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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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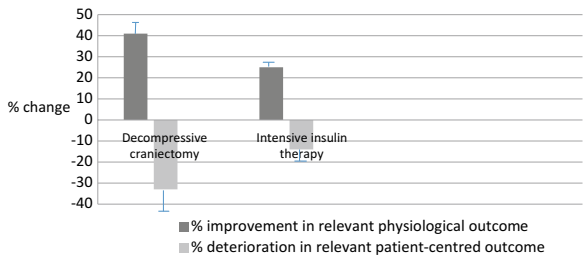

Fig. 1 Changes in physiological status toward normal and associated changes in patient outcomes as shown in large randomized controlled trials of decompressive craniectomy in diffuse traumatic brain injury and intensive insulin therapy. The positive change in physiologically relevant outcome represents 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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Compliance with ethical standards

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Conflicts of interest
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