Section 1 Epidemiology and Outcomes

Chapter 1

The epidemiology of critical illness brain dysfunction

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SUMMARY

Critically ill patients present with a range of alterations which relate to damage or dysfunction of the central nervous system. Acute brain dysfunction is arguably one of the most common forms of organ failure in the intensive care unit (ICU) and is linked directly to adverse short-term outcome. Mounting evidence points to a range of long-term neurological, cognitive, and behavioral changes which substantially impair quality of life following critical illness. Secular trends demonstrate that mortality following severe illnesses such as sepsis and acute respiratory distress syndrome (ARDS) has declined in the past four decades, resulting in a growing population of long-term ICU survivors with unique physical and psychological characteristics. The purpose of this chapter is to outline the epidemiological features of brain dysfunction in critical illness, distinguishing between acute and post-ICU syndromes.

Introduction

A large proportion of hospitalized adults experience acute brain dysfunction which may manifest as anxiety, agitation, delirium, seizures, focal neurological deficits, or coma. The occurrence of brain dysfunction has been linked to adverse short-term outcomes including hospital mortality and prolonged length of stay [1–3], placing significant burdens on caregivers and healthcare services [4,5]. Acute brain dysfunction may also have long-term consequences, with studies suggesting an association between delirium and an increased likelihood of post-discharge death [6], functional disability [7], institutionalization, cognitive impairment [8,9], and dementia [10]. The risk of delirium is particularly high in selected subsets of hospitalized patients such as the elderly and those with pre-existing cognitive impairments [11], subjects with terminal illnesses [12], patients undergoing major surgery [13], and those who are admitted to the ICU [14]. In this chapter we review the frequency, risk factors, and outcomes of critical illness brain dysfunction with a special emphasis on delirium, coma, and seizures.

Incidence and prevalence

Delirium

Delirium is a pathological alteration in mental status associated with inattention, a fluctuating course, and an underlying systemic illness or metabolic imbalance (Table 1.1) [15,16]. The clinical signs of delirium are protean, increasing the likelihood of underrecognition or misdiagnosis [17]. Estimates of delirium frequency are variable depending on methods of identification and populations studied. The frequency of delirium in non-ICU populations ranges from 10% to 18% on general medicine wards and up to 60% in nursing home populations. The incidence of delirium in the ICU is also variably reported, 11% in one large observational study of surgical ICU patients [18] and up to 82% in a selected medical ICU population [1]. In ICU patients older than 65 years of age, up to 70% were found to have delirium [1,14,19]. In medical ICUs nearly 50% of non-ventilated [20] and 60–82% of mechanically ventilated patients [1,21–23] are reported to have delirium. For surgical ICUs similar estimates ranging from 11% to 63% have been reported [18,24]. In a recent study involving 232 patients in 104 ICUs across 11 countries, the point prevalence of delirium was 32.3% [25].

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Table 1.1 Incidence and prevalence of delirium in critical illness.

Reference	Country	Location in hospital	Examination period	Study design	No. of patients enrolled	No. (%) of patients with delirium
[17]	USA	General medical service	12 months	Prospective cohort study	229	50 (22)
[113]	Japan	Medical & surgical ICU	3 months	Prospective cohort study	238	38 (16)
[18]	Turkey	Surgical ICU	2 years	Prospective cohort study	818	90 (11)
[54]	Canada	Medical & surgical ICU	6 months	Prospective cohort study	198	38 (19)
[19]	USA	Medical ICU	8 months	Prospective cohort study	118	51 (43)
[1]; [4]	USA	Medical & cardiac ICU	1 year and 4 months	Prospective cohort study	224	183 (82)
[2]	Taiwan	Medical ICU	6 months	Prospective cohort study	102	22 (22)
[114]	USA	Medical ICU	5 months	Prospective cohort study	143	23 (16)
[20]	USA	Medical ICU	1 year	Prospective cohort study	261	125 (48)
[115]	France	Medical & surgical ICU	8 months	Prospective cohort study	182	95 (52)
[116]	USA	Medical ICU	6 months	Prospective cohort study	93	44 (47)
[117]	Australia and New Zealand	Medical & surgical ICU	6 months	Prospective cohort study	185	84 (45)
[118]	Italy	Surgical ICU	1 year and 4 months	Prospective cohort study	401	117 (29)
[21]	Canada	Medical & surgical ICU	9 months	Prospective cohort study	764	243 (32)
[119]	Canada	Medical & surgical ICU	NA	Prospective cohort study	537	189 (35)
[22]	USA	Medical ICU	2 years	Prospective cohort study	304	214 (70)
[120]	Germany	Surgical ICU	6 months	Prospective cohort study	37	17 (46)
[13]	USA	Surgical ICU	5 months	Prospective cohort study	114	34 (30)
[121]	Taiwan	Medical ICU	8 months	Prospective cohort study	143	31 (21)
[122]	Belgium	Medical & surgical ICU	4 months (Jul–Aug 2006/ Feb–Mar 2007)	Prospective cohort study	172	34 (20)
[23]	USA	Surgical & trauma ICU	3 months	Prospective cohort study	97	68 (70)
[123]	USA	Surgical ICU	4 months	Prospective cohort study	69	41 (59)
[24]	USA	2 surgical ICUs	11 months	Prospective multicenter study	134	84 (63)

