Review

Bench-to-bedside review: Brain dysfunction in critically ill patients – the intensive care unit and beyond

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Published: 24 July 2006
This article is online at http://ccforum.com/content/10/4/223

Critical Care 2006, **10:**223 (doi:10.1186/cc4980)

Abstract

Critical care physicians often find themselves prognosticating for their patients, attempting to predict patient survival as well as disability. In the case of neurologic injury, this can be especially difficult. A frequent cause of coma in the intensive care unit is resuscitation following cardiac arrest, for which mortality and severe neurologic disability remain high. Recent studies of the clinical examination, of serum markers such as neuron-specific enolase, and of somatosensory evoked potentials allow accurate and specific prediction of which comatose patients are likely to suffer a poor outcome. Using these tools, practitioners can confidently educate the family for the majority of patients who will die or remain comatose at 1 month. Delirium is a less dramatic form of neurologic injury but, when sought, is strikingly prevalent. In addition, delirium in the intensive care unit is associated with increased mortality and poorer functional recovery, prompting investigation into preventative and therapeutic strategies to counter delirium. Finally, neurologic damage may persist long after the patient's recovery from critical illness, as is the case for cognitive dysfunction detected months and years after critical illness. Psychiatric impairment including depression or post-traumatic stress disorder may also arise. Mechanisms contributing to each of these entities are reviewed.

Introduction

Among the most difficult things we do as critical care physicians is attempt to predict for a patient or their family the outcome of critical illness. For many individuals, the most pressing question becomes 'Will I (or my loved one) return to my (their) present level of functioning, or will there be a persistent disability?' The answer to this question can be obscure for any patient with critical illness, but prognostication becomes of paramount importance for those in whom issues of neurological injury arise, especially considering 89% of Americans surveyed would not wish to be kept alive if they sustained severe cognitive impairment [1]. This review is intended to highlight recent advances in our understanding and recognition of brain dysfunction – its pathophysiology, significance, and outcomes – from the acute setting to the months following critical illness.

Coma

When a patient fails to respond to his or her environment with any verbal, motor, or psychological interaction, we refer to the patient as comatose. Coma is a common occurrence in the intensive care unit (ICU). It was the primary reason for intubation in approximately 17% of patients in a large international trial evaluating the characteristics of patients receiving mechanical ventilation, occurring more frequently than congestive heart failure, trauma, or pneumonia as an indication to intubate [2]. For comatose patients, the outcome may vary from death or a persistent vegetative state, to various degrees of cerebral disability, or, in the best case, to full neurologic recovery. Because patients' reported preference for ongoing medical care is largely determined by the perceived outcome of each intervention [1], there exists a clear imperative to improve prognostication in coma.

Following drug overdose and trauma, the most common cause of coma in the United States is cardiac arrest [3,4]. Eighty percent of survivors of cardiac arrest will be comatose following resuscitation [5]. Unfortunately, long-term survival rates of cardiopulmonary resuscitation (CPR) remain poor; approximately 29% of patients who suffer out-of-hospital cardiac arrest are alive at 4 hours but fewer than 10% survive to hospital discharge [6,7], while 18% of adults who suffer inhospital cardiac arrest survive to hospital discharge [8]. Because the outcome of cardiac arrest can vary so dramatically – from death or permanent disability to a meaningful, functional recovery – much recent research has focused upon predicting which initial survivors of CPR will go on to enjoy a long-term recovery. Much of this research has

ARDS = acute respiratory distress syndrome; CAM-ICU = Confusion Assessment Method for the ICU; CPR = cardiopulmonary resuscitation; EEG = electroencephalography; GABA = γ-aminobutyric acid; GCS = Glasgow Coma Scale; ICU = intensive care unit; NSE = neuron-specific enolase; PTSD = post-traumatic stress disorder; PROPAC = Prognosis in Post-Anoxic Coma; SSEP = somatosensory evoked potentials.

now been extended to the comatose critically ill population at large, which is then of tremendous use to clinicians in the ICU.

