The Future of Critical Care Lies in Quality Improvement and Education

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The past several decades have witnessed the steady growth of large, multicenter randomized controlled trials (RCTs) in critical care, designed to answer the important questions that challenge us in daily clinical practice. Unfortunately, these major RCTs have failed to deliver on this promise, leaving our field a landscape littered with negative and contradictory evidence (Table 1) (1). Yet, at the same time, outcomes of critical illness have been steadily improving in many settings (2–4). The goal of this perspective is to discuss why this has occurred, and to describe what we believe is a rational path forward as we look to further improve the care we provide to our patients. The available evidence argues that investments in quality improvement and education offer the best next steps to minimize diagnostic error, therapeutic harm, and improve the value and outcomes of care delivered in the intensive care unit (ICU). Prioritizing these efforts now will create a more efficient critical care delivery platform, provide immediate benefits for our patients, and build a strong foundation that will enable future RCTs to more effectively advance our practice.

Poor Return on Investment from RCTs in Critical Care

The past 30 years have taught us that conducting high-quality critical care RCTs is difficult, to the point that some thought leaders have suggested abandoning this practice altogether (5). Some would argue the reason for these failures lies in our lack of understanding of the underlying pathophysiology in the diseases we combat, which limits our ability to develop effective, innovative, and targeted treatments. Our literature is rife with examples of this, including trials examining the use of statins and vitamins in sepsis and acute respiratory distress syndrome (ARDS) (6, 7).

Others might blame the heterogeneity of the patient populations we study, clustered by poorly defined, syndromic conditions with wide variations of age, genetics, comorbidities, stage and severity of illness. The subsequent noise makes identification of true research signals challenging and leads to underpowered studies with conflicting results, as demonstrated in Table 1. The increasing use of novel, pragmatic clinical trial designs using predictive and prognostic enrichment enrollment strategies are a rational choice to address this concern, and have already been successfully applied to cancer research (8, 9).

Expert clinicians have always tailored clinical care according to physiologic, psychological, and social characteristics of individual patients, and recent years have seen a growing interest in precision medicine. But precision medicine in its current form is focused on "big data," including genomics, proteomics, and granular electronic health record (EHR) data sets. One glance at the dizzying array of potential genetic risk factors or cluttered EHR data elements in the medically complex ICU patient tells us these tools are far from ready for clinical use (10). Precision medicine, big data, and novel artificial intelligence algorithms in their current forms risk creating additional complexity,

confusion, and potential harm by distracting clinicians from the well-established best practices that make the greatest difference for our patients.

Still others would argue that RCTs have examined the wrong outcomes altogether. Patients at the extremes of disease severity are likely to survive or die regardless of the intervention they receive, and mortality falls short of measuring more meaningful, patient-centered outcomes (i.e., quality of life, quality of death, and quality of relationships) (11). The critical care research community has made meaningful progress in defining better patient-centered, core outcome measures in recent years, but consistent use of the most appropriate outcome measures in our prospective RCTs remains a clear area for improvement (12, 13).

We would humbly suggest that variations in care quality are perhaps the greatest impediment to our progress, and an important barrier to conducting high-quality RCTs. In theory, subject stratification by center in large, multicenter, randomized trials should control for these variations. In reality,

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Table 1. The challenging landscape of critical care randomized controlled trials

