Delirium and Cognitive Dysfunction in the Intensive Care Unit

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Delirium is an under-recognized, highly prevalent form of organ dysfunction in the intensive care unit (ICU). It is imperative to be aware of risk factors for delirium in the ICU, some of which are modifiable. In the last 5 years, a new tool for detecting delirium among critically ill patients has been validated and found reliable for use at the bedside by psychiatrists and nonpsychiatrically trained personnel as well. The tool, the Confusion Assessment Method for the Intensive Care Unit, has enabled determination of the serious sequelae of delirium, including increased mortality, higher cost, longer length of hospital stay, failure of extubation, and burdensome, long-term cognitive impairment. This article reviews prevention and treatment options, current pharmacologic and nonpharmacologic approaches to delirium, acknowledging limited but improving quality of evidence to date.

Introduction

In 2002, the Society of Critical Care Medicine suggested that all critically ill patients should be monitored both for their level of sedation and for delirium [1••]. With the advent of diagnostic tools to assess for both sedation and delirium since the last version of this topic in 2001 [2], the Society's guidelines have become possible. No longer should delirium be a "part of the scenery," as described in 2001, because the presence of delirium using these tools has been shown independently to predict myriad untoward outcomes.

An understanding of how to prevent and treat delirium is only in its infancy, though numerous medications and several trials have attempted to address this issue among patients in the intensive care unit (ICU). From pharmacologic to nonpharmacologic interventions, progress seems

possible. It is likely as well that subsyndromal delirium—that is, the presence of some delirium features within a patient not otherwise diagnostic of full delirium—may represent a form of brain dysfunction along a spectrum heretofore not described among critically ill patients. This article will update knowledge about how to predict and to measure the frequency of delirium in the ICU, what its consequences are, how potentially to treat or prevent it, and how to begin thinking of delirium within the broader context of acute brain dysfunction in the ICU.

What is Delirium?

Delirium is a disturbance of consciousness that develops acutely, tends to fluctuate, and is associated with inattention, impaired cognition, and perceptual disturbances. Although delirium arguably has a clear definition, there may be significant heterogeneity of the disease, suggestive of complex neuropsychiatric pathophysiology. Attempts to better characterize delirium have resulted in the description of motoric subtypes: hyperactive, hypoactive, and mixed (both hyperactive and hypoactive features) [3,4]. Hyperactive delirium is characterized by increased psychomotor activity and hallucinations or other active perceptual disturbances. Decreased psychomotor activity and inattention frequently constitute hypoactive delirium. Many patients demonstrate a combination of the two types. For instance, in a study by Peterson et al. [5] of 614 consecutive medical ICU patients who were monitored for delirium over 1 year, hypoactive (44%) and mixed (55%) delirium were much more common than pure hyperactive delirium (~ 2%). The majority of patients exhibited hypoactive delirium at some point during their ICU stay, especially patients older than age 65 years [5]. Accordingly, prior assumptions as to the manifestations of delirium, and thus the frequency with which it has been previously detected may be fallacious. Inadequate recognition of a complex disease and reliance upon imperfect tools for detection limited recognition of delirium into the twenty-first century.

For many years, delirium has been described in the literature using such terms as ICU psychosis, encephalopathy of critical illness, septic encephalopathy, acute confusion, neurologic impairment, and toxic confu-

Table 1. Risk factors for delirium

Baseline characteristics	Disease factors	Iatrogenic/ environmental factors
Cognitive impairment	Sepsis	Sedative medications
Comorbidities	Hypoxemia	Analgesic medications
Age	Metabolic derangements	Use of bladder catheter
	Severity of illness score	Anticholinergic medications
		Sleep quality/quantity