Prognosis in coma

Clinical examination

Classically, the main determinant used by clinicians to prognosticate for patients with brain dysfunction has been the clinical neurological examination. In addition to documenting the patient's Glasgow Coma Scale (GCS) [9], the recommended clinical assessment of the comatose patient involves assessment of brainstem reflexes (pupillary, corneal, gag/cough) and vestibular reflexes (oculomotor or 'Doll's eye' and cold caloric testing), as well as assessing for seizure or myoclonic activity.

In their landmark paper describing the utility of the clinical examination in anoxic coma, Levy and colleagues attempt to simplify the pertinent examination. They report that, out of 210 patients, none who had absent corneal or pupillary reflexes at 24 hours or absent motor response at 72 hours ever regained an independent lifestyle [10].

A recent meta-analysis of 11 studies of the clinical examination in comatose patients following cardiac arrest found that various examiners – nurses, residents, and attending physicians – are moderately to substantially in agreement about components of the GCS and brainstem reflexes, with only one study showing diminished precision among less experienced observers [5,11]. The meta-analysis also examined the accuracy of various aspects of the clinical examination performed at differing time points for predicting outcome of post-arrest coma. With a pooled sample size of over 1,900 patients, the proportion of patients dying or having a poor neurologic outcome – severe cerebral disability, coma, or persistent vegetative state – was 77% [5]. At 24 hours, the clinical findings with the highest likelihood values to predict poor outcome were absent pupil response or absent corneal response, with each result indicating that poor outcome was 10 times more likely. At 72 hours post arrest, only an absent motor response accurately predicted death or poor outcome. Both the GCS and the Innsbruck Coma Scale, which combines brainstem reflexes and the GCS, were less predictive than individual motor and brainstem responses for bad outcome. Surprisingly, no element of the clinical examination could accurately predict a good neurologic outcome.

Electrophysiologic and serum markers

Given the imperfection of the clinical examination to guide prognosis, attention has focused on other potential diagnostic methods. Electroencephalography (EEG) has been extensively studied in comatose patients. If the EEG pattern is isoelectric 72 hours after an ischemic event, the chance of survival or even of recovery of consciousness is essentially zero [10,12,13]. If a burst-suppression pattern is observed, there is almost no chance of survival without severe neurologic disability [12,13].

In the recent Prognosis in Post-Anoxic Coma (PROPAC) study [13], EEG was one of the clinical variables examined along with physical examination findings, biochemical variables, and somatosensory evoked potentials (SSEP) to predict outcome of 407 patients who were comatose following CPR. EEG performed modestly well at predicting poor outcome, meaning death or persistent unconsciousness at 1 month. If the EEG had no activity greater than 20 μV at 72 hours post arrest, the positive likelihood ratio of a poor outcome was 17, with no false positives. If the EEG showed burst-suppression activity at 72 hours, the positive likelihood ratio of a poor outcome was 5, with no false positives. Conversely, the finding of status epilepticus by EEG at 72 hours did not increase the likelihood of a poor outcome, with a likelihood ratio of 1. EEG performs less well than SSEP at predicting poor outcome – the likelihood ratio for absent N20 SSEP (see later) at 24 hours was 29, with no false positives – yet a small number of patients with intact SSEP (13%) did have poor prognosis confirmed by EEG alone [13]. As such, EEG at 72 hours post anoxic event may help to determine patients with a low likelihood of survival or regaining consciousness.

Serum markers are another potential prognostic aid that have recently garnered significant attention. Of the many proposed markers, including myelin basic protein, von Willebrand factor antigen, soluble intracellular adhesion molecule-1, neuron-specific enolase (NSE), and S-100β, the latter two have shown considerable promise.

