Delirium: Past, Present, and Future

R. Ryan Field and Michael H. Wall

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R. Ryan Field, MD[1], and Michael H. Wall, MD, FCCM[2]

Abstract

Delirium was described by Hippocrates over 2500 years ago and it remains an important clinical problem today. Work continues to improve definition, prevention, diagnosis, and treatment, but relatively young science remains. Delirium affects 12 500 000 patients and costs $152 000 000 000 every year. Up to 80% of mechanically ventilated patients experience delirium, which exists as a spectrum of acute brain organ dysfunction. Multiple theories exist, including contribution from baseline pathology, medications, surgical inflammation, and environment. Biochemical models point to pathophysiology. Delirium remains largely preventable through planning and subgroup identification. Validated objective assessment models aid diagnosis, whereas protocolized multimodal intervention remains best practice. Pharmacotherapy, as chemical restraint, is reserved for cases of potential harm to self or others. Observation obviates mechanical restraint. The contribution of delirium to cognitive decline remains controversial and concerning. As dollars shrink and cost does not, delirium becomes increasingly important. In an aging population of increasing frailty, delirium will contribute increasingly to long-term morbidity and even mortality.

Keywords

delirium, review, current, treatment, management

Introduction: The Natural History of Delirium

Likely originating in description by another name, delirium began as a syndrome named phrenitis by Hippocrates circa 500 BCE. Phrenitis existed as a syndrome of acute onset of behavioral change, sleep disturbance, and cognitive deficit most commonly associated with the onset of fever. A second syndrome, lethargus, described inertia and dulling of the senses. Hippocrates squarely described these 2 syndromes as existing in spectrum, with free conversion between them (Figure 1).[1]

Celsus, around the first century, described symptom clusters similar to delirium, and for the first time in the literature, described non-fever-sourced causes of the ailment—a claim hotly debated by contemporary minds at the time, including Soranus. Delirium, likely derived from Latin, owing its etymology to the phrase *de lire*, meaning off-track, a common agricultural field plowing reference. In the late 16th century, this phrase contracted to a single word *deliriare*, meaning to be crazy or rave.[1] Not until the medieval period, did a historical account by Procopius describe hallucinations preceding disease with hyperactive and hypoactive variants. Hyperactive variants displayed violence, insomnia, excitement, shouting, and rushing off in flight. Hypoactive variants fell into coma, agnosia for friends and family, and adopted constant sleep and lethargy patterns with no consideration for basic survival, including food and water.[1] By the mid- to late 18th century, prominent minds determined delirium owed its pathophysiology to inflammation of animal spirits, a disturbance in the sleep-wake cycle, and separated delirium without fever as mania or madness.[1] In the early 20th century, Pickett had proposed separation of delirium in the ill and confusion in the elderly. He further postulated that delirium always had a firm organic cause, whereas confusion could source from nonorganic causes. Bonhoeffer described acute exogenous noxae caused by physical illnesses as causative sources. By the late 1950s, Engel and Romano demonstrated reduced cerebral metabolic activity with increased low-frequency wave activity in delirious patients by EEG examination.[1]

Currently, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) defines delirium as acute and fluctuating brain organ dysfunction, presenting with a disturbance of consciousness with reduced ability to focus, sustain, or shift attention. Delirium exists as a change in cognition or the development of a perceptual

[1]University of California–Irvine Health, Orange, CA, USA
[2]Washington University School of Medicine in St Louis, St Louis, MO, USA

Corresponding Author:
Michael H. Wall, Anesthesiology and Cardiothoracic Surgery, Washington University School of Medicine in St Louis, 660 S Euclid Ave, Campus Box 8054, St Louis, MO 63110, USA
Email: wallmi@wustl.edu

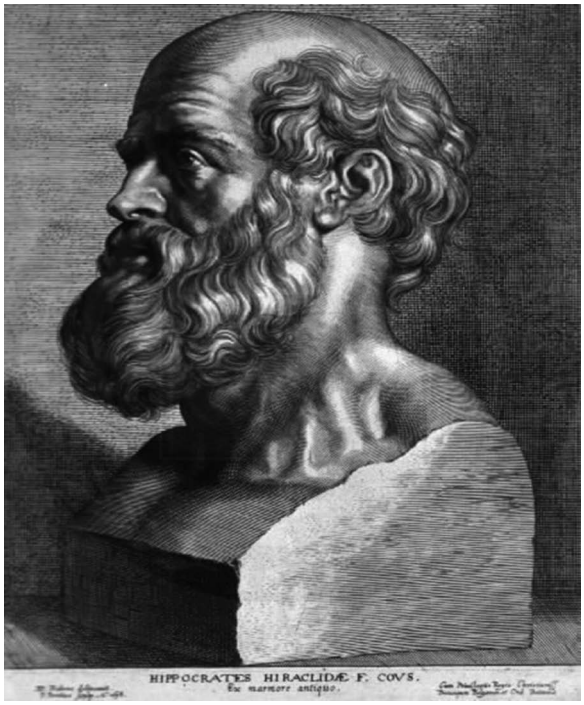


Figure 1. Hippocrates, engraving by Peter Paul Rubens, 1638

disturbance not better accounted for by a preexisting, established, or evolving dementia. Direct evidence from history taking and physical examination or laboratory findings that symptoms are physiological consequences of a general medical condition must be established.[2]

