Toward an Integrated Research Agenda for Critical Illness in Aging

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Aging brings an increased predisposition to critical illness. Patients older than 65 years of age account for approximately half of all intensive care unit (ICU) admissions in the United States, a proportion that is expected to increase considerably with the aging of the population. Emerging research suggests that elderly survivors of intensive care suffer significant long-term sequelae, including accelerated age-related functional decline. Existing evidence-based interventions are frequently underused and their efficacy untested in older subjects. Improving ICU outcomes in the elderly will require not only better methods for translating sound science into improved ICU practice but also an enhanced understanding of the underlying molecular, physiological, and pathophysiological interactions of critical illness with the aging process itself. Yet, significant barriers to research for critical illness in aging exist. We review the state of knowledge and identify gaps in knowledge, research opportunities, and barriers to research, with the goal of promoting an integrated research agenda for critical illness in aging.

Keywords: critical care; elderly; aging

Patients older than 65 years of age account for approximately half of all intensive care unit (ICU) admissions in the United States, a proportion that is expected in increase considerably with the aging of the population. Aging brings an increased predisposition to critical illness, which is commonly explained by the lifelong accumulation of molecular and cellular damage leading to decreased physiologic reserves, leaving the individual less able to respond to stressors and to maintain homeostasis. In addition to the higher risk for developing critical illness, elderly survivors of intensive care may also suffer significant long-term sequelae, including accelerated age-related functional decline (1–3). It is not apparent which aspects of the intensive care experience are responsible for these long-term consequences. Yet it is evident that many evidence-based interventions, although frequently untested in older patients, remain underused in the ICU. Clearly, attempts at improving ICU outcomes in the elderly will require not only better methods for translating sound science into improved ICU practice but also an enhanced understanding of the interactions between the molecular, physiologic, and pathophysiologic mechanisms of critical illness and the physiologic changes associated with aging itself.

(*Received in original form April 30, 2009; accepted in final form June 16, 2010*)

Supported by the National Institute on Aging.

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Am J Respir Crit Care Med Vol 182. pp 995–1003, 2010
Originally Published in Press as DOI: 10.1164/rccm.200904-0630CP on June 17, 2010
Internet address: www.atsjournals.org

Herein, we review the state of knowledge and identify gaps in knowledge, research opportunities, and barriers to research for critical illness in aging, with the goal of promoting an integrated research agenda. Our work involved a three-step process: (*1*) input from National Institute on Aging (NIA) staff to a multiinstitute National Institutes of Health (NIH) program announcement, "Multidisciplinary Translational Research in Critical Care" (4); (*2*) an NIA-sponsored exploratory workshop, "Critical Illness and Critical Care in Older Patients: Translational Approaches," held in Bethesda, Maryland, on September 17 and 18, 2007. This workshop emphasized the aging component of the NIH program announcement, with input and discussion from recognized experts in geriatrics and critical care (Appendix 1); and (*3*) drafting of this narrative summary and review by the authors, followed by feedback and critique from both NIA staff and experts who participated in the workshop. Although this project arose from a workshop held in 2007, every attempt has been made to capture and incorporate key publications that appeared after the workshop was held. We summarize our findings as a series of specific clinical issues and areas of need, followed by select issues in critical care services research, and we conclude with a review of methodological tools for studying critical illness in aging.

DEFINITION OF ELDERLY AND IMPLICATIONS FOR RESEARCH

The definition of "elderly" has been debated extensively in the literature. With increasing longevity, we are now confronted with terms such as the "young old" and the "oldest old." Biologic age varies widely in relation to chronologic age, and there is a distinct need for methods to identify biologic age, not only at the patient level, but also at the organ-system level to better inform patient management and both basic and clinical study design.

However defined, aging brings with it an increased susceptibility to critical illness. For instance, severe sepsis is a quintessential disease of the aged (5). In some disease states, the response to therapeutic intervention is similar in the old and the young, highlighting the health services research needed to ensure sufficient human resources are available as the population ages. However, if the natural history of the disease process or response to therapy varies with age, then research should also focus on enhancing our understanding of disease mechanisms, how they vary with age, and the application of age-directed therapeutic interventions.

