Cognitive Functioning, Mental Health, and Quality of Life in ICU Survivors: An Overview

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KEYWORDS

- Cognitive impairments • Critical illness
- Critical care outcomes • Psychiatric disorders
- Quality of life

There has been increasing awareness of the fact that diseases, treatments, and events (such as surgery or the experience of critical care) often have significant and persistent consequences for cognitive and psychological functioning.[1] Progress in critical care has led to decreased mortality rates among individuals admitted to intensive care units (ICUs). However, for many survivors of critical illness, ICU hospitalization can lead to a life of significant limitations and obstacles, especially with regard to cognitive functioning. Although neurologic dysfunction is not as well studied in the critical care literature as it ought to be, current data suggest a high prevalence of neurologic disturbances in patients with critical illness admitted to medical/surgical (non-neurologic) ICUs.[2–4] Such disturbances can be severe and include encephalopathy and cognitive and psychiatric impairments. Important neurologic disturbances that are common during and after critical care are delirium and long-term cognitive impairments. Emerging research indicates that although these disorders are distinct, they are inextricably linked in critical care. **Fig. 1** shows possible relationships between premorbid state, critical illness, and outcomes. Recent investigations show that delirium is widely prevalent during critical illness and places patients at greater risk for development of cognitive impairment.[5] Further, long-term cognitive impairments may occur in more than half of all ICU survivors and are associated with poor functional outcomes.

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Crit Care Clin 25 (2009) 615–628
doi:10.1016/j.ccc.2009.04.005 **criticalcare.theclinics.com**
0749-0704/09/$ – see front matter