Delirium may present as a hyperactive or hypoactive state and exists in a continuous spectrum of brain organ dysfunction ranging from alert and oriented to coma, including subsyndromal delirium and frank delirium classifications. Whereas hyperactive delirium may be readily recognized, hypoactive delirium may evade suspicion of the most diligent diagnostician and is likely largely underreported. Additionally, patients often meet some but not all criteria for the diagnosis of *DSM-IV* delirium. This population most commonly carries the described pathology of subsyndromal brain organ dysfunction. This is an important patient population with unique impacts on the cost of their health care and disease outcome metrics. Whether subsyndromal or frank, comatose or stuporous, postoperative delirium costs patients a great deal of harm and costs hospitals great sums of money.[3]

Impact: The Harm of Postoperative Delirium

It is found that 20% of 12 500 000 hospitalized patients older than 65 years exhibit delirium every year in the United States alone; 5% to 15% of all patients develop delirium after noncardiac surgery, and 40% of patients presenting for repair of hip fracture develop delirium after spinal anesthesia with deep propofol sedation.[4,5] As many as 80% of all mechanically ventilated patients in the intensive care unit, in particular, may exhibit some form of acute brain organ dysfunction during their intensive care unit stay. Before validated objective assessment tools become widely incorporated into intensivist practice, only 20% of mechanically ventilated patients carried a delirium diagnosis. This is because hyperactive delirium represents 2% to 25% of all cases of delirium.[3,6,7]

Table 1. Analysis of Coincidence of Postoperative Delirium During the Early Postoperative Period and Specific Surgery Type by Percentage[7]

Surgery	Incidence of Delirium (%)
Hip fracture	35-65
AAA	33-54
CABG	37-52
Peripheral vascular	30-48
Head and neck—major	17
Abdominal	5-51
Urological	4-7
Cataract	4

Abbreviations: AAA, abdominal aortic aneurysm; CABG, coronary artery bypass grafting.

Surgery type, although logically involved in risk for postoperative delirium, shows little contribution to its incidence (Table 1).[7] Also, 1-, 6-, and 12-month as well as long-term mortality data all show increased tendency for shortened patient survival, which increases with brain organ dysfunction severity (Table 2).[7,8] Morbidity increases among these patients in kind, increasing length of stay, contributing to extubation failure, and causing new onset dementia[3] (Table 3).

Although human impact always comes before economic impact, financial impact remains important to observe the cost of perioperative cognitive change. Delirium may cost United States hospitals $152 000 000 000 per year.[4] Delirium duration reliably predicts an increased hospital length of stay, yet ultimately, severity of admitting diagnosis and patient comorbidity in the presence of delirium dictate the cost increase. Cost increases range from $9000 per case when low disease severity is present to $15 000 per case when high disease severity is present.[6,9] Considering the prevalence of delirium, this increased cost distributed across 80% of mechanically ventilated perioperative patients, and another portion of spontaneously ventilated patients can quickly cost an average intensive care unit more than $1 000 000 per year. The costs do not stop at hospital discharge. Delirium during

Table 2. Six-Month Mortality Rate of Postoperative, Mechanically Ventilated Patients in the ICU Categorized by Delirium Spectrum Subtype[8]

Patient Spectrum Location	Patient 6-Month Mortality Rate (%)
Normal	5.7
Subsyndromal delirium	18.3
Delirium	25.0
Persistent coma	~100 before 2 months

Table 3. Increased Likelihood of Experiencing Specific Morbidities if ICU Course Characterized by Postoperative Delirium[3]

Morbidity	Increased Likelihood if Delirium Present (Odds Ratio)
Increased length of stay	2×
Failure of extubation at 48 hours	3×
New dementia up to 3 years later	3×

hospitalization shows a positive relationship with functional decline at 1 to 3 months postoperation. Delirium also increases admission to nursing homes and other long-term care facilities at the same time interval, vastly expanding postdischarge economic and human costs.[10]

Pathophysiology: What Causes Delirium?

Historically, although many descriptions of symptoms of delirium surface in various texts, the etiology of delirium only recently shows advances in understanding. Multiple theories exist and one, some, or all may explain the incidence of delirium in postoperative patients. The medication theory focuses on the drugs delivered to a patient and, controversially, points to their chemical neurotoxicity. Cell culture, rodent, and primate models exposed as neonates can show developmental deficits in both social interaction and learning during advancement into adulthood.[11] The surgical theory identifies inflammation from both anesthetics and surgical intervention itself as causative of neuronal change, with circumstantial evidence for this model in young animals.[11]

Factors such as fenestration of the blood-brain barrier changing permeability to neurotransmitters and stress-response sourced increases in circulation of cortisol and catecholamines could further be responsible.[12] The patient theory draws attention from the effect of intervention on

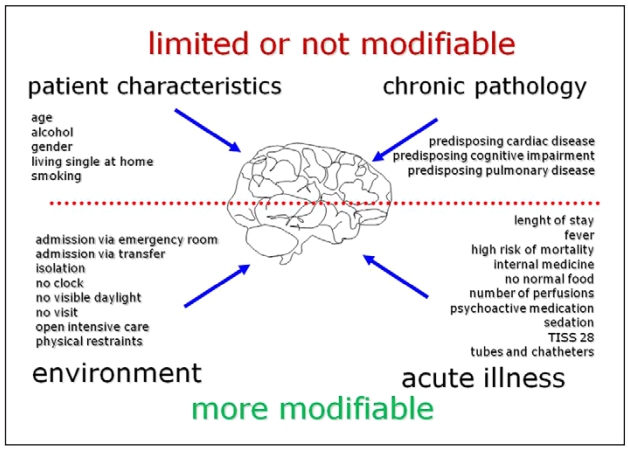


Figure 2. Four domains of risk factors for intensive care delirium
Abbreviation: TISS 28, The Therapeutic Intervention Scoring System–28.[14]

the patient to the preoperative condition of the patient. Factors such as frailty and cognitive deficit may point to the patient and not the drugs or surgery as stimulus to the development of postoperative delirium.[11] The environmental theory credits disorientation as causative or contributory to the overall experience of postoperative delirium.

