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EDITORIAL

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

Jean-Louis Vincent*

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.

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EDITORIAL

Improved survival in critically ill patients: are large RCTs more useful than personalized medicine? We are not sure

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At first sight, personalized medicine and large randomized clinical trials (RCTs) seem to reflect opposite approaches to medicine: one focusing on the single individual, the other on the population of individuals. Accordingly, in critically ill patients, does the "best" therapy depend on the unique characteristics of the patient or does it derive from the outcome analysis of a large population in which a given therapy has been tested? Actually, we believe that comparing personalized medicine and large RCTs is like comparing apples and oranges. Indeed, which are the essences of personalized medicine and which those of the RCTs?

As defined in the Oxford Dictionary of English [1], personalized medicine is "a type of medical care in which treatment is customized for an individual patient". In this sense, we are simply referring to the basic normal medical practice since Hippocrates: we cure a patient, not a population. Within this general statement, a first step to better treat an individual patient (personalization) was (and is) to tailor the treatment according to challenge tests, such as steroid administration after a corticotropin test in septic patients [2] or volume replacement after a fluid challenge [3] or the positive end-expiratory pressure (PEEP) setting after a recruitability assessment [4]. A further step towards the personalized medicine could be the definition of patient clusters or subgroups which better reflect pathophysiological differences and treatment options [5]. The ideal final step should be to customize the medical treatment according to the individual molecular/genetic setup ("precision medicine"). Therefore, in general, "personalized" medicine attempts to better define the patients' characteristics through progressively smaller subgroups, down to the level of the individual genome. Ideally, at the asymptote of this process, each patient will receive a therapy unique to him, with maximal efficacy and minimal side effects. In other words, with the ultimate personalized medicine, the problems due to population heterogeneity will not exist anymore.

The large RCTs are instead not a particular approach to medicine but are just experiments. Mostly, they are designed to find whether a given treatment provides benefits compared to another one. To fully understand the essence of these experiments, however, a few considerations are needed. First, a solid background, derived from experience, observations and physiology, is necessary. From this background, a hypothesis is generated. The RCT is the experiment designed to prove (or disprove) the hypothesis. If the hypothesis is confirmed, the theory is valid; if it is rejected, the theory is wrong. Therefore, the essence of the RCTs is to provide "unquestionable" evidence that a given theory is valid. This occurs if the theory generates a treatment hypothesis which is proved beneficial.

If these are the essences of the personalized medicine and of the RCTs, it is quite clear that, in theory, they are complementary and equally necessary, as summarized in Fig. 1. As shown, the progressive increase in "personalization" allows the defining of more specific groups and subgroups of patients for whom a given treatment, finally, is proved to be beneficial. The asymptote of this process will be—in an ideal world—a degree of personalization so high as to concern a single individual with a therapy unique to him.