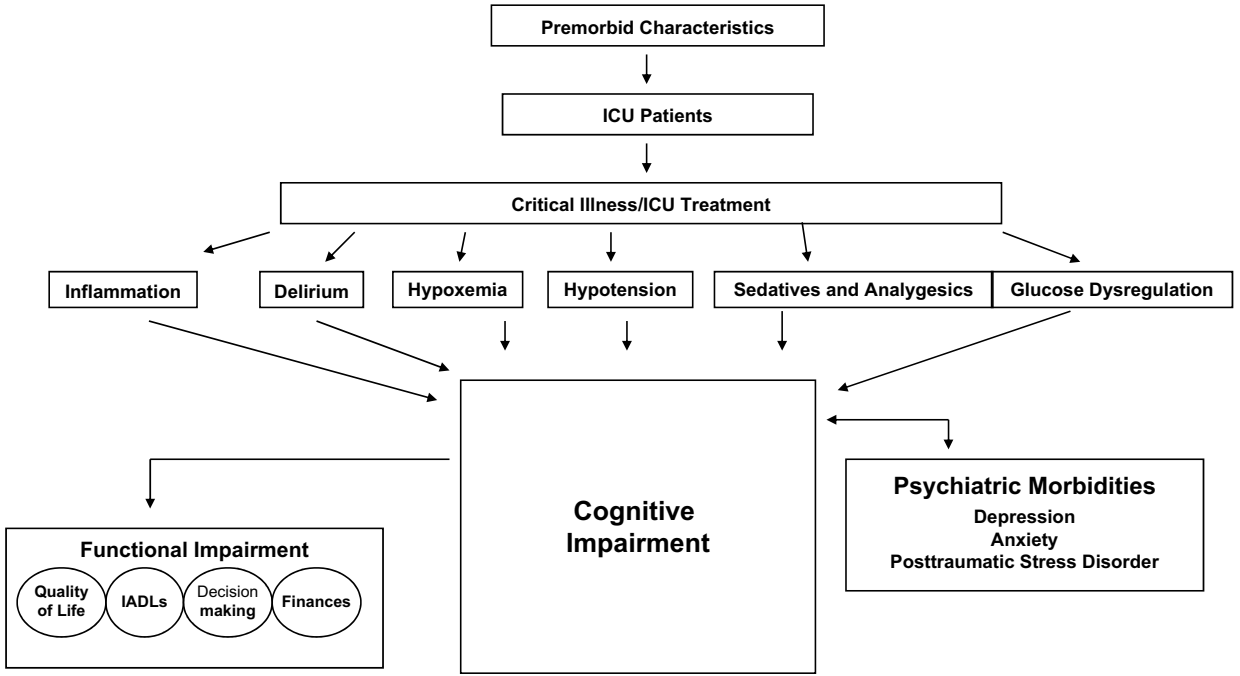

Fig. 1. Relationships between critical illness and outcomes.

DELIRIUM OR ACUTE COGNITIVE OUTCOMES IN ICU PATIENTS

Delirium is a neurobehavioral condition that occurs in a wide variety of health care settings, is associated with adverse outcomes, including death, and is the most common manifestation of acute brain dysfunction during critical illness.[6–8] It is a potentially toxic neuropsychiatric syndrome, characterized by a fluctuating course and pronounced inattention. It is highly prevalent among the hospitalized elderly, affecting between 15% and 20% of hospitalized medical patients,[9] 25% to 65% of surgical patients,[10,11] and as many as 80% of patients in ICU settings.[12] Although delirium was once considered benign, recent evidence has linked it with a variety of adverse outcomes, including prolonged hospitalization, poor surgical recovery, and increased morbidity and mortality.[13–16] Some researchers speculate that delirium may be a marker of subclinical dementia or cognitive impairment that might not otherwise develop for years or decades; indeed, data suggest that common pathogenic mechanisms might underlie development of cognitive impairments in delirium and dementia.[17]

Delirium is linked to poor cognitive outcomes in a variety of patient populations. A review by Maclullich and colleagues,[18] which looked at nine studies published after 2004 on the association between delirium and cognitive decline, documented a strong relationship between these two conditions. Their conclusions echoed those of Jackson and colleagues[19] in the 2004 review on the same topic, which focused on another nine investigations conducted since 2004. Together, these reviews represented a total of 18 investigations—most of them prospective cohort studies—from 1989 to 2008, with a combined total of nearly 4000 patients. These investigations almost uniformly demonstrated, with varying degrees of rigor and sophistication, that the emergence of delirium was a harbinger for greater, more severe, and more persistent neuropsychological decline. Although relevant research to date has focused on the link between delirium and global cognitive impairment, there is emerging evidence to suggest that delirium may be characterized by distinct anatomic patterns and processes.[20] Recent investigations employing sophisticated neuroimaging technologies have demonstrated that delirium results in significant cerebral hypoperfusion in several brain regions, including frontal, temporal, and subcortical regions.[21] Subcortical structures, which appear to mediate key elements of executive functioning, are particularly susceptible to even slight alterations in blood flow because of the small perforating vessels feeding these structures.[22] Evidence from clinical investigations suggests that executive dysfunction commonly develops secondary to reduced blood flow to vulnerable subcortical structures implicated in frontal-subcortical circuitry, even in the absence of frank ischemic injury.[23]

A variety of central nervous system insults, such as stroke and traumatic brain injury, can cause delirium and cognitive impairments, suggesting that widely distributed central nervous system abnormalities likely occur.[24] Neuroimaging data are lacking in critically ill patients with delirium or long-term cognitive impairments. One study found that neuropathologic abnormalities, including significant ventricular enlargement and generalized atrophy, occurred in elderly delirious patients compared with controls.[25] Focal lesions (infarcts and hemorrhage) were observed in frontal and parietal regions in these delirious patients.[25] A study of critically ill patients who underwent CT brain imaging for diminished level of consciousness, confusion, altered mental status, or prolonged delirium found that 61% had abnormalities on brain imaging, including generalized brain atrophy, ventricular enlargement, white matter lesions/hyperintensities, and cortical and subcortical lesions.[26] Although data are limited, future studies using increasingly sophisticated, hypothesis-driven brain imaging techniques

will help advance the understanding of the neurologic effects of delirium, its relationship to cognitive impairments after critical illness, and its treatment, while potentially elucidating neuroscientific mechanisms that are now unknown.

