neurocritical care society Neurocrit Care (2011) 14:463–474
DOI 10.1007/s12028-011-9520-0

REVIEW

Delirium and Sedation in the ICU

Jennifer A. Frontera

Published online: 1 March 2011

Abstract Delirium is defined by a fluctuating level of attentiveness and has been associated with increased ICU mortality and poor cognitive outcomes in both general ICU and neurocritical care populations. Sedation use in the ICU can contribute to delirium. Limiting ICU sedation allows for the diagnosis of underlying acute neurological insults associated with delirium and leads to shorter mechanical ventilation time, shorter length of stay, and improved 1 year mortality rates. Identifying the underlying etiology of delirium is critical to developing treatment paradigms.

Keywords Delirium · Sedation · ICU · Intensive care · Confusion · Neurocritical care

Epidemiology, Etiology, and Pathophysiology of Delirium

Delirium is a descriptive term defined by DSM IV criteria as a fluctuating level of attentiveness with a reduced ability to focus, sustain, or shift attention [1]. Fluctuations in levels of consciousness and/or behavioral disturbances develop rapidly (over hours to days) and are not better accounted for by a preexisting dementia. Additionally, there must be evidence that the disturbance is caused by a medical condition, substance intoxication, or medication side effect [1]. Delirium is common among hospitalized patients, particularly in the ICU setting, where it has been reported to occur in up to 70% of patients, compared to 10% of emergency department patients, 16% of post-acute care patients, and 42% of hospice patients [2–4]. Older patients are particularly susceptible to developing delirium, with up to 50% developing delirium at some point during their hospital stay [5–7]. In prospective studies of general ICU patients, the prevalence of delirium is as high as 80% [8]. In the neurocritical care population, fluctuations in mental status are common. Delirium occurs acutely (within the first 3–4 days) in 13–28% of patients with ischemic stroke, subarachnoid hemorrhage or intracerebral hemorrhage and seems to be more common after intracerebral hemorrhage [9–11]. Though the prevalence of delirium appears to be lower in a neurological population, the methodology for assessing delirium varies in different studies and results are not directly comparable. Additionally, much of the literature addressing delirium in neurological patients includes a mixed population of critically ill and non-critically ill patients. However, in at least one study of ischemic and hemorrhagic stroke patients, delirium was significantly more common in stroke patients compared to patients with acute coronary syndrome [9].

It is important to recognize that delirium is not a disease, but rather a symptom of underlying pathology. The term delirium is sometimes used interchangeably with "acute confusional state" or "encephalopathy" and represents a grab bag of different etiologies. Despite differing, or sometimes multifactorial causes, patients with delirium all have a disruption in the attention and arousal centers of the brain. The ascending reticular activating system (ARAS) stretching from the mid-pontine tegementum to the anterior cingulate is primarily responsible for arousal and attentiveness. The ARAS receives widespread input from the spinal cord, visual and auditory centers, thalamus, hypothalamus, and hippocampus, as well as cortical feedback. Disturbances in any of these areas may lead to delirium. The

J. A. Frontera (✉)
Neuroscience Intensive Care Unit, Departments of Neurosurgery and Neurology, Mount Sinai School of Medicine, One Gustave Levy Place, Box 1136, New York, NY 10029, USA
e-mail: Jennifer.Frontera@mountsinai.org

orbital frontal cortex, cingulate gyrus, frontal projections to the thalamus, anterior and medial thalamic nuclei, fornix, mammillary bodies, hippocampus and caudate are integral to attention, memory and executive function. In neurocritical care patients, lesions along any of these pathways or compression of these medial structures due to hydrocephalus with enlargement of the lateral and third ventricles can lead to alterations in mental status. Abnormalities in neurotransmitters (such as acetylcholine [12, 13], serotonin, dopamine, GABA, tryptophan, melatonin [14], and glutamate [15]) and cytokines (such as interleukins and interferons) [16], have been implicated in the pathogenesis of delirium. Since the pathophysiology of delirium is so complex, it is not surprising that it is often multi-factorial in nature. Some common etiologies of delirium are listed in Table 1. It is important to note that 50% of older patients with delirium have underlying diagnoses of stroke, Parkinson's disease, or dementia (that is often undiagnosed) [17–22].

While all of the etiologic factors that can lead to delirium in the general ICU population also apply to the neurocritical care population, there are specific causes of fluctuating mental status that should be evaluated depending on the acute neurological injury. A disease specific differential diagnosis for neurocritical care patients is presented in Table 2. While it is crucial to explore neurological causes of fluctuating mental status in neurocritical care patients, it is also important to evaluate non-neurological etiologies (medication effect, drug withdrawal, and metabolic disarray) so that these abnormalities do not obscure true neurological deterioration that may require emergent intervention.

Evaluation of Delirium in the ICU

The CAM-ICU scale [23] was specifically developed to identify delirium in the ICU as defined by DSM IV guidelines (Table 3). In a study of 96 mechanically ventilated ICU patients, 471 CAM-ICU assessments were performed in patients with a RASS of −3 to +4 (Table 4) and compared to the gold standard DSM IV definition of delirium. The authors found that delirium, diagnosed by this tool, occurred in 83% of ICU patients for a mean of 2.4 days. The CAM-ICU had a 93–100% sensitivity and a 98–100% specificity when compared to the DSM IV guidelines.

A major limitation of the CAM-ICU scale is that it allows for the determination of delirium to be made in the context of sedative use. In up to 30% of cases, the cause of fluctuating mental status is the sedation medication itself [24]. In fact, though the CAM-ICU scale is meant to be repetitively used, patients may receive varying amounts of

Table 1 Etiologies of delirium or fluctuations in attentiveness in general critical care

Category	Example
Neurological injury	Seizures/Status epilepticus (convulsive, non-convulsive)
	Ischemic stroke/TIA
	Hypoperfusion syndrome
	Intracranial hemorrhage (subdural, subarachnoid, intraparenchymal
	CNS infection (meningitis, encephalitis, abscess)
	Traumatic brain injury
	Posterior reversible encephalopathy syndrome (due to hypertension, medications)
	CNS vasculitis
	CNS inflammatory lesion (multiple sclerosis, ADEM, neurosarcoidosis, Lyme disease, drug effect)
	CNS tumor (primary CNS malignancy, metastasis)
	Paraneoplastic syndrome
Infection	Sepsis/SIRS
	Hyperthermia
	Hypothermia
Metabolic Disarray	Hypoxia
	Hypercapnia
	Acidosis
	Uremia
	Acute liver failure (hyperammonemia)
	Hyper/hypo Na, Ca, Mg, PO4
Endocrine	Hyper/hypo thyroid
	Hyper/hypo parathyroid
	Hyper/hypo glycemia
	Adrenal insufficiency
Nutritional	Acute thiamine deficiency (Wernike's)
	B12 deficiency
	Niacin deficiency
Drugs	Prescription: opiates, benzodiazepines, dexmedetomidine, barbiturates, anti-epileptic medications, neuroleptics, anti-cholinergics, anti-histamines, dopamine agonists, steroids, antibiotics, histamine-2 receptor blockers, Baclofen, cyclobenzapine, anti-depressants, anti-arrhythmics, Beta-blockers, clonidine, digoxin
	Illicit drugs
	Seratonin syndrome
	Neuroleptic malignant syndrome
Toxins	Arsenic, Lead, Ethylene glycol, methanol, cyanide, carbon monoxide
Withdrawal states	EtOH/Benzodiazepine withdrawal
	Opiate withdrawal
Other	Poor pain control
	Sleep deprivation
	Sundowning
	Sensory deprivation: low hearing, low vision, language barrier