The exclusion of elderly subjects from many large-scale clinical trials and their underrepresentation in seminal observational studies has handicapped our ability to inform public policy and research agendas on appropriate management of older individuals. In many instances, clinicians are forced to rely on extrapolation from younger cohorts to guide care of their

elderly patients, as is done for many pediatric patients. Age is a predictor of physical function in adult survivors of critical illness (6), yet age alone is an inadequate predictor of long-term survival or quality of life (7, 8). Unfortunately, commonly used prognostic models are not calibrated for use in the very old and do not address long-term survival or functional outcomes (9).

Medical research will never help patients if clinicians do not adopt practices supported by the evidence (10). Too often treatments that seem likely to be beneficial remain underused. Medical knowledge has undergone explosive growth over the past decade. Yet, even with dissemination of systematic reviews and practice guidelines, it often takes years before evidence-based interventions are translated into routine clinical practice (11). The field of evidence-based quality improvement seeks to develop rigorous methods and decision-support tools for translating sound science into improved practice (12). Such tools could help to stabilize the process of medical care for the elderly, reducing unnecessary variation and inappropriate care while helping to control costs. Better use of existing evidence has the potential to produce greater benefit than could be expected from new drugs or medical breakthroughs, perhaps at less cost to society. In turn, this would set the stage for better observational and experimental studies in all patients, elderly or otherwise.

SPECIFIC CLINICAL ISSUES AND AREAS OF NEED

Cardiology

Cardiovascular disease is a common ICU admitting diagnosis and a frequent comorbid condition complicating the management of critical illnesses. Aging is often associated with decreases in maximal heart rate, ejection fraction, cardiac output, responsiveness to sympathetic stimulation, and vascular compliance. Age-related stiffening of the ventricles can result in diastolic dysfunction, leading to increased risk of pulmonary edema with fluid resuscitation. Elderly subjects are more likely to present with atypical symptoms of myocardial infarction and to have nondiagnostic electrocardiograms, whereas biomarkers of myocardial injury may become less specific with increasing age due to coincident renal insufficiency (13). Furthermore, anticoagulant and antiplatelet therapy are more frequently indicated with increasing age, which comes at the cost of higher risk of bleeding. These age-related changes highlight the importance of developing improved methods for monitoring critical physiologic parameters, particularly through noninvasive measures. The insights provided by the work of Pinsky, Teboul, and others have made identification of inadequate preload more accessible to clinicians, but remain largely ignored (14–16). This indicates the need to focus on tools for translation of research results to clinical practice as well as on pathophysiologic mechanisms. These and other methods could facilitate the early identification and treatment of diastolic heart failure, whereas more basic work could yield an improved understanding of cellular mechanisms of central arterial stiffness and impaired diastolic relaxation.

Mechanical Ventilation

The incidence of acute respiratory failure requiring mechanical ventilation increases 10-fold from age 55 to 85 years. Aging appears to increase the susceptibility to injurious mechanical ventilation (17). Lung-protective ventilation strategies remain underused (18). It is unclear whether lung-protective ventilation and other interventions to prevent pulmonary complications, such as ventilator-associated pneumonia, are as effective in older compared with younger patients. In acute lung injury/acute respiratory distress syndrome (ALI/ARDS), patients 70 years of age or older are twice as likely to die of ALI compared with their younger counterparts. Older survivors recover from respiratory failure and achieve spontaneous breathing at the same rate as younger patients but have greater difficulty being liberated from the ventilator and being discharged from the ICU (19). Among ALI/ARDS survivors, lung volume and spirometric measurements normalize by 6 months, but extrapulmonary functional disability, cognitive dysfunction, and emotional morbidity persist in many patients more than a year after mechanical ventilation (20, 21). A better understanding of the mechanisms leading to extrapulmonary complications of mechanical ventilation would help guide development and testing of potential interventions to minimize these complications. Recent work suggests that a "wake up and breathe" protocol that pairs daily interruption of sedatives with daily spontaneous breathing trials results in improved outcomes for mechanically ventilated patients (22). This approach, like lung-protective ventilation and other evidence-based interventions, requires evidence of efficacy in older populations and better methods of translation from clinical trials to widespread use in clinical practice.

