

Commentary

The staging of sepsis: understanding heterogeneity in treatment efficacy

John C Marshall

Professor of Surgery, Departments of Surgery and Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada

Corresponding author: John C Marshall, jc.marshall@utoronto.ca

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Abstract

Human sepsis is an intrinsically complex disease. Populations of patients enrolled into clinical trials of novel sepsis therapies are notoriously heterogeneous with respect to the inciting cause of their disease, the co-morbid conditions that define its course, and the acute severity of their initial presentation. This heterogeneity is reflected in strikingly variable mortality risks across studies, and probably, though less clearly-established, in variable response rates to a given intervention. In an accompanying article in this issue of *Critical Care*, Macias and colleagues argue that the effectiveness of adjuvant sepsis therapies is not dependent on the baseline mortality risk, since the few "positive" trials that have been published show widely divergent placebo mortality rates. But this analysis assumes that biologically distinct interventions will be equally efficacious in clinically diverse populations, and confuses severity as a population descriptor with severity as a surrogate measure of a biologic state in an individual patient. In a pivotal trial of recombinant human activated protein C (rhAPC) in patients with severe sepsis, an aggregate 6% mortality decrement appeared to be the result of negligible efficacy in the least severely ill patients, and considerably greater efficacy in those who were at greatest risk of dying. A larger follow-up study recruiting low risk patients confirmed this impression, showing a convincing absence of benefit in patients who clinicians judged to be less severely ill. If we accept Macias' argument, we are led to the conclusion that rhAPC is of limited use in the management of severe sepsis. On the other hand, if we view severity as a crude surrogate for a particular pathologic state, we would shift our focus to better defining those populations most likely to benefit from intervention, including patients who may not have met criteria for entry in the original PROWESS trial – those with disseminated intravascular coagulation or acute organ dysfunction from causes other than sepsis. Staging systems that stratify heterogeneous patient populations by risk and by potential to benefit from intervention have proven to be essential to the development of multimodal adjuvant treatment for cancer. They will be no less important in the optimal management of sepsis.

To the casual observer, the patients who inhabit a contemporary intensive care unit must present a single and frightening image.

All are dressed in the same custom issue intensive care unit garb, and all are confined to bed – the passive recipients of a bewildering array of life support technologies. Each has a variable number of plastic tubes emanating from a number of orifices, both anatomic and iatrogenic, and through these tubes is receiving unknown fluids, or expelling those that are only too familiar. Most are on mechanical ventilators, and beds that are capable of quite remarkable contortions. Some are undergoing dialysis, while others seem to be making an agonizing effort to return to a state of coherence and autonomy. But it is their similarities, rather than their differences, that create the most enduring impression.

To the intensivist caring for these patients, however, the picture is much more complex. The course of this otherwise well young woman struggling to survive the consequences of a pregnancy complicated by a placental abruption and disseminated intravascular coagulation may be rendered more complicated by a ventilator-associated pneumonia. But for the elderly man in the next bed, who lacking family or friends to make a decision in the final days of his life was admitted with a further exacerbation of chronic lung disease, the same pneumonia holds the elusive possibility of a dignified death. Across the way is a middle-aged man with an anastomotic leak following an esophagectomy who has now developed acute renal failure, and an elderly woman admitted last night with shock, and a poorly characterized infiltrate on the chest X-ray. For each of these individuals, sustaining life is a relatively simple matter of identifying the physiological insult or insults that comprises an immediate threat, and initiating the appropriate means of exogenous support, be it mechanical ventilation, dialysis, or vasoactive medications. The much greater, and largely unsolved, challenge is to understand the pathological processes that are responsible for potentially lethal organ dysfunction, so that specific treatments that target these might be given.

Sepsis, a syndrome characterized by a dysregulated and destructive response to infection, is a theme common to each of the hypothetical patients above, and to many of the most complex patients cared for in the contemporary intensive care units. A variety of strategies, both proven and potential, have emerged to manage this state: the challenge for the intensivist is understanding when, how, and in whom to use them. This challenge is amplified by the enormous heterogeneity of the patient population, and has spurred attempts to develop stratification models that can resolve this heterogeneity [1-3]. Foremost among these is the still largely theoretical PIRO model that proposes stratifying patients on the basis of measures of 'predisposition', the nature of the acute 'insult', the nature of the host 'response', and the baseline degree of 'organ dysfunction' [3].

Macias and colleagues [4] in this issue of *Critical Care* report the results of one such analysis. Synthesis of the results of a heterogeneous group of pre-clinical studies in animal models suggested the hypothesis that the response to intervention with strategies that target the innate host inflammatory response is dependent on the severity of the inciting insult, reflected in the mortality rate of the placebo population [5]. Macias *et al.* [4] undertook a systematic review of 22 phase III studies of 17 different therapeutic strategies for sepsis, and concluded that there is no evidence of an interaction between baseline mortality risk and the potential to benefit from treatment. While they are to be applauded for undertaking this analysis, in my view, both the question they ask, and the conclusions they draw, miss the mark.