Topic	Seminal Randomized Study	Subsequent Studies	Current Practice
Intensive insulin therapy	Tight glucose control (80–110 mg/dL) decreases ICU mortality (57).	Tight glycemic control offers no benefit, increases mortality among critically ill adults (58). Intensive insulin therapy in medical ICU patients does not significantly reduce mortality (59).	Glycemic control has substantially loosened over the past several decades, largely because of our inability to effectively deliver tight glycemic control without an unacceptable incidence of hypoglycemic episodes.
Recombinant human activated protein C	Activated protein C significantly reduces mortality, especially in patients with sepsis with an APACHE score of $\geqslant$25 (60). Activated protein C significantly reduces 28-d mortality in patients with severe sepsis (61).	Activated protein C does not reduce 28- and 90-d mortality in patients with septic shock (62). Activated protein C offers no benefit in patients with sepsis at low risk of death (APACHE $<$ 25) (63, 64). Activated protein C offers no benefit in children with severe sepsis (65).	These trials have been critiqued extensively for the heterogeneity and differences in their study populations and the use of APACHE score for subset stratification.
EGDT in the treatment of severe sepsis and septic shock	EGDT improves in-hospital mortality, illness severity, 28- and 60-d mortality in patients with severe sepsis and septic shock (66).	A trio of trials do not support the systematic use of EGDT for all patients with septic shock or its inclusion in the Surviving Sepsis Campaign guidelines. EGDT in comparison with usual care or less-aggressive protocols does not improve survival (67–69). Protocol-based resuscitation of patients in whom septic shock was diagnosed in the Emergency Department did not improve outcomes (67). In critically ill patients presenting to the Emergency Department with early septic shock, EGDT did not reduce all-cause mortality at 90 d (68). Following a strict EGDT protocol did not improve outcome (69).	Early fluids, vasopressors, and antibiotics are clearly the proven benefits of the EGDT protocol. There is no clear benefit from early central line placement, RBC transfusion, or dobutamine.
Erythropoietin for critical illness anemia	In critically ill patients, weekly administration of 40,000 units of recombinant human erythropoietin reduces RBC transfusion requirements and increases hemoglobin (70).	The use of epoetin alfa does not decrease RBC transfusion requirements in critically ill patients and may increase the risk of thrombotic events (71).	A process of reduced phlebotomy (Choosing Wisely) is more effective at preventing critical illness anemia than erythropoietin therapy.
Low-dose corticosteroids for septic shock with relative adrenal insufficiency	Among patients with septic shock and relative adrenal insufficiency, administration of corticosteroids reduces 28-d mortality (72).	Hydrocortisone does not improve survival in patients with septic shock (73). In mechanically ventilated patients with septic shock, low-dose hydrocortisone administered for up to 7 d does not reduce 90-d mortality (74).	No clear consensus despite multiple prospective randomized trials and a recent evidence-based guideline
ECMO studies for ARDS	ECMO significantly increases survival without disability at 6 mo among adult patients with severe but potentially reversible respiratory failure compared with conventional management (75).	ECMO for severe ARDS showed no significant benefit of 60-d mortality in comparison with conventional mechanical ventilation (76).	Use of ECMO—and its associated healthcare costs—continues to escalate, despite limited and conflicting data regarding its efficacy.

(Continued)

Table 1. (*Continued*)

Topic	Seminal Randomized Study	Subsequent Studies	Current Practice
Hypothermia in cardiac arrest	Mild therapeutic hypothermia improves neurologic outcome after cardiac arrest. Therapeutic hypothermia increases survival and the rate of favorable neurologic outcome in patients after resuscitation from cardiac arrest (77, 78).	There is no benefit of more aggressive targeted temperature management in unconscious patients after cardiac arrest as compared with 36°C (79).	Use of mild hypothermia after pulseless ventricular arrhythmias is now common practice, but application to other cardiac arrest populations and neurologic injuries remains controversial.
β-Agonists for ARDS	Intravenous β-agonist salbutamol significantly reduced lung water at d 7. There was no significant difference in 28-d mortality compared with placebo (80).	Intravenous salbutamol administration early in the course of ARDS was poorly tolerated, is unlikely to be beneficial, and could worsen outcomes (81).	β-agonists are not commonly used for ARDS treatment.
Early hemodialysis in patients with AKI	Early RRT compared with delayed initiation of RRT in critically ill patients with AKI reduced 90-d mortality (82).	Early vs. delayed initiation of renal replacement therapy in critically ill patients with severe AKI did not show a significant difference in mortality (83).	The timing, dose, and method of RRT in critically ill patients remains controversial and highly dependent on individual practice
Recruitment maneuvers/PEEP	For patients with acute lung injury and ARDS, an "open-lung" ventilation strategy compared to a low-tidal-volume strategy has a similar survival (84). High-PEEP strategy improved lung function and reduced the duration of mechanical ventilation and the duration of organ failure. No difference in mortality compared with low-PEEP strategy was found (85).	An "open-lung" ventilation strategy resulted in increased mortality compared with low PEEP and increased mortality in patients with moderate-to-severe ARDS (86).	The best method to dose PEEP and measure its effects on lung distension remains controversial and subject to institutional practices.