PREVALENCE OF COGNITIVE IMPAIRMENT IN ICU SURVIVORS

The terms *cognitive dysfunction* and *cognitive impairment* are often used synonymously, although *impairment* implies a greater degree of permanence in contrast to *dysfunction*, which refers to an acute condition that may change or improve. Recognizing this distinction, it is perhaps most appropriate to discuss ICU survivors in the context of cognitive impairment, because the neuropsychological deficits that characterize these individuals may improve with time, but tend to be permanent in most cases.[27] Among mechanically ventilated general medical ICU survivors, approximately a third or more demonstrate moderate to severe cognitive impairment 6 months after discharge.[28] Among cohorts composed of both medical and surgical ICU survivors, including those with specific conditions such as sepsis and acute respiratory distress syndrome (ARDS), rates of impairment vary widely in part because of assessment timing and methods.[2,4] Among specific populations, notably patients with ARDS, the prevalence of cognitive impairments is particularly high and persistent, with 46% of patients at 1 year[29] and 25% of patients at 6 years reporting ongoing difficulties.[30] Although highly prevalent, cognitive impairment demonstrated by ICU survivors is also often quite severe. For example, the aforementioned ARDS patients with cognitive sequelae all fell below the sixth percentile of the normal distribution of cognitive functioning, displaying marked neuropsychological deficits in wide-ranging areas, including on tasks requiring memory, executive functioning, and mental processing abilities. Impairment does not impact all domains equally, and deficits in some areas rebound more completely than others.

Significant questions exist related to the relationship between premorbid cognitive functioning and the development of subsequent cognitive impairment among ICU survivors.[27] Although many individuals are cognitively normal before the onset of hospitalization, others,particularly those with multiple medical comorbidities that may impact cognition, such as vascular disease, diabetes, chronic obstructive pulmonary disease, and HIV,may have preexisting cognitive impairments.[31,32] They may be particularly vulnerable to the neurologic effects of critical illness. One of the most provocative issues in this regard is whether individuals with preexisting forms of cognitive impairment, particularly conditions such as mild cognitive impairment (MCI) or Alzheimer disease, which are characterized by a natural history of decline, may worsen more rapidly than they otherwise would after neurologic insults such as those occurring during the ICU stay. Conditions such as Alzheimer disease and its common precursor, MCI, affect large numbers of elderly patients—individuals who increasingly undergo and survive intensive care treatment and major surgery and who may be at particular risk to experience potentially toxic syndromes such as delirium.

PERSISTENCE OF COGNITIVE IMPAIRMENTS

It seems that many ICU survivors experience some or marked improvement in cognitive functioning in the year after hospital discharge (those already in the process of cognitive decline at the time of their critical illness may improve relative to their levels of cognitive functioning at hospital discharge, only to return to a pattern of gradual or accelerated deterioration).[4] However, despite demonstrating a clear trajectory of improvement, many individuals continue to have persistent cognitive impairment with time, infrequently returning to their pre-ICU baseline levels. For example 70%

of ARDS survivors had cognitive impairments at hospital discharge, but 45% had cognitive impairments at 1 year. There was no improvement in the cognitive impairment rate from 1 to 2 years.[33] A retrospective cohort study of 46 ARDS survivors found 25% had cognitive impairments 6 years after ICU treatment; only 21 patients returned to full-time employment, and all patients with cognitive impairments were disabled.[30] A second study in 30 ARDS survivors had impaired memory, attention, concentration, executive dysfunction, and motor impairments when assessed from 1 to more than 6 years post-hospital discharge (mean 6.2 years).[34] These studies suggest that the cognitive impairments in ARDS survivors are persistent, affect employment, and for a subset of the ICU population are resistant to significant improvement.