sional state, among others. However, several, significant modifications in the terminology regarding delirium have occurred over the last 25 years, prompted in part by nosologic standardization from the American Psychiatric Association. Since 1980, the reference standard for diagnosis of delirium by psychiatrists among verbal patients has been the Diagnostic and Statistical Manual of Mental Disorders (DSM). Then in 1990 Inouye et al. [6••] adapted DSM-III-R [7] criteria for delirium for use in non-critically ill patients. The authors formally operationalized the resultant Confusion Assessment Method (CAM) as an algorithmic form using four of the features of delirium as described in the DSM-III-R: acute onset, fluctuating course, altered level of consciousness, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbances (eg, hallucinations, delusions), psychomotor retardation or agitation, inappropriate speech or mood, and sleep/wake cycle disturbance. The CAM required the presence of both 1) acute onset of altered mental status and fluctuation thereof and 2) inattention plus either 3) disorganized thinking or 4) altered level of consciousness. Following successful validation of the CAM and determination of its reliability even when used by nonpsychiatrists, the CAM became the new reference standard for delirium among patients not in the ICU. However, the CAM's adaptation and applicability to a cohort of critically ill patients had not been tested until 2001. Efforts to enhance the feasibility, validity, and reliability of the CAM among patients in the ICU, resulting in the CAM-ICU, have since revolutionized and standardized the detection and monitoring of delirium among the critically ill.

Demographics of Delirium

Approximately 15% to 60% of hospitalized general medical or surgical patients become delirious, with the occurrence highest among older patients [8–11]. The prevalence of delirium among mechanically ventilated ICU patients ranges from 7% to 80%, with the highest rates

among patients older than age 65 years [12,13,14••,15–19, 20••,21,22•,23–25].

Prior supposition has been that the wide variation in prevalence of delirium among cohorts of critically ill patients was due to differences among patient populations or to different severities of illness. Three caveats exist. First, application of tools not intended for use among largely nonverbal cohorts of patients in the ICU (such as the original CAM) may not be appropriate. McNicoll and colleagues [23] compared the CAM with the CAM-ICU in a study of 22 alert, nonintubated patients in the ICU, noting that the two instruments agreed 82% of the time but that the CAM identified delirium in four patients that the CAM-ICU did not. However, the frequent use of sedation and analgesia, even among nonventilated ICU patients, calls into question the validity and reliability of the CAM's verbal assessment, and the authors did not employ a reference standard (ie, formal psychiatric assessment). Second, the most recent revision of the DSM (DSM-IV) has been found to yield a higher prevalence of delirium among than did the DSM-III-R [26,27]. Third, a recent, unpublished, prospective cohort study of critically ill surgical and trauma patients suggests that the prevalence of delirium among that cohort is 68% (Pandharipande, personal communication); therefore, the prevalence of delirium may not, in fact, be any lower among non-medical ICU patients. Accounting for these caveats, the prevalence of delirium among mechanically ventilated ICU patients appears to vary from 50% to 80%, with a range for nonventilated ICU patients from 21% to 68%.

Risk Factors for Delirium

Because there have been relatively few studies, numerous potential risk factors for delirium exist. Moreover, there are likely multiple factors even within a given patient that could lead to delirium. For many patients the ICU represents the intersection of multiorgan dysfunction necessitating mechanical ventilation, which begets sedatives and/or narcotics to ensure patient comfort and patient-ventilator synchrony. Those patients who do not require mechanical ventilation frequently still require or evidence frequent disruptions of sleep (ie, from alarming monitors or intravenous pumps, blood draws, bathing, or changes in positioning to prevent decubitus ulcer formation); moreover, nonventilated ICU patients not uncommonly still require sedatives or narcotics and suffer multiple organ dysfunctions.

For practicality and simplicity, we divide proven or potential risk factors among three categories: 1) host characteristics, 2) features of the acute illness, and 3) environmental or iatrogenic factors (Table 1).

The accumulation of risk factors likely portends development of delirium. In separate cohorts of non-ICU patients, Francis et al. [28] and Inouye and Charpentier [29] noted at least a 60% risk of developing delirium

among patients with three or more risk factors. Critically ill patients easily have at least three risk factors. In fact, in a study of 53 consecutive medical ICU patients, Ely et al. [30] discovered that each patient had a mean ($\pm$ standard deviation) of 11 ($\pm$ 4) delirium risk factors, with a range of 3 to 17. The accumulation of risk factors in critically ill patients undoubtedly contributes to a high prevalence of delirium.