S-100β is the β-subunit of a dimeric calcium-binding protein which is highly brain specific. Serum levels appear to rise in response to astrocyte damage, and circulating elevations have been reported in patients with cerebral ischemia, traumatic brain injury, postcoronary artery bypass cognitive decline, and respiratory failure [14-18]. In addition, S-100β levels are correlated with measures of head injury severity and outcomes [19]. S-100β increases may be associated with systemic inflammation, as the serum trajectory of this protein seemed to mirror a similar increase in IL-8 levels in patients who were 12 hours post cardiac arrest [20]. While the levels of serum S-100β have been proposed as a marker to help prognosticate the extent of brain damage in patients suffering anoxic–ischemic coma, the PROPAC study was unable to validate a cut-off value for this marker [13,21].

NSE is a superior biomarker for coma prognostication. NSE may be envisioned as a marker of neuronal damage because it is a protein-based enzyme found primarily within neurons. Like S-100β, serum levels of NSE rise following traumatic brain injury and correlate with outcome in severe head injury [22-24]. Eighty-eight percent of cardiac arrest patients treated with mild therapeutic hypothermia showed a decline

in NSE levels, and this decrease correlated with a better neurologic outcome at 6 months [25]. In the same study, serum S-100β failed to show a decrement with hypothermia.

Zandbergen and colleagues suggested a cut-off value of NSE greater than 33 μg/l as indicative of poor neurologic outcome following ischemic–anoxic insult, and this threshold was validated by the PROPAC study [13,21]. When the NSE level is above the threshold level at 24 hours post arrest, the likelihood of a poor outcome increases 36-fold. No patient with a serum NSE >33 μg/l had a good outcome [13].

Interestingly, results from NSE analysis and from SSEP analysis appear to be complementary [13]. Unfortunately, the potential utility of NSE is limited by its current availability. At our institution, the serum test is a send-out laboratory test with a 5-day turnover time, despite its relatively modest cost ($185).

Perhaps the most definitive test to determine poor outcome in post-anoxic coma is the SSEP. Because evoked potential waveforms are so integrally related to their corresponding anatomic structures, absence of a specific evoked potential can localize the conduction deficit to within a few centimeters [26]. SSEP are ideal in that they are extremely resistant to being altered by nonpathologic factors, and thus are unaffected by general anesthesia or even barbiturate-induced coma [27,28]. If the N20 signal – triggered by stimulating a median nerve, with expected waveforms then generated in the brachial plexus, upper cervical cord, thalamic nuclei, and primary sensory cortex – is bilaterally absent in a comatose patient, the patient's outcome at best will be a persistent vegetative state [29,30].

In a meta-analysis of SSEP compared with other methods of neurologic testing, SSEP were found superior to pupil examination, to motor response, to EEG, to computed tomography, and to the GCS in predicting a negative outcome, with the specificity and the negative predictive value essentially 100% [31]. In another study, despite receiving long-term intensive care treatment, all 86 patients with bilateral loss of N20 SSEP within 7 days of the onset of coma proceeded to die without awakening from coma [32]. Likewise, the PROPAC study found that, even when measured just 24 hours after the onset of coma from anoxic–ischemic arrest, N20 SSEP that were bilaterally absent invariably predicted either death or a poor neurological outcome [13].

As mentioned previously, the results of SSEP do not completely overlap with NSE or with tests such as EEG. Because both the NSE and SSEP tests are highly specific but are not very sensitive, the PROPAC group tested them in combination to increase the diagnostic yield. The combination of either NSE >33 μg/l or bilaterally absent N20 SSEP identified 66% of comatose patients with a poor prognosis. The addition of EEG at 72 hours, when it revealed either an isoelectric low voltage or a burst-suppression pattern, allowed the identification of an additional small number of patients with poor outcome. In all, 356 of 407 comatose patients (87%) died or remained unconscious at 1 month; the combination of SSEP, NSE, and EEG permitted prediction of this poor outcome for the vast majority (252 of 356, 71%) of these patients within 3 days of their CPR event [13]. Table 1 describes the predictive ability of the most helpful tools to determine poor outcome for comatose patients.