Table 1.1 (cont.)

Reference	Country	Location in hospital	Examination period	Study design	No. of patients enrolled	No. (%) of patients with delirium
[124]	UK	Medical & surgical ICU	3 months	Prospective Jan 2008 Retrospective Nov-Dec 2007	71	22 (31)
[125]	the Netherlands	Medical & surgical ICU	3 months	Prospective cohort study	46	23 (50)
[52]	Belgium	Medical & surgical ICU	8 months (Jan–Apr 2007/Jan–Apr 2008)	Prospective cohort study	523	155 (30)
[126]	11 countries	104 ICUs	1 day	Prospective multicenter study	232	75 (32)
[127]	Greece	Medical & surgical ICU	1 year	Prospective cohort study	161	75 (47)
[128]	the Netherlands	Medical & surgical ICU	1 year	Prospective cohort study	1740	332 (19)
[129]	5 countries	Medical & surgical ICU	4 years and 6 months	Prospective multicenter study	354	228 (64)
[130]	Germany	Surgical ICU	8 months (Aug 2006–Nov 2006/ Feb 2007–May 2007)	Prospective cohort study	418	204 (49)
[131]	the Netherlands	Medical & surgical ICU	1 year	Prospective cohort study	1613	411 (26)

NA, not available; ICU, intensive care unit.

Coma

Coma, a state of unarousable unresponsiveness, is frequently seen in patients with severe neurological insults. However, the epidemiology of coma in non-neurological populations is less well investigated (Table 1.2). Among patients older than 65 years admitted to a medical ICU, up to one third were comatose on admission while close to 10% subsequently developed coma during their stay in the ICU [19]. Among 203 prospectively observed patients with chronic critical illness who were admitted to a respiratory care unit, 61 (30%) were found to be comatose [26]. The highest incidence of coma is reported in survivors of cardiac arrest with 80–90% being comatose acutely and 5–30% remaining unconscious at hospital discharge [27]. Coma is also observed in patients with sepsis-associated encephalopathy. In a prospective case series, 9% of patients who had sepsis were found to be comatose, and the level of consciousness was closely related to mortality [28]. In a large prospective cohort of 275 mechanically ventilated patients, 60% were comatose [1]. In another study diminished level of consciousness was related in up to one quarter of patients with failure to separate from mechanical ventilation [29].

Seizures and status epilepticus

Elucidating the true burden of seizure activity (Tables 1.3 and 1.4) in the ICU depends heavily on the method of detection. The preponderance of seizure activity in this population is non-convulsive in nature, and signs of non-convulsive seizure activity may be subtle (fluctuations in mental status, eye deviation, twitching of eyelids) and intermittent, hence overlooked by routine clinical examination or time-limited electroencephalograpy (EEG). The detection of non-convulsive seizures is increased by continuous EEG monitoring [30,31]. Non-convulsive seizure

Table 1.2 Incidence and prevalence of coma in critical illness.