On chemical and molecular levels, delirium is thought to start with initial insults that lead to biochemical pathway changes starting with neuronal inflammation. After neuronal inflammation develops, downstream neuronal cellular signaling results in neurotransmitter changes. Ultimately, these chemical changes lead to functional changes that manifest as acute brain organ dysfunction.[13]

Prevention Strategies: How Do We Identify Risk and Modify It?

In addition to work regarding the nature of the clinical syndrome and both the exposure and molecular basis contributing to its presence, significant research identifies preoperative risk factors that may contribute to its formation in the postoperative environment. History and physical examination often reveal many of these factors. Patient characteristics such as advanced age, alcohol use, gender, home social interaction, smoking history, and chronic pathologies such as cardiac disease, cognitive impairment, and pulmonary disease all represent items with limited or no room for preoperative modification[14] (Figure 2).

Screening with objective assessments may help identify those with cognitive deficit who otherwise may pass more subjective investigations. The Folstein Mini-Mental State Examination adapted for the screening of dementia and delirium may be most appropriate for the preoperative assessment clinic.[15] Identifying patients at risk by surgery

Table 4. Risk of Delirium for Noncardiac Surgery[a]

Risk Factor	Points
Age >70 years	1
Telephone interview of cognitive state	1
Specific Activity Scale	1
Alcohol abuse	1
Abnormal Na, glucose, K	2
Thoracic surgery	1
Points	**Risk of Delirium (%)**
0	1-2
1-2	8-19
3 or more	45-55

[a]Contribution of patient characteristics to risk for delirium in noncardiac surgery. Factors include age greater than 70 years, identification of dementia or other cognitive deficit in a preoperative telephone interview, identification of reduced baseline activity at home, alcohol abuse, specific serum laboratory abnormality, and/or presentation for thoracic surgery. Points summed to find risk for developing postoperative delirium.[17]

Table 5. Risk of Delirium for Cardiac Surgery[a]

Risk Factor	Points
Mini-Mental State Examination, <24	2
Mini-Mental State Examination, 24-27	1
Albumin < 3.5	1
Depression	1
Prior stroke or TIA	1
Points	**Risk of Delirium (%)**
0	18-19
1	43-47
2	60-63
3+	89-87

Abbreviation: TIA, transient ischemic attack.
[a]Contribution of patient characteristics to risk for delirium in cardiac surgery. Factors include Mini-Mental State Examination score, preoperative serum albumin, and/or symptomatic cerebrovascular disease. Points summed to find risk for developing postoperative delirium.[18]

type may hold some merit, but patient pathology may only allow knowledge of increased risk rather than avoidance of postoperative delirium development, with results varying widely.[7]

Risk assessment scales show a correlation between risk factors and absolute risk for postoperative delirium development. Operation type, complexity, environment, medications, and type of anesthetic all again proved significant (Tables 4 and 5). Leung et al[16] also in 2011, described a frailty index that correlated with an absolute risk factor for

Table 6. Frailty Index[a]

Frailty Indicators	Points
Recent weight loss >10 lbs	1
Symptoms of exhaustion	1
Weak grip	1
Slow ambulation	1
Low activity level	1
Frailty Score	**Delirium (%)**
0	0
1	17
2	29
3	36

[a]Frailty score derived from patient risk factors. Scored by presence of recent weight loss, symptoms of exhaustion, weak grip strength, slow ambulation rate, and low baseline activity level prior to surgery. Points summed to find risk of developing postoperative delirium.[16]

postoperative delirium development with an odds ratio of 1.84 in those patients with a frailty score greater than or equal to 3. Specific frailty indicators included a recent weight loss of greater than 10 pounds, symptoms of exhaustion, weak grip, slow ambulation, and overall low activity levels (Table 6).[16]

Preoperative use of anticholinergics, tricyclic antidepressants, lithium, sedatives and hypnotics, central antihypertensives, antiarrhythmic drugs, and/or anticonvulsants may increase risk for development of postoperative delirium. Medication or substance withdrawal from alcohol, sedatives, and hypnotics may also contribute. Specific poisonings, including exposure to heavy metals, organic solvents, methanol, and ethylene glycol, can provoke delirium.[19]

Hypernatremia, hypercalcemia, and hyperglycemia or hyponatremia, hypocalcemia, and hypoglycemia and/or significant acidosis or alkalosis also increase risk. Hypoxia; end-organ failure; thiamine, B12, or folate deficiency; and hyperthermia or hypothermia may contribute as well. Central nervous system lesions, hemorrhage, or cerebrovascular disease, including infarction could be responsible for or predispose one to delirium. Additionally, vasculitis, epilepsy, sepsis, thyrotoxicosis, and/or myxedema increase risk. Finally, congestive heart failure or acute myocardial infarction can also increase the likelihood of development of postoperative delirium. These risk factors may stem from patient comorbidity and/or iatrogenic causation.[19]

The presence of environmental disturbance, such as admission via an emergency room, admission via outside hospital transfer, isolation, lack of calendar and clock, lack of visible daylight, lack of visitors to the bedside, and presence of mechanical restraints as well as the presence

of acute illness with fever; expected long stay; high risk of mortality; need for consultation or management by internal medicine specialists; decreased oral nutrition; increased amounts of psychoactive medications, including sedatives; and multiple restricting tubes and catheters all represent more modifiable risk factors for the development of postoperative delirium.[14]