Treatment of coma

Recognizing that the probability of poor neurologic outcome following cardiac arrest remains disappointingly high at approximately 77% [5], much interest has been generated by recent trials demonstrating that therapeutic hypothermia can reduce mortality and can improve neurologic outcome.

In a European study of patients following ventricular fibrillation arrest, 275 subjects were randomized either to standard care with normothermia or to therapeutic hypothermia of 32–34°C for 24 hours [33]. Cooling was achieved with an external cooling device over approximately 8 hours. The neurologic outcome at 6 months was favorable (good recovery or moderate cerebral disability) rather than poor (severe cerebral disability, persistent vegetative state, or death) in 55% of cooled patients compared with 39% of controls ($P = 0.009$) [33]. The mortality at 6 months was also significantly reduced in the hypothermia group (from 55% to 41%, $P = 0.02$), and no excess complications were noted in the treatment group [33].

A similar study in Australia applied external cooling for 12 hours to patients who were comatose following CPR for ventricular fibrillation, and likewise found an improvement in outcome as judged by discharge status to home or to a rehabilitation facility, rather than death or discharge to a long-term nursing facility [34]. The Australian study failed to detect a mortality difference between groups. Both clinical trials sedated all patients during the cooling and rewarming period, a mandatory corollary if neuromuscular blockade is used to prevent shivering.

Delirium

While coma is undoubtedly the most dramatic form of brain dysfunction faced in the ICU, it is not the most common. Delirium – defined as an acute, fluctuating change in mental status, with inattention and an altered level of consciousness – occurs in the majority of patients in the ICU. Inattentiveness and a fluctuating level of arousal distinguish delirium from acute anxiety [35], whereas agitation is best described as 'the motor restlessness that accompanies anxiety' [36].

Delirium has been detected in 70–80% of mechanically ventilated patients in the ICU, and in approximately 70% of all ICU patients aged 65 years or older [37-39]. Younger patients have a decreased risk compared with their elders,

Table 1

Prognosis of a comatose patient

Primary assessment	
Glasgow Coma Scale <8?	Patient is comatose
No response to environment?	
At 24 hours	
Clinical examination	
Absent pupillary response?	Probability of a poor outcome, 97%
Absent motor response?	Probability of a poor outcome, 97%
Somatosensory evoked potentials, absent N20 signal bilaterally	Probability of a poor outcome, 100%
Serum neuron-specific enolase ≥33 μg/l	Probability of a poor outcome, 100%
At 72 hours	
Clinical examination	
Absent motor response?	Probability of a poor outcome, 97%
Somatosensory evoked potentials, absent N20 signal bilaterally	Probability of a poor outcome, 100%
Serum neuron-specific enolase ≥33 μg/l	Probability of a poor outcome, 100%
Electroencephalography, isoelectric or burst-suppression	Probability of a poor outcome, 100%

'Poor outcome' is defined as death or persistent coma 1 month later [5,13].

but studies nevertheless find that 57% of patients under age 65 become delirious in the ICU [40].

Each of these studies detected delirium using the Confusion Assessment Method for the ICU (CAM-ICU), an instrument adapted for use in nonverbal patients and validated for its specificity and reliability in determining delirium [37]. Prior to the development of the CAM-ICU, studies regarding brain dysfunction of critically ill patients were hampered by imprecise definitions of delirium, or by reliance upon verbal patients and special psychiatric training for the health care providers involved. The CAM-ICU consists of four features, each with a dichotomous, absent versus present designation. Echoing the accepted definition of delirium, a positive score indicates the presence of acute onset with fluctuating course and inattentiveness, as well as either disorganized thinking or an altered level of consciousness [37].

