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EDITORIAL

Improved survival in critically ill patients: are large RCTs more useful than personalized medicine? No

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Randomized controlled trials (RCTs) are considered the best evidence on which to base change in practice. We all agree that only RCTs can account for unmeasurable factors that may influence the response to a therapeutic intervention. Yet, so many large RCTs have been negative in critically ill patients. Whatever we test does not seem to make a difference to outcomes: the pulmonary artery catheter [1, 2], intracranial pressure monitoring [3], optimal blood pressure levels in septic shock [4], central venous oxygen saturation monitoring [5], blood transfusions, and so the list goes on. We were so proud to have finally developed a drug for sepsis, drotrecogin alfa (activated) [6], but this was such an unexpected and surprising event that another study was performed, which negated the results [7] and the drug was taken off the market. Admittedly, some RCTs have identified interventions that caused harm, and this is of course very important: the best example is the large study of tidal volume in patients with acute respiratory distress syndrome (ARDS) [8]. But, are there any studies that have shown improved outcomes in critically ill patients? In fact, the very few that showed a survival benefit concerned interventions that prevented harm rather than providing benefit: for example, the use of muscle relaxants [9] and prone positioning [10] probably provide benefit in ARDS by limiting barotrauma.

There are several reasons why RCTs are more likely to show harm than benefit, the most important being that our patient populations are very heterogeneous. A good example to illustrate this phenomenon is that of a hypothetical RCT comparing empiric penicillin with placebo in patients with sepsis [11]. Penicillin would be expected to be beneficial in only a very small subset of the patients who have sepsis due to a minority of Gram-positive organisms, and it is more than likely that this effect would be missed in a very large RCT. On the other hand, in the same population, penicillin administration will cause allergic reactions in some patients and these will be easily identified. According to the results of such an RCT, we would abandon penicillin on the basis of no identified clinical benefit and an obvious harmful effect in some patients. And we would be proud that our RCT had identified this toxicity. Fortunately, we are well aware of the importance of antibiotic susceptibility, and such an RCT, in an unselected patient population, would never be performed. This demonstrates the importance of personalized medicine: we need to identify which patients can potentially benefit from the intervention being tested, rather than testing blindly in all.

The multiple negative studies on sepsis drugs provide another example of the need for a more individualized approach. In the past, such studies considered sepsis as being just a pro-inflammatory state, but there is mounting evidence that immunosuppression can also occur, even relatively early [12]. Trials of anti-inflammatory/immunosuppressive agents will likely give negative results if they are tested in patients who are already immunosuppressed, and immunostimulating drugs may well be harmful in patients who have a pro-inflammatory state. We need to characterize the patients' immune status prior to study inclusion to select the most appropriate group of patients for each type of intervention [13].

Similarly, the use of corticosteroids in septic shock is still a hotly debated issue, but the ADjunctive

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Table 1 Some of the problems that can be encountered when performing randomized controlled trials in critically ill patients

	Type of study/example	Hurdle(s)
Essential	New drug	Blinding sometimes difficult
	New technique	Blinding often impossible
	Fever control	Method used to lower body temperature (pharmacological, physical, etc)
	Glucose control	Monitoring technique (e.g., arterial blood vs. capillary sample)
	Blood transfusion	Decision not based only on hemoglobin levels
	Sepsis drugs	Great heterogeneity of patient populations
	Continuous vs intermittent RRT	Result different depending on the patient's condition
Avoidable	Two crystalloid solutions	Blood electrolytes should determine the choice of crystalloid fluids

coRticosteroid trEatment iN criticAlly ilL Patients with Septic Shock (ADRENAL) study that will include 3800 "critically ill" patients is unlikely to provide the definitive answer without some specific selection of patients based on biomarkers. In children with septic shock, Wong et al. [14] showed that specific patterns of gene expression could identify which patients were most likely to benefit from hydrocortisone administration.

There are other reasons why the RCT is not the best option to address all questions in critically ill patients (Table 1). As a first example, RCTs should be double-blind to reduce the risks of bias, but this is sometimes impossible. Some interventions may have a hemodynamic effect that will be easily picked up at the bedside, while others can influence laboratory test results. In one study, granulocyte colony-stimulating factor (GCSF) was unexpectedly associated with a substantial increase in leukocyte count that could not be masked from the clinician [15]. Second, another limitation of RCTs is that the method used to induce the change under investigation can influence interpretation of the results. For example, a study on two different blood pressure levels in septic shock [4] is actually a study of two doses of norepinephrine, a drug that has its own effects. Third, in pragmatic trials, protocol design allows physicians to decide whether or not a patient should be enrolled, potentially creating problems with patient enrollment and randomization. For example, studies on pulmonary artery catheterization included patients only when the physician had decided that the patient could be managed without this intervention. Similarly, for blood transfusion studies, patients were randomized when the doctor felt that the patient could be safely managed without transfusion. In the landmark study by Hebert et al. [16], only 13 % of patients who were potentially eligible were randomized and the study was discontinued before the end for slow enrollment. Fourth, studies comparing two techniques are fraught with the difficulty of using the best technique at the right time for the right patient. Comparing continuous and intermittent renal replacement therapy does not make much sense when it is accepted that continuous techniques are preferred in hemodynamically unstable patients or those with contraindications to anticoagulation, and intermittent techniques are preferred in patients who can be ambulated. Similarly, there is little rationale to compare two crystalloid solutions in heterogeneous groups of patients, because the type of fluid should be selected individually based on electrolyte results. It would be inappropriate to continue to give a saline solution containing 154 mEq/L of chloride to patients who start to develop hyperchloremia [17].

The only common feature of all critically ill patients is that they are "critically ill" and therefore need to be hospitalized in an ICU. This population of patients is highly heterogeneous, with various types and degrees of organ dysfunction, and it is very unlikely that they will respond

similarly to different types of intervention. Rather than considering these patients as identical (as is commonly the case in RCTs), we should try to identify particular features of subgroups of individuals most likely to benefit from specific interventions, e.g., drugs influencing the coagulation system must target patients with coagulopathy, and the administration of gamma-globulins should be guided by blood immunoglobulin levels, etc.

Clinical trials should be based on sound pathophysiologic elements and enroll patients on the basis of specific individual characteristics or biomarkers that identify them as being most likely to respond to the intervention in question. This is the only way to make real progress in this field.

Compliance with ethical standards

Conflicts of interest
The author has no conflicts of interest to declare regarding this manuscript.

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