Table 2 Disease specific etiologies of altered mental status in the neurocritical care population

Neurological disease	Common causes of fluctuating mental status
SAH	Aneurysm rebleed
	Hydrocephalus
	Delayed cerebral ischemia
	Seizures (convulsive and non-convulsive)
	Fever (neurogenic or infectious)
	Meningitis/ventriculitis (in post-surgical patients, patients with external ventricular drains)
	Post-craniotomy pneumocephaly, post-craniotomy cerebro-spinal fluid hypovolemia [72]
	Post-craniotomy epidural/subdural hematoma
Traumatic brain injury	Elevated intracranial pressure
	Cerebral edema
	Contusion, intracerebral hemorrhage, subdural/epidural hemorrhage enlargement
	Delayed intracerebral hemorrhage (DTICH) [73]
	Delayed cerebral ischemia
	Hydrocephalus
	Seizures (convulsive and non-convulsive)
	Dysautonomia, sympathetic storming
	Traumatic dissection with perfusion failure or embolic event
	Fever (neurogenic or infectious)
	Meningitis/ventriculitis (in post-surgical patients, patients with external ventricular drains, or patients with skull fracture)
Stroke	Perfusion failure
	Recurrent embolic stroke
	Capsular warning syndrome
	Edema
	Seizures (convulsive and non-convulsive)
	Fever (neurogenic or infectious)
Brain Tumor	Tumor expansion, malignant deterioration
	Hemorrhage into tumor
	Edema
	Seizures (convulsive and non-convulsive)
	Obstructive hydrocephalus
	Leptomeningitis
	Paraneoplastic syndrome including limbic encephalitis
	Steroid psychosis
Seizures	Recurrent seizures, status epilepticus (convulsive, non-convulsive)
	Post-ictal psychosis/delirium
	Medication toxicity: sedation, hyperammonemia (valproic acid), psychiatric side effects (leviteracetam)
Intracerebral Hemorrhage	Hemorrhage expansion
	Hydrocephalus
	Elevated intracranial pressure
	Edema
	Fever (neurogenic or infectious)
	Seizures (convulsive and non-convulsive)
Hypoxic Ischemic Encephalopathy	Seizures (convulsive and non-convulsive)
	Edema
	Fever (neurogenic or infectious)

sedation during each evaluation. Though it is typical in a neurocritical care setting for sedation to be held to examine a patient, this practice is not standardly applied in other specialty or mixed population ICUs. From a neurologist and neurointensivist's perspective, without eliminating the obvious confounder of sedation upon a patient's mental status, it is impossible to: (1) identify if delirium is present (or levels of sedation are simply different), (2) determine the underlying etiology of delirium, and (3) treat or eliminate the underlying etiology. Additionally, in the setting of sedation, serious neurological events may be occurring and go undetected and untreated. For example, in a neuro-ICU setting, the rates of non-convulsive status epilepticus are as high as 35% [25–28]. Even in patients with no underlying neurological diagnosis, it has been shown that 8–10% of medical ICU patients have seizures, the majority of which are non-convulsive [29, 30]. Seizures in this population are particularly common in patients with sepsis [30]. Similarly, stroke is not uncommon among ICU patients with primary medical diagnoses [31, 32].

A solution to the problem of identifying delirium, but missing a serious underlying neurological condition, is to replace the CAM-ICU with serial neurological exams performed off sedation. Though other rating scales, such as the Delirium Rating Scale [33] have been used in neurological patients, they can be difficult to perform on intubated or critically ill patients. While it has been shown that nurses, physicians, and other health care staff can quickly become proficient at the CAM-ICU [23], an argument can be made that this time would be better spent learning an abbreviated neurological exam (Table 5). A neurological exam not only identifies fluctuations in attentiveness, but also determines if acute neurological injury is present. In a retrospective study of 127 ICU patients who received a neurological consult for an isolated change in mental status, 7% had an ischemic stroke and 1% had a subarachnoid hemorrhage. In this study,

Table 3 Confusion assessment method (CAM-ICU) [23]

Feature 1: Acute onset and fluctuating course
Identify an acute change in mental status from the baseline exam OR
Identify fluctuating changes in mental status or behavior over the past 24 h that may vary in severity
AND
Feature 2: Inattention
Identify an inability to focus attention, easy distractibility or inability to process components of conversation (e.g. count backwards, say months backwards)
AND
Feature 3: Disorganized thinking
If the patient is verbal (and not aphasic): identify illogical or incoherent thought processes, inability to understand proverbs or inability to perform simple calculations (e.g. How many things are in a dozen? Where does a cactus grow?)
If the patient is intubated or nonverbal (and not aphasic): use yes/no questions or letter board to identify illogical or incoherent thought processes (e.g. Can a cat sing? Does wool come from an alligator?)
OR
Feature 4: Altered level of consciousness
Identify if the patient's level of consciousness is anything other than alert (i.e. drowsy, lethargic, stuporous, comatose or agitated/combative)

the neurological exam had a 97% negative predictive value for ruling out acute neurological injury [34]. Most neurointensivists and neurocritical care nurses utilize an abbreviated neurological exam on a serial basis to track a patient's progress. In patients who are other than neurologically intact, a leading indicator can be identified, which demonstrates the patient's best exam (i.e. the patient can reliably count from 20 to 1). If the patient becomes unable to perform this task, then efforts should be mounted to determine why the patient has changed neurologically. It is possible to label this fluctuation in attentiveness as "delirium", but irrespective of the label applied, the cause of the alteration must be identified and treated.

The following is a rational approach to evaluating delirium in the ICU, in both general critical care and neurocritical care patients. First, sedating and toxic medications should be discontinued, if possible. After an appropriate washout period, a neurological exam should be performed to identify any focal features that might lead to localization or etiology. Basic laboratory tests to evaluate for metabolic disarray (e.g. uremia, hyperammonemia, hypoxia, hypercarbia, hypoglycemia, and endocrine dysfunction) should be sent.