Reference	Country	Location in hospital	Examination period	Study design	No. of patients enrolled	No. (%) of patients with coma
[111]	UK	NA	NA	Prospective cohort study	69 (patients with sepsis)	16 (23)
[59]	Israel	Medical ICU	22 months	Prospective cohort study	50 (patients with sepsis)	8 (16)
[132]	Denmark	Medical & cardiac ICU	8 years	NA	231 (patients with cardiopulmonary resuscitation)	116 (50); 28 (12) remained comatose
[133]	4 countries	412 Medical & surgical ICUs	1 day	Prospective multicenter study	1638 (ventilated patients)	(15)
[14]	USA	Medical & surgical ICU	6 months	Prospective cohort study	96 (patients with delirium)	15 (14)
[19]	USA	Medical ICU	8 months	Prospective cohort study	95 (of 118 patients with more than one assessment during ICU stay)	9 (9)
[1]	USA	Medical & cardiac ICU	1 year and 4 months	Prospective cohort study	275 (ventilated patients)	163 (59)
[26]	USA	Respiratory care unit	2 years and 4 months	Prospective cohort study	203	61 (30)
[109]	USA	Medical & cardiac ICU	4 years	Prospective cohort study	58 (patients with cardiopulmonary resuscitation)	58 (100)

NA, not available; ICU, intensive care unit.

Table 1.3 Incidence and prevalence of seizures in critical illness.

Reference	Country	Location in hospital	Examination period	Study design	No. of patients enrolled	No. (%) of patients with seizures
Seizures during intensive care						
[134]	USA	Medical & cardiac ICU	2 years	Prospective cohort study	1758 (without primary neurologic problem)	61 (4)
[44]	USA	Medical ICU	2, 5 years	Retrospective cohort study	201 (without primary neurologic problem)	21 (10)
Seizures following acute ischemic stroke						
[40]	Australia	Stroke unit	1 year and 5 months	Prospective cohort study	1000 (with acute stroke and TIA)	44 (4)
[32]	France	Medical ICU	NA	Prospective cohort study	1640	90 (5)
[135]	Turkey	Department of Neurology	13 years	Restrospective cohort study	1174	180 (15)
[136]	USA	NA	5 years	Prospective population-based study	904 (with first time stroke)	37 (4) early seizures of hospitalized patients

Table 1.3 (cont.)

Reference	Country	Location in hospital	Examination period	Study design	No. of patients enrolled	No. (%) of patients with seizures
[103]	USA	Neurologic ICU	5 years	Retrospective cohort study	46	3 (6)
Seizures following subarachnoid hemorrhage (SAH)						
[37]	Iceland	NA	11 years	Prospective population based study	44 (with SAH due to ruptured aneurysm and survival >6 months)	10 (23) seizures within 2 weeks after SAH
[34]	Spain	Neurosurgical ICU	7 years	Retrospective cohort study	234	38 (16)
[35]	USA	Neurologic ICU	5 years	Prospective cohort study	247	11 (4)
[33]	USA	Neurologic ICU	7 years	Prospective cohort study	116	17 (15) with non-convulsive seizures
[36]	3 countries	43 care centers	7 years and 8 months	Prospective multicenter study	2143 (with SAH due to ruptured aneurysm)	235 (11) seizures early and late after SAH
Seizures following intracerebral hemorrhage (ICH)						
[42]	China	NA	5 years	Retrospective cohort study	1402	64 (5)
[38]	4 countries	NA	2 years and 10 months	Prospective multicenter study	265	28 (11)
[41]	Italy	Neurologic & medical ICU	18 years	Prospective cohort study	761	57 (7)
[103]	USA	Neurologic ICU	5 years	Retrospective cohort study	63	18 (28)
Seizures following hypoxic-ischemic brain injury (HIE)						
[137]	USA	Medical ICU	8 years	Prospective cohort study	114	41 (36)
Seizures following traumatic brain injury (TBI)						
[138]	USA	NA	5 years	Prospective randomized trial	404	14 (3) within 24 h
[43]	USA	NA	NA	Systematic review	Patients with TBI	(12–50)
[139]	USA	Neurologic ICU	8 years	Prospective cohort study	140 (with TBI and cEEG)	32 (23)

cEEG, continuous electroencephalography; HIE, hypoxic-ischemic brain injury; ICU, intensive care unit; NA, not available; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury; TIA, transient ischemic attack.

activity is described in 5% of patients with acute ischemic stroke [32], in 4–16% of patients with aneurysmal subarachnoid hemorrhage [33–37], in 10–30% of patients with intracerebral hemorrhage [38–42], and in 12–50% with head injury [43]. Seizures may occur in critically ill patients without known neurological illness at admission [44]. In comatose patients without any history of epilepsy, non-convulsive seizure activity

Table 1.4 Incidence and prevalence of status epilepticus in critical illness.