Much work continues regarding all facets of postoperative delirium, perhaps none more important than reduction or prevention. In 2010, in a randomized study, patients older than 65 years undergoing spinal anesthesia for hip fracture repair underwent 2 targeted sedation goals. The first targeted a BIS number of greater than 80 versus 50 in the second arm. The authors in the study observed an overall reduction in delirium of 21% at the $P = .02$ level of significance as well as a 0.9-day reduction in postoperative delirium reduction at the $P = .01$ level of significance, suggesting that lighter sedation can reduce the incidence of postoperative delirium in that population.[5]

After surgery, choice of sedation strategy may influence the incidence of delirium. The SEDCOM trial in 2009 examined the association between benzodiazepine sedation and delirium. In a multicenter trial, 375 patients were randomized to dexmedetomidine versus midazolam sedation strategies. Dexmedetomidine decreased delirium (77% vs 54%, $P < .001$) and duration of mechanical ventilation from 3.7 to 1.9 days ($P = .01$).[20] Also in 2009, a randomized study of 118 patients undergoing cardiac surgery showed that dexmedetomidine reduced the incidence of delirium compared with propofol and midazolam (3% vs 50%, $P < .001$).[21]

More recently, in the MIDEX/PRODEX study, the authors carried out a parallel, phase 3, European, large multicenter, randomized, double-blind, and controlled examination of sedation strategies as they relate to delirium. A maximum 14-day intervention randomized the comparison of propofol to dexmedetomidine sedation and midazolam to dexmedetomidine sedation. With comparable baseline characteristics, duration of mechanical ventilation was statistically lower with dexmedetomidine in the MIDEX arm. The authors observed a reduction in time to extubation using dexmedetomidine in both arms: MIDEX ($P = .01$) and PRODEX ($P = .04$). Interestingly, ICU and hospital length of stay were not statistically different; however, median lengths of stay were reduced in both arms.[22]

Postoperative Suspicion: How Do We Diagnose Objectively?

Diagnosis of postoperative delirium in the critically ill is challenging. Because of these challenges, objective assessment tools now find wide use in the clinical environment. Though many exist, the 2 most widely adopted are the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and Intensive Care Delirium Screening Checklist (ICDSC) tools. These tools were designed with different populations and variables controlled, perhaps making direct comparison of these tools likely invalid.[23]

The CAM-ICU specifically focuses on the critically ill and has particular usefulness for the mechanically ventilated and sedated patient. This tool is derived from *DSM-IV* diagnosis and current expert opinion. First, the assessor determines whether the patient exhibits acute and fluctuating changes in cognition. Second, the assessor measures the patient's level of attention. The algorithm then incorporates the level of consciousness of the patient, and finally, the assessor determines the overall level of cognition organization. The scale assigns likelihood based on the aggregate results allowing multiple pathways to diagnose postoperative delirium (Figure 3).[24]

A 2001 publication established an important objective assessment tool to diagnose postoperative delirium. The ICDSC uses a checklist format and score cutoff to determine the presence of postoperative delirium. The scale screens for altered level of consciousness, inattention, disorientation, psychoses, level of psychomotor activity, appropriateness of speech and mood, sleep and wake cycle disturbance, and the fluctuation of symptoms to provide a composite assessment for postoperative delirium (Figure 4).[25]

Following the development of these tools, and likely because of the development of these tools, a potentially clinically important subsyndromal postoperative delirium may describe a previously unrecognized pathology. The presence of some but not all terms to meet the definition of true postoperative delirium may still pose a significant threat to the patients, defined by their postoperative morbidity and mortality above and beyond the risks from surgery in nondelirious patients.[3]

Therapies for Active Delirium

Many methods for treatment of postoperative delirium remain in use. Although the history of delirium reaches into at least the time of Hippocrates, organized, blinded, placebo-controlled, randomized prospective trials only began in the near past to provide evidence for treatment. Protocolized, multimodal interventions remain the mainstay of current thought on treatment of active postoperative delirium.[26] The practitioner should attempt to reverse all obvious underlying causes for delirium, including infection. The practitioner should also treat hypoxia, shock, fever, anemia, and hypoalbuminemia; correct blood chemistry; protect the patient's airway; optimize nutrition; avoid chemical and physical restraint; and maintain patient hygiene.[27]

Pain severity and fluctuation in pain severity may in particular reversibly contribute to delirium in the