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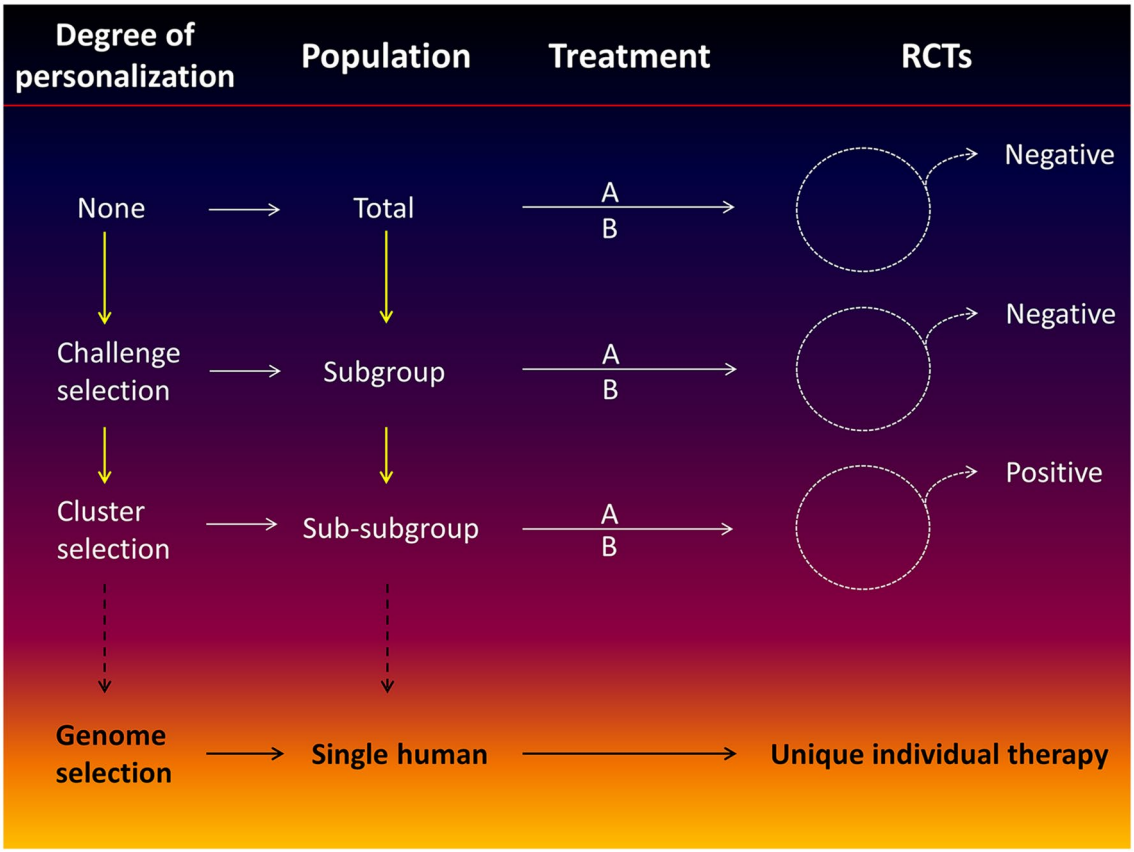

Fig. 1 Increasing the degree of personalization (none, challenge test, cluster definition, genome analysis) allows the progressive decreasing of the heterogeneity of the sample. Accordingly, the chance of success in testing a given treatment in a selected population increases. At present, most of the trials are conducted at a degree of personalization equal to "none". The asymptote of the process of personalized medicine (precision medicine) will ideally be a unique therapy for a single patient, through genome analysis

All this in theory; but what happens in our real life? Most of the treatments tested through RCTs have been performed in a general population of critically ill patients, presenting not with the disease but with a syndrome. The two main paradigms are sepsis and the acute respiratory distress syndrome (ARDS). The theory behind most of the RCTs applied to septic populations is that the sepsis syndrome is caused by a disproportionate/dysregulated inflammatory response of the host. This theory generated the hypothesis that the control of the inflammatory reaction may be of benefit. Accordingly, hundreds of anti-inflammatory treatments (corticosteroids, cytokine antagonists, receptor inhibitors, statins, etc.) have been tested in the last 30 years. All the trials were negative, disproving the hypothesis. The obvious conclusion is that the theory of disproportionate inflammatory response, if applied to the total septic population, is wrong.

Observations, experience and physiological background have told us that an imbalance between oxygen supply and consumption could lead, with time, to multi-organ dysfunction/failure. The hypothesis generated from this theory is that a proper and early correction of the imbalance, indicated by a normalization of the mixed venous saturation, should be of benefit. Actually, the hypothesis was proved right in patients in whom the imbalance was present [6]. However, when applied in RCTs on total septic populations, where the imbalance was not present in most of the patients, no benefit could be demonstrated [7–9]. Unfortunately, in most of the studies carried out in critically ill patients, the degree of personalization was "none" [10]. Further steps are necessary.

The bases of some degree of personalization in critically ill patients are undoubtedly already present. This is particularly true, referring to Fig. 1, for a degree of personalization defined by the response to a challenge test. As an example, there have been several suggestions that the value of PEEP during ARDS should be tailored according to the severity of the syndrome. Most of the "challenge" studies were physiological and identified subgroups of

patients for which a given treatment could be of benefit. Unfortunately, even this first step of the personalization did not translate into RCTs.