Based on the exam and laboratory results, imaging such as head CT or MRI and vascular imaging, such as CT or MR angiography, should be considered. Perfusion imaging (CT or MR) may be useful in patients with suspected flow failure, or vasculopathy. The yield of neuro-imaging depends upon the underlying admitting diagnosis. In a study of 123 medical ICU patients with "altered mental status", new CT findings were present in 26 (21%), including ischemic infarction in 13 (11%), intracerebral hemorrhage in 2 (2%), and tumor in 3 (2%) [35]. Very few studies investigate the utility of MRI in patients with delirium. In a small study of eight delirious medical ICU patients, without focal neurological deficits, meningitis, anoxic brain injury, previously identified brain lesion, baseline cognitive deficits, coma, elevated intracranial pressure or metastatic malignancy, MRI FLAIR, gradient echo, and T2 sequences were performed (DWI was not part of the MRI protocol) [36]. The time from diagnosis of delirium to MRI imaging was not reported. The most common abnormalities on MRI were white matter hyperintensities (75%) and atrophy (12%). No patient had MRI findings that altered treatment, but six of eight patients had

Table 4 Richmond agitation and sedation scale (RASS) [39]

Score	Rating	Description
+4	Combative	Violent, immediate danger to self and staff
+3	Very agitated	Aggressive, removes devices, tubes, catheters
+2	Agitated	Ventilator dyssynchrony, frequent non-purposeful movement
+1	Restless	Anxious but no aggressive movements
0	Alert and calm	
−1	Drowsy	Sustained eye opening and eye contact to voice (>10 s) but not fully alert
−2	Light sedation	Brief eye opening and eye contact to voice (<10 s)
−3	Moderate sedation	Movement or eye opening to voice but no eye contact
−4	Deep sedation	No response to voice, but movement or eye opening in response to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Table 5 Neurological assessment of delirium in the ICU: Delirium is present when there is fluctuation in level of arousal, attentiveness and/or orientation

Step 1	
Assess for fluctuations in mental status	
Mental status assessment[a]	
Arousal	Spontaneously awake, eyes open and alert
	Opens eyes to voice
	Opens eyes to physical stimuli
	No eye opening
Attentiveness	Able to say months backwards from December to January
	Able to count backwards from 20 to 1, but cannot do months backwards
	Able to count from 1 to 10, but cannot do either of the above
	Able to follow complex 2–3 step verbal commands, but cannot do any of the above
	Able only to follow simple verbal commands
	Able only to follow mimicked commands
	Cannot follow commands, but can track visual stimuli
	Cannot track visual stimuli, but saccades to voice
	Does not saccade to voice, but saccades to physical stimuli
	No response to examiner
Orientation	Oriented to person, place and time
	Oriented × 2
	Oriented to self only
Step 2	
Identify localizing abnormalities in the neurological exam	
Cranial nerve exam	
CN II/III	Pupil symmetry and reactivity to light
	Visual field assessment, blink to threat (II, VII, visual pathways)
CN III/IV/VI/VIII	Extraocular movements
	If patient cannot track test Oculocephalic reflex (Doll's eyes maneuver)
	Vesibulo-ocular reflex, hearing
CN V/VII	Corneal response, facial sensation, facial movement
CN IX/X/XII	Gag, tongue movement
Motor exam[a]	
Strength	Test all 4 limbs:
	No drift holding arm or leg out for 10 s
	Drift; limb moves before 10 s, but does not hit bed or support
	Able to move limb against gravity (MRC [74] 3/5)
	Unable to move limb against gravity, but some movement if force of gravity eliminated (MRC [74] 2/5)
	No movement to command
Response to physical stimuli	If patient cannot comply with above motor exam, test response to physical stimuli[b]:
	Localizes to physical stimuli
	Withdraws from physical stimuli
	Flexor posturing (decorticate)
	Extensor posturing (decerebrate)
	Plegia (no movement to physical stimuli) or triple flexion (stereotyped flexion at hip, knee and ankle)

The cranial nerve and motor exam help to identify and localize an underlying neurological injury that may be contributing to delirium

Exam should be performed in patient's native language after sedation has been discontinued for a reasonable amount of time

[a] Within each category responses are listed from best to worst

[b] Patient can have mixed responses

severe abnormalities on 3 month neuropsychiatric testing. Though MRI sequences were incomplete, this study suggests that poor cognitive outcomes may not be due to structural lesions in a subset of delirious patients. While MRI imaging was unrevealing in this small medical ICU cohort, the yield of neuro-imaging in a neurocritical care cohort may be much higher, though little data currently exist to support this assertion.

Continuous EEG to evaluate for seizures or non-convulsive seizures should be entertained in all patients with unexplained delirium. Patients who were able to follow commands 24 h of monitoring will capture 95% of seizures, but only 80% of seizures are detected in comatose patients monitored for 24 h [25]. Therefore, 48 h of continuous EEG may be required in comatose patients. New onset meningitis is exceedingly uncommon in hospitalized patients [37], however, lumbar puncture should be considered in patients with fever and meningismus or patients who have had neurosurgical procedures that might predispose them to CNS infection.

In neurocritical care patients multimodality monitoring can supplement the neurological exam and provide insights into the etiology of fluctuating mental status. Jugular bulb monitoring, brain tissue oxygen monitoring, intracranial blood flow monitoring, and microdialysis can detect changes in cerebral hemodynamics, perfusion, and neurochemistry. These devices may assist in management of blood pressure, osmotic therapy, and hypervolemic hypertensive therapy (in patients with delayed cerebral ischemia) or may support the need for neuro-endovascular or neurosurgical intervention.

Impact of Delirium in the ICU

Delirium has been associated with increased morbidity, mortality, prolonged length of stay and complications such

as fever, tachycardia, and hypertension, which can themselves lead to poor outcome [7, 38]. The implications of delirium in the ICU were explored in a prospective study of 275 mechanically ventilated patients in a medical and cardiac ICU setting [8]. Delirium was diagnosed in patients with a Richmond Agitation and Sedation Scale [39] (RASS) of −3 to +4 (Table 4) who were CAM-ICU positive [23] (Table 3). Coma was defined as response to physical stimuli, but no eye opening, or no response to physical stimuli (RASS −4 or −5). There was no stipulation as to the amount or type of sedation a patient could receive when evaluated. Delirium occurred in 82% of patients and was significantly associated with 6 month mortality (Hazard Ratio 3.2, 95% confidence interval 1.4–7.7, $P = 0.008$), hospital length of stay (Hazard Ratio 2.0, 95% confidence interval 1.4–3.0, $P < 0.001$), and post-ICU length of stay (Hazard Ratio 1.6, 95% confidence interval 1.1–2.3, $P = 0.009$). Each additional ICU day spent in delirium was associated with a 10% increased risk of death (Hazard Ratio 1.1, 95% confidence interval 1.0–1.3, $P = 0.03$). Being in a "coma" in addition to delirium further increased mortality rates and prolonged length of stay. Indeed, 18.5% of patients in this study remained in a persistent "coma" and died, though neither the cause of "coma" nor the cause of death were reported. This study also found that the use of lorazepam and the cumulative lorazepam dose was directly associated with the presence of delirium, while this was not the case for propofol, fentanyl, or morphine. It remained unclear from this study whether delirium was a marker for lorazepam use and if, indeed, lorazepam was responsible for increased delirium, mortality, and prolonged length of stay.