It may be that the effects of ARDS on cognitive functioning are accelerated among patients with specific sorts of vulnerabilities, such as frail elderly, although this proposition has largely been unstudied among critically ill patients. Nevertheless, the idea that the effects of ARDS on cognitive function may be magnified among some individuals, such as geriatric patients with preexisting MCI or dementia, is compelling. Although data are lacking, it may be that some ICU survivors suffer from a clinically distinct condition that is referred to as ''ICU accelerated dementia.'' The phenomenon in which the rate of cognitive impairment increases after medical illness has been observed among other populations, including most notably in the well-known neuroepidemiologic investigation, the Cache County study, which studied progression of dementia in medically ill patients with early Alzheimer disease.[35]

MECHANISMS OF COGNITIVE IMPAIRMENTS

It has been widely recognized that the brain is an immunologically active organ and therefore is vulnerable to systemic inflammatory reactions such as those resulting from sepsis or septic shock, similar to the findings in severe systemic illness. The inflammatory responses are mediated by cytokines, nonantibody proteins that penetrate the blood-brain barrier directly or indirectly to modulate and influence brain activity and potentially alter neurotransmitter release. Studies have shown that increased levels of biologic markers of inflammation, including IL-6 and TNF-α, predict the development of cognitive impairments among older patients without acute illness.[36,37] However, as is true with most cognitive impairments, including the family of dementias, there is probably not a single uniform cause; instead, a number of more or less significant factors interact dynamically with premorbid and genetic variables, resulting in adverse outcomes. Mechanisms of cognitive impairment implicated in the development of brain injury among ICU survivors include hypoxemia,[29] hyperglycemia,[38] delirium duration,[5] and hypotension.[39]

The use of sedatives or analgesics is associated with poor cognitive outcomes in other populations,[40,41] although their role in the development of cognitive impairment after critical illness has been largely unstudied. However, they may be powerfully implicated in the relationship that has been demonstrated between delirium and the emergence of subsequent neuropsychological deficits.[5] That is, sedatives and analgesics, particularly benzodiazepines, contribute to the development of delirium, which in turn is associated with an increased risk for cognitive impairment. Although the specific nature of the relationship between sedatives or analgesics has yet to be fully studied in ICU cohorts and is yet to be elucidated, there are reasons to believe that certain medications or medication classes could contribute to adverse cognitive outcomes, particularly in vulnerable populations. For example, in a recent investigation by Pomara and colleagues,[42] healthy elderly subjects with the *APOE4* allele, a well-known genetic risk factor for Alzheimer disease, experienced more pronounced

cognitive impairment and were slower to recover after acute oral challenge with lorazepam. The cognitive impairment experienced by these subjects was not the result of pharmacokinetic factors, raising the possibility that factors unique to the effects of *APOE4* may have resulted in pronounced vulnerability to drug-related cognitive toxicity. Although the idea that certain genetic alleles may mediate and amplify the effects of specific drugs on the development of cognitive impairment is controversial and not unanimously supported by the literature, it highlights yet another possible mechanism through which neuropsychological deficits in ICU survivors might develop.

DEPRESSION AND ANXIETY IN ICU SURVIVORS

Psychological morbidity, such as depression and anxiety, occurs frequently after critical illness.[43,44] Depression occurs in 25%[33] to more than 50% of survivors of critical illness.[45] Angus and colleagues[45] reported that 50% of ARDS survivors had depression 1 year after treatment, whereas Cheung and colleagues[46] reported a 58% incidence of depression 2 years after ICU discharge. A study of 13 ICUs in four hospitals found that 26% of patients had symptoms of depression 6 months after acute lung injury.[47] Similar rates of depression are reported in 22% to 33% of medical inpatients[48] and in 25% to 28% of patients with cardiac and pulmonary disorders.[49,50] Psychiatric disorders after critical illness may be because of a psychological reaction to the emotional and physiologic stress, sequelae of brain injury sustained as a result of critical illness and its treatment, or both. Medications, physiologic changes, pain, altered sensory inputs, and an unfamiliar environment are all potential contributors in the development of psychological sequelae.[51]