Definition of abbreviations: AKI = acute kidney injury; APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; EGDT = early goal-directed therapy; ICU = intensive care unit; PEEP = positive end-expiratory pressure; RBC = red blood cell; RRT = renal replacement therapy.

unmeasured practice variation and inconsistent application of best—or even usual—practice may jeopardize the success of even the best-designed RCT and frustrate clinicians' ability to consistently and meaningfully apply positive results. A recent systematic review of 65 septic shock RCTs, for example, found a clinically relevant amount of heterogeneity in control group mortality rates that were only partly explained by differences in inclusion criteria, and only weakly associated with reported baseline study population characteristics (14).

A Long Road: Crossing the "Quality Chasm"

There is a more important and pressing need to focus on quality of care—our patients. The real "elephant in the ICU" is the persistence of an unacceptable rate of medical error, omission, and waste that continues to permeate and corrupt our practice environment and degrade the value of the care that we provide (15). In 1999, the Institute of Medicine released its report "To Err is Human" (16), and identified medical error as one of the leading causes of death in the United States. Since that time, the critical care community has worked side by side with other specialties to improve the quality of clinical practice. Unfortunately, the road to close the "quality chasm" has proven longer and more challenging than anticipated. Fifteen years after the original Institute of Medicine report, updates from the Health Foundation in the United Kingdom and the National Patient Safety Foundation in the United States have shown little change in quality and outcomes, despite considerable efforts by legislators, payers, and healthcare organizations (17–19).

A few ready examples demonstrate that the remaining problems are not small. Recognition of ventilator-associated lung injury toward the end of the last century has been a major breakthrough in our field. Yet, a recent large observational study designed to evaluate the incidence, management, and outcome of patients with ARDS in 50 countries found that only 60% of cases were recognized, and 35% received tidal volumes greater than 8 ml/kg predicted body weight (20). In another recent study performed at two U.S. hospitals, physicians initiated low tidal volume ventilation in only 7% of their eligible patients with ARDS. The same physicians reported strong support of low tidal volume use in this setting, and 87% believed that they correctly diagnosed ARDS within 12 hours of onset (21).

Medication errors occur with a median incidence of 106 per 1,000 patient days in adult ICUs, and preventable adverse drug events result in a significant increase in hospital length of stay (22–24). The Choosing Wisely Campaign, an initiative to eliminate expensive, wasteful practices that enjoys the support of all four major U.S. critical care societies, reports slow adoption and limited success (25). The

National Academy of Medicine has recently identified two key areas for improvement: diagnostic error and quality of dying (15, 26). Both of these issues are exponentially more prevalent in the ICU.

Research Priorities in Critical Care

RCTs and quality improvement efforts are not mutually exclusive. In an ideal world, they should be complementary. The practical realities of our current fiscal environment, however, require us to make choices. From fiscal year 2003 to 2017, the National Institutes of Health (NIH) lost 16.4% of its capacity to fund research because of budget cuts, sequestration, and inflationary losses. Despite recent increases in NIH appropriations, current inflation-adjusted dollars remain far below 2003 levels (27). Meanwhile, U.S. healthcare costs continue to rise, with far less than ideal healthcare outcomes when compared with similar developed countries (28).

The National Heart, Lung, and Blood Institute Center for Translation Research and Implementation Science (CRTIS) was created in 2014 to plan, foster, and support research to identify best strategies for successful integration of evidence-based interventions, with a focus on late-stage translational research and implementation science (29). Pragmatic trials have been the cornerstone of CTRIS efforts, and there has been an increase in hybrid RCTs that include an implementation arm. The Agency for Healthcare Research and Quality Patient-Centered Outcomes Research Institute also started supporting clinical effectiveness research in 2013, and now offers support for a mentored career development program for health systems researchers (30).