This question was addressed, in part, by the MENDS trial [40]. This randomized controlled trial of 106 mechanically ventilated medical/surgical ICU patients examined the impact of dexmedetomidine (up to 1.5 μg/kg/h) compared to lorazepam (up to 10 mg/h) during the first 120 h of ICU stay on the development of delirium, diagnosed by the CAM-ICU. Both medications could be titrated to a RASS level dictated by the treating physician and a sedation cessation period was not mandated. The addition of fentanyl to treat pain was allowed. This study excluded those with a history of neurological disease, learning disability, dementia, seizure, liver failure, alcohol abuse, MI, 2nd or 3rd degree heart block, as well as moribund and pregnant patients. Compared to patients who received lorazepam, those randomized to dexmedetomidine had significantly more days without delirium and coma and a trend toward shorter mechanical ventilation time, shorter length of stay (7.5 vs. 9 days, $P = 0.92$) and lower 28-day mortality (17 vs. 27%, $P = 0.18$). There was a lower prevalence of "coma" in the dexmedetomidine group (63 vs. 92%, $P < 0.001$). Though patients on dexmedetomidine spent less time delirious, there was no difference in the prevalence of delirium between the two groups (79 vs. 82%, $P = 0.65$). Other factors that may have contributed to delirium in either group were not adjusted for in the analysis.

The SEDCOM trial [41], published 2 years later, randomized 375 medical/surgical ICU patients to Dexmedetomidine (0.2–1.4 μg/kg/h) versus Midazolam (0.02–0.1 mg/kg/h) titrated to RASS −2 to +1 from enrollment until extubation or 30 days. Patients with acute stroke, uncontrolled seizures, liver failure, dementia, renal insufficiency requiring dialysis, acute MI, 2nd or 3rd degree heart block, EF < 30%, bradycardia or hypotension were excluded. Though the primary outcome measure was the percentage of time within the target sedation range (RASS −2 to +1), delirium was examined as a secondary endpoint using the CAM-ICU. A "daily arousal assessment" was performed during which RASS −2 to +1 patients were asked to open eyes to voice, track the examiner, squeeze the examiner's hand or stick out their tongue and were graded as "awake" if the patient could perform three of the four tasks. There was no mandated sedation vacation time and CAM-ICU assessments could be performed while the patient was receiving sedation. Patients who had a RASS score −5 to −3 had study drug interruption until the RASS score was −2 to 0. Therefore, some patients had drug interruption for an unspecified period of time, while others did not. Indeed, patients with RASS scores of +1 or higher, may have had paradoxical agitation due to sedation medication. The inconsistency in levels of sedation or sedation cessation among patients at the time of CAM-ICU evaluation calls into question the consistency and utility of the dataset. This study found a lower prevalence of delirium in those receiving dexmedetomidine (54%) compared to those receiving midazolam (76.6%, P < 0.001) and similarly, increased delirium-free days (2.5 vs. 1.7. $P = 0.002$) and shorter time to extubation (3.7 days vs. 5.6 days, $P = 0.01$). Though this trial found an association of increased delirium rates in midazolam compared to dexmedetomidine, it did not control for other possible causes of delirium that may have differed between the two groups. Since patients were never examined off sedation, it is not clear that acute neurological injury (stroke, seizure etc.) was excluded as an etiology of delirium.

In a substudy of SEDCOM [41], mortality was found to be significantly lower in patients without delirium (11.9 vs. 30.3% in those with delirium, $P < 0.001$) and the median time to extubation and length of stay were shorter in those without delirium ($P < 0.001$) [42]. There was a dose response effect for the duration of time spent in delirium and the risk of mortality, prolonged ventilation time, and prolonged length of stay. Interestingly, 30-day mortality did not differ between the dexmedetomidine and midazolam group in the larger SEDCOM [41] study (22.6 vs.

25.4%, $P = 0.60$), suggesting that the association of delirium and mortality cannot be explained by a sedation effect alone. Indeed, the authors found that the duration of time spent delirious predicted mortality, mechanical ventilation time and ICU length of stay even after adjusting for age, APACHE-2 score, sepsis, shock, pneumonia, type of ICU, and randomization assignment. This poses the tantalizing question: what was the etiology of delirium in these patients? Unfortunately, none of the trials mentioned thus far address this crucial issue. Is delirium a marker for undiagnosed acute neurological injury (stroke, seizure, etc.), or something else?

In ICU survivors, delirium in the ICU has been associated with long-term cognitive dysfunction. In a prospective cohort study of 99 mechanically ventilated ICU patients surviving $\geq$3 months and enrolled in the Awakening and Breathing Controlled trail [43], cognitive outcomes were assessed at 3 and 12 months by a blinded neuropsychologist administering a battery of nine neuropsychological tests. These tests measured: attention and concentration, information processing speed, verbal memory, visual-spatial construction and delayed visual memory, executive function, language and global mental status. Cognitive impairment occurred in 79% of patients at 3 months and 71% at 12 months. The median duration of delirium in the entire cohort was 2 days. After adjusting for age, education, baseline cognitive status, APACHE II scores, severe sepsis, and exposure to sedative medications in the ICU, increasing days of delirium was associated with worse age-adjusted cognitive scores at 3 months ($P = 0.02$) and 12 months ($P = 0.03$). An increase from 1 day of delirium (25th percentile) to 5 days of delirium (75th percentile) was associated with a decline in cognitive scores by half a standard deviation (5 points) at 3 months and an even greater decline (7 points) at 12 months. The duration of mechanical ventilation, however, was not significantly associated with cognitive scores [44]. This study is unique because after adjusting for causes of delirium such as sepsis, exposure to sedative medication, and severity of illness, the duration of time with delirium was significantly associated with worse cognitive outcomes. Though this study excluded patients with cardiac arrest and neurological deficits that prevented them from living independently (e.g. large stroke, severe dementia), it did not account for any new neurological injury that may have occurred during the ICU stay. Since only 4% of patients in this cohort had the admission diagnoses of hepatic or renal failure or alcohol withdrawal, it is possible that undiagnosed neurological injury was a contributor to the development of delirium. In fact, the patients enrolled in this study were all at high risk for adverse neurological complications of their primary illness. Fifty percent of patients in this study had severe sepsis, which is a risk factor for seizures and status epiletpicus [30]. Additionally, 20% of patients had an admitting diagnosis of myocardial infarction or CHF. The risk of ischemic stroke is increased 5-fold during the first month after diagnosis of CHF [31]. The risk of stroke after MI is 4.6% over 42 months [32] and the risk of seizure after MI is nearly doubled compared to age and gender matched controls [45].