Many different manifestations of delirium are demonstrated by delirious patients. While hyperactive delirium with extensive motor restlessness is easily recognized by caretakers, many critically ill patients will actually manifest lethargy, withdrawal, and psychomotor slowing. This latter form, often referred to as hypoactive or 'quiet' delirium, is frequently unrecognized precisely because the patient is outwardly calm and peaceful. When over 600 consecutive ICU patients were studied for delirium, a mixed-type delirium – involving periods of hypoactivity and withdrawal and occasional periods of restlessness – was found to be the most common motoric subtype [40]. Pure hyperactive delirium was quite uncommon, occurring in fewer than 2% of patients, and exclusively in patients younger than 65 years of age. Strictly hypoactive delirium occurred in 45% of patients, and was the most frequent type of delirium observed in elderly patients [40].

Risk factors

Along with age, a number of other risk factors for the development of delirium have been identified. Mechanical ventilation increases the risk approximately threefold, whereas increasing severity of illness, as determined by the Acute Physiology and Chronic Health Evaluation II score, has a small but significant association with delirium [40]. In the critically ill elderly, the presence of dementia was associated with a 40% increase in delirium (relative risk, 1.4) [39].

A potential risk factor that has received little attention to date is race. A recent study found that Black patients had a significantly increased risk for developing hypoactive delirium as compared with Hispanic or White patients [40].

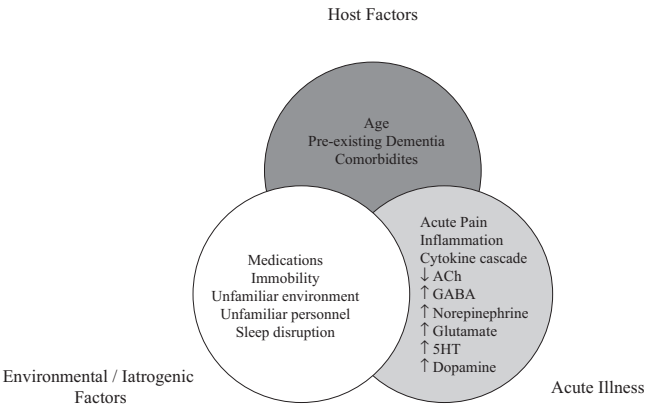
In hospitalized but non-ICU patients, other identified risk factors include visual impairment, hearing impairment, sleep deprivation, immobility, concurrent illness, and polypharmacy [41]. The link between medication and delirium is not wholly understood. Long believed to be the leading iatrogenic cause of delirium, psychoactive medications including analgesics and sedatives have been associated with a higher rate of delirium in some, but not all, studies of critically ill patients [42,43]. Benzodiazepines appear to pose a particular hazard in this regard [43,44].

Associated mortality

While delirium in the ICU remains disappointingly common, we are only beginning to appreciate its deeper significance. Just as we recognize septic shock or acute respiratory distress syndrome (ARDS) as indicators of critical organ dysfunction of the cardiopulmonary systems, delirium may be thought of as a marker of acute central nervous system dysfunction. Lending credence to this argument is the fact that delirium, as measured by the CAM-ICU, is an independent risk factor for mortality in ventilated ICU patients [38,45].

A study of 275 ventilated patients found that delirious patients had more than twice the 6-month mortality rate of nondelirious patients [38]. Delirium was also associated with a longer hospital stay and with a higher rate of cognitive impairment at discharge [38]. In older patients, almost one-half of the patients demonstrating delirium in the ICU continued to be delirious during the post-ICU period, and persistent delirium has been associated with a poor functional recovery following acute illness [39,46].

Figure 1



Potential mechanisms contributing to intensive care unit-associated delirium [18,49,56]. ACh, acetylcholine; GABA, γ-aminobutyric acid; 5HT, serotonin.

