Delirium is characterized by an acute change or fluctuation in mental status, inattention, and either disorganized thinking or an alteration in level of consciousness. It occurs in 35% to 80% of critically ill hospitalized patients. The variability in delirium rates described in the surgical or medical critically ill depends partly on the severity of illness and partly on the type of instrument used to screen for delirium.

Brain dysfunction (delirium and coma) in nonneurologic intensive care unit (ICU) patients has been the subject of increased study in recent years; coma and delirium appear to be independent predictors of longer hospital stay, higher hospital costs, and higher mortality.\(^1\)–\(^3\) Delirium may be associated with prolonged cognitive impairment, impaired activities of daily living, and decreased quality of life in survivors of critical illness.

DEFINITIONS AND CATEGORIES OF DELIRIUM

Delirium can be diagnosed in ICU settings by psychiatrists and trained nonpsychiatric personnel. It can be detected in mechanically ventilated and other nonverbal patients using validated instruments such as the Confusion Assessment Method for the ICU\(^4\) and the Intensive Care Delirium Screening Checklist (ICDSC).\(^5\) Verbal communication limits descriptions of specific symptoms in intubated patients. Agitation and slowing occur frequently (in more than 90% of patients), and specific symptoms may be markers of prognosis.\(^6\)

SUBSYNDROMAL DELIRIUM

Subsyndromal delirium occurs when patients have one or more delirium symptoms but do not meet criteria for full-blown clinical delirium.\(^7\) This clinical syndrome is well described in the geriatric literature. In the ICU, its identification is possible with the ICDSC, a graded scale at the patient’s bedside, with clinical criteria rated from zero to eight.\(^7\) Delirious patients have four clinical abnormalities or more. Patients with no abnormalities (ie, an ICDSC of 0) are considered cognitively normal. Those
with ICDSC ratings of one to three items are labeled as having “subsyndromal delirium.” Subsyndromal delirium affects roughly one-third of the critically ill, as reported in the only paper published to date on the subject. This incidence, when combined with the number of patients considered delirious with the ICDSC, adds to a combined 70% incidence of delirium-like cognitive abnormalities. It is possible that the discrepancies in incidence descriptions for delirium (35% by some and 80% by others) are related to separate identification or confounding of these two syndromes. Whether subsyndromal delirium constitutes a graded step in the spectrum of brain dysfunction severity (from normal to subsyndromal delirium to delirium) or not is unclear. Although subsyndromal delirium resembles delirium in that it is associated with longer hospital stay and a higher probability of dependent living upon hospital discharge, it does not have the same risk factors and is probably preventable.

PREVENTION

Delirium has untoward consequences, on the one hand, and potentially preventable associated factors, on the other. Studies addressing delirium prevention and prophylaxis can be separated into those evaluating nonpharmacologic, pharmacologic, and combined (pharmacologic and nonpharmacologic) approaches.

Nonpharmacologic Delirium Prevention

Controversy exists as to whether factors associated with delirium are causative. Nonpharmacologic intervention aims to prevent or reverse these potential contributors. Although no studies have been published to date on nonpharmacologic delirium prevention in the ICU, two prevention strategy studies in non-ICU patients deserve mention. The first to successfully demonstrate the effectiveness of nonpharmacologic intervention targeted specific aspects of care in a high-risk medical geriatric population. Treated patients underwent systematic orientation; therapeutic activities designed to lessen cognitive impairment; early mobilization; nonpharmacologic minimization of psychoactive drug use; prevention of sleep deprivation; enhancement of communication, including provision of eyeglasses and hearing aids; and early intervention for volume depletion. The incidence of delirium was 9.9% with this intervention compared with 15.0% in the group receiving usual care (odds ratio [OR], 0.60; 95% confidence interval [CI], 0.39, 0.92). In those patients who did develop delirium, exposure to “preventive” measures did not change the severity or the duration of delirium or any of the complications associated with it.

The second nonpharmacologic intervention study, the first randomized clinical trial, allocated hip fracture patients to “standard care” versus care in which treating physicians requested a routine geriatric consultation. The consultation incorporated standardized recommendations targeting 10 domains: systemic oxygenation monitoring, as a surrogate for oxygen delivery to the brain; fluid and electrolyte balance; pain management; minimization of psychoactive drug use; optimal bowel and bladder function; nutrition; early mobilization; prevention of postoperative complications; appropriate environmental stimuli; and treatment of delirium symptoms. A 77% adherence to the geriatric consultant’s recommendations was achieved in this study, and the total cumulative incidence of delirium during hospitalization was 32% in the proactive geriatric-consultation group versus 50% in the “usual care” group (OR, 0.48 [95% CI, 0.23, 0.98]; relative risk [RR], 0.64 [95% CI, 0.37, 0.98]).

