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EDITORIAL

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Mortality is the only relevant outcome in ARDS: no

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Introduction

The design of a prospective clinical trial requires careful consideration of outcomes to be targeted. Traditionally, mortality has been the most relevant and coveted outcome for prospective clinical trials in acute respiratory distress syndrome (ARDS). However, recently the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), ARDS Network has developed the NHLBI-funded Prevention and Treatment of Acute Lung Injury (PETAL) Network. This shift reflects the sentiment that many experts have regarding the future of ARDS outcomes research. Specifically, the notion that mortality should be the preferred outcome for ARDS trials is no longer a valid argument. This contribution to the editorial debate presents reasons why other outcomes besides mortality are relevant to the future design of ARDS trials.

ARDS survivors have substantial morbidities

Herridge and colleagues published an important paper in 2003, which described the difficulties that ARDS survivors had with regard to function and quality of life [1]. This young cohort (median age 45 years) was remarkably dysfunctional, particularly with regard to physical function assessments [2]. Less than half were able to return to work. A follow-up report by the same group 5 years after ARDS showed that this cohort continued to have severe physical limitations, suggesting that such problems are likely permanent. A recent longitudinal trial of 203 ARDS survivors from 12 hospitals participating in ARDS Network randomized trials reported similar findings [3]. Previous studies have shown clearly that survival without a level of physical or cognitive function that is similar to pre-illness level is not desirable. Indeed, patients may prefer death to living with substantial physical and/or mental dysfunction following serious illness [4, 5]. Since ARDS survival has improved substantially over the last 15 years [6], it is clear that many more patients will be dealing with long-term complications related to ARDS.

ARDS survival is improving so that targeting mortality as the only relevant outcome is no longer practical

There are several prospective trials in ARDS that have shown a survival benefit. These include the Amato et al. [7] protective ventilation strategy, the ARMA low tidal volume study [8], the ACURASYS neuromuscular blockade trial [9], and the PROSEVA prone positioning study [10] (Talmor et al. [11] did not show a survivor benefit if one adheres to the traditional $P < 0.05$ statistical cutoff). However, as survival continues to improve, the mortality target will become progressively more difficult to hit. Furthermore, while mortality may seem to be an utterly objective endpoint at first glance, there are important subjective factors that actually may affect this outcome. First, the timing of mortality measurement is

critical. Previous outcomes studies have measured ICU mortality, hospital mortality, 28-day mortality, 60-day mortality, 90-day mortality, 6-month mortality, and 12-month mortality. How is a discharge to hospice care on day 33 recorded? How do geographic locations with widespread availability of long-term acute care hospitals (LTACs) compare to places that do not have such options? For example, LTACs are relatively common in the USA, but not in European countries. Such variables may impact decisions about treatment options or goals of care. Certainly, mortality outcomes are extremely important; but to suggest that they cannot be subject to extrinsic variables that can influence results is not accurate.

There are valid, existing outcomes other than mortality

There are many outcomes in critical care research that are of interest to scientists and clinicians. Clearly, the definitions of these outcomes are not uniform [12, 13]. This is perhaps most evident in the recent move away from the endpoint called "duration of mechanical ventilation" (which can be shortened by death) to the endpoint called "ventilator-free days". Schoenfeld and Bernard first suggested this change for the ARDSNet in 2002 [14]. It stands to reason that a similar approach to other traditional endpoints (e.g., ICU-free days, hospital-free days) may be worth considering, though, to date, such endpoints have not received widespread use. The fact that there is not a uniform definition of non-mortality endpoints does not invalidate their values. Every endpoint has limitations (see discussion of mortality above); accordingly, it is incumbent upon both researchers and readers of the literature to acknowledge such variations. The call for a more consistent approach to defining outcomes in ARDS research (indeed, all of critical care research) is a welcome change [15], though such changes may be difficult to implement.

There are also endpoints that have only recently been recognized as worthy of attention. For example, ICU delirium is a well-recognized outcome that portends a poor prognosis [16]. Recent work has identified ICU delirium to be associated with long-term cognitive dysfunction [17]. Such relatively new information must be recognized when outcomes are being considered.

Conclusions

The management of ARDS is changing. Evidence-based strategies continue to demonstrate improved outcomes and mortality continues to fall. The prospect of more ARDS survivors requires a change in the traditional focus of mortality as the primary outcome of interest. While mortality certainly will remain an important outcome, it should not be the only relevant one.

Conflicts of interest None.

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