Perhaps the most universal and potentially modifiable risk factor among critically ill patients is exposure to psychoactive medications such as sedatives and analgesics. Ely et al. [30] identified exposure to benzodiazepines or narcotics in 98% of patients in an ICU cohort. In a cohort of 216 medical and surgical ICU patients, Dubois et al. [16] found that morphine was the strongest predictor of delirium in a multivariable model, with an increase in odds of at least sixfold over 5 months. Additionally, in a cohort of 198 mechanically ventilated medical and cardiac ICU patients, Pandharipande et al. [31] found that lorazepam had an independent and dose-related temporal association with delirium. The risk for daily transition to delirium increased by 20% per milligram of lorazepam (odds ratio [OR] = 1.2/mg; 95% CI, 1.1–1.4; P = 0.003) after adjusting for 11 relevant covariates. Despite a trend toward significance, midazolam and fentanyl did not significantly portend the same risk. It is possible that delirium represents an idiosyncratic reaction to psychoactive (or other) medications, accounting for some of the difference in the limited data to date. Further evaluation of the role of psychoactive medications commonly used in the ICU is warranted to further elucidate mechanisms and the role of these medications in the development of delirium. Efforts to minimize the use of sedatives and analgesics have been strongly encouraged for ventilated patients [32••]. Additionally, alternative medications should be sought, such as dexmedetomidine in place of lorazepam for sedation.

Another important and common risk factor, though unalterable, among hospitalized patients is older age. Increasing age has been shown to independently predict delirium among non-ICU patients [33,34]. However, this relationship has been unproven among ICU patients older than age 65 years, who account for nearly 60% of all ICU patient-days [35]. Some have suggested that this disconnect may be due to a generally faulty assumption that the risk factors outside the ICU are the same as those within. For example, in a cohort of 216 critically ill medical and surgical patients in whom the overall prevalence of delirium was low (19%), the authors were unable to show that common risk factors for delirium (eg, age) outside the ICU were significant among the critically ill [16]. Likewise in a cohort of 818 surgical ICU patients, age was not associated with delirium using logistic regression. However, this population was young compared with typical ICU populations [13]. Moreover, both of these studies suffered from insufficient power

Figure 1. Diagnosis of delirium with the Confusion Assessment Method for the ICU (CAM-ICU). See <http://www.icudelirium.org>. Adapted from Inouye et al. [6••].

or methodologic problems, potentially limiting their ability to detect differences among patients older than age 65 years. Finally in 2006, Pandharipande et al. [31] demonstrated that age significantly increases risk for development of delirium. The authors noted a statistically significant, 2% increase in probability of transition to delirium for each year beyond age 65 years, even after controlling for relevant covariates.

How Do We Measure Delirium in the ICU?

At best, and despite its prevalence, medical doctors and intensivists have markedly underdiagnosed delirium since its nosologic inception in 1980 [36–38]. After the 1987 revision of the DSM, Inouye et al. [6••] developed and validated a tool (the CAM) to assess hospitalized patients for delirium. Other tools for use outside the ICU were subsequently developed and tested with varying degrees of success [39,40]. However, they were not practical for use in critically ill patients because they required verbal responses, took at least 5 to 10 minutes to complete, were not found valid and reliable among ICU patients, or were not demonstrated to be associated with clinical outcomes. Hence, delirium continued to be under-recognized in the ICU population.

Efforts to create an instrument to objectively evaluate for delirium among ICU patients began in 1996 and led to the development and validation of the Cognitive Test for Delirium [41,42] and the Intensive Care Delirium Screening Checklist [17]. The abbreviated version of the Cognitive Test for Delirium was presented in 1997 by Hart et al. [42] after evaluation in 19 delirious patients (15 critically ill). Although it took but a few minutes to complete and was shown to discriminate well among delirium, dementia, depression, and schizophrenia (P < 0.0001), the abbreviated Cognitive Test for Delirium was not evaluated in a cohort of ICU patients, not all of whom were delirious. In contrast, when the Intensive Care Delirium Screening

Figure 2. Kaplan-Meier analysis of delirium in the intensive care unit and 6-month survival. Adapted from Ely et al. [20••], with permission.

Checklist was first reported in 2001, it was heralded as valid among a general population of ICU patients. Using a consulting psychiatrist who served as the reference standard rater, the checklist of eight different delirium features derived from DSM criteria predicted delirium with 99% sensitivity but only 64% specificity, using a cutoff of four or more features as indicating delirium. Because of the low specificity, the authors concluded that the checklist was most appropriate for use in screening for (rather than diagnosing) delirium.