These efforts, although laudable, fall far short of the need. A pitiful 0.1% of U.S. annual healthcare expenditures are dedicated to health services research (31). Research and institutional spending priorities must be refocused to invest more heavily in quality improvement, dissemination, and implementation efforts. This strategy offers the greatest potential to benefit the most people in the shortest period of time—and that time for action is now.

A Time for Revolution

Physicist and philosopher Thomas Kuhn, best known for his invention of the concept of paradigm shift, tells us that "under normal conditions the research scientist is not an innovator but a solver of puzzles, and the puzzles upon which he concentrates are just those which he believes can be both stated and solved within the existing scientific tradition. Then there are revolutions. A new science arises out of one that has reached a dead end. Often a revolution has an interdisciplinary character—its central discoveries often come from people straying outside the normal bounds of their specialties" (32).

Kuhn's words are a call to arms for intensivists frustrated with large-scale RCTs powered for mortality and ill-suited to address the struggling critical care delivery environment in which we practice. We must stage a revolution, returning to the roots of scientific innovation and refocusing our efforts to transform our critical care practice into a highly reliable environment focused on truly meaningful, patient-centered outcomes before we can generate real progress in critical care research. We must recognize and openly acknowledge that although medical science has advanced exponentially over the past century, our understanding of best methods of clinical practice lags far behind.

Translating Quality Improvement Lessons: From Anesthesiology to Critical Care

Anesthesiology, a discipline closely related to critical care medicine, provides a rich example to contrast the benefits of quality and process improvement on meaningful patient outcomes. In the 1950s, anesthesia-related harm and death were a true public health concern (33). The introduction of safety standards, improved training, and integration of human factor considerations has caused anesthesia-related mortality to drop from 64 to 0.4 deaths per 100,000 cases over the past 50 years (34). The same period of time produced only one large randomized clinical trial in this discipline, which yielded negative results (35).

The practice of critical care is more complex than the operating room, but a similar system-based approach has already been used in our subspecialty with some success. Although aspirin administration had no effect in our ARDS prevention trial, implementation of a lung injury prevention checklist was associated with a 50% lower incidence of ARDS than anticipated based on lung injury prediction scores across participating hospitals (36). These findings confirmed previously described declines in hospital-acquired ARDS, for the most part due to a systematic approach to quality improvement in hospital care delivery (2). A recent prospective randomized trial failed to demonstrate a reduction in delirium duration with neuroleptic administration, but documented a significant reduction in its incidence after implementation of a standardized ABCDE bundle (E. W. Ely, M.D., written communication, November 2018) (37, 38). Similarly, a retrospective observational cohort study of more than 100,000 patients with sepsis from 171 ICUs in Australia and New Zealand demonstrated a decrease in mortality from 35% to 18% over 10 years due to improvements in supportive care, despite numerous RCTs over the same period that refuted the "proven" practices of early goal-directed therapy guided by continuous central venous oxygen saturation monitoring and use of recombinant activated protein C (3). With an estimated 30 million cases of sepsis worldwide each year, the potential benefits of a quality improvement intervention that impacts survival, quality of life, and quality of death by even a few percent in the global population are staggering (39).

The Way Forward

The first step toward meaningful progress is to regain our focus on compassionate, patient-centered clinical practice. We must reduce the administrative burden that dehumanizes modern critical care and reengage clinicians in empathetic, meaningful bedside support of our critically ill patients and their families. This is an ethical imperative and does not need examination in an RCT (40). Effective decision-making and care delivery in the complex ICU environment require a distributed cognitive network—a well-coordinated healthcare team working in a practice environment that is adapted to accommodate the limits of human cognition. Our group has a long history of

innovation in computerized detection of complex syndromes and human-centered graphical EHR displays that have been shown to reduce cognitive load and proactively, but sensibly, assist people in their tasks using principles of human factor engineering (41–43). This work to develop an "intelligent clinical environment" must continue, in order to free critical care teams from their computers and return them to their patients' bedsides.