Potential mechanisms

In evaluating the possible mechanisms underlying delirium, much interest has centered on the brain's response to injury and its subsequent inflammatory response (Figure 1). Early research focused on ischemic brain injury. More recently, attention has shifted to an inflammation hypothesis of delirium. When confronted with systemic infections, the central nervous system evokes a cytokine cascade that can induce cell infiltration and tissue damage, which could in turn affect neuronal activity, resulting in delirium [18,47-49]. A study of patients undergoing surgery for hip fracture lends credence to the theory that inflammation drives brain injury; complications including postoperative delirium were significantly associated with higher levels of C-reactive protein, an acute-phase reactant stimulated by acute inflammation [50].

Another active area of interest concerns dysregulation of neurotransmitter systems, including acetylcholine, γ-aminobutyric acid (GABA), dopamine, serotonin, and norepinephrine. Drugs with anticholinergic properties have long been known to precipitate cognitive dysfunction. Even more intriguing, acetylcholine activates pathways that have been shown to inhibit proinflammatory cytokine synthesis and to protect against both ischemia-reperfusion injury and endotoxemia, suggesting that deficits in acetylcholine may trigger a neuroinflammatory response [51]. GABA activity, which typically depresses neuronal excitability, is implicated in hepatic encephalopathy and alcohol or benzodiazepine withdrawal [18]. Benzodiazepines and most other sedative hypnotics act via GABA-receptor stimulation, and many of them impair cognitive function at least acutely. Dopamine, which tends to have excitatory effects, has been implicated as a risk factor for delirium when given exogenously, and endogenous dopaminergic hyperfunction via upregulated dopamine receptors is thought to underlie schizophrenia and to possibly contribute to the development of delirium [52].

Prevention and treatment of delirium

Most research on the prevention of delirium to date has focused on hospitalized but not critically ill patients. The Yale Delirium Prevention Trial used a targeted intervention to minimize six risk factors common to hospitalized patients, by providing orientation activities, early mobilization, efforts to prevent sleep deprivation and to avoid the use of psychoactive medications, and use of hearing aids and eyeglasses to improve communication [53]. By applying this intervention, delirium was reduced from 15% in controls to 9.9% in the study group [53]. Unfortunately, at 6 months there was no sustained improvement in cognitive or functional outcomes for the study group [41].

In critically ill patients, only one small preliminary trial on the prevention of delirium has been published in abstract form. Forty-two patients undergoing elective cardiac surgery were randomized to postoperative sedation with dexmedetomidine, propofol, or midazolam at the time of sternal closure. In the dexmedetomidine group 8% of patients developed delirium, compared with 50% in those patients sedated with either propofol or midazolam [54]. This difference was not statistically significant given the small number of patients, but the finding is intriguing since dexmedetomidine, an α-agonist, is thought to spare the GABA-receptor pathway, and may potentiate endogenous sleep-promoting pathways [55].

Treatment of delirium in the ICU is a largely unstudied territory. Just as in non-ICU patients, once delirium is identified in ICU patients, management should focus upon identifying potential precipitating factors, providing supportive

care, and preventing further complications [56]. Once life-threatening complications such as hypoxemia, hypoperfusion, metabolic derangements, severe pain, and infection have been excluded, attention should turn to the patient's medications and environment in an attempt to minimize any factor that might exacerbate delirium. Reorientation, mobilization, provision of family support and of hearing or visual aids, attention to the patient's comfort, including proper positioning and removal of unnecessary catheters, and attempts to encourage a normal sleep–wake cycle may all help to attenuate cognitive impairment.

Small studies report the improvement of sleep among critically ill patients who were randomized to receive a 6-minute back massage or to receive therapeutic touch by a specially trained nurse [57,58]. A study in patients recovering from orthopedic surgery found decreased delirium and faster readiness to ambulate for patients randomized to receive music therapy in their recovery room [59]. Such alternative therapies, although untested, may have a role in treating delirium once it arises. Pharmacologic therapies to treat the symptoms of delirium should be reserved for patients demonstrating agitation with risk for self-harm, including pulling at catheters or endotracheal tubes, and should occur only after nonpharmacologic treatment has been initiated.