Since all of the above studies excluded patients with primary neurological diagnoses, this literature is not directly generalizable to the neurocritical care population. It should be mentioned, however, that none of the aforementioned trials assessed for secondary neurological complications that may have occurred during the ICU stay and could explain delirium in the study cohort. In neurocritical care patients, risk factors for delirium include age, poor vision, poor admission clinical status, left-sided stroke, hemispheric stroke, intracerebral hemorrhage (ICH), cardioembolic stroke, neglect, aphasia, intraventricular hemorrhage, hydrocephalus, pre-existing cognitive impairment, medications (particularly anti-cholinergics), and medical complications [9–11, 46]. As with general ICU patients, delirium is associated with increased mortality and worse outcomes. In one study of 156 patients aged $>$65 years with ischemic stroke or ICH, delirium (diagnosed by DSM IV criteria within 3 days of admission) was associated with a 12 month mortality rate of 41% compared to 17% in those without delirium [11]. Additionally, Functional Independence Measure (FIM) and Mini-Mental State Examination scores were significantly worse at 1 and 6 months after admission in those with delirium. Delirium lasting $>$24 h was significantly related to mortality at 6 months and worse FIM scores than delirium lasting $\leq$24 h. Unfortunately, when assessing outcomes, this study did not adjust for age, stroke type, or underlying severity of illness. Additionally, it is unclear how many of these patients were critically ill and the underlying etiologies for delirium were not explored. Others have found 1 month mortality rates as high as 30% in delirious ischemic stroke and ICH patients compared to 1.7% in those without delirium, though these analyses were also not adjusted [10]. Increased length of stay and institutionalization, as well as long term disability are also associated with delirium [9–11]. In a prospective study of ICH, SAH, and ischemic stroke patients, 76% of patients with delirium had moderate disability or death (modified Rankin Score 3-6) compared to 33% of those without delirium [9]. Future prospective studies are needed to better delineate the impact of delirium in the neurocritical care population.

The above literature has identified the fact that delirium is associated with increased risk of death and poor cognitive outcome. While sedation use is associated with the development of delirium, other unspecified factors are

clearly contributing. The diagnosis of delirium may, infact, be a marker for unrecognized neurological events (i.e. stroke or seizure). Though it is possible that an entirely different or novel mechanism for acute brain injury is occurring in delirious ICU patients, common and treatable adverse neurological events should be evaluated. Determining the underlying etiology of delirium is critical if adequate treatment strategies are to be addressed.

The Argument for Limiting Sedation in the ICU

Though evidence suggests that delirium is associated with worse outcomes independent of sedative effect, the MENDS [40] and SEDCOM [41] trials suggest that sedation can contribute to the prevalence of delirium and the duration of time spent delirious. Furthermore, in order to drill down on the etiology of delirium, it is critical that the contribution of sedation be eliminated from the equation. Frequent arguments for sedating patients include the concept that sedation prevents patients from accidentally harming themselves or self-extubating, or that it is more "humane" to keep an intubated patient sedated. In fact, that literature does not support either of these concepts. Daily interruption of sedation has been shown not only to be safe, but also to improve outcomes and is now a routine component of most ventilator weaning protocols. In a landmark trial of 128 mechanically ventilated medical ICU patients randomized to daily sedation interruption until the patient awakens versus sedation interruption at the discrepancy of the treating physician, those receiving a sedation vacation spent 2.4 fewer days on the ventilator ($P = 0.004$) and had a significantly shorter length of stay (6.4 days vs. 9.9, $P = 0.02$) [47]. Though this study included agitated and uncomfortable patients, there was no difference in the rates of accidental extubation. Stopping sedation also allowed physicians to identify neurological injury. Significantly more patients in the control group never awakened from a coma (20%) and died in a coma (17%) compared to the sedation interruption group (9 and 8%, respectively). This may be because serious neurological illness went undiagnosed and untreated in the control group. Conversely, more head CTs and MRIs were performed on the control group than the sedation interruption group, presumably because these studies were unnecessary in the context of a reassuring, unsedated neurological exam.

This study was followed by the multicenter Awakening and Breathing Controlled Trial, which randomized 336 mechanically ventilated patients to either sedation interruption followed by a spontaneous breathing trial or continued sedation with a spontaneous breathing trial [43]. As in the Kress trial [47], those in the intervention group had significantly more ventilator-free days and a shorter ICU and hospital length of stay. In addition, 1 year mortality rates were lower in the intervention group (44 vs. 58%, $P = 0.01$). The number needed to treat to prevent one mortality was only 7. Though there were more self-extubations in the treatment group (10 vs. 4%, $P = 0.03$), there was no difference in re-intubation rates, and the rate of tracheostomy was lower in the intervention group (13 vs. 20%, $P = 0.06$).

Aside from improved performance during spontaneous breathing trials, sedation interruption can allow patients to participate in other tasks, such as physical therapy. In a randomized trial of 104 mechanically ventilated ICU patients, 49 received sedation interruption followed by a standardized physical therapy protocol (which included an escalating pathway of passive ROM followed by active supine activities followed by transfers and finally performance of routing activities of daily living), while 55 patients underwent sedation interruption and physical therapy at the discretion of the treating physician [48]. Significantly more patients in the intervention group had a return to independent functional status at hospital discharge (59 vs. 35%, $P = 0.02$). The time from intubation to achieving ADL milestones such as getting out of bed, standing, marching in place, transferring to a chair and walking, were also significantly shorter in the intervention group. Similarly, patients who received the physical therapy protocol had higher Barthel index scores (measure of activities of daily living), shorter duration of mechanical ventilation, and a trend toward shorter ICU length of stay. This study was also able to demonstrate significantly less delirium in the ICU and hospital in the intervention group. Along with the Kress [47] and Awakening and Breathing Controlled trial [43], this study demonstrates that sedation interruption is not only safe, but also improves outcomes and may ameliorate delirium.