There is little data available about risk factors for depression in survivors of critical illness. Depression is positively associated with longer ICU lengths of stay, longer duration of mechanical ventilation, and greater number of days on sedatives.[52] Two additional studies support the relationship between longer ICU lengths of stay and depression.[43] No information is available regarding factors related to longer ICU lengths of stay that lead to the development of depression. That is, it is not known if it is the time or the longer exposure to other factors such as sedatives or glucose dysregulation that results in depression. For example, a recent study found that hypoglycemia during ICU treatment was associated with greater symptoms of depression 3 months after acute lung injury.[47] Other factors related to depression are higher body mass index, premorbid depression or anxiety, and mean ICU benzodiazepine dose.[47] A study in 13 ICUs from four hospitals found depression at 6 months was related to surgical but not medical or trauma ICU admission, maximum organ failure score, and mean benzodiazepine dose.[53]

Although the above studies are starting to assess relationships between critical illness and ICU treatment with development of depression, research is in its infancy; additional studies are needed to determine risk factors, mechanisms, and potential treatments. Daily sedative interruption did not reduce the prevalence of depression at hospital discharge, but did reduce the rate of depression at 1 year.[54] A study that assessed prevalence of antidepressant treatment found that 37% of ARDS patients were taking antidepressant medications 2 months after ICU discharge.[44] Little is known regarding whether treatment of depression with antidepressant medications improves outcomes.

There is limited information on generalized or nonspecific anxiety in critically ill populations. The prevalence of nonspecific anxiety is less frequently reported than depression, but the rate of anxiety ranges from 23% to 41%.[43,54] The rates of anxiety in ICU survivors is higher than that observed in medical inpatients (5%–20%),[55] but

similar to the reported rates of 10% to 40% observed in patients with pulmonary disorders.[56] Potential mechanisms of depression and anxiety in ICU survivors include organ dysfunction, medications, pain,[52] sleep deprivation, ICU treatment, elevated cytokines,[57] stress-related activation of the hypothalamic-pituitary axis, hypoxemia, and neurotransmitter dysfunction due to brain injury. The most frequently identified anxiety disorder is posttraumatic stress disorder (post traumatic stress disorder [PTSD], see discussion in the next section). The prevalence of psychological morbidity is high and research is in its early stages. Future investigations should assess mechanisms, risk factors, and possible interventions.

POST TRAUMATIC STRESS DISORDER IN ICU SURVIVORS

PTSD was once believed to result primarily from experiences such as combat, assault, and exposure to a natural disaster. Experts have recognized that a somewhat broader array of events may indeed be traumatic to individuals, including life-threatening illnesses and surgical procedures. A significant literature has emerged in this regard, particularly as it relates to the development of PTSD after the diagnosis of cancer. Researchers and clinicians are focusing on another experience believed to contribute to PTSD and PTSD symptoms—critical illness and the events associated with ICU hospitalization—although a debate on the prevalence and severity of PTSD in ICU survivors is ongoing.[58]

