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Delirium: An Emerging Frontier in Management of Critically Ill Children

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Abstract

1. Introduce pediatric delirium and provide understanding of acute brain dysfunction with its classification and clinical presentations.
2. Understand how delirium is diagnosed and discuss current modes of delirium diagnosis in the critically ill adult population and translation to pediatrics.
3. Understand the prevalence and prognostic significance of delirium in the adult and pediatric critically ill population.
4. Discuss the pathophysiology of delirium as currently understood.
5. Provide general management guidelines for delirium.

Keywords

brain dysfunction; confusion; delirium; encephalopathy; pediatric; critical care; psychosis

INTRODUCTION

Acute brain dysfunction is a common and significant complication associated with critical illness. Unfortunately, the development of delirium, or acute brain dysfunction, is largely considered an expected and trivial component of critical disease.^{1–3} With the advent of well

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validated and reliable diagnostic instruments for delirium in critically ill adults, there has been rapid and significant progress in the body of knowledge on this topic.⁴ Furthermore, better understanding of delirium has prompted new recommendations for delirium monitoring to be a component of daily usual care for all ICU patients.⁵ Delirium remains essentially unrecognized in the pediatric critical care setting due to inability of prompt diagnosis and uncertainty of clinical significance. Therefore, the pediatric knowledge base regarding delirium occurring during critical illness drastically lags behind adult literature. Fortunately, there are ongoing studies in both Europe and the United States to develop and implement pediatric instruments by which to diagnose and monitor delirium in critically ill children. This article provides an overview of the diagnosis, clinical significance, pathophysiology, and treatment of delirium based on adult studies, and highlights the emerging and exciting areas of pediatric delirium research.

DEFINITION

Delirium is a disturbance of consciousness and cognition that develops acutely with a fluctuating course of inattention and an impaired ability to receive, process, store, or recall information.^{6;7} Historically, *delirium* was used to describe an agitated and confused person, while *lethargus* was used to depict a quietly confused person.¹ ICU literature traditionally describes delirium as “ICU psychosis, ICU syndrome, acute confusional state, encephalopathy, and acute brain failure.”^{1;8;9} The remarkable variation in terminology for delirium (acute brain dysfunction) has greatly limited successful collaboration within the medical community.⁴ To this end, the American Psychiatric Association (APA) recently recommended that “delirium” be consistently used to describe the “acute state of brain dysfunction” in critical care literature.⁶

Clinical Presentation and Subtypes

Delirium presents with a wide-range of symptoms and a continuum of psychomotor behavior.^{10;11} Hypoactive delirium is characterized by apathy, decreased responsiveness, and withdrawal,¹⁰ historically a condition referred to by Neurologists as “encephalopathy.”⁴ Patients with hypoactive delirium are often assumed erroneously to be thinking clearly. Hypoactive delirium does not commonly arouse concern by the medical team, which leads to minimal monitoring or treatment despite these patients being at substantial risk for poor outcomes.^{2;12;13;13} Hyperactive delirium is characterized by restlessness, agitation, and emotional lability,¹⁰ classically referred to as “delirium” by physicians across a wide-range of disciplines.⁴ Combative patients with hyperactive delirium are perceived to be at greatest risk for self-extubation and self-inflicted harm and therefore are closely monitored and administered substantial doses of sedatives and narcotics to diminish their symptoms.¹⁴ However, the administration of standard sedatives to mask symptoms of delirium may actually contribute to worse clinical outcomes in these patients.

A recent study of subtype prevalence in a large cohort of adult medical ICU patients demonstrated that hypoactive delirium was considerably more common than hyperactive delirium (43.5% versus 1.6%), while a combined clinical picture referred to as “mixed delirium” was the most frequently observed (54.1%).¹¹ The high prevalence of hypoactive delirium in critically ill patients may contribute to its under-recognition, particularly in critically ill children.^{6;15} When the brain does not have the capacity to function normally, the imbalance of neurotransmitter release and cellular damage as currently understood will be expressed clinically in various ways. Transition from one clinical expression of delirium to another does not describe a “new condition,” rather a fluctuation in brain function. Psychiatrists and increasingly intensivists use “delirium” to appropriately refer to all motoric subtypes (hypoactive, hyperactive and mixed) of acute brain dysfunction, as patients will often fluctuate between these clinical states over time.⁴

Though the prevalence of all motoric subtypes of delirium have not been adequately described in the pediatric population, Turkel and colleagues¹⁵ suggest that symptomatology may be very similar between children and adults. Manifestations of delirium most commonly reported in both adults and children include: impaired alertness, inattention, fluctuation in mental status, confusion, and disturbances in sleep-wake cycles.¹⁵ However, there is concern that pediatric delirium may be extremely subtle and complicated by the developmental variability in clinical presentations. Pediatric delirium may also be associated with other neuropsychiatric symptoms such as purposeless actions, inconsolability, and signs of autonomic dysregulation.¹⁶ Recognition of differences in delirium presentation between children and adults highlights the need for a pediatric focused diagnostic approach to delirium in the PICU.^{15;17;18}

DIAGNOSIS

Intensivists are experts in identifying and treating multi-organ failure. Modern technology provides the ability to monitor organ function decisively; pulmonary dysfunction via compliance curves, pulse oximetry and blood gases, cardiac dysfunction via blood pressure, electrocardiography, and indices of oxygen delivery, and renal dysfunction via urine output and serum creatinine.¹ However, the systematic monitoring of the central nervous system, has been inadequate in the identification of disturbances of consciousness and content, otherwise *delirium*. Consciousness consists of two distinct components: 1) *arousal*, or the appearance of wakefulness, and 2) *the content of consciousness*, or the sum of mental function.¹⁹ While we routinely monitor arousal using the Glasgow Coma Scale (GCS)²⁰ and/or various sedation scales such as the Modified Motor Activity Sedation Scale (MMASS)²¹ or the Ramsay Agitation Sedation Scale (RASS),²² our assessment of the content of consciousness has been extremely limited. See **Box 1** for commonly used terms in the assessment of delirium.^{1;23}

Historically, psychiatric consultation using DSM-IV criteria, family and nurse interviews, and patient examination has been required to assess content of consciousness and ultimately diagnose *delirium*.²⁴ Delirium is diagnosed based on four major DSM-IV criteria: 1) An acute onset or fluctuation in the 2) disturbance of consciousness which leads to the inability to focus, shift or maintain attention, 3) An altered level of cognition which may present with disorientation, language disturbance, memory deficit, or perceptual disturbances, 4) directly triggered by a general medical condition.^{7;16} Many clinicians assume agitation or hallucinations must be present for diagnosis of delirium. While these features may be present, they are not required.²⁵ A complete psychiatric evaluation is both time consuming and limited by available personnel and patient needs, and frankly unrealistic in the ICU setting. Furthermore, delirium is a syndrome that represents brain dysfunction as currently assessed by specialists in both psychiatry and neurology. It is a clinical expression of brain dysfunction caused either from primary disease of the brain, or secondary from a variety of complications associated with critical illness. Therefore, tools which can be used at the bedside for rapid diagnosis and ongoing monitoring of delirium in critically ill patients are vital to exploring this new frontier of pediatric critical care medicine.