One study documented the incidence of delirium in 49 patients randomized to early physiotherapy and occupational therapy versus 55 patients randomized to routine care. There were fewer days of delirium in the ICU [2.0 (0.0, 6.0) vs 4.0
and in the hospital [2.0 (0.0, 6.0) vs 4.0 (2.0, 8.0); \( P = .017 \)] in the early mobilization group. Likewise, there were a lower percentage of ICU days with delirium [33.0% (0.0%, 58.0%) vs 57.0% (33.0%, 69.0%); \( P = .015 \)] and percentage of hospital days with delirium [25.0% (0.0%, 43.0%) vs 39.0% (22.0%, 62.0%); \( P = .009 \)] in the early mobilization group. \(^{10}\) Risk factors for delirium between groups were similar.

The features that link these studies are careful and systematic assessments of non–life-threatening patient characteristics, medications, and needs. Most of the interventions focus on dimensions that are not part of the culture of most ICUs. Some interventions, for instance prevention of sleep deprivation, may be challenging to implement in an ICU where sleep is abnormal in the majority of patients. \(^{11}\) Further, it is a secondary consideration in the context of caring for acute emergencies. Other interventions, such as early mobilization, have been shown to be of benefit but are nonetheless not yet part of routine practice.

Until ICU-based delirium prevention studies are available, it seems reasonable to implement patient-focused care, and to broaden this perspective to include reorientation, communication, mobilization, and minimization of pharmacologic exposure. At the very least, it is difficult to see how such approaches, when administered by well-educated health care professionals, could place the patient at risk.

### Pharmacologic Delirium Prevention

Aizawa and colleagues\(^ {12}\) hypothesized that sleep disturbances are critical factors in the etiology of postoperative delirium. In this study, patients were admitted to the ICU after abdominal surgery and were then randomized to pharmacologic sleep-wake cycle adjustment or to conventional care. The “Delirium Free Protocol” involved nightly routine administration of intramuscular diazepam at 20:00 hours and intravenous 8-hour long infusions of flunitrazepam and meperidine. The incidence of delirium in the 7 days after surgery was significantly lower in the intervention group (5% vs the controls’ 35%) \( \text{OR, 0.10 [95\% CI, 0.01, 0.89]; RR, 0.14 [95\% CI, 0.02, 1.06]} \).\(^ {12}\) However, the protocol caused some sedation upon waking, and this may have interfered with delirium assessment.

There are no trials evaluating antipsychotic drugs or anticholinesterase inhibitors for delirium prevention in the ICU. Outside the ICU, a trial evaluating prophylactic haloperidol was not effective in preventing delirium but did reduce its severity and duration. \(^ {13}\) A second study that compared donepezil with placebo reported an incidence of delirium of 18.8% after surgery in treatment and placebo groups (\( \text{RR, 1.2 [95\% CI, 0.48, 3.00]} \)).\(^ {14}\)

Dexmedetomidine has been compared with midazolam in the sedation of critically ill patients. \(^ {15}\) The prevalence of delirium during sedative treatment was strikingly lower in dexmedetomidine-treated patients: 54% \( (n = 132/244) \) versus 76.6% \( (n = 93/122) \) in midazolam-treated patients (95% CI, 14%–33%); \( P<.001 \)).\(^ {15}\) Dexmedetomidine-treated patients were more likely to develop bradycardia (42.2% \( [103/244] \) vs 18.9% \( [23/122] \); \( P<.001 \)).\(^ {15}\) It can be speculated that dexmedetomidine, a potent central alpha-2-receptor antagonist, which is described for the treatment of alcohol withdrawal, has a potential role to play in delirium prevention or treatment. Conversely, the benzodiazepines used in the nondexmedetomidine group may have contributed to the increased incidence of delirium. \(^ {16}\)

### Combined Pharmacologic and Nonpharmacologic Prevention

The use of sedatives\(^ {16,17}\) and analgesics\(^ {18}\) has been linked to delirium, particularly in the context of excessive sedation. The author’s group implemented and compared, in a PRE-POST fashion, a symptom-driven protocol in a single tertiary ICU. \(^ {19}\) They
routinely distinguished among the clinical features of pain, agitation, and delirium and provided protocolized pharmacologic and nonpharmacologic approaches that were individualized to specific symptoms. After the institution of this protocol (POST), more patients remained cognitively intact (32.5% PRE vs 41.2% POST; \(P = .004\)). The rate of delirium was similar (34.7% PRE vs 34.2% POST; \(P = .9\)), but the number of patients manifesting subsyndromal (ie, subclinical) delirium was significantly less in POST. There was no difference in antipsychotic use between the PRE and POST groups.

Combined pharmacologic and nonpharmacologic prevention strategies are challenging and onerous to implement in any inpatient unit. Problems with adherence to protocols have been described, and they likely limit the effectiveness. Further studies are needed but, of necessity, are likely to be limited in scope and in number. Risk stratification may aid in identifying patients most likely to benefit from multimodal interventions. Strategies to improve intervention implementation and adherence, such as shared “owner”ship” and interactive education, may also serve to improve interdisciplinary protocols. Such combined approaches are likely to be an integral part of any delirium intervention package.