Sedation and Analgesia

Excess sedative and analgesic use is associated with a variety of short- and long-term complications, including greater incidence of delirium, neuromuscular weakness, and prolonged mechanical ventilation, as well as increased ICU length of stay. Older adults may be more susceptible to these complications compared with younger adults. Daily interruption of sedation improves outcomes (23), yet remains underused. Better methods for assessing adequacy of sedation and analgesia, such as bispectral index (24) and other objective monitors, have the potential to reduce an overuse of these medications. Studies of newer sedatives acting through different central nervous system receptors, such as remifentanil (25) and dexmedetomidine (26, 27), may guide therapeutic choices to improve outcomes.

The Aging Immune System

By measures established in younger people, such as response to influenza vaccination, the immune system becomes less responsive with age, a concept referred to as immunosenescence. Yet, some aspects of the immune system actually become more active, or remodeled (28). For example, clonotypic T-cell receptor diversity decreases with aging, but there is also *de novo* expression of other types of receptors, many of which are natural killer cell–related and may endow novel functions to aging T cells. A more thorough understanding of immune-function changes with aging is needed to understand innate and adaptive immune-system responses to critical illness in older adults. This knowledge is important for tailoring effective immunomodulatory interventions and for determining optimal measures of immune-system function in critical care settings.

Nosocomial Infections

Older adults may be at greater risk for nosocomial infections and subsequent mortality compared with younger patients (29), although there is some evidence that older adults may be less likely to develop ventilator-associated pneumonia (30). Simple evidence-based interventions that can reduce rates of catheter-related bloodstream infections (31) and ventilator-associated pneumonia (32) remain underused in the ICU setting. Older adults placed in isolation may be at higher risk for delirium and functional impairments (33). More rapid methods of diagnosing or excluding bacterial infections have the potential to reduce isolation, antibiotic overuse, and emergence of multidrug-resistant organisms. Further research is necessary to understand

whether older adults are more likely to be colonized and subsequently infected by antimicrobial-resistant organisms than younger patients and whether local age-specific antibiograms may be useful in guiding empiric therapy of community- or hospital-acquired infections in older adults.

Sepsis

Both the incidence and absolute number of cases of severe sepsis increase exponentially with age, making severe sepsis a quintessential disease of the elderly (5). Furthermore, case fatality rates increase dramatically with increasing age. Drotrecogin alfa appears equally effective in old and young subjects, with similar bleeding risk (34), yet remains underused. The institution of sepsis care bundles was associated with lower hospital mortality for patients with severe sepsis independent of age, although regardless of intervention status, age remained a significant predictor of morality (35). Key additional issues in the effective management of sepsis in older adults are largely unexplored, including the role of corticosteroids, identification of essential components of early goal-directed therapy (36), the influence of age-related comorbidities, and the appropriateness of specific vasopressors to aging physiology. Despite extensive study, our understanding of the pathophysiology and molecular mechanisms of severe sepsis remains limited, hampering the development of effective drug treatments to prevent or treat sepsis-related organ failure.