Adult ICU Diagnostic Tools

In the adult population several delirium screening tools have been created and validated against formal psychiatric assessments as the reference standard. The Delirium Rating Scale (DRS),²⁶ Confusion Assessment Method for the ICU (CAM-ICU),^{27;28} and the Intensive Care Delirium Screening Checklist (ICDSC)²⁹ are reliable screening tools for delirium in adult critically ill patients. Of these, the CAM-ICU^{27;28} and the ICDSC²⁹ are validated for use by non-psychiatric trained medical professionals in the ICU setting. The CAM-ICU is the most commonly used diagnostic tool for delirium of critical illness, also validated for use in patients who require mechanical ventilation and are therefore non-verbal. With the ability for prompt

diagnosis of delirium in critically ill adults,^{25;30–32} there has been an explosion of literature on prevalence, associated outcomes, risks, and treatment of this disease state.

Pediatric ICU Diagnostic Tools

There is currently no validated instrument to diagnose and monitor pediatric delirium in the ICU setting by non-psychiatric trained clinicians. The adult tools previously described in their current form cannot be applied to the pediatric population due to differences in developmental expression of cognition between these diverse populations. Unfortunately, the lack of age-appropriate diagnostic tools in children leaves little known regarding the incidence, clinical presentation, response to treatment, and consequence of pediatric delirium in the ICU.^{15;17;18}

The Pediatric Anesthesia Emergence Delirium Scale (PAED) screens children as young as 2 years of age for emergence delirium (ED) following anesthesia during the postoperative period.³³ Emergence delirium (ED) is defined as a disturbance in mentation following general anesthesia which is associated with hallucinations, delusions, or confusion, manifested by frequently observed symptoms such as restlessness, involuntary physical activity, and extreme agitation.³⁴ What has been referred to as ED by anesthesiologists would in large part be considered hyperactive delirium. The PAED Scale is made up of 5 items which are scored 0–4 with a final summation, of which the degree of ED increases directly with the total score (**Box 2**).³³ Two salient features of delirium are represented in this scale; 1) disturbance of consciousness (Items A and C), and 2) changes in cognition (Item B).⁷ The limitations of the scale are easily recognized due to its subjective nature and lack of validation against DSM-IV criteria for diagnosis of delirium. The purpose of the scale is to identify hyperactive delirium, which is the least common form of delirium described in the critically ill. This scale may provide a foundation for the creation of tools to diagnose all subtypes of delirium, particularly that occurring in children less than 5 years of age.

The Pediatric Confusion Assessment Method for the ICU (pCAM-ICU) has recently been developed by the Vanderbilt Pediatric Delirium Group (Figure 1). This tool is an adaptation of the adult CAM-ICU. The pCAM-ICU has recently been validated to diagnose delirium using psychiatric assessment as the reference standard in critically ill children aged 5 years and older. The pCAM-ICU is the first bedside tool for diagnosis of delirium in ventilated and non-ventilated critically ill pediatric patients by non-psychiatric trained caregivers. A rapid diagnosis of delirium by clinicians could guide critical therapeutic decisions such as maneuvers to improve cerebral oxygen delivery, choice of sedative and analgesic medications, and influencing the timing of extubation. Preliminary data from the validation study of the pCAM-ICU demonstrates excellent sensitivity and specificity for screening and diagnosing delirium. Pilot implementation studies are ongoing at several centers in the U.S. and in one European center.

The pCAM-ICU mirrors diagnosis of delirium by the CAM-ICU with a two-step approach; 1) assessment of *level of consciousness* using a standardized sedation scale, and 2) assessment of *content of consciousness* using the pCAM-ICU. The level of consciousness for both tools is evaluated by the Richmond Agitation-Sedation Scale (RASS),^{35;36} which ranges from –5 (comatose) to +4 (combative), with 0 describing an alert and calm patient (Table 1). By design, the pCAM-ICU requires an interactive patient in order to assess content of consciousness. Therefore, patients with a RASS score of –4 or –5, those who require physical stimulation for arousal or do not arouse, are defined as being in a comatose state and cannot be assessed for delirium. This does not mean that the patient does not have brain dysfunction, simply that the patient cannot be adequately assessed for content of consciousness by the pCAM-ICU. If a patient has a level of consciousness other than comatose, they are then evaluated on four key features of delirium diagnosis based on DSM-IV criteria to include: 1) acute onset of mental

status changes or a fluctuating course, AND 2) inattention, with EITHER 3) altered level of consciousness, OR 4) disorganized thinking.

The pCAM-ICU diverges from the traditional CAM-ICU in Features 2 and 4 where “inattention” and “disorganized thinking” are evaluated. Due to limitations in developmental expression of cognition, the assessments for both “inattention” and “disorganized thinking” required adaptation in order to differentiate children with and without delirium. In particular, the Attention Screening Examination (ASE) pictures used in Feature 2 were replaced with bold-colored non-threatening figures that children could easily recognize (Figure 2). In addition, the questions used for evaluation of “disorganized thinking” were substituted with those of age-appropriate content. The pCAM-ICU may emerge as a beneficial tool due to its foundation on DSM-IV criteria of delirium diagnosis, and therefore the ability to diagnose and screen for all subtypes of delirium to include the most prevalent and most subtle subtype hypoactive delirium. The limitation of this tool is the inability to use it in children younger than 5 years of age. It is recognized that the evaluation of the content of consciousness will be a challenge in young children and infants. Refinement of the pCAM-ICU for this age group will be required.

