Critical Care Evidence—New Directions

**During the past decades,** intensivists have learned how to care for critically ill patients and enable many to survive illnesses that previously would have been fatal. For example, the mortality rates associated with acute respiratory distress syndrome (ARDS) and with sepsis have both declined markedly during this interval. Improved short-term survival has resulted not only from better understanding of individual diseases but also (and perhaps more importantly) from optimizing intensive care unit (ICU) organization, standardizing best practices, and improving processes of care delivery.

Even though this decline in short-term mortality is a major achievement, it has spawned new challenges. Increasingly, patients who survive serious illness experience “chronic critical illness” that continues well beyond ICU discharge and often culminates in long-term morbidity and mortality. For example, about 3 of 5 sepsis survivors exhibit persistent cognitive decline or disability after hospital discharge. Prevention of such disability, with its attendant emotional and economic costs for patient, family, and society, has become a therapeutic priority. Earlier interventions to prevent the need for ICU admission and to avoid the adverse consequences of ICU care are beginning to receive justified emphasis. Achieving further improvements in survival and quality of life for patients with critical illness may require different approaches to understanding disease processes, conducting research, and developing new therapies.

In March 2014, a group of 24 experts in critical care research and practice held a meeting (the 2014 Brussels Round Table) at the 34th International Symposium on Intensive Care and Emergency Medicine (Brussels, Belgium). As described in this Viewpoint, the purpose of the round table was to share ideas regarding the potential for recent advances in biophysics and molecular medicine and for newly developed biological, analytical, and statistical approaches to advance the science and practice of critical care medicine. The need to personalize critical care according to physiologic responses to disease and treatment was emphasized in the context of the patient’s innate physiology, chronobiology, immunology, and attempts to adapt.

**Scientific Methods**

The scientific methods on which intensivists currently rely to gather evidence may not be sufficient to guide practice and improve outcomes. Population heterogeneity, complexity of interventions and disease, time dependence of disease characteristics, disrupted diurnal physiology and control mechanisms, variations in sensitivity to treatment, and adaptive biological responses complicate therapeutic endeavors. Although diversity of disease expression and requirements to personalize care are not unique to critical illnesses, these factors are especially relevant to the ICU environment and its clinical problems. Syndromes such as ARDS and sepsis are multifaceted entities, and clinical experience suggests that patients respond to them in different ways.

Strenuous, costly, and time-intensive attempts to define best therapy by randomized clinical trials (RCTs) that combine disparate patient phenotypes have occasionally provided definitive answers (eg, benefit from lower tidal volumes in patients with ARDS) but more often have yielded inconclusive results (eg, use of corticosteroids for ARDS or sepsis). Randomized clinical trials and meta-analyses often help define the roles of new management approaches and the limits of older ones. However, heterogeneity within and between RCTs and low rates of attempted replication often limit strength of evidence and relevance to the care of the individual patient; this may be compounded by slow adoption of new techniques to report RCTs in ways that allow individualized interpretation of heterogeneous treatment effects.

At present, an approach trying to normalize acute physiologic derangements often remains the basis for bedside decisions regarding immediate problems at hand. Identifying the clinical phenotypes that are more likely to benefit rather than be harmed from interventions such as prone positioning, muscle relaxation, or use of corticosteroids is crucial for safe and effective care. New methods—many derived from electronic monitoring, sample analysis, medical documentation, and data evaluation—are now available with the potential to help address these shortcomings.

**Highlighting the Challenges**

At the bedside, interactions among comorbidities and cointerventions limit the efficacy of management strategies and may predispose to complications arising from their use. For example, protracted deep sedation during mechanical ventilation may delay extubation and influence mortality. Likewise, effectiveness is limited by insufficient understanding of the mechanisms of chronic critical illness, imprecision of diagnosis, and failure to account for the dynamics of disease. Personalization of care presents both a major challenge and an opportunity for progress.