Developed in 2001, the CAM-ICU is the only delirium assessment tool for use in critically ill patients that has been validated against a reference standard rater in multiple cohorts [14••,15,21]. Building upon the work of Inouye et al. [6••], Hart et al. [41,42], and others [43] as well as the DSM-IV [44], Ely et al. [14••] created the CAM-ICU (Fig. 1) for use by nonpsychiatrists in mechanically ventilated patients. When features 1 and 2 and either feature 3 or feature 4 are present, a patient is said to be delirious or “CAM-ICU positive.” In the largest validation cohort of 111 medical ICU patients using the CAM-ICU and as compared with reference standard raters, two study nurses demonstrated high sensitivity (93%–100%), high specificity (98%–100%), and high inter-rater reliability ($\kappa = 0.96$; 95% CI, 0.92–0.99) [14••]. Importantly, the CAM-ICU also distinguishes delirium from coma—defined as the state of unarousability, unawareness of the environment, and absence of spontaneous interaction or awareness of the interviewer—and dementia. Requiring on average less than 2 minutes to complete, the CAM-ICU has been validated, and its reliability has been confirmed in other languages and at least one other region of the world [21]. Its ease of use among nonpsychiatrists also makes the CAM-ICU practical [45•]. Subsequent revisions of the CAM-ICU, including use of the validated Richmond Agitation Sedation Scale

to monitor level of consciousness [46–48] and a greater reliance upon a form of the Vigilance A random letter test [43] rather than the picture recognition tool for the attention screening examination, are being incorporated in ongoing clinical trials. The development of a simple, objective, brief, valid, reliable, and widely accepted, bedside assessment tool for critically ill, often mechanically ventilated, patients has revolutionized the detection of delirium but has also revealed its serious sequelae.

Outcomes and Prognostic Significance of Delirium in the ICU

With an effective tool to diagnose delirium, the next step was to determine the independent association of delirium with multiple, clinically significant endpoints. Over the last 5 years, much has been learned about the impact of delirium both while in the hospital and for up to 2 years after the hospitalization. On a daily basis, delirium and/or altered levels of consciousness contribute to an increased risk of complications related to the complex bedside monitoring, drug delivery [16], and life-supporting therapies that are commonplace in ICUs. Given that most patients who develop delirium survive to hospital discharge, these long-term sequelae will likely prove to be more burdensome than currently imagined.

Mortality

Increased risk of death among delirious, non-critically ill patients for up to 2 years has been previously identified [49,50]. Over the last 5 years, additional data on critically ill patients have shown a similar impact of delirium, though not always during the immediate hospitalization period [12,16,24]. Lin et al. [21] demonstrated a 13-fold increased risk for in-hospital death among 111 mechanically ventilated patients. Furthermore, Ely et al. [20••]

prospectively followed 275 mechanically ventilated, medical ICU patients for 6 months from the time of hospital discharge and noted a threefold increase in the risk of death by 6 months, even after adjustment for age, severity of illness, comorbid conditions, coma, and the use of sedatives and analgesics (adjusted hazard ratio = 3.2; 95% CI, 1.4–7.7; $P = 0.008$) (Fig. 2).

Cost

Costs of care in the ICU are significantly higher among those who develop delirium than those who do not. Milbrandt et al. [51] reported in 2004 that the costs to care for a delirious, critically ill patient were significantly higher than for patients who never became delirious, even after controlling for several covariates. The costs of caring for delirious, critically ill patients were a median \$9014 and \$14,730 higher for ICU and hospital stays, respectively. At least part of this increase would likely be accounted for by longer lengths of stay.

Length of stay

That ICU delirium independently prolongs both ICU and hospital length of stay has been demonstrated in at least four studies. The first, a cohort of 238 critically ill patients, revealed that the median ICU length of stay was three times longer for delirious patients than nondelirious patients (15 vs 5 days, respectively; $P = 0.0001$) and that delirium persisted for a median of 5 days [12]. Subsequently, using multivariable analysis to evaluate the association of delirium and hospital length of stay in a cohort of 48 medical ICU patients, Ely et al. [30] demonstrated that of delirium, severity of illness, age, gender, race, and duration of sedative and analgesic drug administration, delirium was the strongest predictor ($P = 0.006$). These results were then confirmed in two, large, follow-up cohorts of more than 250 patients that showed a 41% to 100% increase in hospital length of stay for delirious patients after controlling for multiple covariates [20••,25].

