Types of Brain Dysfunction in Critical Illness

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Many patients in the ICU develop a global alteration in cognitive function that may be structural or metabolic in origin [1]. Terms used to describe these disturbances include delirium, acute confusional state, organic brain syndrome, acute organic reaction, cerebral insufficiency, brain failure, ICU psychosis, and encephalopathy. Etiology-specific terms, such as septic encephalopathy or hepatic encephalopathy, have been used when there is a strong presumption regarding the causative mechanism. It has been postulated that many of these disorders are clinical expressions of a pathophysiologic spectrum, collectively referred to as “critical illness brain syndrome” [2], “critical illness–associated cognitive dysfunction” [3], or “critical illness encephalopathy” [1]. Recently, there has been an effort to rationalize this terminology and to classify brain dysfunction in the ICU as either delirium or coma, using validated clinical criteria [4–7].

Coma

Clinical assessment

In the clinical realm consciousness is described in terms of two primary neurologic functions: arousal or wakefulness, and awareness of self and of the environment [8]. Awareness is the content of consciousness and includes multiple cognitive domains including perception, attention, memory,
executive function, and motivation. The anatomic substrate of arousal is the reticular activating system, a neuronal system extending from the pontine and midbrain tegmentum and projecting to the cerebral hemispheres through the thalamus, and to the basal forebrain [9]. The anatomic basis of awareness as a unified conscious field has not been determined; however, components of conscious awareness, such as perception and attention, have been associated with activation of discrete anatomic systems [10–12].

Coma is characterized by a severe disruption in arousal and awareness. It is differentiated from transient states, such as syncope or concussion, by duration of greater than 1 hour. Coma rarely lasts for more than 4 weeks and in most cases evolves toward phenomenologically distinct states including recovery of consciousness, the vegetative state, the minimally conscious state, or brain death [13]. Plum and Posner [8] proposed a simple, four-part neurologic evaluation of comatose patients, including an assessment of the level of consciousness, brainstem function, motor activity, and respiratory pattern. Coma is characterized by limited vocal and motor activity, nonpurposeful responses to external stimuli including noxious ones, an absence of sleep-wake cycles, alterations in brainstem reflexes, markedly slowed electroencephalographic activity, and decreased cerebral metabolism.

The level of consciousness has been described with semiquantitative terms, such as somnolence, stupor, lethargy, and obtundation; however, clinical validity and reliability of these terms is uncertain, and many clinicians prefer describing wakefulness with the help of quantitative scoring systems, such as the Glasgow Coma Scale (GCS) [4]. The GCS has limitations, including a low sensitivity to subtle changes in arousal; a failure to assess brainstem function; and the difficulty with obtaining a verbal score in patients who are endotracheally intubated, sedated, or aphasic. Alternative scoring systems that integrate brainstem findings include the Glasgow Liege Score [14] and the recently proposed Full Outline of UnResponsiveness score [15]. Additional scales have been developed to provide a more detailed description of cognitive function in patients who have consciousness disorders [16].

Etiology and pathogenesis

Coma is associated with structural or functional disruption of bilateral cerebral hemispheres, or bilateral or midline injury to diencephalic or brainstem structures, inactivating key elements of the reticular activating system. Common causes of coma include direct or primary cerebral disorders resulting from trauma, cerebrovascular disease, neuroinfectious or neuroinflammatory diseases, seizures, and brain tumors. Systemic alterations that are associated with coma include cardiopulmonary arrest, pharmacologic and toxic exposures, sepsis, severe metabolic and physiologic derangements, and endocrine insufficiency. Several neurotransmitter systems have been implicated in consciousness, including cholinergic, glutamatergic, adrenergic, serotonergic, and histaminergic neurons. Pharmacologic agents, toxins,
or metabolic processes that interfere with these neurotransmitters can impair arousal and attention.