Acute disease evolves from onset through phases of recovery and healing. Innate repair processes are initiated soon after the initial insult occurs, but little is currently known about how critically ill patients attempt to recover or how interventions aid or inhibit recovery. Many interventions currently used for rescue, ie, the early aggressive life support needed to compensate for cardiopulmonary deterioration, have harmful potential if they are inappropriately applied or sustained. For example, a catecholamine-based resuscitation strategy focused on boosting cardiac index and systemic oxygen delivery actually produced worse outcomes among critically ill patients.

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Preclinical data, such as those derived from laboratory studies, are essential for pathophysiologic knowledge and trial design and may be the sole source of data when experimentation is required that cannot be conducted among patients or when addressing rare critical illness phenotypes. Animal models are based on experimentally induced disturbances that usually diverge from naturally occurring human illness, precluding the replication of disease dynamics and time course. This deficiency of relevant analogues is particularly evident for chronic critical illnesses. Development of appropriate experimental animal models or other preclinical research models should be considered a high priority of future research agendas.

Retargeting Research Objectives

In critical illness, as in other domains of medical care, better understanding is needed regarding the likely effects of treatments for the individual patient, identifying good candidates and appropriately timing pharmacologic and nonpharmacologic interventions. Methods for identifying, monitoring, and encouraging adaptive processes have substantially expanded in recent years, offering the promise of helping to promote time-sensitive, personalized medicine. For example, an individual patient with sepsis may require immune suppression or immune enhancement at different points during the illness, according to dynamic host responses. Immune monitoring and immune therapies directed toward these goals are available in many institutions. Predispositions to respond, resist, or encounter problems from certain therapies applied in critically ill patients could be identified by analyses of genetic polymorphisms. Examples include corticosteroids for asthma, medications for cardiovascular disease, and anti-infective agents.6 The evolving tool kit includes molecular assays ("omics") and gene mapping; mathematical modeling; precision phenotyping; biomarker profiling for disease identification, severity, and response to treatment; chronobiology; innovative trial design and intentional analysis for heterogeneous treatment effects; and novel analytical techniques. Computerized technologies have been leveraged to refine both scrutiny of clinical data and genetic and molecular analyses. Whatever the practice environment and resources, trend analysis and identification of physiologic patterns of response deserve renewed emphasis.

Clinical and Research Directions

Delivery of critical care and research into critical illness would benefit from more precisely identifying target populations—through biochemistry, genetic profiling, and better phenotype delineation. Approaches that lie closer to the fundamental biology, eg, proteomics, transcriptomics, and other biomarkers of condition and response, should be deployed at the bedside to detect and track the progress of critical illness. Opportunities to better assess needs and treatment effects within complex and changing physiology include functional monitoring of hemodynamic responses and adequacy of treatment and "big data" approaches. Research will need to characterize the various factors that contribute to chronic critical illness, such as innate disease, individual predisposition, and therapeutic interventions. Challenging current care delivery processes merits careful consideration when gathering the clinical evidence base. A strong mechanistic rationale is advisable prior to planning and executing an RCT. Investigators should consider novel methods for study design (eg, dynamic "adaptive" design for trials) and data analysis (eg, prespecified examination for heterogeneity of treatment effect). Cooperative approaches to data sharing and access to "open" databases are needed.

Conclusions

During the past few decades substantial progress has been made in the care of patients with critical illness. However, several key developments are necessary to further improve outcomes: (1) preclinical studies need realistic models of acute and chronic critical human illnesses; (2) retrospective and prospective observational studies should leverage rapidly evolving digital technology with big-data capability for analysis and patient monitoring; and (3) RCTs should consider novel designs and incorporate appropriate biomarkers to facilitate a personalized approach to evidence development and care delivery. These suggestions are expected to improve acute outcomes and long-term quality of life for critically ill patients and represent a starting point for setting new directions in critical care medicine and research.

ARTICLE INFORMATION

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