Anemia and Transfusion Practices

Anemia is common among community-dwelling elders, not only due to nutritional deficiencies and chronic disease but also because of several mechanisms that are potentially unique to this age group. These include inflammatory dysregulation, blunting of the hypoxia/erythropoietin sensing mechanism, sarcopenia, alterations in stem cell physiology, decrease in sex steroids, and polypharmacy (37). Anemia in the very elderly ($\geqslant$85 yr) appears to be associated with an increased risk of death, independent of comorbidity (38). In the ICU, anemia is widespread and results in frequent transfusions. The anemia of critical illness is consistent with an underproduction of red blood cells (RBCs), although frequent blood withdrawal for testing purposes is also to blame. Erythropoietin levels are inappropriately low and the response to endogenous erythropoietin is blunted. Treatment with recombinant human erythropoietin, however, does not reduce the incidence of RBC transfusion and is associated with increased incidence of thrombotic events in the ICU setting (39). RBC transfusion or erythropoietin treatment may improve survival in select populations of critically ill patients (39, 40). Further research is needed to understand the pathophysiology of anemia of critical illness and to determine age-related thresholds for transfusion, optimal hemoglobin concentration, and whether transfusion is an important component of early goal-directed therapy (36).

Renal Function

Aging is associated with reduced glomerular filtration rate, impaired sodium and potassium handling, and diminished renal concentrating capacity. Older adults may be at higher risk for acute kidney injury (AKI), less likely to recover from AKI, and possibly more susceptible to the adverse effects of intermittent hemodialysis (41, 42). Models of severe sepsis using older animals appear to reproduce much of the AKI syndrome in humans; however, models of AKI recovery are lacking. Key unanswered issues include goal-directed therapy targeting renal function; optimal modality, dosing, and timing of renal replacement therapy; and valid biomarkers of renal function and injury, measured both continuously and/or at the bedside.

Fluid Management

Elderly ICU patients present unique fluid management challenges due to normal age-related changes and to the increased prevalence of both clinical and subclinical comorbidities. These include systolic and diastolic dysfunction, chronic renal insufficiency, endocrinopathies, hypoproteinemia, malnutrition, and reduced muscle mass, all of which result in increased susceptibility to fluid and electrolyte imbalances. Excessive intravenous fluid administration puts patients at risk for pulmonary edema, ileus, and delayed wound healing. Within the ICU, there is a strong correlation between fluid overload and subsequent mortality, morbidity, and length of stay (43). Improved noninvasive or minimally invasive methods of monitoring fluid status tied to protocols guiding hemodynamic management are needed, but will require validation to ensure that their use improves outcomes. Better understanding of the role of colloid osmotic pressure and extracellular antioxidants in fluid resuscitation of older adults might also direct therapeutic decisions.

Nutrition

Aging is associated with changes in body composition, including a decrease in muscle mass with a concomitant increase in total body fat. Furthermore, gastrointestinal changes with aging can affect nutrient intake and assimilation (44). The consequence of these changes is that standardized nutrient requirements for younger adults cannot be generalized to older adults. Serum albumin levels decline modestly with increasing age independent of underlying disease (44). Malnutrition may occur in up to 74% of hospitalized elderly patients (45) and contributes to immune dysfunction, poor wound healing, altered pharmacokinetics of many drugs, and increased mortality. Clearly defining caloric goals and specific nutritional needs for elderly patients, for example, through metabolic cart studies and a more comprehensive understanding of intermediary metabolism, should help guide approaches to enteral and parenteral nutrition. Lipid formulations for total parenteral nutrition in the United States are composed entirely of omega-6 fatty acids with potentially deleterious effects on inflammation and subsequent outcomes (46, 47). A variety of pharmaconutrients show potential as inexpensive therapeutic adjuncts, including omega-3 fatty acids (48), glutamine (49), arginine (50), antioxidants (51), and creatine, yet all of these require further evaluation in aging patients. Tight blood glucose control in critically ill patients was equally harmful in old and young patients, likely due to frequent episodes of severe hypoglycemia (52). As such, enhanced strategies for glucose control, including real-time glucose monitoring (53), have the potential to maximize clinical benefit of tight glucose control while minimizing risk of hypoglycemia.