PREVALENCE AND PROGNOSTIC SIGNIFICANCE

Delirium in Critically ill Adults

Brain dysfunction is very common in adults with critical illness. Delirium has been observed in 60–80% of ventilated adult ICU patients, and 40–60% of non-ventilated adult ICU patients.^{29;31;37–40} The high incidence of delirium during critical illness makes its associations with morbidities and adverse outcomes in survivors extremely important. Most notably, critically ill patients with delirium have more failed and self-extubations,^{30;41} prolonged requirement of mechanical ventilation,^{30;31} inadvertent removal of catheters,³⁰ prolonged hospital stay,^{30;40} higher health-care costs,⁴² and increased mortality.^{31;43;44} Alarming, delirium is associated with a threefold increase in risk of death in adults after controlling for presence of coma, severity of illness, and preexisting comorbidities.³¹

The development of delirium during hospitalization has been implicated in the development of complications for survivors such as long term cognitive impairment (LTCI) and post-traumatic stress disorder (PTSD).^{32;45;46} Critical illness alone leads to neuropathologic changes, ultimately associated with neurologic dysfunction.⁴⁷ Evidence from a total of 11 studies totaling ~500 adult patients, suggests that 25% to 78% of patients develop LTCI following critical illness.^{48–56} There is mounting evidence that the causal link between critical illness and the development of LTCI is delirium,⁵⁷ with many studies demonstrating delirium as one of the strongest predictors for LTCI in survivors.^{25;31;32;58;59}

The physiologic and psychiatric consequences of critical illness has just begun to be recognized.^{60;61} Indeed, experts almost uniformly acknowledge that experiencing life-threatening illnesses often leads to acute stress disorder (ASD) and post-traumatic stress disorder (PTSD).^{60–63} Review of 20 adult studies demonstrate that the reported rates of PTSD symptoms in adult ICU survivors may be over 40% and easily eclipse the rates occurring in other medical populations.^{60;61;64} With the associations between critical illness and PTSD, an important risk factor for its development may be delirium.⁶⁵

Delirium in Critically Ill Children

Pediatric delirium in the critically ill population remains in its infancy regarding diagnosis, treatment, and associations of risk. Prevalence literature on pediatric delirium is biased towards general medical populations which exhibit hyperactive symptoms that have triggered consultation by psychiatric services. In one of the largest pediatric retrospective studies on

delirium, Turkel and colleagues,²⁴ reported that of 1,027 consecutive patients evaluated by the child psychiatric service, 84 patients (9%) carried a diagnosis of delirium. Schieveld and colleagues,¹⁶ reported that of 877 critical care patients prospectively referred to the child psychiatry service, 40 patients (4.5%) were diagnosed with delirium. Both studies describe patient cohorts that were identified through clinical symptoms associated with hyperactive delirium, which is reported as the least common manifestation of delirium in the critically ill.¹¹ Therefore, the true prevalence of pediatric delirium in critical care population remains unknown.

The actual prognostic significance of pediatric delirium during critical illness is also limited by few prospective studies, none of which include patients on mechanical ventilation. In a large retrospective study, Turkel and colleagues²⁴ revealed increased morbidity and a 20% mortality rate in children diagnosed with delirium. In the critically ill pediatric population, mortality alone may not be a realistic outcome measure for the significance of delirium and potential treatment effects since mortality is a relatively rare event with rates of 3–15% nationally. As the diagnosis of pediatric delirium increases, the use of functional outcome measures in addition to monitoring mortality will be important to truly describe the effects of brain dysfunction.⁶⁶

Critical illness causes acute and chronic organ dysfunction, which may include progression to long-term neurologic sequelae in the pediatric patient.⁶⁷ Research is limited in the area of long-term cognitive impairment (LTCl) in pediatrics, however recent investigations using validated rating scales suggest that a significant percent of pediatric patients develop unfavorable neurocognitive and functional morbidity following critical illness.⁶⁸ Alievi and colleagues⁶⁹ assessed outcomes of 443 PICU survivors using validated functional outcome scales, finding that PICU treatment and critical illness contributed to considerable declines in neurocognitive and functional performance in a significant proportion of this study cohort. Fiser and colleagues⁷⁰ also used functional outcome scales to prospectively assess a cohort of 11,106 patients following critical illness. They found that patients with mild to moderate disability at PICU discharge subsequently had neurocognitive and functional impairments which affected school performance. With early pediatric research showing evidence of LTCl following critical illness, it will be imperative to evaluate the relationship between the development of delirium and LTCl.

PTSD is prevalent among children with chronic illnesses such as cancer,⁷¹ though little is known about the prevalence and adverse consequences of PTSD in pediatric survivors of critical illness.^{62;72} Children may rely on coping resources more easily disrupted by the ICU environment compared with their adult counterparts, in addition to a less sophisticated ability to effectively process psychologically complex issues associated with life-threatening events.⁶² Specifically, children's resilience to trauma may heavily rely on the maintenance of routine and presence of parents, both of which are disturbed in the PICU. While in a state of delirium, both children and adults commonly experience psychotic symptoms and delusions of a profoundly disturbing nature. Memories of these thought distortions, in turn, can trigger the dysregulation of the HPA axis, presenting clinically with the symptoms of avoidance, anxiety, and hyper vigilance, characteristic of PTSD. Existing literature in patients with chronic mental illness suggest that memories of psychotic episodes frequently form the basis for PTSD.⁷³ A similar dynamic appears to be at work in critically ill pediatric patients, with one recent investigation suggesting a link between delusional (as opposed to factual) memories and symptoms of PTSD.⁷⁴ These reports highlight the necessity for prompt delirium diagnosis and the subsequent ability to look at associations with brain dysfunction during critical illness and the long-term effects it initiates.

ETIOLOGY

Delirium is a neurobehavioral manifestation of imbalances in the synthesis, release, and inactivation of neurotransmitters that normally control cognitive function, behavior, and mood.⁷⁵ Many different global pathways are involved in the development of brain dysfunction. What begins as the stimulation of numerous diverse pathways, may converge onto few specific neural pathways that ultimately affect both arousal and the content of consciousness and cause delirium. Ultimately, understanding the cellular response to critical illness, including neurotransmitter activity and neuro-receptor expression, may lead to innovative diagnostic and treatment modalities. Neurotransmitter imbalance, impaired oxidative metabolism, and inflammation are all implicated in the development of delirium.^{25;75–78}

Three specific neurotransmitter systems are involved in the development of delirium including: the glutamatergic, dopaminergic, and cholinergic pathways.^{79–81} The cerebral cortex, striatum, substantia nigra, and thalamus are critical neuroanatomic areas that are most sensitive to alterations in neurotransmitter balances.⁸² The thalamus, in particular, operates as a filter for information flowing to the cerebral cortex. When neurotransmitter balance through disease or psychoactive medication administration becomes altered, thalamic dysfunction may lead to sensory overload and hyperarousal (hyperactive delirium).^{82;83}

Dopamine is a key neurotransmitter thought to be responsible for modulation of behavior, mood, and cognitive function.⁸⁶ The effect of dopamine on cortical function appears to fluctuate following an inverted U-shaped curve based on concentration and specific receptor mediation.^{87;88} In general, dopamine deficiency leads to extrapyramidal symptoms, while dopamine excess is associated with a range of psychotic disorders.⁸⁹ A balance in dopamine appears to be crucial and a deficiency or excess of dopamine in the setting of delirium may be associated with hypoactive or hyperactive subtypes respectively.