Reference	Country	Location in hospital	Examination period	Study design	No. of patients enrolled	No. (%) of patients with SE
Status epilepticus during intensive care						
[134]	USA	Medical & cardiac ICU	2 years	Prospective cohort study	1758 (without primary neurologic problem)	6 (0.3)
[68]	USA	NA	2 years	Prospective population-based study	166 (with 204 SE episodes)	41–61/100,000 per year
[45]	USA	Medical ICU	2 years	Retrospective cohort study	236 (comatose patients)	19 (8) with NCSE
[31]	Switzerland	Medical ICU	3 years	Retrospective cohort study	537 (performed EEGs)	88 (16) with NCSE
Status epilepticus following acute ischemic stroke						
[135]	Turkey	Department of Neurology	13 years	Restrospective cohort study	1174	7 (0.6)
[136]	USA	NA	5 years	Prospective population-based study	904 (with first time stroke)	10 (1)
[140]	USA	NA	9 years	Retrospective population-based study	718,531	1415 (0.2) GCSE
Status epilepticus following subarachnoid hemorrhage (SAH)						
[33]	USA	Neurologic ICU	7 years	Prospective cohort study	113	12 (11) with NCSE
Status epilepticus following intracerebral hemorrhage (ICH)						
[141]	China	NA	5 years	Retrospective cohort study	1402	11 (1)
[41]	Italy	Neurologic & medical ICU	18 years	Prospective cohort study	761	8 (1)
[140]	USA	NA	9 years	Retrospective population-based study	102,763	266 (0.3) GCSE
Status epilepticus following hypoxic-ischemic encephalopathy (HIE)						
[108]	Switzerland	Medical ICU	7 years and 8 months (retrospective), 2 years (prospective)	107 from a retrospective, 74 from a prospective cohort study	181 (with HIE and treated with therapeutic hypothermia)	6 (3)
[137]	USA	Medical ICU	8 years	Prospective cohort study	114	17 (15) with SE; 19 (17) with myoclonic SE
Status epilepticus following traumatic brain injury (TBI)						
[105]	USA	Neurologic ICU	3 years	Retrospective cohort study	20 (with moderate to severe TBI)	7 of 10 patients with seizures had SE

EEG, electroencephalography; GCSE, generalized convulsive status epilepticus; HIE, hypoxic-ischemic brain injury; ICU, intensive care unit; NA, not available; NCSE, non-convulsive status epilepticus; SAH, subarachnoid hemorrhage; SE, status epilepticus; TBI, traumatic brain injury.

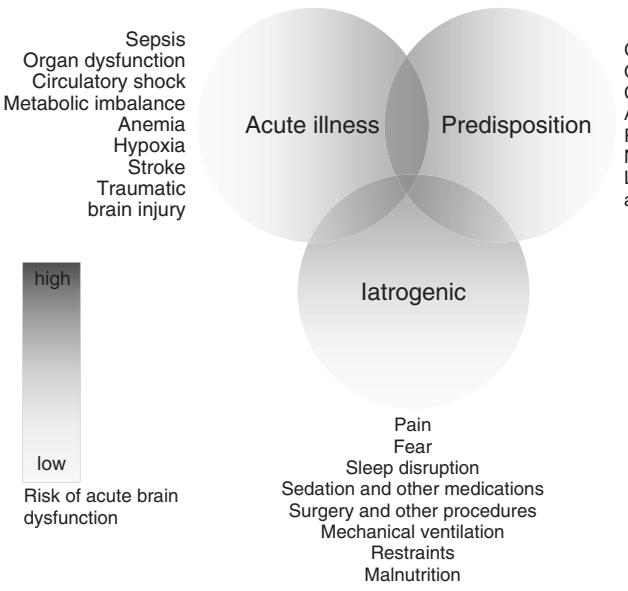

Figure 1.1 The interplay of risk factors for critical illness-associated brain dysfunction.

was detected in 8% of cases [45]. In one observation, over 80% of all status epilepticus was non-convulsive in nature [46].