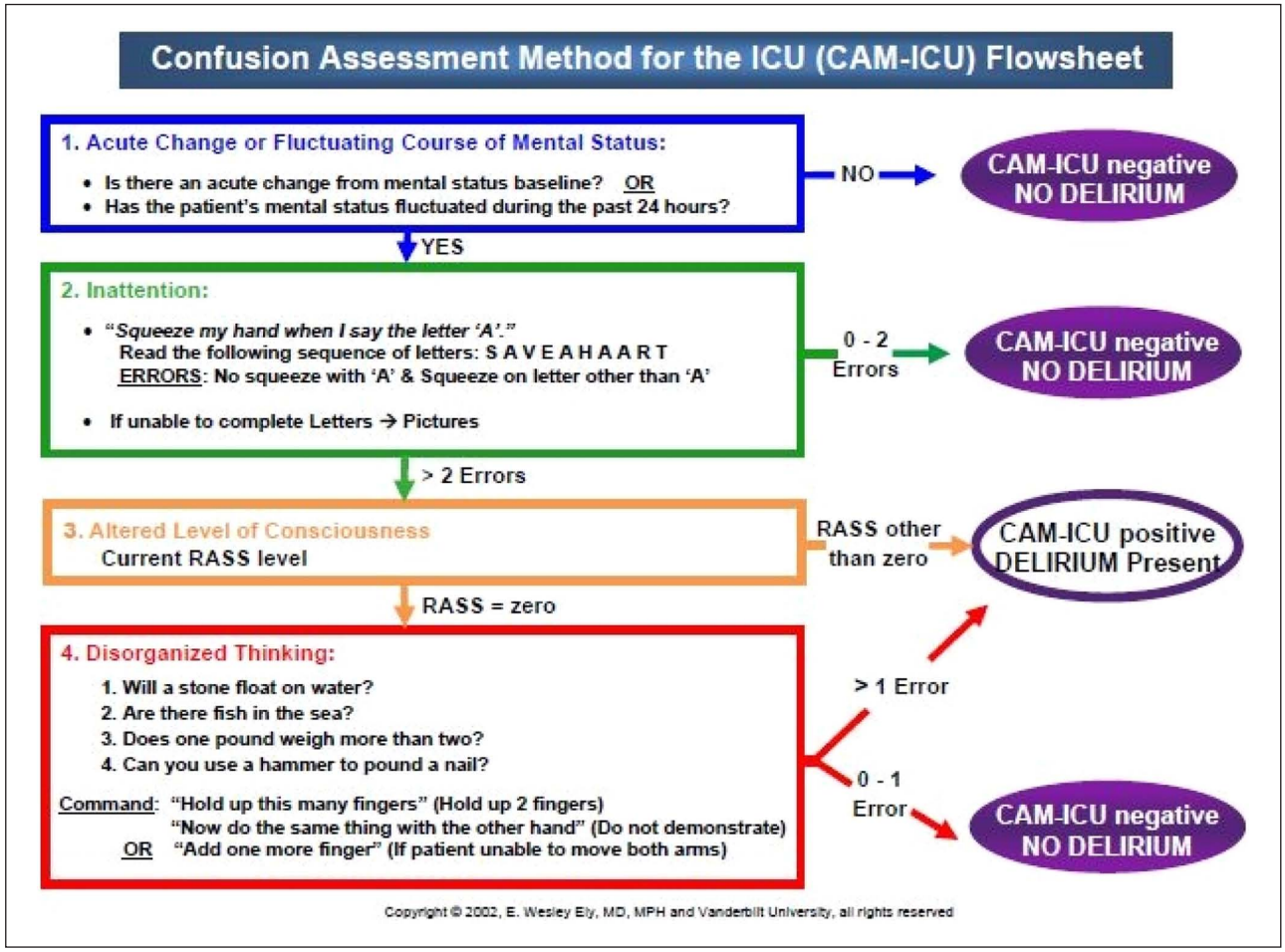


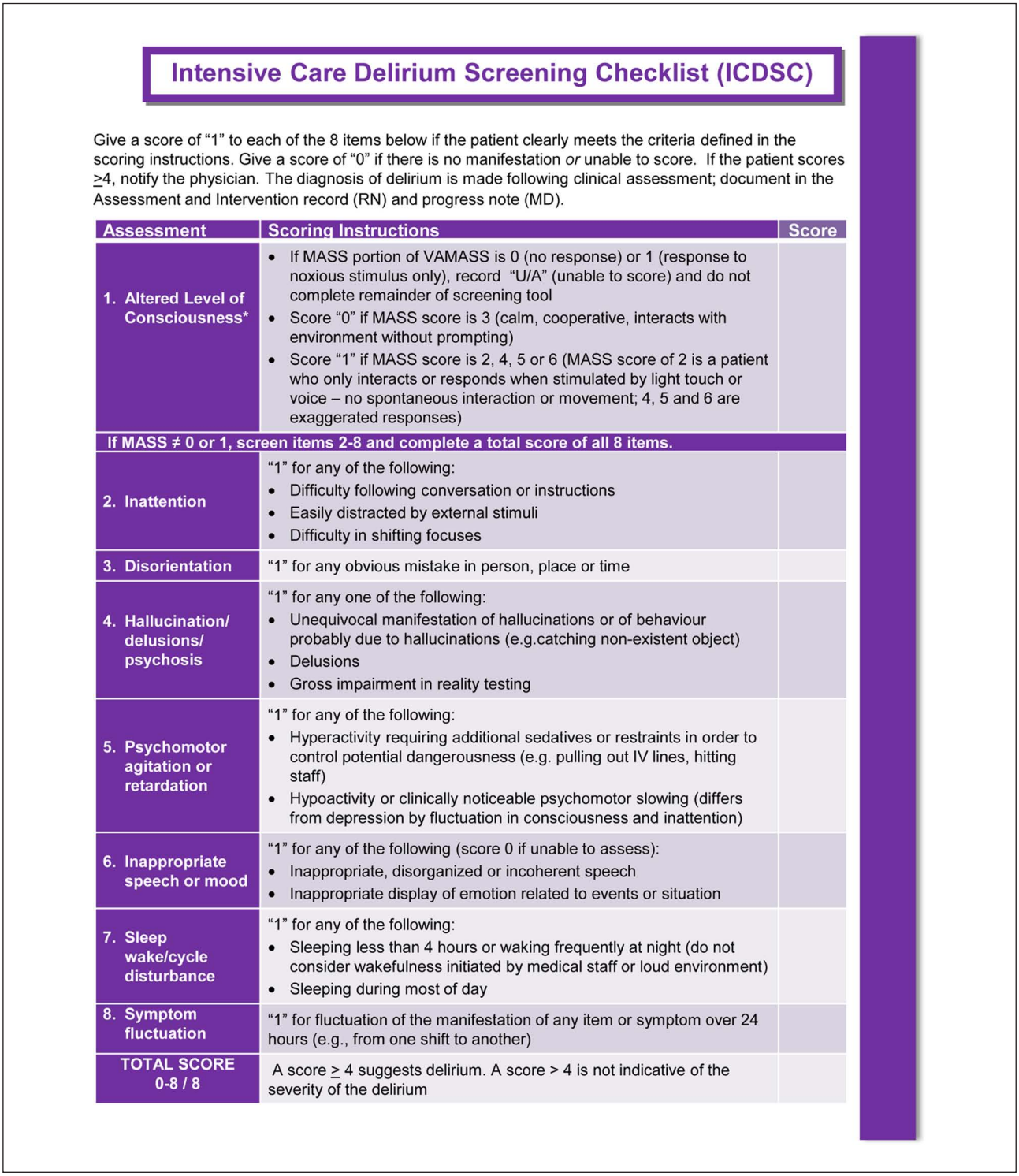
Figure 3. CAM-ICU worksheet for objective diagnosis of delirium[24]