Gamma amino butyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system (CNS).⁷⁸ Global and persistent inhibition of CNS arousal through GABAergic stimulation may cause disruption in cerebral functional connectivity and lead to unpredictable neurotransmission causing a constellation of acute brain dysfunction and long term cognitive impairment.^{25;84;85} Many common sedatives utilized in the ICU setting like benzodiazepines and propofol have high affinity for the GABAergic receptors and contribute to delirium through interference in sleep patterns and production of a central-mediated acetylcholine deficient state.^{78;82;86}

Scarcity of acetylcholine has been linked to the development of delirium in critical illness.⁹⁰ Hyperactive delirium or psychosis associated with anticholinergic excess provides insight into the dysfunctional state of acetylcholine deficiency.⁷⁸ Numerous studies have demonstrated that the development of delirium and an increase in symptom severity of delirium is directly increased with the use of commonly used ICU drugs with significant anticholinergic properties.^{91–93}

Both adults and pediatric patients present with similar types of critical illness such as trauma, septic shock, myocardial insufficiency, and respiratory failure. There are numerous mechanisms including hypoperfusion and inflammation by which critical illness may lead to organ dysfunction. Hypoperfusion of tissues is recognized as one of the leading causes of organ dysfunction, and may contribute to the development of delirium.⁸² Whether due to decreased oxygen delivery or increased oxygen demands, neural ischemia leads to the inability to 1) maintain ionic gradients causing cortical depression,^{94;95} 2) balance neurotransmitter synthesis, release, and metabolism,^{96–100} and 3) eliminate neurotoxic by-products from normal metabolism processes or disease states.^{96;97;99}

Inflammation is another common and significant contributor of multi-organ dysfunction in the critically ill.¹⁰¹ Inflammation initiates a cascade of activity that results in endothelial damage, thrombin formation, and ultimately microvascular compromise.¹⁰² Animal studies have demonstrated that inflammatory mediators cross the blood-brain barrier,¹⁰³ increase vascular permeability in the brain,¹⁰⁴ and result in electroencephalographic (EEG) alterations consistent with those seen in septic patients diagnosed with delirium.¹⁰⁵ The diffuse slowing on EEG is thought to represent a reduction in cerebral oxidative metabolism or “cerebral insufficiency.”^{106;107} Girard and colleagues¹⁰⁸ recently demonstrated that a significant increase in key biomarkers of coagulation and inflammation were associated with the development of delirium amongst adult critical care patients.

RISK FACTORS

The cause of delirium in the critically ill is multi-factorial and associated with numerous risk factors.⁸² These risk factors can be categorized into three main groups: 1) predisposing factors or host factors, 2) precipitating factors including the severity and type of presenting illness, and 3) iatrogenic or environmental factors occurring in the ICU.^{2;6;109–114} In critically ill adults, the most common risk factors are older age, preexisting cognitive impairment, severity of illness in the ICU, and exposure to sedatives (Table 2).^{6;38;44;115;116} There remains a dearth of literature on risk factors specific for the development of pediatric delirium in the critically ill.

Predisposing risk factors for pediatric delirium may be similar to those observed in adults including age, genetic predisposition, chronic neurologic illnesses, or psychiatric disease. Clearly genetic risk factors may impact pediatric and adult patients alike. Polymorphisms of Apolipoprotein E4, previously linked to the development of Alzheimer’s disease¹¹⁷ and poor patient outcomes in the setting of closed head injury and intracranial hemorrhage,^{118;119} have recently been linked with delirium. Ely and colleagues demonstrated a significant association between the Apo E4 polymorphism and duration of delirium in adult critical care patients.¹²⁰ Leung and colleagues also demonstrated that an Apo E4 carrier status was associated with a higher risk for development of delirium in patients postoperative from noncardiac surgery.¹²¹ Similar studies into genetic risk factors and other predisposing risk factors for the development of pediatric delirium need to be performed.

Iatrogenic Factors

Iatrogenic risk factors in the ICU which significantly contribute to the development of delirium include sleep deprivation and administration of sedatives and analgesics.^{6;114;116;122} ICU patients sleep on average 2 hours per day,¹²³ of which less than 6% is comprised of random eye movement sleep. Sleep deficiency may detrimentally affect protein synthesis, cellular and humoral immunity, energy expenditure, and ultimately organ function.¹²³ Excessive noise, diagnostic procedures, pain, fear, and frequency of patient-care activities are some recognized sources of sleep deprivation within the ICU.^{82;124} However, exposure to sedatives and analgesics, mechanical ventilation, and other disease associated complications may have even greater roles in affecting sleep patterns in the critically ill.¹²⁴

Sedative Administration

Patients who require mechanical ventilation routinely receive sedative and analgesic medications to reduce pain and anxiety, per guidelines by the Society of Critical Care Medicine (SCCM).⁵ Although the use of sedation and analgesia may facilitate patient care and safety,^{125;126} their use may also depress spontaneous ventilation and prolong the requirement of mechanical ventilation leading to greater costs and complications.^{127–130} Patients on mechanical ventilation are often sedated to the point of stupor or coma in order to improve

oxygenation, alleviate agitation, and to prevent them from removing support devices. When patients emerge from the effects of sedation, they may do so peacefully or in a combative manner, therein experiencing the hypoactive or hyperactive form of delirium, respectively.¹

Multiple adult studies have shown significant associations with the administration of sedatives and the development of delirium,⁴⁴ of which benzodiazepines are the most commonly implicated.^{113;116} Psychoactive medications represent a significant iatrogenic cause of delirium^{13;114;131}, with a relative risk for delirium of 3 to 11 times.^{13;113} The temporal relationship between sedative administration and ICU delirium was recently examined by Pandharipande and colleagues,¹¹⁶ where lorazepam was found to be an independent risk factor for the daily transition to delirium (OR, 1.2; 95% CI, 1.2–1.4). Though administration of midazolam and lorazepam has been consistently shown to be associated with the development of delirium, studies have been less consistent on the relationship between delirium and opioids.⁶

Greater than 90% of infants and children supported on mechanical ventilation receive psychoactive medications, most commonly combinations of opioids and benzodiazepines.^{132;133} Recently, Colville and colleagues reported that of 102 consecutive children aged 7–17 years admitted to the PICU, 1 out of 3 reported having delusional memories following discharge. Delusional memories were significantly associated with a longer duration of psychoactive medication administration during PICU stay.⁷⁴ This association of sedative exposure and the delusional memories highlights the likelihood that pediatric patients may have a significant risk of delirium during critical illness.