Of particular interest for ICU clinicians and research is the role of memory in mediating the development of PTSD, because a key impetus for employing strategies to keep critically ill patients heavily sedated has been the concern that memories of their ICU experience could facilitate the development of PTSD.[59] The importance of specific *explicit memories* (memories pertaining to facts and events, which are accessible to consciousness)[24,25] in the generation and maintenance of PTSD is difficult to estimate because they are the basis for nightmares, flashbacks, and intrusive thoughts, and they contribute to avoidant and reexperiencing symptoms. Although a detailed treatment of these issues is beyond the scope of this review, the authors briefly discuss several key findings from the literature as they relate to ICU populations. The preponderance of evidence suggests that the absence of episodic memory for a traumatic event is protective against the development of PTSD; most studies have shown that the risk of PTSD is markedly lower in individuals unable to recall a traumatic event than in those with explicit memory for the event(s).[26,60–63] The literature is not unanimous and is quite narrow in scope, with virtually all relevant studies having been conducted on victims of motor vehicle accidents or other traumas with concomitant traumatic brain injury.[64] Theories of information processing suggest that traumatic memories can be encoded *implicitly* during periods of impaired consciousness and may provide the basis for the generation of PTSD symptoms even if patients are not consciously aware of the memories.[65–68] Also, during periods of impaired consciousness, the encoding of emotional experiences such as panic or severe pain appears to be sufficient for the generation of PTSD symptoms.[69]

Many ICU patients report little, if any, conscious awareness of their critical illness, although as Jones and colleagues[70] have reported, delusional memories, often having violent and paranoid themes, are pervasive among these individuals. Among patients with delirium, particularly hyperactive delirium, psychotic symptoms including visual hallucinations are particularly common.[71,72] These hallucinations and delusions can be extremely gripping and are often characterized by paranoid and traumatic themes involving physical or sexual assault or torture. As is frequently the case, these hallucinations are integrated by patients into a narrative that sometimes involves benign

actual events and, as such, tend to be entrenched. Even after hallucinations dissipate, their effects may persist in the form of delusional memories, particularly for those patients who remain convinced that the aversive experiences they remember actually happened. Importantly, sedative medications may be one factor that mediates the development of delusional memories.[73] Delusional memories may exist in the absence of factual memories, and factual memories provide markers of reality and may serve to orient the patient. For example, in one study, daily sedative interruption was associated with fewer symptoms of PTSD,[54] suggesting that even limited factual memories from brief awakening may reduce PTSD. In addition, delusional memories tend to be stable with time and are significantly more persistent than factual memories.[74] Delusional memories may be more refractory to the normal cognitive processes of habituation and reappraisal because they are not well integrated into the long-term memory. Although research is limited, the presence of delusional memories of the ICU is associated with increased levels of anxiety and PTSD.[75,76]

QUALITY OF LIFE IN ICU SURVIVORS

Health-related quality of life has emerged as an important measure of outcome in a variety of disease states and may be particularly important after ICU treatment, where interventions can maintain life but may lead to significant morbidity. Although definitions differ slightly across disciplines, health-related quality of life is defined as a set of causally linked dimensions of health, with biologic/physiologic, mental, physical, social function, cognitive, and health perceptions.[44] Critically ill patients with severe sepsis[77] and prolonged mechanical ventilation[78] have significantly lower quality of life. The quality-of-life scores for ARDS survivors are very low at extubation and then increase substantially at 3 months, with only slight additional improvement by 1 year.[44] The reduced quality of life occurs primarily in physical domains (eg, physical functioning, bodily pain, and role physical)[44] and is associated with pulmonary symptoms,[44] abnormal pulmonary function,[79] and persistent muscle wasting and weakness.[80] The perturbations in quality of life appear to be profound as Rothenhäusler and colleagues[30] state: "…the success of intensive care management of severe diseases such as ARDS is no longer judged solely by its effects on survival but by its influence on patients' psychosocial well-being."

Dowdy and colleagues,[81] in a recent meta-analysis of health-related quality of life in ARDS survivors, found that ARDS survivors consistently had lower quality-of-life scores compared with matched, normative controls at all time points after ICU discharge (from hospital discharge up to 66 months later). The magnitude of the quality-of-life differences between critically ill patients and healthy controls represent a moderate decline in physical domains and mild-to-moderate decline in emotional domains, particularly early after ICU discharge. Improvements in quality of life are uneven and are time- and domain-specific.[33] The greatest gains occur in physical functioning, social functioning, and role physical in the first 6 months, with only modest additional improvements thereafter. Role physical is the singular domain where improvement continues throughout the first several years.[33] Although quality-of-life scores improve with time in most longitudinal studies, these improvements do not necessarily reflect clinical meaningful changes in function. As Herridge and colleagues[80] state, health-related quality of life "will be profoundly influenced by the patient's prior health status and her expectations for a return to premorbid functional status."