postoperative patient.[28] Multimodal therapy, such as the use of acetaminophen, may reduce the need for opiates and reduce pain severity fluctuation reducing risk for the development of delirium.[29] Scheduling analgesia with patient refusal orders may provide superior relief compared with PRN administration.

In 2005, a parallel 2-group design examined this difference. The study observed no differences in total analgesics consumed; however, pain scores lowered from 4.1 to 1.8 (P = .009) with scheduled analgesia, and the highest pain score lowered from 5.6 to 2.9 (P = .018), showing less fluctuation in severity.[30] Oral opiates may have an edge over intravenous opiates for decreasing delirium incidence with an odds ratio of 0.4 (95% confidence interval = 0.2-0.7).[31] In 2006, a small pilot cohort of older patients received gabapentin with spine surgery, resulting in a reduction of postoperative delirium from 42% to 0% (P = .045).[32]

Environmental modification with frequent orientation to day of the week, date, time, and time of day as well as providing social interaction and creating an environment amenable to sleep during nighttime hours all help. Removal of all invasive lines, tubes, and other mechanical restraints paired with early ambulation may further increase patient freedom. Frequent evaluation of the need for escalation or deescalation of care can help patients further optimize their chances of keeping orientation.[14,33]

Although experts mostly agree that the use of pharmacotherapy to treat delirium should be a last resort, a Cochrane review, in 2009, identified low-dose haloperidol as the first-line pharmacotherapy for delirium, which concurs with general intensivist practice. Several studies in the review compared haloperidol to atypical antipsychotics with little statistically significant difference in outcomes and side effects; however, when patients required high-dose haloperidol to treat their delirium, a small increase in extrapyramidal symptoms occurred. For this reason, many intensivists switch to atypical antipsychotics when low-dose haloperidol yields insufficient improvement in symptoms.[34]



Intensive Care Delirium Screening Checklist (ICDSC)

Give a score of "1" to each of the 8 items below if the patient clearly meets the criteria defined in the scoring instructions. Give a score of "0" if there is no manifestation *or* unable to score. If the patient scores ≥4, notify the physician. The diagnosis of delirium is made following clinical assessment; document in the Assessment and Intervention record (RN) and progress note (MD).

Assessment	Scoring Instructions	Score
1. Altered Level of Consciousness*	• If MASS portion of VAMASS is 0 (no response) or 1 (response to noxious stimulus only), record "U/A" (unable to score) and do not complete remainder of screening tool • Score "0" if MASS score is 3 (calm, cooperative, interacts with environment without prompting) • Score "1" if MASS score is 2, 4, 5 or 6 (MASS score of 2 is a patient who only interacts or responds when stimulated by light touch or voice – no spontaneous interaction or movement; 4, 5 and 6 are exaggerated responses)	
If MASS ≠ 0 or 1, screen items 2-8 and complete a total score of all 8 items.		
2. Inattention	"1" for any of the following: • Difficulty following conversation or instructions • Easily distracted by external stimuli • Difficulty in shifting focuses	
3. Disorientation	"1" for any obvious mistake in person, place or time	
4. Hallucination/ delusions/ psychosis	"1" for any one of the following: • Unequivocal manifestation of hallucinations or of behaviour probably due to hallucinations (e.g.catching non-existent object) • Delusions • Gross impairment in reality testing	
5. Psychomotor agitation or retardation	"1" for any of the following: • Hyperactivity requiring additional sedatives or restraints in order to control potential dangerousness (e.g. pulling out IV lines, hitting staff) • Hypoactivity or clinically noticeable psychomotor slowing (differs from depression by fluctuation in consciousness and inattention)	
6. Inappropriate speech or mood	"1" for any of the following (score 0 if unable to assess): • Inappropriate, disorganized or incoherent speech • Inappropriate display of emotion related to events or situation	
7. Sleep wake/cycle disturbance	"1" for any of the following: • Sleeping less than 4 hours or waking frequently at night (do not consider wakefulness initiated by medical staff or loud environment) • Sleeping during most of day	
8. Symptom fluctuation	"1" for fluctuation of the manifestation of any item or symptom over 24 hours (e.g., from one shift to another)	
TOTAL SCORE 0-8 / 8	A score ≥ 4 suggests delirium. A score > 4 is not indicative of the severity of the delirium	

Figure 4. ICDSC worksheet for objective diagnosis of delirium. Ventilator assisted (VA) Motor Assessment Scoring Scale (MASS) used to assess whether or not patient can be screened for postoperative delirium in the ICU. Ventilated patients receive an additional α score (A-D), but this does not change how the patient is assessed. If the patient is, at least, responsive to voice or touch, then the patient can be assessed, and the MASS or VAMASS numerical score is greater than one[25]

Current Best Practice

There is no better time to improve surgical outcome and lower delirium incidence than in the clinic prior to surgery. At a minimum, older people should receive an objective preoperative screening for dementia if its presence would change decision making or improve informed consent. Assessment of modifiable risk factors and identification of poorly modifiable risk factors should be considered. For example, if a nonsurgical medical trial, interventional approach, or less-invasive surgical approach can yield satisfactory results, patients may benefit more from a reduced exposure to development of postoperative delirium than from any extra advantages they may receive from gold standard surgical intervention.