The US Food and Drug Administration has not currently approved any medication for the treatment of delirium. If medication is to be used, choices include antipsychotics such as haloperidol or resperidone, benzodiazepines, or antidepressants with hypnotic effects. A recent retrospective study suggests that the use of haloperidol in mechanically ventilated patients is associated with reduced hospital mortality, but delirium was not assessed as part of the study [60]. Postulated mechanisms for the observed decrease in mortality include hypotheses that haloperidol may decrease the administration of sedative medication, or that it may potentiate central-nervous-system-mediated anti-inflammatory pathways, including the direct inhibition of certain pro-inflammatory cytokines by haloperidol [60,61]. While some guidelines suggest haloperidol as the treatment of choice for ICU delirium [35], its side effects may include extrapyramidal effects, acute dystonias, malignant hyperthermia, hypotension, and, most worryingly, prolonged QT syndrome leading to *torsade de pointes* [62].

Atypical antipsychotics such as olanzapine or resperidone may have a decreased incidence of side effects, but the risk profile remains unchanged and there is little published experience using these medications in critically ill patients [63].

Benzodiazepines are generally to be avoided in the delirious patient, as their use has been associated with increased rates of delirium and paradoxical excitation or agitation.

Residual neuropsychiatric effects of critical illness: cognitive dysfunction and post-traumatic stress disorder

To survive critical illness in the modern ICU, where up to one-third of patients may succumb to their disease, is a justifiable cause for happiness. As mortality from ARDS, renal failure, and other disorders decreases, however, the logical corollary is that more patients are living to experience potential long-term complications of critical illness [64-66]. Increasingly, practitioners are recognizing that a significant proportion of survivors of critical illness will be affected by neuropsychological complications, which can impair their health status and functional outcome, cognitive abilities, or emotional and psychological health.

Critically ill patients frequently manifest cognitive impairment. One study of ICU patients aged 65 years or older found that 30–40% of patients screened positive for pre-existing dementia at the time of hospitalization [67]. At hospital discharge, 50% of another prospectively studied group of mechanically ventilated ICU patients had detectable neuropsychologic abnormalities, and one-third of the total group remained cognitively impaired 6 months later [68]. Neurocognitive dysfunction appears to improve with time, although not to normalize. A study of mixed medical and surgical ICU patients found that 35% of survivors of critical illness manifested profound cognitive impairment at 3 months, whereas only 4% were severely impaired at 9 months [69].

The neuropsychiatric dysfunction of some patients takes the form of post-traumatic stress disorder (PTSD), characterized by the development and persistence of intrusive recollections, avoidance symptoms, and hypervigilance 1–3 months after a traumatic event. In addition to the strain the disorder itself places upon social functioning and psychological health, PTSD is implicated in increased rates of depression, substance abuse, and suicide attempts [70,71].

Among survivors of ARDS, one study reported that over 27% of patients self-reported symptoms that would characterize them as having PTSD [72]. This was a strikingly higher proportion of PTSD-affected individuals than was found in groups of patients who had undergone disfiguring maxillofacial surgery or in groups of soldiers who had spent considerable time peace-keeping in Cambodia [72]. In addition, patients who reported memory of more than one traumatic experience from the ICU were far more likely to report symptoms of PTSD, suggesting that the number of adverse recollections might predispose patients to developing PTSD [72].

To further study this issue, a group prospectively examined the relationship between memory, delusions, and PTSD with standardized interviews 2 weeks following patients' critical illness, and again 8 weeks later. Distinguishing factual memories from delusional ones, the development of PTSD symptoms were predicted only by the presence of delusional

memories without recall of factual events [73]. In fact, the presence of factual memories – despite being memories of unpleasant events – seemed protective against subsequent PTSD symptoms [73]. A similar study found that patients who reported PTSD-related symptoms 3 months after their critical illness recalled fewer factual memories of their ICU stay immediately after ICU discharge [74].