Outcomes of coma

Although coma is reported frequently in studies of patients who have primary neurologic or neurosurgical disorders, the epidemiology and impact of coma in the general ICU is less well understood. Among survivors of cardiac arrest, 80% to 90% are comatose for varying lengths of time, and 5% to 30% are comatose at discharge [17]. In large-scale studies of critically ill patients receiving mechanical ventilation, 15% to 20% are comatose [18,19], and coma has been implicated in up to one quarter of patients who fail to separate from mechanical ventilation [20]. In a cohort of elderly patients (> 65 years) admitted to the medical ICU, nearly one third were comatose on admission, and 8% subsequently developed coma [21]. In a study of sepsis-associated encephalopathy, 16% of patients who had sepsis were comatose (ie, GCS < 8), and the level of consciousness of these patients was linked closely to mortality [22]. Among 203 patients who had chronic critical illness and were admitted to a respiratory care unit, 61 (30%) were comatose [23].

Coma has considerable prognostic significance in patients with both primary and secondary mechanisms of brain injury. Coma has been identified as a powerful predictor of death and functional outcomes in patients who have ischemic stroke [24], intracerebral hemorrhage [25], traumatic brain injury [4,26], and cardiac arrest [27,28]. Among 558 patients who were admitted to the ICU, coma was the strongest independent predictor of death and length of stay [29]. In a cohort of 15,973 medical and surgical ICU patients, admission GCS was a leading predictor of mortality [30]; of note, coma developing in the setting of sepsis was linked to worse survival than was post-traumatic coma [29]. The GCS is an integral component in the most widely used intensive care prognostic scoring systems [31–37].

Other consciousness disorders

Brain death

Coma must be distinguished from brain death, which represents a complete and irreversible loss of brain and brainstem function. It is recognized clinically by the absence of consciousness, cranial nerve activity, flexion or extension motor responses, and spontaneous breathing [38]. Before a diagnosis of brain death can be made, conditions that confound neurologic assessment must be ruled out, in particular physiologic or metabolic derangements, severe hypothermia, and recent exposure to toxic or pharmacologic agents that impair consciousness or muscle activation. Although not necessary for the clinical diagnosis, the electroencephalogram (EEG) in brain death is silent [39] and cerebral metabolism is absent [40]. It is widely accepted that a clinical diagnosis of brain death is necessary and sufficient to
diagnose death of the organism; however, there are differences in brain death diagnostic methodology between countries, states, and even between institutions, and critical care providers should familiarize themselves with local policies and norms. The cadaveric organ donation paradigm evolved out of the realization that patients who are brain dead may sustain cardiovascular activity, splanchnic function, and pulmonary gas exchange for a limited period of time, provided that organ support is provided.

**Locked-in syndrome**

Coma must also be differentiated from the locked-in syndrome, which is not a consciousness disorder but can be confused with one. The locked-in syndrome is caused by focal injury to the ventral pons, which leads to quadriplegia and anarthria, but preserved arousal and awareness [41]. Etiologies include brainstem infarction or hemorrhage, multiple sclerosis, and central pontine myelinolysis. In its classic presentation, patients who have locked-in syndrome can express themselves only by blinking and by vertical eye movements. Alternative presentations may occur in patients who have injuries of the rostral pons and midbrain, in whom even eye movements are lost (total locked-in syndrome) [42]. States analogous to locked-in syndrome may occur in patients who have severe forms of Guillain-Barré syndrome and those receiving neuromuscular blocking drugs. It is imperative to consider the possibility of a locked-in syndrome in patients who present acutely with an unexplained alteration in consciousness. If a total locked-in syndrome is suspected based on the presence of midbrain or diencephalic injury, the diagnosis can be substantiated with the help of EEG or functional neuroimaging which will reveal normal patterns of cortical activation [13].

