CURRENT KEY DEVELOPMENTS

Sepsis and septic shock: inching forwards

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Introduction

Large epidemiological studies and clinical trials in patients with sepsis all show that the overall mortality rate is approximately 35%. If one restricts the analysis to patients with more advanced disease, septic shock, the mortality increases to 65% or more. It is worth emphasising that these alarming figures represent the outcome of 'standard of care' treatment: in other words, this is a condition in which at least one third of patients die, *despite* treatment on an intensive therapy unit receiving full supportive care and appropriate antibiotics. Why is it that this common condition remains so challenging, despite all our efforts to improve the outcome?

Improving recognition

It has been said that sepsis is one of those conditions that every doctor recognises but few would be able to define. Would that this were so: paradoxically, the debates about how precisely to define sepsis have probably clouded the fact that, certainly in its earlier stages, it is frequently missed and it is only when the patient develops full-blown shock that sepsis is recognised. There is a clear link between the number of organ failures and the outcome: sepsis in the absence of organ failure has a predicted mortality of approximately 15%, but if three or more organs fail the mortality exceeds 70%, irrespective of treatment.[1]

Most discussions about how to define sepsis take as their starting point the joint consensus document produced by the American College of Chest Physicians and the Society of Critical Care Medicine, published in 1992.[2] While this provided a much-needed basis for epidemiological and clinical studies, increasing experience with its use suggested that it failed to capture many of the subtle presentations of the condition. This prompted a reappraisal and a second consensus conference, the upshot of which was a long list of symptoms and signs, any or all of which could feature as manifestations of sepsis.[3] This approach is not helpful, certainly to the junior bedside clinician, and has prompted some to question whether 'sepsis' as a discrete or specific diagnosis is still a useful concept. Perhaps it would be more meaningful to acknowledge that what we are really dealing with is a particular infection, say pneumonia or peritonitis, which in some cases is complicated by organ failure(s).[4]

What is certainly clear is that doctors (and particularly junior doctors) need better training in how to recognise the early clinical features of this condition. It is striking (and in my opinion disappointing) that sepsis is not mentioned at all either in the core competencies or the syllabus for the Modernising Medical Careers programme.[5]

Improving treatment

Treating septic patients involves complex decisions in a variety of different therapeutic areas. Patients must receive appropriate oxygenation, may need cardiovascular support, antibiotic therapy, or surgical interventions as well as specific treatment of underlying conditions. Ideally this is done in an intensive care unit but in some parts of the world access to experienced intensive care specialists is limited and, in any case, the evidence base in this field is weak or even non-existent. These problems led to an international group of experts to establish what they called the Surviving Sepsis Campaign, and to try to draw together a group of recommendations, as far as possible based on the principles of evidence-based medicine, to guide the management of septic patients. The guidelines, first published in 2004,[6] were updated in 2008.[7] They provide a useful source of advice on the basic principles of managing such patients, but there are three areas of recent interest that remain highly controversial and bear brief mention.

Corticosteroids

Pharmacological doses of corticosteroids to treat septic shock were first proposed 20 years ago, but were ultimately shown not to be helpful.[8] Much more recently studies were undertaken that seemed to show that some septic patients were effectively Addisonian and that low dose steroid replacement was beneficial, particularly in patients with severe cardiovascular failure.[9] Although widely adopted because it was seen to be cheap and unlikely to do harm, this approach remains highly controversial. Recent data from CORTICUS, a 500-patient multicentre study of patients with less severe sepsis, showed that low dose steroids did not alter mortality, although they did reduce the time to shock reversal, an intriguing finding that is likely to add further fuel to the controversy in this area.[10]

Strict glycaemic control

Although it has long been recognised that septic patients have severely deranged metabolic function and may require insulin to control blood sugar, Van den Berghe and colleagues have proposed that much tighter glycaemic control (target blood glucose 4.4–6.1 mmol/l) can reduce morbidity and/or mortality.[11,12] As more data accumulate, the general applicability of this approach has been questioned, not the least because there is a real risk of unappreciated hypoglycaemia.[13]

Novel specific therapies

The landmark study by Bernard *et al* showing a survival benefit for drotrecogin alfa (activated) (activated protein C) led to

registration by both the European Medicines Agency and the Food and Drug Administration, and approval from the National Institute for Health and Clinical Excellence for its use in defined clinical settings.[14,15] Nevertheless, the lack of a second confirmatory clinical trial and the failure of the ADDRESS study in lower-risk patients means that many intensivists remain uncertain about the precise role of this drug.[16]

What is encouraging – and in some senses surprising, given the difficulty in making headway in this field – is that novel agents continue to come forward from the basic science arena. For instance, there is currently much interest in the possibility that Toll like receptors (in particular TLR4) may be good therapeutic targets and two large clinical trials of small molecule antagonists have begun.[17,18] What is clear is that driving down the mortality in this condition remains a major unmet medical need.

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Antimicrobials: past, present and uncertain future

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It is hard to imagine the practice of medicine without antibiotics. Life-threatening infections, such as meningitis, endocarditis, bacteraemic pneumonia and puerperal sepsis, would again prove fatal. Minor community-managed infections would be associated with slower recovery, higher complication and hospital admission rates, while surgical practice would see steep rises in postoperative infectious complications. Aggressive chemotherapy and transplant procedures would prove impossible.

Why create this scenario? Antibiotics are unique among therapeutic agents. Although prescribed for diseases, syndromes and symptom complexes, they target pathogenic organisms rather than an intrinsic host-derived pathophysiological process. Furthermore, their efficacy is eroded as resistance emerges and disseminates. There is therefore a requirement for surveillance of resistance, encouragement of prudent prescribing and observance of practices that reduce the risk of resistant pathogens emerging or disseminating. Continuous technological innovation is essential to ensure an adequate flow of new drugs, vaccines and diagnostics to manage existing and emerging infections. Currently this process is in a state of imbalance.

The dominance of β-lactam antibiotics (penicillins and cephalosporins) emphasises the fundamental importance of Fleming's discovery of penicillin and the landmark identification of the 6-aminopenicillanic acid nucleus by Rolinson and colleagues which presaged structure-based drug design.[1,2] The legacy is remarkable and includes the aminopenicillins (eg amoxicillin), the isoxazolyl penicillins (eg meticillin, flucloxacillin) and the piperazinyl penicillins (eg piperacillin). This laid the technical know-how for the development of the cephalosporins whose derivatives have proved the work horse antibiotics in hospital and community practice for four decades. Currently, the elusive target of a cephalosporin active against methicillin-resistant *Staphylococcus aureus* (MRSA) appears in site with the trialling and imminent licensing of ceftibiprole.

Antimicrobial science has proved innovative not only in discovering new compounds but in defining the myriad and ever-increasing mechanisms of microbial resistance. Enzymatic