TREATMENT STRATEGIES

The clinical approach to prevent and/or treat delirium may vary and be driven by different goals; 1) prevention through controlling precipitating risk factors, 2) management of delirium symptoms (psychosis or agitation), and/or 3) treatment of delirium through resolution of its underlying cause or modulation of the neurochemical cascade.⁸² Multidisciplinary approaches to the prevention and overall management of delirium in critically ill adults and children have yet to be adequately studied. However, well-studied treatment protocols for delirium in non-critically ill patients may provide some insight into delirium management in ICU populations.⁶ In general the treatment of delirium in the ICU setting requires: 1) an accurate delirium diagnosis, 2) means of consistent monitoring and re-evaluation, 3) therapeutic intervention for hyperactive manifestations that may cause patient harm, 4) avoidance of risk factors to include certain ICU medications which may exacerbate delirium severity, and 5) diagnosis and treatment of the underlying etiology if possible.⁸²

Non pharmacologic Management

Iatrogenic risk factors for delirium in the ICU setting are numerous and fundamentally avoidable. Inouye and colleagues¹³⁴ conducted a study of a multicomponent delirium intervention protocol in critically ill adults, consisting of : a) cognitive stimulation and patient reorientation, b) consistent nonpharmacologic sleep, c) exercise and early mobilization, d) use of hearing aids or glasses, and e) timely removal of indwelling catheters.. The protocol reduced delirium incidence significantly from 15% in the usual-care group to 9.9% in the intervention group. Other adult randomized controlled trials of similar multicomponent therapies have also shown similar improvements in the occurrence of delirium.^{135;136} Schievelde and coworkers¹⁶ instituted an intervention strategy for critically ill children with delirium to include parental presence, pictures of familiar people and objects, familiar music, and involvement of a child psychiatrist. All surviving patients demonstrated reduction of the assessed severity of delirium.

The goal of any multicomponent approach to delirium treatment and prevention will be based on minimizing risk factors. Some of the most common risk factors are infection, electrolyte abnormalities, sleep deprivation, and medication exposure.⁶ Maintaining as normal environment as possible within the ICU setting allows for consistent patient orientation and ultimately reassurance. As part of this approach, promoting normal circadian light rhythm with light and noise control is likely to be paramount. Family involvement, adherence to patient routines, and removal of restraints when appropriate may specifically impact pediatric ICU patients. A mainstay of both prevention and treatment focuses on appropriate use and even avoidance of certain GABAergic agents such as benzodiazepines and propofol.¹³⁷ Sedatives and analgesics are clearly intended to provide patient comfort through pain control and anxiety relief, which in many instances may decrease the risk of developing delirium.¹³⁸ However, over sedation must also be avoided as its association with transition to delirium is well documented and the usefulness of validated sedation scales and daily interruption of sedatives are shown to significantly improve outcomes.^{127;129;139}

Pharmacologic Management

Pharmacologic therapy for delirium in the ICU may be a helpful adjunct to the needed multicomponent approach to patient care. Once risk factors for delirium have been minimized, along with the alleviation of complications from critical disease such as hypoxia, hypoglycemia or shock, pharmacologic therapy can be considered.⁶ Although medications used for delirium may improve cognition, there are many psychoactive effects which may worsen a patient's sensorium and lead to prolonged cognitive impairment.²⁵ Until prospective, randomized, double-blinded studies demonstrate clear treatment benefit of antipsychotic drugs, one must use great caution and administer the minimal doses required for potential benefit.

Haloperidol (Haldol) is a conventional antipsychotic most frequently used for the treatment of delirium.¹⁴⁰ Haloperidol antagonizes the D2 receptor in numerous higher cortical pathways, leading to restoration of hippocampal function.^{25;82} With inhibition of the dopamine-2 receptor, the effects of dopamine excess are controlled and symptoms such as unstructured thought patterns and hallucinations can be alleviated.²⁵ However in hypoactive delirium that is associated with dopamine scarcity versus excess, treatment with haloperidol may exacerbate the severity of delirium and prolong psychomotor retardation or even promote catatonic features.⁸² SCCM guidelines currently recommend that adult patients with hyperactive delirium be treated with haloperidol though the optimal dosing regimen has yet to be defined in clinical trials.⁶ Successful treatment of hyperactive delirium in pediatric ICU patients with haloperidol was reported by Schievel and colleagues¹⁶ using a loading dose of 0.15 to 0.25 mg intravenous followed by 0.05 to 0.5 mg/kg every day for maintenance. In patients who could tolerate oral medication, an atypical antipsychotic, risperidone (Risperdal), was provided as a loading dose of 0.1 to 0.2 mg followed by 0.2 to 2.0 mg every day as maintenance. Schievel and colleagues reported that the majority of treated patients had beneficial effects most noted immediately following the loading dose.

Atypical antipsychotics such as risperidone, olanzapine (Zyprexa), and ziprasidone (Geodon) are considered alternatives to haloperidol for delirium treatment. The clinical benefit of this class of drugs is the global impact on not just dopamine receptors but also effects on serotonin, acetylcholine, and norepinephrine neurotransmission.¹⁴¹ Patients with hypoactive delirium may benefit from the global effect on neurotransmitter equilibrium versus traditional focus on dopamine suppression. Skrobik and colleagues¹⁴¹ completed a nonrandomized trial comparing haloperidol to olanzapine in 73 adult ICU patients. Though resolution of delirium was similar in both groups, the side effects were greatly decreased in those patients receiving olanzapine.