ALCOHOLIC PATIENTS

Alcoholic patients deserve special mention. About 1 in 10 North Americans purportedly consumes excess alcohol and is therefore at risk for alcohol withdrawal. In addition, alcoholism contributes to as many as 21% of admissions to ICU. Validated questionnaires (eg, CAGE questionnaires or Clinical Institute Withdrawal Assessment for Alcohol Scales) are not routinely administered in the critical care setting. Alcoholism doubles the incidence of delirium without necessarily developing into alcohol withdrawal syndrome. Screening for alcohol consumption should be part of every ICU admission case history, whenever feasible.

DELIRIUM TREATMENT

**Nonpharmacologic**

Addressing delirium management in the ICU requires routine screening for its presence. Validated pedagogic interventions targeting nurses are useful in establishing reliable delirium screening. Early delirium recognition and management in the medical and surgical ICU setting may aid in delirium resolution and shorten the length of stay. Although interventions focused on increasing exposure to daylight, avoiding use of restraints, and boosting family contact are endorsed by intensivists and other caregivers, none of these interventions have been rigorously evaluated.

**Pharmacologic**

Delirium is distressing for patients, families, and caregivers. Pharmacologic sedation of the agitated or frightened patient is therefore broadly perceived as desirable. Although no double-blind, randomized, placebo-controlled trial has ever established the efficacy or safety of any antipsychotic medication in the management of delirium, administration of antipsychotics is endorsed by guideline recommendations, and it is part of routine clinical practice for the majority of intensive care specialists.

Any discussion of antipsychotic medication as a category is complicated by the variety and the differences in the receptor-adherence profiles characteristic to each. All conventional and atypical antipsychotics appear to be equally efficacious in the treatment of psychosis, and at present there is no evidence of differential effects on delirium. Two studies evaluating antipsychotic use in the ICU have been
published. In the first, delirious patients able to tolerate enteral nutrition were randomized to receive enteral olanzapine or intravenous haloperidol. Both groups of patients improved with time in their delirium severity score. Benzodiazepine requirements, which reflected the need for sedation, decreased equally in both groups. Patients in the olanzapine arm had less extrapyramidal side effects than those receiving haloperidol. In the second study, 30 delirious patients able to tolerate enteral nutrition were randomized to receive quetiapine (50 mg every 12 h) or placebo in addition to as-needed intravenous haloperidol. Patients receiving quetiapine achieved a “nondelirium” score (ie, Intensive Care Delirium Checklist score <4) faster, had a shorter ICU stay (54 vs 138 hours, \( P < .007 \)), spent less time agitated (6 vs 36 hours, \( P = .03 \)), and required a shorter treatment duration. It is not clear whether these findings are generalizable, as the studies are limited by their inclusion of patients able to tolerate enteral drugs, thereby limiting the generalizability of the findings.

There are no intravenous second-generation antipsychotics available for ICU use. The use of other sedatives, such as benzodiazepines, has generated much scientific and academic interest over the last 10 years; however, the focus has been the titration of sedation and the disadvantages of its excess rather than optimal therapy for agitation. Well-established sedation scales, such as the Richmond Agitation and Sedation Scale, are better validated for sedation than for agitation. Optimal pharmacologic treatment of delirium in the ICU thus remains to be established.

THE SPECIFIC CASE OF DELIRIUM AND ALCOHOL WITHDRAWAL

Pharmacologic interventions shown to be beneficial in the prevention of alcohol withdrawal have been best described with the administration of sedatives. Although providing alcohol to patients stratified to be at high risk for alcohol withdrawal seems effective, the heterogeneity in the design of the studies and the potential risks of alcohol administration preclude the recommendation of this practice. Benzodiazepines, major tranquilizers, and central alpha-blockers, alone or in combination, are the cornerstone of conventional alcohol withdrawal symptom management. The addition of phenobarbital and propofol, in addition to titrated benzodiazepines, not only benefits patients but also reduces the necessity for intubation in patients admitted to the ICU with alcohol withdrawal syndrome (AWS). Titrating sedative drugs to patient need benefits the critically ill. For alcoholic patients, this is particularly true; however, screening for patients at risk and use of an appropriate alcohol withdrawal scale (AWS or Clinical Institute Withdrawal Assessment) is essential. In the context of careful titration, administering additional sedation early in the course of alcohol withdrawal symptoms in ICU patients yields a better outcome.

SUMMARY

Little is known of nonpharmacologic and pharmacologic delirium prevention and treatment in the critical care setting. Trials emphasizing early mobilization suggest that this nonpharmacologic approach is associated with an improvement in delirium incidence. Titration and reduction of opiate analgesics and sedatives may improve subsyndromal delirium rates. All critical care caregivers should rigorously screen for alcohol abuse, apply alcohol withdrawal scales in alcoholic patients, and titrate sedative drugs accordingly. No nonpharmacologic approach or drug has been shown to be beneficial once delirium is established. Considering the importance and the consequences of delirium in the critical care setting, studies to further address prevention and rigorous trials addressing pharmacologic intervention are urgently needed.
REFERENCES