Redoubling our efforts to support the ongoing international focus on patient safety and healthcare quality are the next steps on our journey to success. Society consensus statements argue that the combination of an effective organizational structure and processes of care, built on a backbone of quality improvement, is how our community will achieve high-quality critical care outcomes (44). Numerous efforts to date clearly demonstrate that this approach can support improvements in patient safety, decrease preventable death, shorten length of stay, and lower costs. Interprofessional ventilator liberation protocols, central line–associated bloodstream infection prevention strategies, and adherence to evidence-based best practices through checklist interventions or telemedicine oversight are just a few of these examples (45–48). The way forward starts with the application of lean technology to streamline care delivery processes and eliminate harmful and wasteful interventions (49), using the Choosing Wisely campaign and the Declaration of Vienna to provide a detailed road map on the critical care journey toward zero harm (50, 51). The intelligent clinical environment offers opportunities to accelerate this process as well, through real-time identification of patients with or at risk of receiving interventions that do not comply with evidence-based best practice and the delivery of accurate and timely feedback to their providers. These data can also be used to identify process failures and practice patterns that can inform and accelerate customized quality-improvement efforts targeted at specific system concerns.

Academic medical systems have an important role to play as centers of innovation, both to improve current care system practices and to train the next generation of healthcare leaders to champion future health systems research (52). From these efforts, the science of healthcare delivery has grown into an interdisciplinary field that demands interprofessional collaboration between individuals with expertise in informatics, systems engineering, human factors, quality improvement, and implementation science (53). Within healthcare, many of these disciplines require further integration and maturation and would benefit from robust engagement with community critical care centers and more deliberate attention to incentives and dissemination methods to speed their progress. Similarly, the critical care community has to strengthen its collaborations outside the ICU, given the profound impact events before and after ICU admission have on patient-centered outcomes. The current emphasis on pragmatic clinical trials and health services research must increase, and with it the funding support it receives. Reducing wasteful and inefficient care at the institutional level offers another important source of long-term support for these efforts.

If addressing human factors and developing a culture of safety, teamwork, communication, adequate staffing, and compassionate and patient-centered care are priorities, we must ensure that high-impact journals publish quality-improvement and health services research studies (21, 54). This responsibility for more effective dissemination must also be shared with academic researchers, however, who need to adopt a more systematic approach to the study of healthcare delivery through the discipline of implementation science. Only by using and advancing commonly accepted conceptual frameworks will these investigators speed both generalizability and the adoption of their results (53).

The third step on this journey is to partner with the medical education community to speed dissemination of practice innovations at the institutional level and beyond. Why medical educators? The Accreditation Council of Graduate Medical Education Clinical Learning Environment Review program now requires all accredited training programs to engage in robust patient safety and quality activities, with the goal of vertical alignment and integration with institutional quality and safety efforts to accelerate improvements in healthcare delivery (55). This provides an army of ready volunteers—clinician educators and trainees—who are expert at local practice processes and have demonstrated enthusiasm and ability to be willing champions and advance our cause.

The last critically important step along our pathway to excellence is the careful and consistent application of tools to better measure meaningful, patient-centered outcomes. Thirty years ago, Dunstan stated that "the success of intensive care should not be with statistics of survival only, [but should be measured by the] quality of lives preserved or restored, [the] quality of the dying in patients in whose best interest it is to die, and [the] quality of relationships involved" (56). In parallel with achieving the goals of safe, reliable, error-free clinical practice, we need to finish the work of refining and validating pragmatic tools to measure meaningful patient-centered outcomes that take into account patient preferences and prior physical, psychosocial, and cognitive functioning. Once established, the critical care community must actively partner with the Centers for Medicare and Medicaid Services and similar international bodies to incentivize their use, to better measure the performance of our healthcare systems. Finally, reliable clinical practice and meaningful outcome assessments are also necessary prerequisites to perform thoughtful experiments (RCTs) to determine causality and evaluate the effects of novel interventions. For example, randomization is needed for testing intriguing but unproven hypotheses, such as the physiologic effects of a combination of vitamin C, thiamine, and corticosteroids in sepsis (6).

Our healthcare system is in crisis, and our critical care delivery platform faces many challenges. Our patients, physicians, and healthcare teams need solutions quickly, and the time for action is now. Quality improvement and education will show us the best path to close the quality chasm, and pave a firm foundation for future pragmatic RCTs to provide the answers we need both for our practice and our patients. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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