Interestingly, patients are not alone in their risk of developing PTSD. Several studies have found high rates of PTSD symptoms in family members of ICU patients, especially those related to patients who had unfavorable outcomes from their illness and those who participated in end-of-life decision-making for their loved one [75,76]. Depression may also be more common in survivors of critical illness. While a detailed overview of the literature supporting this assertion is beyond the scope of this paper, the reader is directed to an excellent review recently published by Weinert [77].

The mechanisms by which critical illness-associated neuropsychiatric dysfunction occur are not precisely understood. Multiple factors undoubtedly contribute, some of which are well documented. Hypoxemia has been associated with cognitive decline in populations with ARDS and chronic obstructive pulmonary disease, with longer amounts of time spent hypoxic correlating with deficits in memory, attention, speed of processing, visuo-spatial skills, and executive function [78,79]. At 1 year, 30% of one cohort of ARDS survivors demonstrated global cognitive decline and 78% demonstrated impairment in at least one cognitive domain [78].

Delirium may be another potentiator of neuropsychological injury. In addition to increased mortality rates, patients suffering delirium during the ICU stay were nine times more likely to demonstrate cognitive impairment on hospital discharge compared with nondelirious patients [38]. The only study to examine the link between delirium and long-term neurocognitive dysfunction in critically ill patients was underpowered to find a significant relationship, but it did find a trend toward increased duration of delirium in cognitively impaired patients [68]. Nonetheless, delirium is not necessary for the development of cognitive dysfunction; one study found that between 30% and 50% of nondelirious patients demonstrated memory and problem-solving deficits 2 months after their critical illness [80].

Medication, particularly sedatives and psychoactive agents, administered during and after critical illness may also play a role. In mechanically ventilated patients who were randomized to either routine sedation or a daily sedative interruption, patients receiving daily sedative interruption demonstrated trends toward a lower incidence of PTSD and toward a better psychosocial adjustment to illness [81]. In addition to receiving smaller daily and total amounts of sedatives, the group receiving sedative interruption also had 2 days fewer on the ventilator and 3 days fewer in the ICU than the control group [82]. The beneficial effect of sedative interruption on psychological well-being might be ascribed to a decreased medication amount, to a decreased time on the ventilator, or to different memory processing among the intervention group, highlighting the complexity of potential contributing factors. Patient factors – including advancing age, declining educational level, or coexisting depression or anxiety – may each pose additive risks for the development of cognitive decline following critical illness.

We are only beginning to comprehend the scope of neurocognitive sequelae following critical illness. To date, research has focused on identifying the different forms of neurocognitive impairment and establishing each form's prevalence and risk factors. As such, we do not yet know how best to prevent or treat ICU-related cognitive impairment. For some aspects of the problem, significant inroads have been made. For example, studies of patients at risk for PTSD following trauma or burns have led to a number of potential preventative measures, including adequate pain control with morphine and empiric use of propranolol following trauma [83,84]. In addition, given the evidence that acquisition of factual memories in the ICU is protective against the development of PTSD, we advocate daily interruption of sedatives for all ventilated patients in the ICU, to allow daily neurologic assessment and daily readjustment of sedative to the patient's needs [82]. Once PTSD has developed, cognitive behavioral therapy is generally the mainstay of therapy, but this may be supplemented by use of selective serotonin receptor inhibitors [85].

Perhaps most importantly we are learning that it is only by recognition of our patients' vulnerability to neurocognitive impairment that we may appropriately screen and diagnose them. When we have the opportunity to follow patients out of the ICU, we must actively investigate their cognitive, emotional, and psychological state. Patients and family members should be warned about potential neurologic outcomes, and should be reassured about the commonality of their experiences. Because we may not care for our patients once they have survived their critical illness, we must share with our primary care colleagues our hopes and concerns for patients' psychological health, just as we do regarding their physical health. By bridging our care with this crucial follow-up, we are likely to improve our patients' longitudinal outcomes.

Competing interests

The authors declare that they have no competing interests.

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