Failure of extubation

As is the case with longer ICU and hospital stays among delirious patients, the potential for delirium to contribute to extubation failure necessarily subjects patients to risk of complications. For example, failure of extubation patients to the risks of prolonged ventilation or of reintubation, including such complications as nosocomial pneumonia [52] and death [53]. That abnormal mental status significantly predicts failure of extubation has been previously studied [54,55]. Nearly 10% of delirious, intubated patients in one study versus 2.3% of nondelirious, intubated patients self-extubated [16]. Recently we have also demonstrated that the presence of delirium, specifically as determined by the CAM-ICU, is associated with a nearly threefold increased risk for reintubation within 48 hours of pre-dominately planned extubations [56].

Long-term cognitive impairment

In addition to the predisposition of cognitive impairment among critically ill patients for the development of delirium, it appears that delirium may also independently cause or result in greater occurrence and severity of cognitive impairment for up to 3 years after ICU stay. In a review of nine prospective studies evaluating a total of 1885 hospitalized medical and surgical (non-ICU) patients, Jackson et al. [57••] found that intrahospital delirium increased the likelihood of dementia as much as threefold up to 3 years from the time of hospital discharge. A smaller study that stringently examined 34 previously mechanically ventilated patients demonstrated that although “normal” at baseline almost one third were neuropsychologically impaired by standardized neuropsychologic batteries at 6 months following hospital discharge [58]. More recently, Hopkins et al. [59] have confirmed the high prevalence of cognitive impairment among previously critically ill patients long after discharge from the hospital. An area ripe for future investigation, the likely role of delirium in contributing to long-term cognitive impairment suggests the need for larger, prospective cohort studies to better identify risk factors for persistence of neurocognitive dysfunction. As with mortality, cost, length of stay, and failure of extubation, the presence of long-term cognitive impairment among critically ill patients represents a significant, lasting burden for patients and their families.

Strategies for Optimal Management

With the development of effective diagnostic tools such as the CAM-ICU and the Richmond Agitation Sedation Scale, the Society of Critical Care Medicine’s recommendations to monitor for delirium and sedation level in all critically ill patients are easier to follow—and to do so frequently. However, for them to take their place alongside such stalwart, multidisciplinary interventions in the ICU as deep venous thrombosis prevention or antibiotics, evidence that altering the occurrence or course of delirium decreases the frequency of untoward outcomes is essential. Likely, this will require targeted prevention strategies and specialized, multidisciplinary interventions, both nonpharmacologic and pharmacologic.

Nonpharmacologic approach

Although several clinical trials of multicomponent, nonpharmacologic interventions have been performed [11,60,61], none targeted the ICU and all have met with modest, post-discharge success. The largest such trials in the literature are those conducted by Inouye et al. [11] and Lundström et al. [61]. The former, a nonrandomized trial of patients older than age 70 years admitted either to a specialized ward or to a regular unit, featured an intervention protocol. The protocol targeted such features as cognitive stimulation, reorientation prompts, a sleep protocol, visual

and hearing aids, reminders to prevent volume depletion, and walking/exercise. The incidence of delirium among the intervention as compared with those who received usual care was significantly lower, 9.9% versus 15.0%, respectively ($P = 0.02$). Unfortunately, neither the severity of delirium nor the recurrence rates differed between the two groups, and subsequent follow-up of the patients 6 months after hospital discharge did not demonstrate sustained benefits overall [62]. However, the highest-risk delirious patients (arguably those most similar to critically ill patients) did report higher health and functional status scores at 6 months than did high-risk, nondelirious patients. The more recent trial by Lundström et al. [61] incorporating a nurse-driven, multifactorial intervention program among 400 patients older than age 70 years resulted in significant reductions in duration of delirium (30% absolute risk reduction, $P = 0.001$) and hospital length of stay (3-day reduction, $P < 0.001$). We hope long-term follow-up will yield promising results and anticipate that interventions to prevent or diminish the consequences of delirium among both noncritically ill and ICU patients will remain fundamental to management of delirium in the future.

