appropriate antibiotic, there are no differences in the way that we would treat the patient. It seems that the clinical picture of sepsis is in effect a 'final common pathway' that results from activation of the host response to overwhelming infection; by the time we see it, it is no longer possible to differentiate the process that initiated it. This reality is nicely illustrated by a recent paper [8] that looked at gene expression profiles in a clinical rather than laboratory setting. Although profiles were clearly different in septic compared to control patients, the investi-

gators could not distinguish Gram-positive from Gram-negative sepsis. As Fry pointed out in an accompanying editorial [9], it looks as though sepsis is a 'generic' response to infection.

That goes to the heart of a debate that has been frustrating clinicians for too long. Sepsis is a real phenomenon - we see it every day in the intensive care unit - but it is too generic (diverse) to have a meaningful pathophysiological description or definition [10]. If instead we were to ask, 'Pneumonia - does the nature of the infecting organism matter?', we would get a very clear and unambiguous answer. As long as there is no real evidence that knowing the organism is important in terms of selecting specific adjunctive therapy, the debate is moot. However, as soon as we identify a form of therapy that is specific to the type of infection - an effective anti-endotoxin, for example, or a Toll-like receptor blocker that preferentially blocks activation by Gram-positive bacteria - then it will be time to describe patients' infections much more accurately: *E. coli* pneumonia or staphylococcal empyema [11]. 'Sepsis' will still be a useful term, but it will no longer be fit for purpose.

## Competing interests

The author declares that they have no competing interests.

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