Though continuous sedation has long been the paradigm in most ICU settings, this concept was recently challenged in a single center randomized trial of 140 mechanically ventilated patients who received either no continuous sedation, but as needed morphine or haloperidol (which could be converted to a continuous infusion if necessary) or continuous sedation with daily sedation interruption until awakening [49]. Those not receiving continuous sedation had significantly more days off the ventilator, and shorter ICU and hospital length of stay. Additionally, there was a trend toward lower ICU mortality (22 vs. 38%, $P = 0.06$), though there was no difference in hospital mortality rates. Although data were analyzed on an intention to treat basis, 18% of patients in the no continuous sedation group required a continuous infusion at some point during the study. Agitated delirium occurred in 20% of the no sedation group and 7% in the continuous sedation group ($P = 0.04$), but there may be a diagnosis bias reflecting the

difficulty of diagnosing delirium in sedated patients. It is important to note that this study was conducted with 1:1 nurse to patient staffing. Since using as needed medication dosing is labor intensive, the results of this study may not be generalizable to ICUs with less generous staffing models. Nevertheless, the cost savings in shorter length of stay and fewer mechanical ventilation days may offset the expense of higher staffing ratios.

Overall, limiting sedation allows for faster liberation from mechanical ventilation, shorter length of stay, better functional outcome at discharge, lower mortality rates, and possibly less delirium. Use of intermittent, as needed sedation appears to be efficacious and may further limit the total duration of exposure to sedation compared to continuous infusions.

Treatment of Delirium in the ICU Setting

The first step in treating delirium is to address the underlying etiology. This requires sedation cessation, followed by a neurological exam and an appropriate investigative evaluation as outlined above. As a first step, supportive measures, including non-pharmacologic strategies, can be effective in preventing and treating delirium. Sleep deprivation may contribute significantly to delirium [50]. Not only do ICU patients spend fewer hours sleeping, but sleep quality, architecture and, circadian rhythms are also altered [14]. Since up to 40% of ICU patients are sleep deprived [51], simple strategies to increase sleep include keeping shades open and the lights on during the day and off at night, and limiting nighttime exams and interruptions in sleep. These strategies are also helpful to reduce reversal of sleep/wake cycles. Limiting sensory deprivation by providing patients with glasses, hearing aids, calendars, and clocks can also help prevent delirium. In non-English speaking patients, having ready access to staff or family members for translation can be important for re-orientation. The use of physical restraints should be limited since this can lead to pressure ulcers, skin breakdown, aspiration and, in fact, worsened delirium. Restraint use has been associated with a 3-fold increase in the odds of persistent delirium [19]. Verbal re-orientation, ambulation, and observation may be more effective methods of managing agitation. In a study of 852 elderly hospitalized patients, a protocol of orientation, cognitive stimuli, non-pharamcologic sleep aids, early mobilization, minimization of restraints, visual and hearing aids, and prevention of dehydration resulted in a significant reduction in the number of delirium episodes and the number of days spent in delirium compared to a control group [52]. In neurocritical care patients, non-pharmacologic options of treating delirium are preferred to sedatives since it is crucial to preserve the ability to easily perform a neurological exam.

Delirium has traditionally been treated with sedative medications, however, as mentioned above, these very medications may induce or worsen delirium. Old paradigms for treating delirium have promulgated the use of lorazepam infusions [53], though more recent data from the MENDS [43] and SEDCOM [41] trials would suggest that this is an outdated approach. In fact, a prospective study of ICU patients found lorazepam increased the risk of incident delirium by 20% [54]. It should be mentioned, however, that benzodiazepines are the most appropriate treatment for alcohol or benzodiazepine withdrawal.

Nicotine withdrawal has been associated with agitation and delirium in neurocritical care patients [55]. In a study of general critical care patients, a history of smoking prior to admission was independently associated with higher rates of agitation, but not delirium. Nicotine abstinence was related to higher incidences of self-removal of catheters and the need for sedatives, neuroleptics, and restraints [56]. Nicotine replacement therapy to ameliorate the effects of withdrawal has been controversial. In a retrospective study of medical ICU patients, nicotine replacement therapy was associated with increased mortality after adjusting for severity of illness and invasive mechanical ventilation [57]. In a study of subarachnoid hemorrhage patients, nicotine replacement therapy was associated with lower rates of mortality at 3 months, but paradoxically, an increased risk of delirium and seizures [58]. The authors surmise that delirium was increased in the nicotine replacement cohort because delirium related to nicotine withdrawal was a primary indication for replacement therapy and because coincident alcohol use was higher in the nicotine replacement cohort compared to controls. Additionally, seizures were more common in the nicotine replacement group and may have been the cause of delirium. Prospective studies examining the efficacy of nicotine replacement therapy in critically ill patients are needed.

First generation antipsychotics, such as haloperidol (Haldol), have been commonly used to treat delirium in doses that are alarmingly high. Some studies have advocated haloperidol 5 mg IV followed by doubling of the dose every 20 min [59]. Others have suggested infusion rates of 10 mg/h with increases of 5 mg/h every 30 min as needed [60]. In fact, haloperidol doses of 1,200 mg/day and >200 mg/day $\times$ 15 days have been reported [61, 62]. Safety data for these doses of typical neuroleptics are based on only a handful of case reports [60, 63]. In one case series, eight patients with agitation refractory to benzodiazepines and narcotics were treated with 3–25 mg/h of haloperidol. Of this group, five patients survived, two developed a tremor, one developed 3rd degree heart block, and one ventricular tachycardia [60]. Adverse reactions to antipsychotics

include extra-pyramidal movement disorders, neuroleptic malignant syndrome, and sudden death. Extra-pyramidal side effects are higher with high dose typical neuroleptics and include akathisia, acute dystonic reaction (more common in young men), Parkinsonism (more common in older women), and tardive dyskinesia (more common in older patients receiving 1st generation antipsychotics for a prolonged period of time). Additionally, antipsychotic medications carry a black box warning of sudden death. In a study of 90,000 medicaid patients, both typical and atypical antipsychotics were found to double the rate of sudden death compared to non-use [64]. This study also found a dose-related effect on the risk of death, presumably due to the cardiac repolarization effects, prolonged QTc, and risk of arrhythmia. Other studies have found an increased risk of mortality in elderly and demented patients when antipsychotics are used to treat delirium. In these studies, risk seems to be greater soon after initiation of antipsychotics and more pronounced with conventional neuroleptics [65, 66].