**Pharmacologically induced coma**

The treatment of neurologic emergencies, such as refractory status epilepticus or intracranial hypertension, can involve the deliberate induction of a coma-like state with sedative or anesthetic agents [43–45]. Agents that are used commonly for this purpose include barbiturates [44,46], propofol [47], and midazolam [46], all of which are responsible for reductions in cerebral metabolism and cerebral blood flow. Pharmacologically induced coma can abolish virtually all clinical evidence of brain or brainstem activity, and confounds the clinician’s ability to diagnose coma or brain death.

**Vegetative state**

One of the possible outcomes of coma is the vegetative state (VS). In contrast to comatose patients in whom there is an absence of arousal and awareness, patients in a VS have no awareness of self or of the environment but retain signs of arousal [48]. Patients who are in a VS open their eyes spontaneously but do not react in any meaningful way to environmental
cues; in particular, they are unable to follow visually a moving person or object nor can they fixate on these objects or persons, and they do not follow any commands. The VS is the result of extensive damage to the cerebral cortex with relative sparing of the brainstem; its most frequent causes are traumatic brain injury and cardiac arrest. Emerging data from functional neuroimaging and electrophysiologic studies indicate that variable degrees of cortical activation may occur in patients who meet clinical criteria for the VS [49–54]. Patients who remain in a VS for longer than 1 month are classified as having a persistent vegetative state [55,56].

**Minimally conscious state**

Patients in a minimally conscious state (MCS) have a profound alteration in consciousness but are differentiated from the VS because they present with occasional, inconsistent, but unequivocal signs of self or environmental awareness [57]. Minimally conscious state subjects might sporadically follow commands, attend to recognizable objects or voices, initiate meaningful speech, or engage in purposeful movement; however, these behaviors are never obtained in a predictable or reliable fashion. Like the VS, the minimally conscious state occurs in the setting of catastrophic hemispheric brain injury; however, recent investigations with functional imaging and evoked potentials suggest that the minimally conscious state involves a lesser degree of cortical impairment than does the VS, perhaps as a result of preserved function in corticocortical and corticothalamic tracts [49,58–61]. The long-term outcomes of patients in a minimally conscious state have not been well studied; however, significant recovery of neurologic function has been reported [62]. In a recent report, thalamic deep-brain stimulation was used to restore significant neurologic function in a patient who was in a prolonged minimally conscious state following severe head injury. The authors reported recovery of motor skills allowing the patient to feed himself and communicate with the outside world [63].

**Management of coma**

The acute onset of coma is a medical emergency that requires a swift and structured management approach incorporating concurrent resuscitative, diagnostic, and therapeutic efforts [64]. Initial resuscitation should assess and treat airway, breathing, and circulatory dysfunction and in the setting of trauma, the cervical spine should be immobilized. During and immediately following initial stabilization, attention should be directed to diagnosing and treating common and rapidly reversible metabolic and pharmacologic causes of coma, including hypoglycemia and intoxication with opioids or benzodiazepines. Systemic derangements, such as hypertension, hypotension, hypoxemia, anemia, acidosis, hypothermia, and hyperthermia, should be identified and corrective measures instituted. Resuscitative measures should be accompanied by a focused diagnostic evaluation to identify the underlying
etiology or precipitating factor leading to coma. This includes a structured neurologic assessment, serum chemistries and complete blood count, arterial blood gas, and toxicology screens [64]. In nearly all instances of acute coma, an emergent brain CT is mandated. CT has high sensitivity for acute intracranial hemorrhage, hydrocephalus, and brain edema, and moderate sensitivity for abscess or tumor. CT is frequently unrevealing in hyperacute ischemic stroke and toxic-metabolic or hypoxic-ischemic coma. Moreover, some investigators have questioned the value of CT in the diagnostic work-up of comatose patients in the ICU who do not have focal neurologic deficits or seizures [65]. Patients who have unexplained coma and normal or equivocal CT findings should undergo MRI, which is sensitive to changes induced by acute ischemic stroke, cerebral venous sinus thrombosis, brain edema, brain tumor, inflammation, cerebral abscess, and diffuse axonal injury. Studies in patients in the ICU who have sepsis or after cardiac surgery suggest that MRI can detect lesions that are not suspected by clinical examination or CT [66,67]. When central nervous system infection or inflammation is suspected, or if a diagnosis of intracranial aneurysm rupture is being entertained and CT is unrevealing, lumbar puncture should be obtained, although the diagnostic yield for infectious causes is low in patients who do not have immune compromise and have not had a neurosurgical procedure [68]. Finally, an EEG should be sought if history or physical examination is suggestive of seizure activity or when occult nonconvulsive status epilepticus is suspected. Nonconvulsive status may be diagnosed in up to 20% of patients in the ICU who have unexplained alterations in consciousness [69,70].