Genome-wide association studies (GWAS), in general, try to find the association between outcome (or other phenomena, such as response to drugs) and specific variants at the genomic level. If associations are found, it is possible either to better personalize the treatment or to identify potential novel targets for therapy, prevention or development of biomarkers for risk stratification. While the GWAS approach is increasingly used in oncology [11, 12], in critical care it is still in its infancy and primarily confined to sepsis research. In sepsis due to pneumonia, Rautanen and colleagues identified a strong association between common variants in the *FER* gene and reduced risk of death [13]. Christaki and Giamarellos-Bourboulis recently reviewed the issue, concluding that a more personalized approach based on genomics will be possible in the next decade [14]. Similar conclusions were reached by Pinheiro da Silva and Cerquiera César Machado, discussing the actual status of personalized medicine for sepsis [15].

In conclusion, both personalized medicine and RCTs are, in theory, beautiful instruments for increasing our knowledge. As for which instrument, however, the results will depend on how they are used and integrated. At present, there is a very large space for improvement in the personalization of treatment, even without genomics, as the basis for a more meaningful use of RCTs.

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EDITORIAL

Improved survival in critically ill patients: are large RCTs more useful than personalized medicine? Yes

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Introduction

The daily practice of critical care medicine is both personalized and protocolized. For example, in a 24-year-old with severe ARDS, low tidal volume ventilation with permissive hypercapnia would be applied, but not if severe traumatic brain injury and marked intracranial hypertension were also present. In this way, treatment is personalized. In contrast, based on the findings of a large randomized controlled trial (RCT) [1], in all ICU patients with hyperglycemia, a target of between 8 and 10 mmol/L (144–180 mg/dL) might be prescribed irrespective of other clinical circumstances. In this way, treatment is RCT-based and protocolized.

Such differences are often seen to represent an ideological conflict. This is not the case. All medicine is personalized by definition: doctors and nurses treat individuals, not populations. What is controversial is the usefulness of applying RCT findings at an individual and population level compared with making decisions based on mentorship, experience, and physiological reasoning. This controversy invites reflection on some key aspects of personalized versus large RCT-based medicine.

Personalized medicine is delivered on the basis of the interpretation and integration of many forms of evidence. This is inevitable as each patient and each situation is different, dynamic, complex, and the prism through which all previous knowledge must be interpreted and applied. In this way, personalized medicine and medicine based on large randomized controlled trials are complementary. However, personalized treatment cannot advance the field of modern medicine at the population or the individual level because it does not provide reproducibility, and because, in a single patient, outside of the obvious, clinicians cannot really ever know whether their actions help or harm the patient or are irrelevant.

All clinicians are attracted by the belief that their actions are important or even life-saving. However, individual cases do not provide robust, unbiased information to guide other clinicians under similar circumstances. For example, personalized medicine has previously advocated the widespread application of arsenic, leeches, blood-letting, lobotomy, and enemas. In contrast, large RCTs have identified that many modern previously accepted treatments [10–13] adversely affect patient outcomes. This makes it possible for such treatments to be discarded and for patient care to be made safer.

Critical care physicians respond to physiological changes with multiple interventions and see the rapid modifications delivered by such interventions. They are highly likely to have a biased view of the impact of their interventions, both because of the immediacy of physiological changes that occur in critically ill patients and because they are generally both the initiator and the judge of the physiological value of these interventions. Such physiological "success" is seductive by analogy because, in extreme situations of impending death, it can be clearly life-saving. However, outside of such extreme situations, physiological success has been repeatedly shown to be dissociated from clinical success (Fig. 1). Moreover, although clinicians give importance to increasing cardiac output, as shown in the 1990s by their commitment to supranormal oxygen delivery [2] and more recently to early goal-directed therapy [3], patients care little about that. They care instead about