Questions to ask may include the following: If a surgical intervention is long, can it be made shorter? Can the surgical methodology choice shorten postoperative inpatient care? Can less sedated or anesthetized interventions provide equal or acceptable results? Can surgical and anesthetic methodologies improve hemodynamic stability during the case, avoiding periods of extreme hypertension and hypotension? Can a less-intense level of postoperative care with less interruption, more access to visitors, and more environmental orientation provide similar vigilance and outcome? Given this patient's risk for postoperative delirium, is he or she still appropriate for ambulatory care and/or an outpatient surgical center? How will the patient receive support after hospital discharge?

Prior work suggests that some medications may contribute to the risk for developing postoperative delirium. It may be prudent to identify, limit, or avoid, if possible, several drug classes. Opiates increase the likelihood of developing delirium by up to 250%. Benzodiazepines may increase the likelihood by as much as 300%. Dihydropyridines can possibly increase the likelihood of postoperative delirium development by 240%, whereas antihistamines may increase risk by as much as 180%. There is probably no association with neuroleptics or digoxin. Controversy remains regarding the use of histamine 2 blockers, tricyclic antidepressants, antiparkinsonian drugs, steroids, nonsteroidal anti-inflammatory drugs, and anticholinergics.[35]

The patient, surgeon, and anesthesiologist should start careful and coordinated conversations with patients regarding their risk, understanding of it, and the components going into the physician's recommendation regarding the risk versus benefit ratio. Risk for postoperative delirium in identified high-risk patients may reasonably warrant inclusion in patient consent paperwork. Once the informed decision is made to proceed with the least-invasive surgery and the least-deep and shortest-duration anesthetic, periods of extreme hypotension and hypertension should be avoided, and pain should be well controlled.

After surgery, postanesthesia care unit (PACU) discharge should include surveillance for signs of developing acute brain organ dysfunction, and any changes to appropriate disposition should be made at this point in consultation with the surgical team. The least-frequent observation level appropriate should be utilized in high-risk patients to minimize disruption to the sleep-wake cycle and maximize access to visitation and social interaction. Clearly visible daylight and moonlight, calendars, clocks, television, newspapers, and other time-oriented references should be made available to the patient. All hearing, visual, and other aids should be in use as early as possible to decrease sensory deprivation and increase environmental immersion and reception. All unnecessary lines should be removed at the earliest possible time.

For mechanically ventilated patients, daily sedation holidays and spontaneous breathing trials remain best practice.[36] Sedation should be as light as possible to reduce delirium incidence and should be assessed by objective assessment tools such as the Richmond Agitation and Sedation Scale and Ramsay Sedation Scale.[7] Early intervention with physical and occupational therapy in both mechanically ventilated and extubated patients with and without delirium should be used.[37]

Patients should be encouraged by all staff to be wakeful during the day and restful during appropriate sleeping hours. Refusable and scheduled multimodal analgesia and patient-controlled analgesia with recurrent evaluation of its efficacy should continue after PACU discharge whenever possible. Particular attention should be paid to reducing pain severity fluctuation. The shortest duration of hospital stay and the minimum amount of time possible at each level of care should be observed.

Delirium should be actively screened for on a per-shift basis, and primary care teams should be notified immediately of any positive result, including subsyndromal signs. A thorough investigation into underlying causes should be carried out, and a determination should be made on how best to improve the patient's environment and maintain the safety of both the patient and others. In the geriatric population, a geriatric medicine consult may be reasonable before as well as after the development of delirium in the early postoperative environment, particularly to examine drug regimens. Delivering care in a ward specially designed for geriatric care may improve outcomes for these patients.

Pharmacotherapy should be used as only a method to reduce harm to self or others and should be considered a form of chemical restraint. Mechanical restraints should be used for the shortest duration possible. A 1-to-1 patient sitter is always preferable to mechanical restraint when the patient does not pose an unreasonable risk of harm to others. Careful consideration of support and care type for patient disposition from the hospital as well as establishment of postdischarge screening for postoperative cognitive decline after delirium may be appropriate.

Conclusion

Along history's course through the separation of abnormal from normal, through the recognition of brain organ dysfunction with acute identifiable cause and that with often progressive, slow, insidious, and lasting development, postoperative delirium remains hotly researched and debated. It took more than 2000 years to aptly identify, diagnose, and suggest basic treatment for postoperative delirium. It is unlikely to take 2000 years more to make great strides in prevention, care, and postdelirium support.

As health care dollars shrink, and cost of care does not, delirium will become increasingly important to operating economically efficient hospitals and ambulatory surgical centers. For the first time in our history, as we live to ages largely unachievable previously and as medicine slowly reduces the severity and incidence of age-related disease, we stand poised to make a large impact not only on the surgical care we can deliver but also on the long-term cognitive impact of that care on quality of life. The journey toward these end goals begins in the surgical clinic and finishes with supportive postdischarge care.