The authors' conclusion that baseline mortality risk does not impact the potential for benefit or harm derives primarily from the observation that the three clinical trials showing a statistically significant beneficial treatment effect have placebo mortality rates ranging from 31% to 61%, whereas an apparent lack of efficacy in other trials occurs across a spectrum of baseline mortality risk. There are several important flaws in this analysis. First, it proceeds from the simplistic assumption that agents that target highly diverse aspects of a complex disease process will be equally efficacious in all patients with sepsis. But this is clearly not the case. Vasoactive medications, for example, are only of use in the septic patient with refractory hypotension, and mechanical ventilation does not help the patient without respiratory insufficiency; indeed, intervention in the absence of a clearly established need may generate harm. Similarly, treatment with recombinant human activated protein C (rhAPC) improves survival in patients who are more severely ill, as measured by Acute Physiology, Age, and Chronic Health Evaluation (APACHE) II score or the number of failing organs [6], a conclusion suggested by a subgroup analysis of the pivotal PROWESS study and confirmed in a recently published and much larger multicenter trial [7]. On the other hand, intervention with anti-tumor necrosis factor therapy appears to be of benefit primarily in patients without

Table 1
Efficacy of drotrecogin alpha activated as a function of baseline severity of illness in phase III trials

APACHE II score	28 Day mortality (%)		Odds ratio	95% CI	p
	Placebo	rhAPC			
≤24					
PROWESS	19.1	18.7			
ADDRESS	16.0	16.9			
Pooled	16.8	17.4	1.04	0.86-1.26	0.72
>24					
PROWESS	43.1	31.5			
ADDRESS	24.8	29.4			
Pooled	38.0	30.9	0.73	0.57-0.94	0.01
Overall mortality	22.4	21.0	0.92	0.79-1.06	0.26

APACHE, Acute Physiology, Age, and Chronic Health Evaluation; CI, confidence interval; rhAPC, recombinant human activated protein C.

established organ dysfunction [8], while the detrimental effects of blood transfusion are most apparent in patients with lower severity of illness [9]. Pooling data from a biologically disparate group of studies serves to obscure, rather than to illuminate, a treatment-severity interaction.

Moreover, the analysis confuses severity as a population descriptor with severity as a descriptor of individual patients within that population. Assuming that the potential to respond to treatment varies across unknown or undefined characteristics of patients within a study population, then the absence of an effect in a trial reflects one of three possibilities: that the agent is truly lacking in clinical efficacy; that the absence of activity reflects benefit in some patients, and harm in others; or that the agent is efficacious, but the magnitude of that activity is too small to be detected given the size of the population studied, or that a larger effect is diluted by the absence of activity in some patients.

Thus, if the agent truly works in the population of interest, an inappropriate conclusion of no effect may reflect either concomitant harm or dilution of the true effect by the inclusion of patients who could not benefit. Harm is a very real concern in studies of novel therapies for sepsis, whether a consequence of inappropriate dosing or titration or of unanticipated biological activity [10,11]. The problem, however, of inappropriately minimizing efficacy through the inclusion of patients who have no chance of benefiting is an even greater concern to the clinician, whose objective is to target the right treatment to the right patient, and to avoid treating those who have no chance of benefit. A recent example illustrates this problem (Table 1).

rhAPC (or drotrecogin alpha activated) was approved by North American and European regulatory agencies for the treatment of severe sepsis and septic shock on the basis of a multicenter trial showing a 6.1% absolute mortality reduction

in patients receiving the agent. Secondary analyses suggested that the potential to benefit from treatment was not homogeneous throughout the population, but rather restricted to patients with greater severity of illness at trial entry, and led to restrictions on the use of drotrecogin alpha activated and a requirement that a second trial evaluate efficacy in a lower risk population. That study, recently published, confirmed the absence of efficacy in a lower risk population [7]. If we pool data from the two published phase III trials of rhAPC in sepsis, treatment increases the probability of survival by 7.1% in the sickest patients, those with APACHE II scores of 25 or higher. But now the mortality benefit across the entire population is only 1.4%, even smaller than that seen in other sepsis trials [12] and no longer statistically significant. Should rhAPC be relegated to the ignominious scrap heap of other 'failed' sepsis therapies or 'negative' sepsis trials? I would argue no. But it is entirely likely that we will hear this line of argument with increased vehemence in the wake of the publication of the ADDRESS trial [7].

The flaw here – and in Macias and colleagues' line of reasoning as well – is that populations of patients with patients with sepsis are intrinsically heterogeneous in both their baseline risk of adverse outcome and their potential to respond to intervention. Failing to acknowledge that heterogeneity by increasing the relative proportion of patients who cannot benefit from intervention only serves to mask a potential treatment effect. Conversely, a more careful targeting of specific therapeutic strategies to more biologically homogeneous groups of patients is essential to developing effective adjuvant treatment. High dose corticosteroid therapy was shown to be ineffective or even harmful in patients with severe sepsis [13,14], whereas pharmacological doses of steroids improve the survival of patients with refractory septic shock and relative adrenal insufficiency [15]. Goal-directed hemodynamic management is very efficacious early in the course of severe sepsis and septic shock [16], but ineffective if delayed [17]. Anti-tumor necrosis factor therapy has a marginal impact when given to a heterogeneous population of patients with sepsis [12,18], but is much more efficacious when given to patients without significant organ dysfunction at study entry [8]. In contrast, rhAPC is more effective in patients with greater degrees of organ dysfunction [6].

The unmet challenge in sepsis research is not the identification of therapeutic targets, but the development of sensible, robust, and validated methods of stratifying patients, analogous to those that currently guide the use of adjuvant therapy in oncology. Baseline mortality risk or severity of illness measured by a non-specific physiological scale such as APACHE is one crude system of stratification. But mortality risk is a poor surrogate for the complex pathological processes that define the evolution of sepsis, and more sophisticated systems must be developed. To fail to do so is to discard the prospect of biologically rational and clinically effective therapy for this common and lethal process.

Competing interests

The author(s) declare that they have no competing interests.

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