Risk factors

Delirium

Although the biological mechanisms underlying delirium remain incompletely understood, the identification of risk factors may help develop mechanistic hypotheses. Research indicates that delirium is associated with a broad range of risk factors which may be broadly considered in terms of medical and neurological conditions preceding critical illness, physiological and metabolic alterations induced by critical illness, and iatrogenic exposures in the ICU (Figure 1.1) [47–50].

Delirium develops most commonly in susceptible patients who are exposed to precipitating factors [50]. The probability of developing delirium in the ICU increases after the age of 65 years with the odds of transitioning to delirium rising by 2% for every year above that threshold [51]. Risk factors for the development of delirium include prior cognitive impairment [19,22,52], lower educational achievement [53], malnutrition, stroke, epilepsy, depression, hypertension [21], renal insufficiency [22], smoking [54], alcohol use [21], use of illicit substances [17], fever, and infections [17,18]. In a prospective multicenter study of 523 patients, the development of delirium was significantly associated with prior cognitive impairment (OR 2.4), smoking (OR 2.0), daily use of more than three units of alcohol (OR 3.2), and living alone (OR 1.9) [52]; environmental risk factors in the ICU were isolation (OR 2.9), the absence of family or friend visits (OR 3.7), the absence of visible daylight (OR 2.4), and the use of physical restraints (OR 33.8) [52].

Coma

Coma results from structural or metabolic alterations affecting brainstem ascending reticular arousal systems (ARAS), diencephalon, or cerebral hemispheres. Structural causes of coma impair consciousness either by directly compressing or destroying the ARAS or by distorting tissues so that they secondarily compress the ARAS or its projections [55]; this may be caused by tumors, hematomas, abscesses, and swelling caused by inflammatory processes. To be associated with coma, lesions must involve bilateral or paramedian brainstem, diencephalon, or hemispheres [55]. Non-structural processes that are associated with coma include pharmacological exposures and intoxication [56–58], sepsis [59], severe metabolic and physiological derangements [60,61], endocrine insufficiency [62,63], as well as cardiopulmonary arrest [64,65].

Different pharmacological agents in particular can interfere with neurotransmitters critically involved in maintaining arousal and awareness: these include cholinergic, glutamatergic, adrenergic, serotoninergic, and histaminergic neurons [66].

Seizures and status epilepticus

Physiologic, metabolic, inflammatory, and pharmacological exposures occurring in the setting of critical illness may decrease the threshold for seizures, possibly via disinhibition of central nervous system neurons. The development of status epilepticus during critical illness might then reflect the unmasking of an underlying, but previously unrecognized epileptic disorder. Status epilepticus has a bimodal age distribution with peaks during the first years of life and during the decades above 60 years of age [67]. Epidemiological studies have identified low subtherapeutic serum levels of antiepileptic drugs in patients with epilepsy, remote brain insults, and acute stroke as the most common risk factors for seizures in hospitalized patients [67–69]. Additional epileptogenic factors include hypoxic-ischemic encephalopathy, metabolic disorders, and history of alcohol abuse [67]. Pharmacologic agents used in critically ill patients have been associated with seizure risk; these include anesthetics [70], antiviral and antibacterial agents (i.e., cephalosporins [71–73], theophylline [74], iphosphamide [75–77]), immunomodulatory drugs (i.e., methotrexate [78]), chemotherapeutic drugs, respiratory agents (i.e., theophylline, phenylpropanolamine [74]), antiarrhythmic drugs, as well as neuroleptics, antidepressants, and lithium [79]. Sleep deprivation and hyperventilation are additional factors which may further increase the risk for seizures.