Drug therapy

That nonpharmacologic interventions to prevent a disease are prudent is no surprise. However, with a widening array of medications at our disposal, physicians are tempted to act when faced with medical abnormalities. Accordingly, the temptation to seek pharmacologic interventions for diseases such as delirium in the ICU frequently outpaces the scientific evidence to support their use. In a 2004 survey of 912 intensivists, 92% considered delirium a substantial problem in the ICU despite only 40% routinely screening for it. Yet, 79% reported that delirium requires active intervention and 66% felt haloperidol should be the treatment of choice, followed by lorazepam (12%) and atypical antipsychotics (4%). Despite this impulse to intervene pharmacologically with haloperidol and the support of this position by both the Society of Critical Care Medicine [1•] and the American Psychiatric Association [63], there are no randomized, placebo-controlled trials to confirm the efficacy of haloperidol in either the prevention or the treatment of delirium. Not surprisingly, no drugs have Federal Drug Administration approval for the prevention or the treatment of delirium. Through 2005, anecdotal evidence, uncontrolled trials, and a few randomized trials comparing haloperidol with neuroleptics or benzodiazepines constitute the basis for professional societies' recommendation of haloperidol.

Antipsychotics such as haloperidol and the "atypicals" (eg, olanzapine, risperidone, ziprasidone, aripiprazole, quetiapine) are thought to exert their antidelirium effect in at least two ways. First, the drugs are thought to "normalize" cerebral function by disinhibition of acetylcholine, blockade of dopamine

receptors, and activation of serotonin receptors. Second, some data suggest that haloperidol may exhibit anti-inflammatory effects upon the production of proinflammatory cytokines [64,65].

The atypicals do not have intravenous formulations. As such, those who have or are investigating haloperidol as compared with an atypical antipsychotic must rely upon either enteral or intramuscular administration. Nonetheless, intravenous haloperidol is not only common but recommended [1•,66,67], with a protocol of escalating dose (eg, doubling every 30 minutes until desired effect) noted in professional guidelines [1•].

Pharmacokinetics is important with antipsychotics, as with all drugs, in portending risk of adverse events. The half-life of haloperidol is approximately 21 hours, with peak plasma concentrations noted within 2 to 6 hours of dosing (enteral) or 20 minutes (intramuscular). Notable side effects of the drug can include hypotension that antagonizes adrenaline (especially in parenteral form), dose-dependent QTc prolongation leading to cardiac tachyarrhythmias such as *torsades des pointes* [68–70]—particularly among those with pre-existing cardiac disease and in those who receive a more than 35 mg cumulative dose—extrapyramidal symptoms [71], neuroleptic malignant syndrome [72], dysphoria [73], or laryngospasm [74]. Meanwhile, the atypical antipsychotics typically have half-lives of at least 20 hours, with the exception of ziprasidone (approximately 7 hours). Peak plasma concentrations are typically reached within 5 to 8 hours following enteral ingestion, though risperidone reaches peak concentration within 1 hour, or within 1 hour for drugs administered intramuscularly. In contrast to haloperidol, the atypical antipsychotics cause few side effects usually, though weight gain and hypotension are not uncommon, and there may be an increased risk of hyperglycemia or diabetes with the drugs [75]. The risk of extrapyramidal symptoms or neuroleptic malignant syndrome is lower by design.

Data supporting the use of haloperidol either alone or versus other medications are limited. Evidence for the potential benefit of haloperidol, however, was recognized by Milbrandt et al. [76]. In a cohort of 989 mechanically ventilated ICU patients, those who received haloperidol within the first 48 hours were 16% less likely to die during the hospitalization [76]. One explanation for this finding is the purported anti-inflammatory effect of haloperidol.

The only prospective trials to our knowledge to evaluate the efficacy of treatment of delirium in the ICU with antipsychotics are fraught with limitations but provide reassurance as to the safety of so-called "atypical" antipsychotics. One unblinded study evaluated the efficacy and safety of enteral olanzapine as compared with enteral haloperidol in the treatment of 73 ICU patients who screened positive for delirium according to DSM-IV criteria [22•]. Although there was

no difference in the development of delirium between the treatment groups, the study confirmed the safety of olanzapine, as none of the patients in the olanzapine arm but six patients in the haloperidol arm experienced extrapyramidal symptoms. In addition to a simplistic randomization scheme, a predominance of surgical ICU patients, and a low severity of illness score (mean Acute Physiology and Chronic Health II score of 12.7), the low overall prevalence of delirium (21%) relative to other ICU cohorts calls into question the generalizability of this study's results. Although the trial did not intend to answer the question of whether olanzapine is equal or superior to haloperidol, it did suggest that the former is no more, and perhaps less, harmful. Moreover, similar results were found in a separate trial comparing haloperidol with risperidone [77]. Again, delirium scores decreased during drug administration in both groups ($P < 0.05$), but there was no difference in the scores between the two treatment groups ($P = 0.51$). A placebo-controlled study comparing placebo with haloperidol and an atypical antipsychotic would most appropriately address this question.