In the future, large-scale trials will continue to elucidate the process of preoperative identification of high-risk patients and further define how operative stimuli and pharmacotherapy contribute, perhaps even on the pharmacogenomic level; more targeted therapies for treatment of active delirium will come to market as treatment protocols become more commonplace. Focus will continue to sharpen as more attention is placed on the costs associated with the care of these patients and the morbidity and mortality that occur in parallel. Patients will increasingly benefit from prevention, early recognition, and efficient therapy as these goals are met.

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References

1. Adamis D, Treloar A, Martin FC, Macdonald A. A brief review of the history of delirium as a mental disorder. *Hist Psychiatry*. 2007;18:459-469.
2. American Psychiatric Association Task Force. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatiric Association; 2000.
3. Miller RR, Wesley EE. Delirium and cognitive dysfunction in the intensive care unit. *Semin Respir Crit Care Med*. 2006;27:210-220.
4. Greene NH, Attix DK, Weldon BC, et al. Measures of executive function and depression identify patients at risk for postoperative delirium. *Anesthesiology*. 2009;110:788-795.
5. Sieber FE, Zakriya KJ, Gottschalk A, et al. Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. *Mayo Clin Proc*. 2010;85:18-26.
6. Ely E, Gautam S, Margolin R, et al. The impact of delirium in the intensive care unit on hospital length of stay. *Intensive Care Med*. 2001;27:1892-1900.
7. Rudolph JL, Marcantonio ER. Postoperative delirium: acute change with long-term implications. *Anesth Analg*. 2011;112:1202-1211.
8. Ely E, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*. 2004;291:1753-1762.
9. Milbrandt EB, Deppen S, Harrison PL, et al. Costs associated with delirium in mechanically ventilated patients. *Crit Care Med*. 2004;32:955-962.
10. Rudolph JL, Inouye SK, Jones RN, et al. Delirium: an independent predictor of functional decline after cardiac surgery. *J Am Geriatr Soc*. 2010;58:643-649.
11. Crosby G, Culley DJ. Surgery and anesthesia: healing the body but harming the brain? *Anesth Analg*. 2011;112:999-1001.
12. Chaput A, Bryson G. Postoperative delirium: risk factors and management: continuing professional development. *Can J Anesth*. 2012;59:304-320.
13. Fricchione G, Nejad S, Esses J, et al. Postoperative delirium. *Am J Psychiatry*. 2008;165:803-812.
14. Van Rompaey B. Risk factors for delirium in intensive care patients: a prospective cohort study. *Crit Care Med*. 2009;13:R77.
15. O'Neill D, O'Shea B, Walsh JB, Coakley D. Screening for dementia and delirium using an adapted Folstein mini-mental state examination. *Ir Med J*. 1989;82:24-25.
16. Leung JM, Tsai TL, Sands LP. Preoperative frailty in older surgical patients is associated with early postoperative delirium. *Anesth Analg*. 2011;112:1199-1201.
17. Rudolph JL, Jones RN, Rasmussen LS, et al. Independent vascular and cognitive risk factors for postoperative delirium. *Am J Med*. 2007;120:807-813.
18. Rudolph JL, Jones RN, Levkoff SE, et al. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. *Circulation*. 2009;119:229-236.
19. Johnson JC. Prevention and management of perioperative delirium. In: Pignolo RJ, Keenan MA, Hebela NM, eds. *Fractures in the Elderly: A Guide to Practical Managment*. Totowa, NJ: Humana Press; 2011:101-114.
20. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients. *JAMA*. 2009;301:489-499.
21. Maldonado JR, Wysong A, van der Starre P, et al. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. *Psychosomatics*. 2009;50:206-217.

22. Jakob SM, Ruokonen E, Grounds R, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA*. 2012;307:1151-1160.
23. Devlin J, Fong J, Fraser G, Riker R. Delirium assessment in the critically ill. *Intensive Care Med*. 2007;33: 929-940.
24. Ely E, 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;286:2703-2710.
25. Bergeron N, Dubois MJ, Dumont M, et al. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive Care Med*. 2001;27:859-864.
26. Lundström M, Edlund A, Karlsson S, et al. A multifactorial intervention program reduces the duration of delirium, length of hospitalization, and mortality in delirious patients. *J Am Geriatr Soc*. 2005;53:622-628.
27. Inouye SK. Delirium in older persons. *N Engl J Med*. 2006;354:1157-1165.
28. Hughes CG, Pandharipande PP. The effects of perioperative and intensive care unit sedation on brain organ dysfunction. *Anesth Analg*. 2011;112:1212-1217.
29. Schug SA, Sidebotham DA, McGuinnety M, et al. Acetaminophen as an adjunct to morphine by patient-controlled analgesia in the management of acute postoperative pain. *Anesth Analg*. 1998;87:368-372.
30. Paice JA, Noskin GA, Vanagunas A, Shott S. Efficacy and safety of scheduled dosing of opioid analgesics: a quality improvement study. *J Pain*. 2005;6:639-643.
31. Vaurio LE, Sands LP, Wang Y, et al. Postoperative delirium: the importance of pain and pain management. *Anesth Analg*. 2006;102:1267-1273.
32. Leung JM, Sands LP, Rico M, et al. Pilot clinical trial of gabapentin to decrease postoperative delirium in older patients. *Neurology*. 2006;67:1251-1253.
33. Thomason J, Ely EW. Delirium in the intensive care unit is bad: so what is the confusion? *Crit Care Med*. 2004;32: 2352-2354.
34. Lonergan E, Britton AM, Luxenberg J, Wyller T. Antipsychotics for delirium. *Cochrane Database Syst Rev*. 2007;(2):CD005594.
35. Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. *Age Ageing*. 2011;40: 23-29.
36. 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;371:126-134.
37. 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;373:1874-1882.