Physical Function, Disability, and Rehabilitation

Sarcopenia is an aging-related condition characterized by loss of skeletal muscle mass and is associated with decreased strength, gait imbalance, falls, fractures, disability, and increased risk of hospitalization (54). Skeletal muscle loss is due in part to increasing catabolic signals, such as proinflammatory cytokines, and diminishing anabolic signals, such as growth hormone and testosterone. Strategies for decreasing or preventing muscle loss may include growth hormone secretagogues, such as ghrelin (55) and MK-0677 (56), localized expression of insulinlike growth factor-1 (57), inhibition of nuclear factor kappa B (58), angiotensin-converting enzyme inhibitors (59), and myostatin antagonism (60).

Muscle weakness and deconditioning are common in ICU survivors, yet there is a distinct lack of detailed data on physical, functional, and health-related quality of life outcomes in elderly

ICU survivors. Risk factors and pathophysiologic mechanisms underlying ICU-associated muscle weakness and deconditioning are not well understood but may include severity of illness, acute inflammation, exposure to corticosteroids and neuromuscular blockers, and prolonged bed rest (61). Elderly individuals appear to be particularly sensitive to the effects of bed rest. After 10 days of bed rest, healthy older adults had greater losses in lower extremity muscle mass and strength than after 28 days of bed rest in younger subjects (62, 63). Older muscle is less able to repair itself after prolonged unloading, in part due to loss of muscle satellite proliferative potential, which is reversed by the application of insulinlike growth factor-1 (64).

Early physical activity during acute illness may prevent weakness and promote earlier recovery of functional independence (65, 66), yet this intervention remains untested in randomized trials and it is unclear if early mobility gains will translate into sustained improvement in functional status. Other interventions complementing early activity, such as early nutrition, attention to blood glucose control (67), sedation interruption to facilitate exercise (68), minimizing the use of restraints or other devices that restrict movement, avoidance of neuromuscular blockers and high-dose steroids, and early tracheostomy (69), could provide additional benefit. More advanced possibilities exist, such as drugs to modulate the inflammatory response, anabolic hormones, and nutraceuticals. Insight may be gained by studying hibernating animals, which show little muscle and bone loss despite prolonged immobilization (70). Regardless of the chosen intervention, it will be important to select outcome measures that reflect functionality and return to independent living.

Critical Illness-associated Cognitive Dysfunction

Cognitive dysfunction (CD) is common in critically ill patients both during acute illness and after discharge. In the ICU, CD manifests as delirium, a form of acute organ dysfunction that is associated with increased mortality, length of stay, and cost. Chronically, CD manifests as difficulties with memory, attention, executive function, processing speed, spatial abilities, and general intelligence, which may persist long after ICU discharge. Older patients are particularly susceptible to both acute and chronic cognitive dysfunction, especially when there is preexisting dementia or mild cognitive impairment (71, 72). Yet even without baseline dementia, older adults have a greater likelihood of cognitive decline after hospitalization than those who were not hospitalized (73). Patients who develop delirium during their hospital stay subsequently have greater rate of decline on cognitive tests and increased likelihood of developing dementia (74), in what has been termed "ICU-accelerated dementia" (75).

Although there are clearly defined risk factors for critical illness–associated CD, there is limited understanding of the basic mechanisms of brain dysfunction, protection, and recovery in the critically ill. Animal models and biomarkers of CD are needed to better understand its pathogenesis and to identify potential targets for therapeutic intervention. Easy-to-use tools could help to rapidly screen subjects for subtle evidence of post-ICU CD, not only at hospital discharge but later via telephone or in ICU follow-up clinics. This, in turn, would facilitate identification of patients who could benefit from cognitive rehabilitation, which is commonly used in patients with stroke and anoxic or traumatic brain injury, but is untested in nonneurologic critical illness.