All antipsychotics have potentially serious side effects. The most concerning adverse effects include torsades de pointes, malignant hyperthermia, extrapyramidal movement disorders,

hypotension, glucose and lipid dysregulation, laryngeal spasm, and anticholinergic effects such as constipation, urinary retention and dry mouth.²⁵ Any patient with prolonged QT or with significant cardiac arrhythmias should avoid treatment with antipsychotics. Schievel and colleagues¹⁶ demonstrated that of 40 pediatric critical care patients treated for delirium with typical and atypical antipsychotics, only two patients developed acute dystonias which required further intervention. Although atypical antipsychotics are associated with fewer side effects, there remains a lack of well-designed randomized, placebo-controlled trials studying the efficacy of either typical or atypical antipsychotics for the treatment or prevention of delirium in adult or pediatric critically ill patients.⁶

The use of sedatives, such as benzodiazepines, is a mainstay of treatment for agitation and withdrawal syndromes in the pediatric ICU. However, administration of lorazepam (Ativan) is now recognized to be a significant risk factor for the development of delirium in the ICU.^{113;116} A novel α_2 -receptor agonist, dexmedetomidine (Precedex), has been used in the ICU setting for sedation and was not shown to have an association with the development of delirium. Maldonado and colleagues¹³⁷ were able to demonstrate that of patients sedated after sternal closure, only 8% of those receiving dexmedetomidine developed delirium compared with 50% of patients treated with either propofol (Diprivan) or midazolam (Versed). Recently, Pandharipande and colleagues¹⁴² completed a double-blinded, randomized controlled trial in which ICU patients treated with dexmedetomidine compared with lorazepam spent fewer days in coma and had more neurologically appropriate days. Pediatric studies of dexmedetomidine have been limited to patients treated for emergence delirium following anesthesia. These studies demonstrate less analgesic withdrawal complications with the use of dexmedetomidine.^{6;143}

SUMMARY

Delirium is a syndrome of acute brain dysfunction that commonly occurs in critically ill adults and most certainly is prevalent in critically ill children all over the world every year. The dearth of information in the incidence, prevalence, and severity of pediatric delirium stems from the simple fact that there have not been well-validated instruments for routine delirium diagnosis at the bedside. This article reviewed the emerging solutions to this problem, including description of a new pediatric tool called the pCAM-ICU. In adults, delirium is responsible for significant increases in both morbidity and mortality in critically ill patients. The advent of new tools for use in critically ill children will allow the epidemiology of this form of acute brain dysfunction to be studied adequately, will allow clinical management algorithms to be developed and implemented following testing, and will present the necessary incorporation of delirium as an outcome measure for future clinical trials in pediatric critical care medicine.

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Reference List

1. Ely EW, Siegel MD, Inouye SK. Delirium in the intensive care unit: an under-recognized syndrome of organ dysfunction. *Semin Respir Crit Care Med* 2001;22(2):115–126. [PubMed: 16088667]
2. Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. *JAMA* 1990;263(8):1097–1101. [PubMed: 2299782]
3. Inouye SK. The dilemma of delirium: clinical and research controversies regarding diagnosis and evaluation of delirium in hospitalized elderly medical patients. *Am J Med* 1994;97(3):278–288. [PubMed: 8092177]

4. Morandi A, Pandharipande P, Trabucchi M, Rozzini R, Mistraletti G, Trompeo AC, et al. Understanding international differences in terminology for delirium and other types of acute brain dysfunction in critically ill patients. *Intensive Care Med* 2008;34:1907–341915.
5. Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* 2002;30(1): 119–141. [PubMed: 11902253]
6. Pandharipande, P.; Ely, EW. Scoring and Managing Delirium in the PICU. In: Shanley, TP.; Zimmerman, JJ., editors. *Current Concepts in Pediatric Critical Care - Society of Critical Care Medicine*. Mount Prospect, IL: Society of Critical Care Medicine; 2008. p. 69-77.
7. American Psychiatric Association Diagnostic and statistical manual of mental disorders. Vol. Fourth edition. Washington, DC: American Psychiatric Association; 2000. text revision
8. Justic M. Does "ICU psychosis" really exist? *Crit Care Nurse* 2000;20(3):28–37. [PubMed: 11876211]
9. McGuire BE, Basten CJ, Ryan CJ, Gallagher J. Intensive care unit syndrome: a dangerous misnomer. *Arch Intern Med* 2000;160(7):906–909. [PubMed: 10761954]
10. Meagher DJ, Trzepacz PT. Motoric subtypes of delirium. *Semin Clin Neuropsychiatry* 2000;5(2): 75–85. [PubMed: 10837096]
11. Peterson JF, Pun BT, Dittus RS, Thomason JW, Jackson JC, Shintani AK, et al. Delirium and its motoric subtypes: a study of 614 critically ill patients. *J Am Geriatr Soc* 2006;54(3):479–484. [PubMed: 16551316]
12. O'Keefe ST, Chonchubhair AN. Postoperative delirium in the elderly. *British Journal of Anaesthesia* 1994;73:673–73687.
13. Inouye SK, Schlesinger MJ, Lydon TJ. Delirium: a symptom of how hospital care is failing older persons and a window to improve quality of hospital care. *Am J Med* 1999;106(5):565–573. [PubMed: 10335730]
14. Ely EW, Truman B, May L, Gordon S, Francis J, Margolin R, et al. Validation of the CAM-ICU for delirium assessment in mechanically ventilated patients. *J Am Geriatr Soc* 2001;49:S2.
15. Turkel SB, Trzepacz PT, Tavare CJ. Comparing symptoms of delirium in adults and children. *Psychosomatics* 2006;47(4):320–324. [PubMed: 16844890]
16. Schievelld JN, Leroy PL, van OJ, Nicolai J, Vos GD, Leentjens AF. Pediatric delirium in critical illness: phenomenology, clinical correlates and treatment response in 40 cases in the pediatric intensive care unit. *Intensive Care Med*. 2007
17. Martini DR. Commentary: the diagnosis of delirium in pediatric patients. *J Am Acad Child Adolesc Psychiatry* 2005;44(4):395–398. [PubMed: 15782088]
18. Schievelld JN, Leentjens AF. Delirium in severely ill young children in the pediatric intensive care unit (PICU). *J Am Acad Child Adolesc Psychiatry* 2005;44(4):392–394. [PubMed: 15782087]
19. Plum, F.; Posner, J. *The diagnosis of stupor and coma*. Philadelphia, PA: F.A. Davis Co.; 1980.
20. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet* 1974;181–184. [PubMed: 4129874]
21. Devlin JW, Boleski G, Mlynarek M, Nerenz DR, Peterson E, Jankowski M, et al. Motor Activity Assessment Scale: a valid and reliable sedation scale for use with mechanically ventilated patients in an adult surgical intensive care unit. *Crit Care Med* 1999;27(7):1271–1275. [PubMed: 10446819]
22. Ramsay MA, Keenan SP. Measuring Level of Sedation in the Intensive Care Unit. *JAMA* 2000;284:441–284442.
23. Trzepacz, PT.; Baker, RW. *The Psychiatric Mental Status Examination*. Oxford, UK: Oxford University Press; 1993. p. 202
24. Turkel SB, Tavare CJ. Delirium in children and adolescents. *J Neuropsychiatry Clin Neurosci* 2003;15:431–15435.
25. Pandharipande P, Jackson J, Ely EW. Delirium: acute cognitive dysfunction in the critically ill. *Curr Opin Crit Care* 2005;11(4):360–368. [PubMed: 16015117]
26. Trzepacz PT, Mittal D, Torres R, Kanary K, Norton J, Jimerson N. Validation of Delirium Rating Scale Revised-98: comparison to the delirium rating scale and cognitive test for delirium. *J of Neuropsychiatry and Clin Neurosciences* 2001:13229–13242.

27. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med* 2001;29(7):1370–1379. [PubMed: 11445689]
28. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, 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(21):2703–2710. [PubMed: 11730446]
29. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive Care Med* 2001;27(5):859–864. [PubMed: 11430542]
30. Ely EW, Gautam S, Margolin R, Francis J, May L, Speroff T, et al. The impact of delirium in the intensive care unit on hospital length of stay. *Intensive Care Med* 2001;27(12):1892–1900. [PubMed: 11797025]
31. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004;291(14):1753–1762. [PubMed: 15082703]
32. Jackson JC, Gordon SM, Hart RP, Hopkins RO, Ely EW. The association between delirium and cognitive decline: a review of the empirical literature. *Neuropsychol Rev* 2004;14(2):87–98. [PubMed: 15264710]
33. Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. *Anesthesiology* 2004;100(5):1138–1145. [PubMed: 15114210]
34. Wilson TA, Graves SA. Pediatric considerations in a general postanesthesia care unit. *J Post Anesth Nurs* 1990;5(1):16–24. [PubMed: 1693959]
35. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002;166(10):1338–1344. [PubMed: 12421743]
36. Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA* 2003;289(22):2983–2991. [PubMed: 12799407]
37. Dubois MJ, Bergeron N, Dumont M, Dial S, Skrobik Y. Delirium in an intensive care unit: a study of risk factors. *Intensive Care Med* 2001;27(8):1297–1304. [PubMed: 11511942]
38. McNicoll L, Pisani MA, Zhang Y, Ely EW, Siegel MD, Inouye SK. Delirium in the intensive care unit: occurrence and clinical course in older patients. *J Am Geriatr Soc* 2003;51(5):591–598. [PubMed: 12752832]
39. Pandharipande P, Costabile S, Cotton B, Morris J, Frizzell J, Fraley M, et al. Prevalence of delirium in surgical ICU patients. *Crit Care Med* 2005;33(12 Suppl):A45.
40. Thomason JW, Shintani A, Peterson JF, Pun BT, Jackson JC, Ely EW. Intensive care unit delirium is an independent predictor of longer hospital stay: a prospective analysis of 261 non-ventilated patients. *Crit Care* 2005;9(4):R375–R381. [PubMed: 16137350]
41. Salam A, Tilluckdharry L, Amoaeng-Adjepong Y, Manthous CA. Neurologic status, cough, secretions and extubation outcomes. *Intensive Care Med* 2004;30:1334–1339.
42. Milbrandt EB, Deppen S, Harrison PL, Shintani AK, Speroff T, Stiles RA, et al. Costs associated with delirium in mechanically ventilated patients. *Crit Care Med* 2004;32(4):955–962. [PubMed: 15071384]
43. Lin SM, Liu CY, Wang CH, Lin HC, Huang CD, Huang PY, et al. The impact of delirium on the survival of mechanically ventilated patients. *Crit Care Med* 2004;32(11):2254–2259. [PubMed: 15640638]
44. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y. Incidence, risk factors and consequences of ICU delirium. *Intensive Care Med* 2007;33(1):66–73. [PubMed: 17102966]
45. Jackson JC, Gordon SM, Girard TD, Thomason JWW, Pun BT, Dunn J, et al. Delirium as a risk factor for long term cognitive impairment in mechanically ventilated ICU survivors (under review). *Am J Respir Crit Care Med* 2007;175:A22.
46. Hopkins RO, Jackson JC. Long-term neurocognitive function after critical illness. *Chest* 2006;130(3):869–878. [PubMed: 16963688]
47. Insel K, Morrow D, Brewer B, Figueredo A. Executive function, working memory, and medication adherence among older adults. *J Gerontol B Psychol Sci Soc Sci* 2006;61(2):102–107.

48. Heaton RK, Marcotte TD, Mindt MR, Sadek J, Moore DJ, Bentley H, et al. The impact of HIV-associated neuropsychological impairment on everyday functioning. *J Int Neuropsychol Soc* 2007;10317–10331.
49. Hinkin CH, Castellon SA, Durvasula RS, Hardy DJ, Lam MN, Mason KI, et al. Medication adherence among HIV+ adults. *Neurology* 2002;591944–591950.
50. Stewart JT, Gonzalez-Perez E, Zhu Y, Robinson BE. Cognitive predictors of restiveness in dementia patients. *Am J Geriatr Psychiatry* 1999;7259–7263.
51. Allen SC, Jain M, Ragab S, Malik N. Acquisition and short-term retention of inhaler techniques require intact executive function in elderly subjects. *Age Ageing* 2003;32(3):299–302. [PubMed: 12720616]
52. Kalhan R, Mikkelsen M, Dedhiya P, Christie J, Gaughan C, Lanken PN, et al. Underuse of lung protective ventilation: analysis of potential factors to explain physician behavior. *Crit Care Med* 2006;34(2):300–306. [PubMed: 16424706]
53. Biederman J, Petty C, Fried R, Fontanella J, Doyle AE, Seidman LJ, et al. Impact of psychometrically defined deficits of executive functioning in adults with attention deficit hyperactivity disorder. *Am J Psychiatry* 2006;631730–631738.
54. Evans JD, Bond GR, Meyer Ps, Kim HW, Lysaker PH, Gibson PJ, et al. Cognitive and clinical predictors of success in vocational rehabilitation in schizophrenia. *Schizophr Res* 2004;70331–70342.
55. McGurk SR, Mueser KT. Cognitive and clinical predictors of work outcomes in clients with schizophrenia receiving supported employment services: 4 year follow-up. *Adm Policy Ment Health* 2006;33598–33606.
56. Washburn, am; Sands, LP. Social cognition in nursing home residents with and without cognitive impairment. *J Gerontol B Psychol Sci Soc Sci* 2006;61174–61179.
57. Gunther ML, Jackson JC, Ely EW. The Cognitive Consequences of Critical Illness: Practical Recommendations for Screening and Assessment. *Critical Care Clinics* 2007;23(3):491–506. [PubMed: 17900482]
58. Jackson JC, Hart RP, Gordon SM, Shintani A, Truman B, May L, et al. Six-month neuropsychological outcome of medical intensive care unit patients. *Crit Care Med* 2003;31(4):1226–1234. [PubMed: 12682497]
59. Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson-Loehr V. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999;160(1):50–56. [PubMed: 10390379]
60. Tedstone JE, Tarrier N. Posttraumatic stress disorder following medical illness and treatment. *Clinical Psychology Review* 2003;23409–23448.
61. Jackson JC, Hart RP, Gordon SM, Hopkins RO, Girard TD, Ely EW. Post-traumatic stress disorder and post-traumatic stress symptoms following critical illness in medical intensive care unit patients: assessing the magnitude of the problem. *Crit Care* 2007;11(1):R27. [PubMed: 17316451]
62. Ward-Begnoche W. Posttraumatic stress symptoms in the pediatric intensive care unit. *J Spec Pediatr Nurs* 2007;12(2):84–92. [PubMed: 17371552]
63. Kangas M, Henry JL, Bryant RA. Posttraumatic stress disorder following cancer: A conceptual and empirical review. *Clinical Psychology Review* 2002;22499–22524.
64. Davydow DS, Gifford JM, Desai SV, Needham DM, Bienvenu OJ. Posttraumatic stress disorder in general intensive care unit survivors: a systematic review. *Gen Hosp Psychiatry* 2008;30(5):421–434. [PubMed: 18774425]
65. Girard TD, Shintani AK, Jackson JC, Gordon SM, Pun BT, Henderson MS, et al. Risk factors for posttraumatic stress disorder symptoms following critical illness requiring mechanical ventilation: a prospective cohort study. *Crit Care* 2007;11(1):R28. [PubMed: 17316452]
66. Fiser DH, Tilford JM, Roberson PK. Relationship of illness severity and length of stay to functional outcomes in the pediatric intensive care unit: a multi-institutional study. *Crit Care Med* 2000;28(4):1173–1179. [PubMed: 10809301]
67. Van Vliening TE, Tuokko HA, Cramer K, Mateer CA, Hultsch DF. Awareness of financial skills in dementia. *Aging Ment Health* 2004;8374–8380.