The timing of quality-of-life assessment may influence the findings either by exaggerating or by underestimating patient perception of their quality of life relative to their

critical illness and ICU treatment. Survivors may have shifting perceptions of their illness and recovery, leading to different responses with time, without a similar objective change in their actual capabilities. Conversely, report improvements in quality of life might be more relevant than objective changes in capabilities in predicting willingness and ability to contribute to society. The influence of the ''ICU experience,'' such as invasive procedures and the amount and quality of caregiver support, on health-related quality of life scores has not been assessed. Given the importance of quality of life as a measure of global outcome in survivors of critical illness, it is imperative that clinicians understand that brain function, musculoskeletal function, and other components of medical care that influence quality of life should also be assessed.

Neurocognitive impairments are a major determinant of the ability to return to work, work productivity, life satisfaction, and reduced quality of life.[82] Two studies found that ARDS patients with cognitive impairment had lower quality of life compared with patients without cognitive impairment.[82] Rothenhäusler and colleagues[30] found that ARDS patients with and without neurocognitive impairments had lower quality of life compared with age- and gender-matched healthy controls. Alternatively, decreased quality of life was not associated with neurocognitive impairments in ARDS survivors or with executive dysfunction in a critically ill medical population.[83] Depression and anxiety are also associated with decreased quality of life for all domains, except physical functioning.[39] A study in patients with acute lung injury found that depression and psychosocial symptoms were associated with lower life satisfaction, but not with physical problems or limitations.[44] Depression correlated with poor functional status and decreased ability to perform activities of daily living in patients with chronic obstructive pulmonary disease.[84] Decreased quality of life on the psychosocial domains (eg, role emotional, mental health, and vitality) is associated with PTSD in ARDS patients.[43] Greater PTSD symptoms are associated with reduced quality-of-life scores.[85] Psychiatric disorders and their relationships with decreased quality of life are undoubtedly multifactorial. Data to date indicate that cognitive and emotional functions are associated with lower quality of life after critical illness. The effects of critical illness and ICU therapies extend well beyond hospital discharge and often lead to significant neurocognitive and psychiatric morbidities and reduced quality of life in survivors.[33,80] The observed morbidities and their adverse impact on quality of life raise questions regarding possible interventions to improve outcomes in these patients.

SUMMARY

The significant and sometimes permanent effects of critical illness on wide-ranging aspects of functioning are increasingly recognized. Among the areas affected are acute and long-term cognitive functioning, depression, anxiety, PTSD, and quality of life. These and other areas are increasingly being studied and indeed are increasingly the focus of clinical attention and investigations. These conditions have been a focus of attention for more than a dozen years, with much improvement occurring in the ability to characterize these phenomena. For instance, in intervening years, it has been learned that cognitive impairment is highly prevalent and functionally disruptive and that it occurs in wide-ranging domains. Key questions remain unanswered with regard to vital questions such as determining causes, risk factors, and mechanisms as well as the degree to which brain injuries associated with critical illness are amenable to rehabilitation. Little remains known about the effects of critical illness on elderly ICU cohorts and on the neurologic functioning of individuals with preexisting impairment versus those who are normal. Few data exist regarding the development

of strategies designed to prevent the emergence of neuropsychological deficits after critical illness. Although great progress has been made and is ongoing, a pressing need exists for additional investigation of cognitive impairment and other conditions, such as PTSD and quality of life after critical illness, that will seek to untangle the many pertinent questions related to this condition and that will ultimately offer help and hope to the thousands of survivors affected by this condition.

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