Typical and atypical neuroleptic use for the treatment of delirium has been compared in an ICU setting in two small well-designed studies, however, the utility of these agents remains unclear. When haloperidol (Haldol) and ziprasidone (Geodon) were compared to placebo in a randomized controlled trial of 100 mechanically ventilated ICU patients, there was no difference in the number of days spent in delirium or coma, nor was there a difference in mechanical ventilation days, ICU length of stay or mortality [67]. In this study, the average daily doses of haloperidol and ziprasidone were 15 and 113 mg/day, respectively. At these doses, there was no difference in the incidence of akathisia or extra-pyramidal syndrome compared to placebo. In another randomized, placebo controlled study, 36 patients with delirium in the ICU received either quetiapine (Seroquel) at escalating doses up to 200 mg every 12 h or placebo [68]. Patients receiving quetiapine (median daily dose of 110 mg) spent significantly less time delirious or agitated and had a trend toward better functional status at discharge. More somnolence was observed in the quetiapine group. Interestingly, it is not uncommon for physicians to use quetiapine in low doses (below anti-psychotic thresholds, such as 25–50 mg) to promote restoration of normal sleep-wake cycles. It is possible that simply restoring normal sleep may attenuate delirium.

While benzodiazepines may induce or worsen delirium (except in the case of alcohol or benzodiazepine withdrawal), and the role of antipsychotics in treating ICU delirium is unclear, pharmacologic pain control is an important component of managing delirium. It has been long recognized that inadequate analgesia is a strong risk factor for delirium [69]. In one study, severe pain increased the risk of delirium 9-fold [70]. Pain control is also important for limiting post-ICU conditions such as post-traumatic stress disorder (PTSD). In a study of 696 ICU military patients without serious traumatic brain injury, 35% developed PTSD. In a multivariate analysis, adequate pain control with morphine significantly reduced the risk of developing PTSD [71]. Aggressive assessment and treatment of pain is important in preventing and managing delirium.

Conclusions

Fluctuating attentiveness, or delirium, is common in ICU patients. Delirium has been associated with increased mortality and poor cognitive outcome, but unfortunately, the etiology of delirium in the ICU has not been well characterized in major studies. Serious neurological insults, such as stroke or seizure, may be underdiagnosed or labeled as delirium in the general ICU setting. Furthermore, little research exists addressing the diagnosis of delirium and its etiologies in the neurocritical care population. It is incumbent upon the scientific community to adequately investigate the causes of delirium in the ICU and characterize the neurological and cognitive risks of ICU care. Limiting sedation and/or using dexmedetomidine, rather than midzaolam or lorazepam, may help attenuate the risk of developing delirium and allow for identification of acute neurological injury, as well as shorten mechanical ventilation time, improve length of stay, reduce mortality rates, and improve functional outcome. Prospective studies addressing the frequency and cause of mental status fluctuation and its impact on functional and cognitive are needed.

Conflict of interest None.

References

1. American Psychiatric Association. Diagnostic and statistical manual. 4th ed. Washington, DC: APA Press; 1994.
2. Kiely DK, Bergmann MA, Murphy KM, Jones RN, Orav EJ, Marcantonio ER. Delirium among newly admitted postacute facility patients: prevalence, symptoms, and severity. J Gerontol A Biol Sci Med Sci. 2003;58:M441–5.
3. Lawlor PG, Gagnon B, Mancini IL, et al. Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. Arch Intern Med. 2000;160:786–94.
4. McNicoll L, Pisani MA, Zhang Y, Ely EW, Siegel MD, Inouye SK. Delirium in the intensive care unit: occurrence and clinical course in older patients. J Am Geriatr Soc. 2003;51:591–8.
5. Dyer CB, Ashton CM, Teasdale TA. Postoperative delirium. A review of 80 primary data-collection studies. Arch Intern Med. 1995;155:461–5.
6. Francis J. Delirium in older patients. J Am Geriatr Soc. 1992; 40:829–38.

7. Inouye SK, Rushing JT, Foreman MD, Palmer RM, Pompei P. Does delirium contribute to poor hospital outcomes? A three-site epidemiologic study. J Gen Intern Med. 1998;13:234–42.
8. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004;291:1753–62.
9. Caeiro L, Ferro JM, Albuquerque R, Figueira ML. Delirium in the first days of acute stroke. J Neurol. 2004;251:171–8.
10. McManus J, Pathansali R, Hassan H, et al. The course of delirium in acute stroke. Age Ageing. 2009;38:385–9.
11. Sheng AZ, Shen Q, Cordato D, Zhang YY, Yin Chan DK. Delirium within three days of stroke in a cohort of elderly patients. J Am Geriatr Soc. 2006;54:1192–8.
12. Dysken MW, Skare SS, Burke MS, Mach JR Jr, Galka T, Billington CJ. Intrasubject reproducibility of growth hormone-releasing hormone-stimulated growth hormone in older women, older men, and younger men. Biol Psychiatry. 1993;33:610–7.
13. Tune L, Carr S, Cooper T, Klug B, Golinger RC. Association of anticholinergic activity of prescribed medications with postoperative delirium. J Neuropsychiatry Clin Neurosci. 1993;5:208–10.
14. Figueroa-Ramos MI, Arroyo-Novoa CM, Lee KA, Padilla G, Puntillo KA. Sleep and delirium in ICU patients: a review of mechanisms and manifestations. Intensive Care Med. 2009;35:781–95.
15. Flacker JM, Lipsitz LA. Neural mechanisms of delirium: current hypotheses and evolving concepts. J Gerontol A Biol Sci Med Sci. 1999;54:B239–46.
16. Stefano GB, Bilfinger TV, Fricchione GL. The immune-neurolink and the macrophage: postcardiotomy delirium, HIV-associated dementia and psychiatry. Prog Neurobiol. 1994;42:475–88.
17. Dasgupta M, Dumbrell AC. Preoperative risk assessment for delirium after noncardiac surgery: a systematic review. J Am Geriatr Soc. 2006;54:1578–89.
18. Fick DM, Agostini JV, Inouye SK. Delirium superimposed on dementia: a systematic review. J Am Geriatr Soc. 2002;50:1723–32.
19. Inouye SK, Zhang Y, Jones RN, Kiely DK, Yang F, Marcantonio ER. Risk factors for delirium at discharge: development and validation of a predictive model. Arch Intern Med. 2007;167:1406–13.
20. Lundstrom M, Edlund A, Bucht G, Karlsson S, Gustafson Y. Dementia after delirium in patients with femoral neck fractures. J Am Geriatr Soc. 2003;51:1002–6.
21. Pisani MA, Murphy TE, Van Ness PH, Araujo KL, Inouye SK. Characteristics associated with delirium in older patients in a medical intensive care unit. Arch Intern Med. 2007;167:1629–34.
22. Rudolph JL, Jones RN, Rasmussen LS, Silverstein JH, Inouye SK, Marcantonio ER. Independent vascular and cognitive risk factors for postoperative delirium. Am J Med. 2007;120:807–13.
23. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001;286:2703–10.
24. Francis J. Drug-induced delirium: diagnosis and treatment. Auckland: Mairangi Bay; 1996.
25. Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology. 2004;62:1743–8.
26. Jordan KG. Neurophysiologic monitoring in the neuroscience intensive care unit. Neurol Clin. 1995;13:579–626.
27. Privitera M, Hoffman M, Moore JL, Jester D. EEG detection of nontonic-clonic status epilepticus in patients with altered consciousness. Epilepsy Res. 1994;18:155–66.
28. Vespa PM, O'Phelan K, Shah M, et al. Acute seizures after intracerebral hemorrhage: a factor in progressive midline shift and outcome. Neurology. 2003;60:1441–6.
29. Towne AR, Waterhouse EJ, Boggs JG, et al. Prevalence of nonconvulsive status epilepticus in comatose patients. Neurology. 2000;54:340–5.
30. Oddo M, Carrera E, Claassen J, Mayer SA, Hirsch LJ. Continuous electroencephalography in the medical intensive care unit. Crit Care Med. 2009;37:2051–6.
31. Alberts VP, Bos MJ, Koudstaal PJ, et al. Heart failure and the risk of stroke: the Rotterdam Study. Eur J Epidemiol. 2010;25:807–12.
32. Loh E, Sutton MS, Wun CC, et al. Ventricular dysfunction and the risk of stroke after myocardial infarction. N Engl J Med. 1997;336:251–7.
33. Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. Psychiatry Res. 1988;23:89–97.
34. Benbadis SR, Sila CA, Cristea RL. Mental status changes and stroke. J Gen Intern Med. 1994;9:485–7.
35. Salerno D, Marik PE, Daskalakis C, Kolm P, Leone F. The role of head computer tomographic scans on the management of MICU patients with neurological dysfunction. J Intensive Care Med. 2009;24:372–5.
36. Morandi A, Gunther ML, Vasilevskis EE, et al. Neuroimaging in delirious intensive care unit patients: a preliminary case series report. Psychiatry (Edgmont). 2010;7:28–33.
37. Warshaw G, Tanzer F. The effectiveness of lumbar puncture in the evaluation of delirium and fever in the hospitalized elderly. Arch Fam Med. 1993;2:293–7.
38. Inouye SK. Delirium in hospitalized older patients. Clin Geriatr Med. 1998;14:745–64.
39. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond agitation-sedation scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166:1338–44.
40. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA. 2007;298:2644–53.
41. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA. 2009;301:489–99.
42. Shehabi Y, Riker RR, Bokesch PM, Wisemandle W, Shintani A, Ely EW. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. Crit Care Med. 2010;38:2311–8.
43. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet. 2008;371:126–34.
44. Girard TD, Jackson JC, Pandharipande PP, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Crit Care Med. 2010;38:1513–20.
45. Adelow C, Andersson T, Ahlbom A, Tomson T. Prior hospitalization for stroke, diabetes, myocardial infarction, and subsequent risk of unprovoked seizures. Epilepsia. 2011;52(2):301–7.
46. Caeiro L, Ferro JM, Claro MI, Coelho J, Albuquerque R, Figueira ML. Delirium in acute stroke: a preliminary study of the role of anticholinergic medications. Eur J Neurol. 2004;11:699–704.
47. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med. 2000;342:1471–7.
48. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009;373:1874–82.
49. Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet. 2010;375:475–80.

