

Sepsis research: where have we gone wrong?

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Sepsis is defined as the host response to invasive infection.¹ The definition underlines an evolving awareness that the clinical syndrome arises through the response of the host, rather than the direct effects of the infecting microorganism. It further suggests the hypothesis that modulating the response of the host — independent of measures to control infection — might improve the outcome for critically ill patients with sepsis.

This promise is compelling. Sepsis is the leading cause of death for critically ill patients admitted to an intensive care unit, and the predominant cause of morbidity in those who survive. Even though sepsis commonly afflicts patients with significant co-morbidities, survival is clearly possible, even in the most extreme cases. Thus, the contemporary mortality rate of some 30% over 1 month must be seen as unacceptably high — analogous to mortality rates for myocardial infarction three or four decades ago.

But, despite a strong biological rationale and no shortage of potential therapeutic targets, attempts to modulate the host response over the past two decades have been profoundly disappointing. Even when efficacy has been demonstrated in clinical trials, the magnitude of benefit is small.² I argue here that this results not from any intrinsic impossibility of treating sepsis as a disease, nor a lack of biologically efficacious interventions, but rather from shortcomings in three domains of clinical investigation — conceptual, methodological, and organisational.

Conceptual challenges

Perhaps the greatest failing in contemporary research on sepsis has been the assumption that sepsis is a simple disease with a uniform course and pathogenesis, rather than a complex group of diseases with divergent, and even contradictory, biological mechanisms.³ Even more, we have assumed that the parameters of this disease can be established by the consensus of experts, rather than by more objective and specific parameters.

The concept of sepsis is attributed to Hippocrates who believed that living tissues have endogenous mechanisms of breakdown that are either beneficial or harmful.⁴ *Sepsis* was the process associated with putrefaction and rotting, while *pepsis* was tissue breakdown by digestion or fermentation. With the recognition that microorganisms initiate the processes of sepsis (as well as many of those of *pepsis*), the term sepsis became synonymous with severe bacterial infection. More recently, with the unravelling of the innate

host immune response, it has become apparent that the condition we call sepsis reflects a response of the host, rather than any intrinsic property of the microorganism. Moreover, this host response is not specific to viable microorganisms, but a more general danger response that can be elicited by killed microorganisms, microbial products and injured tissues.

Sepsis, then, is primarily a concept that delineates a group of diseases: the concept is that morbidity is driven by the response of the host. However, the diseases are remarkably heterogeneous in their triggers, clinical course and ultimate prognosis. Indeed, just as cancer defines a concept — the uncontrolled proliferation of abnormal cells — and a broad group of diseases, sepsis is a category, not a single process.

Thirty years ago, scientists and policymakers spoke earnestly about the possibility of a cure for cancer. Today, the phrase is used predominantly by quacks and charlatans, for we have accepted the notion that there is no single cure for cancer, but rather many different potential cures for specific cancer types and stages. For example, surgical resection of the rectum may be curative for an early stage rectal cancer, but is of no value in the management of childhood leukaemias. The drug herceptin prolongs the survival of a subgroup of women with breast cancer, but would be ineffectual in the treatment of astrocytoma. Oncologists long ago realised that cancers must be divided into biologically homogeneous groups and then staged to optimally define therapy. Indeed, it is only the evolution of staging systems such as the TNM (tumour, node, metastases) system that has permitted the promise of adjuvant therapy for cancer to be realised.

Similar clinical heterogeneity is apparent in patients and animal models of sepsis. For example, in animal models of bacterial challenge, the response to neutralisation of tissue necrosis factor (TNF) depends highly on the model.⁵ Neutralisation of TNF improves survival in models of challenge with endotoxin or systemic challenge with gram-negative organisms. On the other hand, neutralising TNF actually worsens outcome if the challenge organism is *Streptococcus pneumoniae*, or a *Candida* or *Listeria* sp. Finally, there is no evidence of efficacy against complex challenges, such as caecal ligation and puncture.