**Delirium**

*Clinical features*

Delirium is a global disturbance in cognitive function characterized by impaired attention and associated with changes in the level of consciousness, disorganized thinking, and a fluctuating course [71–73]. Contrary to coma, patients with delirium retain elements of arousal and awareness. Delirium frequently precedes or follows comatose states, and is linked to the same types of global cerebral or systemic physiologic and metabolic insults that have been associated with coma. Alternatively, delirium has been associated with focal brain injury involving, in particular, frontal, right parietal, and basal ganglia structures [74,75]. Delirium may be unrecognized or misdiagnosed as another disorder, such as depression or dementia, in up to 84% of cases [76]. In the ICU, failure to diagnose delirium may occur because of infrequent neurologic assessments, the fluctuating nature of delirium, and a perception that alterations in mental status are a normal response to acute illness [77].

The *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association proposes a clinical definition of delirium that has been widely accepted [73]. The *Diagnostic and Statistical Manual*
of Mental Disorders criteria for delirium include a disturbance of consciousness with impaired attention; a change in cognitive function (eg, memory impairment, disorientation, or language disturbance) or a perceptual disturbance; the disturbance develops over a short period of time (hours to days) and fluctuates; and the history, physical examination, or laboratory data suggest that the abnormalities are caused by a general medical condition and are not better accounted for by a pre-existing dementia. Delirious patients are classified into three behavioral or motoric subtypes: (1) hyperactive delirium, in which patients are agitated, loud, combative, and likely to inflict significant harm on themselves or others; (2) hypoactive delirium, in which they are withdrawn and have minimal interaction with health providers or family; and (3) mixed delirium, in which hyperactive and hypoactive traits are present. Recent data suggest that the hypoactive and mixed forms of delirium may be significantly more prevalent than the purely hyperactive type [78,79].

Much effort has been devoted to creating objective scoring systems for detecting and monitoring delirium clinically in a reliable fashion. Nearly all of these scores are adapted from the criteria set forth in the Diagnostic and Statistical Manual of Mental Disorders. To be clinically useful, bedside scoring systems need to account for characteristics of critically ill patients (eg, endotracheal intubation, mechanical ventilation, sedation), which can hinder traditional cognitive assessment. Delirium scoring systems that were developed specifically for the ICU include the Confusion Assessment Method for the ICU [5], the ICU Delirium Screening Checklist [80], and the Delirium Detection Score [81].

Epidemiology and outcome

Delirium occurs in up to 30% of patients who are admitted to general medical wards [76,82] and in 10% to 60% of surgical populations [83,84], with particularly high rates observed in patients who sustained hip fracture or underwent cardiac surgery [85,86]. The highest rates of delirium are reported in patients who are admitted to the ICU, with prevalences of 50% to 90%, depending on the delirium scoring instrument used and the population studied [5,18,87]. Delirium in the ICU has been associated with an increased risk for death, prolonged mechanical ventilation, and longer duration of ICU and hospital stay [18,87–90].