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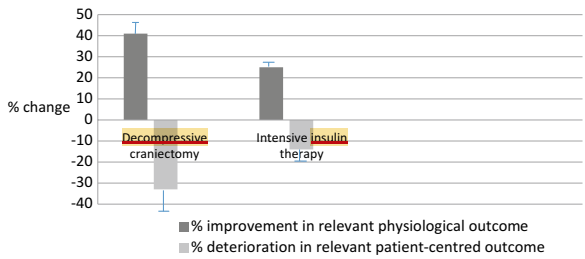

Fig. 1 Changes in physiological status toward normal and associated changes in patient outcomes as shown in large randomized controlled trials of decompressive craniectomy in diffuse traumatic brain injury and intensive insulin therapy. The positive change in physiologically relevant outcome represents the significant percentage improvement in intracranial pressure [13] and glycaemia [1] toward the normal value. The negative change in relevant outcome represents the significant percentage increase in the primary patient-centered trial outcomes of neurological disability [13] and mortality [1] seen in association with such physiological improvement

being pain- and discomfort-free, getting extubated, leaving the ICU and hospital alive, and returning to the same or even better function than before their illness. These patient-centered goals are crucial to judging the usefulness of a particular kind of approach because the effect of interventions on 'patient-centered' outcomes can only be answered by appropriately powered RCTs and cannot be determined by inductive physiological reasoning and a 'personalized' approach.

Why personalized medicine cannot answer patient-centered questions

Outside of the obvious, personalized medicine is a tautological pathway of care: if clinicians apply a particular intervention and the patient "gets better" (typically defined by physiological changes), they will then believe this is because of their actions (but cannot prove this is true). If the patient gets worse, they will believe it is despite their enlightened actions (but cannot prove this is true). This approach cannot determine whether a given treatment delivers patient-centered improvements in outcome. It is personalized medicine, but logically and paradoxically *personalized to the clinician, not the patient*. Personalizing hospitals and doctors might be the only way personalized medicine can improve patient outcomes [4, 5] and yet, paradoxically, is never advocated by its protagonists. Given the divergent behavior (practice variation) of individual clinicians in equivalent situations, personalized medicine is logically indefensible: clinicians applying their divergent "right treatment" cannot all be right. Such clinicians often cannot even agree on why patients die [6]. Logically, some, maybe many, and perhaps all must be wrong. Thus, personalized medicine represents a form of "random behavior within boundaries". The words 'random' and 'boundaries' indicate that decisions are profoundly affected by chance because they change unpredictably from doctor to doctor and hospital to hospital but do so within certain boundaries. This is because certain interventions (e.g., the administration of certain drugs or surgical procedures) are either prohibited by law or not undertaken because of training, education or peer review.

Faced with such criticisms, the antagonists of large RCTs regularly point out some of their limitations: the need for large sample size, long study duration, lack of power to evaluate plausible effects, inability to have sufficiently large subgroups, heterogeneity of patients enrolled, variability of accompanying treatment in different ICUs and high cost. However, trial technology is rapidly evolving to address such shortcomings [7, 8], and the cost of random (highly variable and chaotic) medicine is much greater than that of randomized medicine.

Despite their shortcomings, there is currently nothing more useful to drive practice change and improve patient outcomes than large RCTs. As mortality continues to decrease, the differences between treatments for which uncertainty of effectiveness exists (equipoise) become smaller. Thus, the number needed to treat (NNT) to detect them is increasing. Yet, these treatment effects matter dramatically at a population level. Even a NNT of 1 in 50 or 1 in a 100 for a ubiquitous and cheap ICU treatment has profound public health significance [9, 10] if applied globally and may save 200,000 lives/year [11]. Several toxic treatments have only been identified through large RCTs [12–15]. Yet, bedside clinicians could never perceive such an effect. They can only observe differences in blood pressure, or cardiac output, or in other physiological variables. They cannot answer the question of whether an intervention to change physiological parameters achieves better patient-centered outcomes. Only large RCTs can help address such questions. The task of modern critical care doctors should simply be to facilitate more widespread inclusion of RCTs into every aspect of their daily practice and to make it easier to conduct RCTs that are powered to detect small treatment effects and evaluate such effects in subgroups. Only then can we apply a kind of personalized medicine that is evidence-based rather than eminence-based.

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