As suggested by the first admonition of the Hippocratic Oath, it may be as important what medications we do not use as those we do use to alter the occurrence and course of delirium. Almost all ICU patients require and receive sedatives and analgesics, particularly during the early part of their ICU stay, and avoidance of harmful medications during that time seems prudent. Little evidence exists to date to guide this type of decision, but in a study by Breitbart et al. [78], the authors randomized 30 hospitalized and subsequently delirious patients with AIDS to receive either lorazepam ($n = 6$), chlorpromazine ($n = 13$), or haloperidol ($n = 11$) [78]. They found that either haloperidol or chlorpromazine significantly reduced the delirium score as compared with lorazepam ($P < 0.001$), leading the authors to suggest that lorazepam alone is ineffective in decreasing delirium symptoms. That it is a known risk factor further validates the assertion that outside well-known drug withdrawal syndromes, benzodiazepines are not recommended for routine treatment of delirium. Moreover, when used, they should be used in the context of sedation protocols that employ intermittent bolus sedation, if at all possible [32••,79,80].

Even though minimal data beyond consensus opinion exist currently to guide prevention or treatment decisions in ICU delirium, the CAM-ICU provides an effective tool to evaluate the safety and efficacy of non-pharmacologic and pharmacologic interventions alike. Several, ongoing, randomized, and/or placebo-controlled trials should begin to clarify the indications for use of the typical and atypical antipsychotics and the indications for use of other agents (such as dexmedetomidine) for sedation.

Spectrum of Acute Brain Dysfunction

In addition to delirium, other forms of brain dysfunction such as coma, stupor, and subsyndromal delirium may represent a continuum of acute brain dysfunction. Subsyndromal delirium is perhaps best defined as the presence of some, but not full, criteria for delirium [81–84]. In the case of the CAM-ICU, that could mean disorganized thinking despite normal levels of consciousness and attention or a fluctuating level of consciousness despite preserved attention and thinking. Distinction of these subtypes of brain dysfunction may be pertinent in light of the prevailing notion that increasing severity of delirium is associated with worse outcomes outside the ICU [81–83]. For example, Marcantonio et al. [83] compared 504 patients who remained CAM negative (not delirious) or who became CAM positive (delirious) or CAM intermediate (subsyndromal delirium, those with one or more CAM features but not diagnostic of delirium) during their stay at post-acute skilled nursing facilities. They found that patients with subsyndromal delirium had intermediate 6-month mortality rates (25.0%, 18.3%, and 5.7% for delirious, subsyndromal delirium, and “normal” patients, respectively), intermediate rehospitalization rates, and intermediate rates of complications, even after adjusting for age, pre-existing dementia, and medical comorbidity. Identification of similar phenomenology of acute brain dysfunction in the ICU might help better target therapeutic interventions.

Conclusions

Since 2001 our knowledge of delirium in the ICU has changed dramatically. Not only has there been greater understanding, if persistent under-appreciation, of the prevalence of delirium among the critically ill, but also attempts to identify risk factors for delirium specifically in the ICU have increased and occasionally provided targets for modification. With the additional development of the CAM-ICU, the independent association of delirium with untoward outcomes from mortality to long-term cognitive impairment has been possible to describe. Now, further efforts to determine appropriate interventions and management of delirium must come to the fore. Placebo-controlled trials for treatment of delirium are on the horizon. In avoiding harmful medications or pursuing beneficial ones, the prevention and treatment of delirium or any of the various subtypes along the continuum of acute brain dysfunction in the ICU will require a multidisciplinary approach. Diligent investigation, including large cohort studies will help identify potential new targets for intervention in the years ahead.

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Papers of particular interest, published recently, have been highlighted as:

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- Of major importance

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The original validation study of the CAM, which is now the most common method of diagnosing delirium by nonpsychiatrists. This instrument was adapted for use in intubated, mechanically ventilated ICU patients to form the CAM-ICU.

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