Outcomes

Delirium

The occurrence of delirium during hospitalization has been associated with adverse outcomes including prolonged hospital stay [1,14,80], institutionalization after hospital discharge [2,81], longer duration of mechanical ventilation [24], and increased risk of death both acutely [1] and in the long term [6]. In a systematic review on delirium in elderly hospitalized patients, Witlox *et al.* found that delirium was linked to poor outcomes independently of age, comorbid illness, or dementia [82]. The overall hazard ratio for death in this context was reported as high as 1.95 after a mean follow-up period of 22.7 months. In a meta-analysis, these authors found a nearly two and a half fold increased odds of long-term institutionalization in studies of patients who had delirium when acutely ill. Delirium has also been linked to long-term cognitive impairment. In a recent single-center cohort study of 99 mechanically ventilated patients, severe cognitive impairment was identified in 62% at 3 months and in 36% at 12 months [83]; in this same study, the likelihood of developing cognitive impairment was linked to the duration of delirium in the acute setting. The risk of dementia following delirium has been addressed in only a few studies so far. Witlox *et al.* found a 12.5 (95% CI, 1.86–84.21) increased odds for the development of dementia in patients who had delirium when hospitalized [82]. In addition to the burden imposed on affected patients, delirium also has a substantial economic impact, reflected by increased costs [4]. Healthcare costs are estimated to be nearly twice as high for hospitalized patients who develop delirium when compared with those who do not [4,5].

Coma

Coma has been identified as a major predictor of death and poor outcomes in patients with ischemic strokes [84], intracerebral hemorrhage (ICH) [85], traumatic brain injury (TBI) [86,87], anoxic brain injury [84,88,89], and sepsis [28, 84]. Coma is a major factor contributing to prolongations in mechanical ventilation and ICU length of stay [90]. In a study of 558 ICU patients, the presence of coma was identified as the strongest independent predictor of death and length of stay besides cardiopulmonary resuscitation and shock [91]. In a sample of almost 16,000 patients, the admission Glasgow Coma Scale (GCS) had a strong but non-linear relationship with hospital mortality [92]; in this study, a low initial GCS in patients with sepsis was associated with a higher mortality than in patients with head trauma [92]. This result was mirrored in a more recent study of 232 patients with sepsis-associated encephalopathy whose 28-day mortality was 56% compared with 35% in septic patients without encephalopathy ($p = 0.013$) [93].

Seizures and status epilepticus

The case fatality rate in patients with status epilepticus is reported between 3.5% and 46% [46,67,94–96].

Distinguishing the effects of an initial brain insult from the added consequences of epileptic activity is challenging. The overall mortality of status epilepticus is reported from prospective single-center studies between 14% and 20% [97,98], excluding patients with status epilepticus following hypoxic-ischemic encephalopathy, and up to 26% including hypoxic-ischemic encephalopathy [46,67]. For generalized convulsive status epilepticus (GCSE), overall mortality was reported between 3.5% and 18% [99–101], and for non-convulsive status epilepticus (NCSE), 18% [102].

Outcome may depend not only on the type of seizures, but also on the underlying condition. For example, NCSE or seizures have been demonstrated to increase mortality in patients with TBI and with ICH [103,104]. Seizures emerging after TBI are associated with episodic or long-lasting increases of intracranial pressure [105] while seizures complicating ICH have been associated with hematoma expansion [106]. In anoxic-ischemic encephalopathy, the emergence of seizures and *malignant* EEG patterns are independent predictors for poor outcome [107–109]. Continuous EEG monitoring provides independent prognostic information in patients with poor-grade subarachnoid hemorrhage (SAH), even after controlling for clinical and neuroradiological indices of severity [33]. Seizures following ischemic stroke are related to increased resources utilization and decreasing 30-day and 1-year survival [110]. In patients with sepsis who are monitored with EEG, non-convulsive seizures and periodic epileptiform discharges are detected frequently and are also shown to be associated with poor outcome [44]. Furthermore, EEG abnormalities are linked with the severity of brain dysfunction in septic encephalopathic patients and correlate with dysfunction of other organs [111,112]. Initial diffuse slowing in the theta range (waves of 4–8 Hz) is seen in patients with mild encephalopathy, while diffuse marked slowing in the delta range (waves of less than 4 Hz), then generalized emergence of triphasic waves, and finally suppression or a generalized burst-suppression pattern are seen in more severe forms of encephalopathy.

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