Mental Health

Psychiatric symptoms and disorders, including depression, anxiety, and post-traumatic stress disorder, affect 15 to 35% of ICU survivors (76) and present a distinct threat to long-term recovery from critical illness. Elders may be particularly vulnerable, due to concomitant medical illness, when they lack a supportive social network or if they live alone. Informal caregivers of ICU survivors, typically family members, also have an increased risk of psychiatric symptoms, with greatest risk among those caring for the oldest patients (77). The safety and efficacy of antidepressants in critically ill patients is unknown. Daily sedation interruption may reduce the occurrence of post-traumatic stress disorder (78), and self-help booklets provided during recovery may decrease symptoms of anxiety and depression (79). Understanding the causal pathways that lead from acute medical stress to mood disorders and neuropsychiatric conditions will allow more precise targeting of preventive interventions.

Patient-centered Care in Advanced Critical Illness

Despite similar overall hospitalization rates in England and the United States, there is considerably greater use of intensive care services at the end of life in the United States, especially among the elderly (80). Approximately one in four older Americans dies in the ICU, and most are unable to participate in decision making because of the severity of their underlying illness (81). There is substantial individual variability in older adults' preferences for care in the setting of advance illness (82). Older patients generally prefer less aggressive care than younger patients (83). Medicare beneficiaries prefer treatment focused on palliation rather than life extension (84). Even so, many older patients want cardiopulmonary resuscitation and care focused on life extension (83). Unfortunately, physicians are frequently unaware of patient preferences for end-of-life care (85). Patients who prepared advance directives received care that was strongly associated with their preferences, yet only two of three who lacked decision-making capability had advanced directives (86). Older age is associated with greater likelihood of being refused ICU admission, reduced treatment intensity in the ICU, and higher rates of decisions to withhold life-sustaining treatment. At times, such decisions are made without consideration of patient or family preferences and with misperceptions about quality of life or ability to benefit from care (83, 85, 87–89). Taken together, these findings highlight the need for better methods of eliciting patient preferences, fostering high-quality surrogate decision making, predicting postillness quality of life, and ensuring that treatment reflects an individualized understanding of the patient as a person.

Delivery of Critical Care

Early management of precipitating critical events may contribute to improved long-term outcomes. For critical illness that develops outside of the ICU, initial care could potentially be provided in the prehospital setting, such as in skilled nursing facilities. Further research is needed to explore the benefits, risks, and feasibility of providing critical care interventions in these settings. Organizational characteristics of ICUs are related to differences in treatment intensity and outcomes (90, 91). Clinicians and hospital leaders should consider the potential impact of ICU organizational characteristics on outcomes in elderly patients. Intensivist involvement is associated with lower mortality and reduced hospital length of stay (92). The demand for intensivists is expected to outpace supply, largely because of population aging, and directly threatens the ability to deliver efficient population-level critical care. Furthermore, because critical care settings are associated with high mortality, increasing demand, and highly variable outcomes, small improvements in care have the potential to yield large absolute mortality reductions, highlighting the importance of finding better methods for translating sound science into improved ICU practice.

METHODOLOGICAL TOOLS FOR STUDYING CRITICAL ILLNESS IN THE ELDERLY

Translational Approaches

Translational research involves the bidirectional flow of information between bench and bedside. The ability to build on clinical observations to ask additional questions at the molecular level, as well as to move basic research into clinical applications, is key to improving ICU care. Human translational approaches may help elucidate mechanistic interactions between aging processes and critical illness. However, more sophisticated experimental models of aging are needed, including animal models and *in vitro* studies of tissues from older humans. Current animal-based methods include the use of older animals in studies of mechanisms and management; the development and use of transgenic models of accelerated aging, such as telomerase knockouts, and the introduction of Western diets in animal models of aging.

Complex Systems

A complex system is an interdependent group of components that act together to form a unified whole not possible with any of the individual parts. Application of complex systems biology to critical illness is one potentially useful approach to understanding complex disease–disease and disease–aging interactions in critical illness. Such research studies might include interactions among renal, cardiovascular, and pulmonary systems through gene expression studies, signaling pathway characterization, or mathematical modeling. For example, complex systems analyses may identify ways in which inflammation and repair in the elderly differ from that in younger adults and how these differences impact the development and progression of acute organ failure. Other applications could include using measures of overall variation, frequency, and severity of disorder to determine prognosis, and using continuous multiorgan variability analysis for goal-directed therapeutic interventions (93).