50. Yildizeli B, Ozyurtkan MO, Batirel HF, Kuscu K, Bekiroglu N, Yuksel M. Factors associated with postoperative delirium after thoracic surgery. Ann Thorac Surg. 2005;79:1004–9.
51. Krachman SL, D'Alonzo GE, Criner GJ. Sleep in the intensive care unit. Chest. 1995;107:1713–20.
52. Inouye SK, Baker DI, Fugal P, Bradley EH. Dissemination of the hospital elder life program: implementation, adaptation, and successes. J Am Geriatr Soc. 2006;54:1492–9.
53. Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med. 2002;30:119–41.
54. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology. 2006;104:21–6.
55. Mayer SA, Chong JY, Ridgway E, Min KC, Commichau C, Bernardini GL. Delirium from nicotine withdrawal in neuro-ICU patients. Neurology. 2001;57:551–3.
56. Lucidarme O, Seguin A, Daubin C, et al. Nicotine withdrawal and agitation in ventilated critically ill patients. Crit Care. 2010;14:R58.
57. Lee AH, Afessa B. The association of nicotine replacement therapy with mortality in a medical intensive care unit. Crit Care Med. 2007;35:1517–21.
58. Seder DB, Schmidt JM, Badjatia N, et al. Transdermal nicotine replacement therapy in cigarette smokers with acute subarachnoid hemorrhage. Neurocrit Care. 2011;14:77–83.
59. Adams F. Emergency intravenous sedation of the delirious, medically ill patient. J Clin Psychiatry. 1988;49(Suppl):22–7.
60. Riker RR, Fraser GL, Cox PM. Continuous infusion of haloperidol controls agitation in critically ill patients. Crit Care Med. 1994;22:433–40.
61. Levenson JL. High-dose intravenous haloperidol for agitated delirium following lung transplantation. Psychosomatics. 1995; 36:66–8.
62. Sanders KM, Murray GB, Cassem NH. High-dose intravenous haloperidol for agitated delirium in a cardiac patient on intra-aortic balloon pump. J Clin Psychopharmacol. 1991;11:146–7.
63. Seneff MG, Mathews RA. Use of haloperidol infusions to control delirium in critically ill adults. Ann Pharmacother. 1995;29: 690–3.
64. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med. 2009;360:225–35.
65. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA. 2005;294:1934–43.
66. Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med. 2005;353:2335–41.
67. Girard TD, Pandharipande PP, Carson SS, et al. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. Crit Care Med. 2010;38:428–37.
68. Devlin JW, Roberts RJ, Fong JJ, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. Crit Care Med. 2009;38:419–27.
69. Lynch EP, Lazor MA, Gellis JE, Orav J, Goldman L, Marcantonio ER. The impact of postoperative pain on the development of postoperative delirium. Anesth Analg. 1998;86:781–5.
70. Morrison RS, Magaziner J, Gilbert M, et al. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. J Gerontol A Biol Sci Med Sci. 2003;58: 76–81.
71. Holbrook TL, Galarneau MR, Dye JL, Quinn K, Dougherty AL. Morphine use after combat injury in Iraq and post-traumatic stress disorder. N Engl J Med. 2010;362:110–7.
72. Komotar RJ, Mocco J, Ransom ER, et al. Herniation secondary to critical postcraniotomy cerebrospinal fluid hypovolemia. Neurosurgery. 2005;57:286–92. (discussion-92).
73. Brown CV, Zada G, Salim A, et al. Indications for routine repeat head computed tomography (CT) stratified by severity of traumatic brain injury. J Trauma. 2007;62:1339–44. (discussion 44–5).
74. Medical Research Council. Aids to the examination of the peripheral nervous system, Memorandum no. 45. London: Her Majesty's Stationary Office; 1981.