Risk factors and pathogenesis

Delirium generally develops in a susceptible patient who is exposed to one or several precipitating factors [91]. Host factors that have been associated with an increased risk of delirium include older age, male gender, pre-existing cognitive impairment or dementia, poor functional status, lower educational achievement, malnutrition, substance or ethanol use, and
coexisting medical conditions [18,21,84,92,93]. Precipitating factors for delirium include primary neurologic diseases; infection; shock; hypoxia; electrolyte imbalances; surgery; exposure to neuroactive pharmacologic agents, in particular opioids and benzodiazepines; substance withdrawal; mechanical ventilation; bladder and central venous catheterization; restraints; and sleep deprivation [18,21,87,93].

The neural mechanisms of delirium are not well explained. Research indicates that delirium is associated with a broad range of pathologic events, including neurotransmitter imbalances, inflammation, specific neuroanatomic lesion patterns, and electrophysiologic changes [3,94,95]. Taken together, these data are consistent with a view of delirium as a syndrome of global cerebral insufficiency analogous to organ system failures observed in sites remote from the brain [71,96,97].

The term “septic encephalopathy” has been used to characterize patients who have sepsis and an alteration in mental status that is associated with diffuse slowing on EEG and normal cerebrospinal fluid and neuroimaging [22,98–100]. This form of encephalopathy develops in 23% to 71% of patients who have sepsis, and it is associated with a significantly increased risk for death [101]. Brain histopathology from patients who died with sepsis demonstrates an array of injury mechanisms, including disruption of the blood-brain barrier, cerebral edema, tissue infarction, hemorrhage, vascular thrombosis, microabscesses, and neuronal cell death [102–104]. MRI techniques, in particular diffusion-weighted imaging and MR spectroscopy, may allow in vivo identification of cerebral injury that is not detectable with CT [67,105,106].

Management of delirium

The management of delirium includes prevention strategies, the identification of precipitating factors, and pharmacologic therapy. Prevention strategies have been proposed as multicomponent care bundles promoting patient reorientation; sleep; noise reduction; physical therapy and mobilization; avoidance of, or early removal of, catheters and physical restraints; and provision of eyeglasses and hearing aids. Prevention bundles have been associated with a significantly reduced incidence of delirium [107]; however, the feasibility and efficacy of such measures in the ICU have not been determined.

The cornerstone of delirium management is the identification of precipitating factors. Physiologic, metabolic, and pharmacologic precipitants should be investigated aggressively, and whenever possible corrected or eliminated. Common precipitants of delirium in the ICU include primary brain injury, exposure to sedative and analgesic medications, drugs with anticholinergic properties, substance withdrawal, sepsis, respiratory failure, shock, mechanical ventilation, intravascular catheters, and sleep deprivation.

Pharmacologic therapy specifically directed at delirium is indicated when there is a concern for patient safety (eg, hyperactive delirium); in patients
who remain delirious after elimination of precipitants; and in cases where precipitating factors are unknown or cannot be removed promptly (eg, mechanical ventilation). The antipsychotic agent haloperidol reduces symptoms of delirium in patients with HIV [108], and has been advocated for the pharmacologic management of delirium in the ICU [109]. There are no placebo-controlled randomized trials evaluating the efficacy and safety of antipsychotic agents in the ICU. Haloperidol was associated with decreased hospital mortality in a retrospective study of 989 mechanically ventilated patients (no information was given on the incidence of delirium in this population and the reasons why haloperidol was administered) [110]. In a randomized head-to-head comparison that was undertaken in 73 ICU patients, haloperidol and olanzapine were found to be safe and associated with comparable declines in the ICU Delirium Screening Checklist [111]. A phase II randomized, placebo-controlled trial is evaluating haloperidol and ziprasidone to prevent delirium in mechanically ventilated patients in the surgical or medical ICU [112]. Benzodiazepines may be helpful for treating or preventing delirium that is associated with alcohol and sedative withdrawal; however, in other types of delirium, these agents have been associated with exacerbation and prolongation of symptoms [108,113]. In a recent randomized trial of 106 mechanically ventilated medical and surgical ICU patients, sedation with the \( \alpha_2 \)-agonist dexmedetomidine resulted in a reduced incidence of delirium or coma and more time at the targeted level of sedation than lorazepam [7].