The recognition that sepsis is not a single disease stimulated interest in developing staging or stratification systems analogous to the TNM system.⁶ One such candidate model is the PIRO system, which suggests that stratification

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according to predisposition, insult, response and organ dysfunction can ultimately aggregate patients into homogeneous populations for therapy.⁷ The system is at present an abstract concept awaiting refinement and validation through large natural-history studies, but its appeal is intuitive. For example, if we are evaluating a new antibiotic with activity against methicillin-resistant staphylococci, the appropriate population for study might be stratified as follows:

- P: Absence of other immediately life-limiting conditions.
- I: Documented infection with methicillin-resistant *Staphylococcus aureus*.
- R: Clinical evidence of infection to suggest that the organism is truly infecting and not simply colonising.
- O: Absence of significant organ dysfunction.

On the other hand, if we are evaluating a novel anticoagulant, the PIRO model might appear as:

- P: Genetic predisposition to a procoagulant state.
- I: Any insult that induces coagulopathy.
- R: Biochemical evidence of coagulopathy or hypercoagulability.
- O: Significant organ dysfunction.

In contrast, contemporary clinical sepsis trials recruit patients based on the non-specific physiological criteria of sepsis syndrome and systemic inflammatory response syndrome (SIRS). Criteria for sepsis syndrome were originally proposed by investigators planning a study of high-dose corticosteroids for septic shock.^{8,9} The criteria were based on consensus rather than data, and have never been shown to define a biochemically homogeneous group of patients.¹⁰ Nonetheless, and despite the failure of these criteria to identify an appropriate population for treatment with corticosteroids, they continue to be used and, perhaps not surprisingly, to reveal their inadequacy in delineating a target population.

Methodological challenges

The methodological challenges of sepsis research are numerous. We lack large-scale natural-history studies of either clinical course or biochemical evolution that might better define appropriate populations for intervention and characterise the specific morbidities amenable to treatment. Trial design proceeds on the naive assumption that a scientific experiment is better informed by opinion than by data from intensive natural-history studies. Beyond the fact that the criteria for SIRS are all simply components of the APACHE II score, there is no evidence to suggest that tachycardia, tachypnoea, hyperthermia or hypothermia, and leukopenia or leukocytosis better identify a patient population that might benefit from therapy with antibiotics, haemodialysis, corticosteroids or activated protein C. In

addition, although 28-day all-cause mortality is used as the primary endpoint for sepsis trials, this time point reflects expert opinion rather than robust data showing it is the best measure of short- or long-term clinical efficacy.

While investigators would obviously like to demonstrate a clinically important effect on a patient-centred outcome measure, such as mortality, refining the research enterprise to do so first requires proof of principle. Beyond evidence of biological activity in simple animal models of disease, this proof of principle has been largely lacking in sepsis trials. For example, it is unthinkable that an intervention that prevents stroke by controlling blood pressure could have this effect in the absence of an early impact on blood pressure, or that an agent designed to normalise glucose levels could have long-term benefit if this effect was not evident early on. However, this hypothesis is rarely tested in sepsis trials. When a given mediator is targeted in a population of patients, it is rare that the population is evaluated to determine the presence of the mediator, and equally rare that the effects of intervention on the levels of that mediator or related molecules are evaluated. Similarly, if patients are entered into a clinical trial on the basis of tachycardia and tachypnoea, it stands to reason that an effective therapy would have an early and favourable influence on these physiological parameters. That it does in no way implies long-term clinical efficacy, but, if it does not, then it is hard to believe that these parameters are appropriate criteria for trial entry.¹¹

Failure to evaluate measures of early biological activity not only dooms trials, but may result in patient harm. In a large clinical trial of nitric oxide inhibition, treatment resulted in a striking increase in mean arterial pressure that was associated with an increased risk of death from pulmonary hypertension and cardiac causes.¹² Demonstration of biological efficacy permits the investigator to titrate therapeutic intervention to a desired physiological or biochemical target, increasing both efficacy and safety.