Patient–clinician interactions can also be considered a complex system, with emergent properties that can frequently only be studied definitively in the clinical setting. Here the issue of effective translation tools, which enable different clinicians to reproduce decision-making, becomes an important experimental attribute. Such tools are needed to enable rigorous research of elderly subjects in the clinical setting.

Functional Genomics of Critical Illness

Functional genomics is the systematic evaluation of dynamic changes in gene function and products through computational biology and high-throughput techniques, such as microarray analyses. Potential applications of functional genomics to critical illness in older adults include understanding complex interactions among age-related changes in physiologic systems, examining unique patterns of gene expression in response to injury, improving disease diagnosis and prognostication, and identifying polymorphisms associated with individual response to, and toxicity of, drug therapy. A recent NIH symposium focused on the practical applications and limitations of these techniques in critical illness (94).

Biomarkers

Biomarkers are quantitative measures that permit diagnosis and assessment of disease processes and monitoring of responses to treatment. Biomarker development has lagged significantly behind therapeutic development. Reliable biomarkers of organ function and injury could increase the likelihood of therapeutic success when they are able to identify subtle dysfunction before permanent injury has occurred. Biomarkers may be particularly useful for monitoring progression of critical illness in older patients who may already have derangements of multiple physiological systems before a precipitating event. Also needed are prognostic biomarkers, such as polymorphisms in cytokine and other genes associated with altered risk of sepsis or death from sepsis (95). Finally, biomarkers may prove useful to stratify or subgroup patients for clinical trials and to individualize therapy. The Food and Drug Administration's Critical Path Initiative provides a framework for biomarker qualification for regulatory purposes (96).

Stem Cell Biology

Stem cell biology has received much attention for its potential applications to regenerative medicine, such as in burns, trauma, spinal cord injury, and diseases currently treated through solid organ transplantation. With aging, stem cell numbers may be reduced and their function and migratory ability impaired. Stem cell technology may be promising in replacement of impaired organ function from sepsis or in myocardial infarction, yet the role of this approach in older patients with critical illness remains unexplored.

Additional Considerations

Critical illness and aging often involve derangements in multiple organ systems, and statistical analyses of critical care interventions should account for interactions among multiple systems. Given high mortality rates in the ICU, deaths require careful statistical attention through analyses such as intention-to-treat, joint modeling, and multiple conditional outcomes. Outcomes of multicomponent (bundled) interventions are sometimes challenging to interpret because of difficulty in identifying the effective component(s), whereas factorial designs can efficiently reveal interactions among interventions, although such trials are often difficult to implement. As new discoveries and pathways are identified using complex systems analysis, functional genomics, and other emerging techniques, rigorous clinical trials will be necessary to demonstrate benefit of specific interventions. Furthermore, with the exponential increase in quantity and complexity of data available, it will be increasingly important to develop tools that enable clinicians to use this new information in a manner that will be reproducible, lead to more credible clinical research than currently possible, and enable translation of research into practice.

CONCLUSION

Improving outcomes of critical illness in the elderly will require not only better methods for translating sound science into improved ICU practice but also an enhanced understanding of the underlying molecular, physiological, and pathophysiological interactions of critical illness and aging processes. Significant gaps in knowledge and barriers to research of critical illness in aging exist, and specific clinical issues and areas of need present a myriad of potential research opportunities. Although a variety of methodological tools are available for studying critical illness in the elderly, many remain underused. Innovative approaches to research questions and broad collaborations to include state-of-the-art technology promise to enrich this important area of geriatric care.

Author Disclosure: E.B.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.E. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.N. received $10,001–$50,000 from the NIH/NIA for serving as a scientific advisor for anemia clinical trials and more than $100,001 from the NIH in sponsored grants for investigator-initiated clinical research. E.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. D.C.A. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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