### Cognitive dysfunction after critical illness

In recent years, considerable evidence has accrued to indicate an association between critical illness and long-term cognitive impairment [114]. Cognitive impairment is one component in an array of chronic morbidities that have been recognized in survivors of critical illness [115]. The importance of understanding long-term outcomes is underscored in longitudinal studies that show a decline in hospital mortality of critical illnesses [116–118] and randomized trials that demonstrate increased survival with targeted therapeutic interventions for patients who have sepsis and acute lung injury [119,120]. Observational prospective and retrospective cohorts indicate that subjects evaluated months and years following critical illness have decreased survival, functional outcome, and quality of life [121–124]. These data collectively indicate that the number of ICU survivors is increasing, and that many of these survivors have chronic and invalidating sequelae.

**Clinical assessment**

Cognitive function can be evaluated with the help of simple screening tools, such as the Mini Mental State Examination [125], or with more detailed neuropsychologic batteries that separately assess specific cognitive
domains including visual memory, verbal memory, verbal fluency, attention, executive function, visuospatial performance, and fine motor skills [126]. Although the rational interpretation and comparison of neuropsychologic test data are a matter of considerable debate, a widely accepted methodology is to compare test scores before and after a specific event, or to compare them with a population norm.

It has been suggested that cognitive dysfunction is overlooked, underrecognized, and misdiagnosed in the ICU and subsequently [114]. Many providers in the ICU and in rehabilitation medicine are not familiar with cognitive assessment, and standard medical history and physical examination techniques fail to detect abnormalities identified with neuropsychologic batteries. Moreover, cognitive impairments may be erroneously attributed to other processes, such as concurrent psychoactive medication use, substance use, or psychiatric disorders, in particular depression.

Epidemiology and outcome

Cognitive outcomes following critical illness have been reported in a small number of prospective and retrospective cohort studies [127–132]. These studies focused on survivors of acute respiratory distress syndrome (ARDS), patients in the medical ICU, and patients in the multidisciplinary ICU. Twenty-five percent to 78% of patients who were enrolled in these studies had evidence of cognitive impairment when evaluated with neuropsychologic tests 6 to 24 months following ICU or hospital discharge. Variability in reported prevalences may reflect differences in study design (prospective versus retrospective); neuropsychologic tests administered; time to follow-up; and populations studied.

In a landmark study, Hopkins and colleagues [129] reported a reduction in performance in one or more cognitive domains in 43 (78%) of 55 ARDS patients who were assessed at 1 year. In a separate cohort of 74 ARDS survivors, the prevalence of cognitive impairment was 46% at 1 year and 47% at 2 years [130]. In a retrospective analysis of ARDS survivors who were assessed a median of 6 years after ICU discharge, Rothenhausler and colleagues [128] found cognitive impairment in 11 of 46 subjects (24%). Similar observations have been made in other subsets of ICU patients. Jackson and colleagues [127] observed cognitive dysfunction in 11 (32%) of 34 survivors of the medical ICU who were interviewed at 6 months; they also noted a higher incidence of depression and lower premorbid educational status among cognitively impaired patients compared with nonimpaired patients. In a cohort of 51 patients who were discharged from a medical-surgical ICU, Sukantarat and colleagues [131] noted cognitive impairment in 35% of study subjects at 3 months, with improved test scores when the patients were re-evaluated 6 months later. Finally, a recent report on 30 patients in the ICU who did not have delirium and who were assessed at 2 months found impairments in memory tests in 25% and in problem-solving tests in 50% [132].
It is helpful to consider post-ICU cognitive function within a framework of long-term physical, mental, social, and financial indicators [133,134]. Psychiatric symptoms are reported in 15% to 50% of patients following critical illness. In a seminal report on a cohort of ARDS patients, 51% were not working when they were evaluated at 1 year, and quality of life as assessed by the 36-item Short-Form General Health Survey was significantly less than that in an age- and gender-matched normative population [121]. A systematic review found that decreased quality of life was reported consistently across studies of survivors of ARDS [123]. It is believed that relationships exist between post-ICU cognitive impairment and psychiatric morbidity, decreased social interaction, and quality of life, yet data to support these relationships are scarce.