Organisational challenges

A critique of the failings of sepsis research inevitably brings the lack of leadership within the critical care community into sharp focus.

Most clinical research in the field of sepsis is initiated and conducted by pharmaceutical companies whose primary motivation is the prospect of developing an expensive drug that can be marketed to many hundreds of thousands of patients. This breeds conservatism. It discourages attempts to delineate more focused populations of patients for study, and encourages studies whose design is driven more by regulatory requirements than by the imperatives of good clinical science.

Both within the critical care community and within industry, we have steadfastly refused to learn from our past mistakes. There is now overwhelming evidence that the models of sepsis research we have used can — regardless of the intervention studied — typically improve survival rates in the order of 2%.^{2,13} There is also evidence that regional and international variability in clinical practice can effectively conceal a therapeutic effect, and, conversely, that evidence of activity is most striking when studies are done in a small number of experienced centres with standardised treatment protocols. Nonetheless, the contemporary model of sepsis research comprises large international trials recruiting patients on the basis of generic physiological criteria. This intransigence is frustrating. Even when a trial shows evidence of clinical efficacy — as it did in the case of the PROWESS study for activated protein C¹⁴ — the inherent shortcomings of clinical trial design breed skepticism.

Finally, we have failed to engage other stakeholders in meeting this extraordinarily complex scientific challenge. Patient awareness of the problem of sepsis is minimal. The problem also has a low profile among world health bodies, granting agencies, and regulatory authorities.

Conclusions

The challenge of modulating the host response in sepsis is enormously complex. Two decades of experience have provided us with rich insights into the reasons that studies fail, and have pointed to new directions for future research. It is time we listened.

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References

- 1 Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992; 101: 1644-55.
- 2 Marshall JC. Such stuff as dreams are made on: mediator-directed therapy in sepsis. *Nat Rev Drug Discov* 2003; 2: 391-405.
- 3 Marshall JC. Rethinking sepsis: from concepts to syndromes to diseases. *Sepsis* 1999; 3: 5-10.
- 4 Majno G. The ancient riddle of sigma eta psi iota sigma (sepsis). *J Infect Dis* 1991; 163: 937-45.
- 5 Lorente JA, Marshall JC. Neutralization of tumor necrosis factor in preclinical models of sepsis. *Shock* 2005; 24 Suppl 1: 107-19.
- 6 Marshall JC, Vincent JL, Fink MP, et al. Measures, markers, and mediators: toward a staging system for clinical sepsis. A report of the Fifth Toronto Sepsis Roundtable, Toronto, Ontario, Canada, October 25-26, 2000. *Crit Care Med* 2003; 31: 1560-7.
- 7 Levy MM, Fink MP, Marshall JC, et al; SCCM/ESICM/ACCP/ATS/SIS. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31: 1250-6.
- 8 Bone RC, Fisher CJ, Clemmer TP, et al. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med* 1987; 317: 653-8.
- 9 Bone RC, Fisher CJ, Clemmer TP, et al. Sepsis syndrome: a valid clinical entity. *Crit Care Med* 1989; 17: 389-93.
- 10 Casey LC, Balk RA, Bone RC. Plasma cytokines and endotoxin levels correlate with survival in patients with the sepsis syndrome. *Ann Intern Med* 1993; 119: 771-8.
- 11 Marshall JC, Vincent JL, Guyatt G, et al. Outcome measures for clinical research in sepsis: a report of the 2nd Cambridge Colloquium of the International Sepsis Forum. *Crit Care Med* 2005; 33: 1708-16.
- 12 Lopez A, Lorente JA, Steingrub J, et al. Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. *Crit Care Med* 2004; 32: 21-30.
- 13 Zeni F, Freeman B, Natanson C. Anti-inflammatory therapies to treat sepsis and septic shock: a reassessment. *Crit Care Med* 1997; 25: 1095-100.
- 14 Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344: 699-709. □