Etiology and pathogenesis

The pathogenesis of cognitive sequelae following critical illness is largely speculative. According to one view, impaired cognition represents a neurodegenerative process that develops in vulnerable hosts (eg, pre-existing neurologic or cognitive dysfunction) who are exposed to brain dysfunction or damage during critical illness. Such exposures include hypoxemia, hypotension, anemia, fever, hyperglycemia, systemic inflammation, sepsis, various pharmacologic agents, renal failure, and liver failure; however, data to substantiate this hypothesis are scarce [135]. Recently, two studies suggested a link between the duration of delirium and the apolipoprotein E4 gene polymorphism, which is known to be implicated in the pathogenesis of dementia [136,137]. One cohort study that compared characteristics of patients who did and did not have post-ICU cognitive impairment found no difference between groups regarding severity of illness, organ dysfunction, admission diagnosis, and delirium [127].

Two interrelated lines of evidence provide important clues regarding the mechanisms that underlie the long-term cognitive sequelae of critical illness. First, there is a relationship between delirium and cognitive dysfunction, although the precise nature of this relationship is far from well understood [91]. Dementia or poor premorbid cognitive status is identified consistently as a leading risk factor for delirium [18,84], whereas delirium, in turn, may substantially increase the risk for long-term cognitive deterioration. In cohorts of elderly medical inpatients who were not in the ICU, subjects who were diagnosed with delirium during their hospitalization were significantly more likely to develop subsequent dementia and had higher mortality [138,139]. Although such an association has not been demonstrated in ICU patients, it remains an appealing and testable hypothesis [140]. Second, it has been suggested that cognitive dysfunction may result from occult brain injury. Histopathologic and neuroimaging studies indicate specific patterns of brain injury in association with events, such as severe hypoxemia [141,142], sepsis [67,102,103], or acute lung injury.
A brain CT study of ARDS survivors indicated significant brain atrophy and hydrocephalus ex vacuo when compared with matched control subjects. Gunther and colleagues recently hypothesized that brain atrophy in ICU survivors may be a morphologic correlate of a decrease in functional connectivity between the posterior parietal, medial temporal, and prefrontal cortical areas induced by severe illness or sedative drugs. Taken together, these data suggest a theoretic framework in which delirium or encephalopathy are clinical markers of an acute brain injury process that develops subsequently as cognitive impairment, and therapies aimed at preventing or treating delirium might have an impact on long-term cognitive function.

Summary

Recent research highlights a spectrum of cerebral dysfunction acquired in critical illness, which may take the form of coma, delirium, or cognitive impairment. These disorders are common and may be responsible for deterioration in the physical and mental well-being of survivors of the ICU. Advances have been made in recognizing brain dysfunction in critical illness and in delineating its impact, yet fundamental questions regarding its etiology, pathogenesis, and natural history remain unanswered. These questions need to be addressed with a combination of basic science, translational, and clinical approaches. Large-scale cohort studies are necessary to provide insight into the complex relationships between post-ICU cognitive impairment, events occurring in the ICU, and premorbid function. The neural substrates of delirium should be explored using functional and metabolic brain imaging protocols. There is a need to elucidate the role of systemic insults, such as hypoxemia, shock, inflammation, and sepsis, and brain injury mechanisms. The postulated toxic effects of commonly administered drugs (eg, sedatives and analgesics) should be investigated using experimental and epidemiologic paradigms. Results from these studies provide a mechanistic framework for designing effective prevention and treatment strategies to decrease the long-term burden of critical illness.

References