68. Hopkins RO. Does critical illness and intensive care unit treatment contribute to neurocognitive and functional morbidity in pediatric patients? *J Pediatr (Rio J)* 2007;83(6):488–490. [PubMed: 18074052]
69. Alievi PT, Carvalho PR, Trotta EA, Mombelli FR. The impact of admission to a pediatric intensive care unit assessed by means of global and cognitive performance scales. *J Pediatr (Rio J)* 2007;83(6):505–511. [PubMed: 18074054]
70. Fiser DH, Long N, Roberson PK, Hefley G, Zolten K, Brodie-Fowler M. Relationship of pediatric overall performance category and pediatric cerebral performance category scores at pediatric intensive care unit discharge with outcome measures collected at hospital discharge and 1- and 6-month follow-up assessments. *Crit Care Med* 2000;28(7):2616–2620. [PubMed: 10921604]
71. Geffen DB, Blaustein A, Amir MC, Cohen Y. Post-traumatic stress disorder and quality of life in long-term survivors of Hodgkin's disease and non-Hodgkin's lymphoma in Israel. *Leuk Lymphoma* 2003;44(11):1925–1929. [PubMed: 14738144]
72. Rees G, Gledhill J, Garralda ME, Nadel S. Psychiatric outcome following paediatric intensive care unit (PICU) admission: a cohort study. *Intensive Care Med* 2004;30(8):1607–1614. [PubMed: 15112035]
73. Jones C, Griffiths RD, Humphris G, Skirrow PM. Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. *Crit Care Med* 2001;29(3):573–580. [PubMed: 11373423]
74. Colville G, Kerry S, Pierce C. Children's factual and delusional memories of intensive care. *Am J Respir Crit Care Med* 2008;177(9):976–982. [PubMed: 18244955]
75. Trzepacz PT. Update on the neuropathogenesis of delirium. *Dement Geriatr Cogn Disord* 1999;10:330–334.
76. Trzepacz PT. Delirium. Advances in diagnosis, pathophysiology, and treatment. *Psychiatr Clin North Am* 1996;19(3):429–448. [PubMed: 8856810]
77. Meagher DJ, Moran M, Raju B, Gibbons D, Donnelly S, Saunders J, et al. Phenomenology of delirium. Assessment of 100 adult cases using standardized measures. *Br J Psychiatry* 2007;190:135–141.
78. Gunther ML, Morandi A, Ely EW. Pathophysiology of delirium in the intensive care unit. *Crit Care Clin* 2008;24(1):45–65. [PubMed: 18241778]
79. Pavlov VA, Wang H, Czura CJ, Friedman SG, Tracey KJ. The cholinergic anti-inflammatory pathway: a missing link in neuroimmunomodulation. *Mol Med* 2003;9:9125–9134.
80. Webb JM, Carlton EF, Geeham DM. Delirium in the intensive care unit: Are we helping the patient? *Critical Care Nursing Quarterly* 2000;22:247–260.
81. Crippen, D. Treatment of agitation and its comorbidities in the intensive care unit. In: Hill, NS.; Levy, MM., editors. *Ventilator Management Strategies for Critical Care (Lung Biology in Health and Disease)*. New York: Marcel Dekker, Inc.; 2001. p. 243–284.
82. Maldonado JR. Delirium in the acute care setting: characteristics, diagnosis and treatment. *Crit Care Clin* 2008;24(4):657–722. [PubMed: 18929939]
83. Gaudreau JD, Gagnon P, Roy MA, Harel F, Tremblay A. Association between psychoactive medications and delirium in hospitalized patients: a critical review. *Psychosomatics* 2005;46(4):302–316. [PubMed: 16000673]
84. Gunther ML, Jackson JC, Wesley EE. Loss of IQ in the ICU brain injury without the insult. *Med Hypotheses*. 2007
85. Hopkins RO, Jackson JC. Assessing neurocognitive outcomes after critical illness: are delirium and long-term cognitive impairments related? *Curr Opin Crit Care* 2006;12:388–394.
86. Bloom, FE.; Kupfer, DJ.; Bunney, BS., et al. *Amines. Psychopharmacology: the fourth generation of progress*. New York: Raven Press; 1995. p. 1287–1359.
87. Meyer-Lindenberg A, Kohn PD, Kolachana B, Kippenhan S, Inderney-Leo A, Nussbaum R, et al. Midbrain dopamine and prefrontal function in humans: interaction and modulation by COMT genotype. *Nat Neurosci* 2005;8(5):594–596. [PubMed: 15821730]
88. Meyer-Lindenberg A, Nichols T, Callicott JH, Ding J, Kolachana B, Buckholtz J, et al. Impact of complex genetic variation in COMT on human brain function. *Mol Psychiatry* 2006;11(9):867–877. [PubMed: 16786032]

89. Bloom, FE.; Kupfer, DJ.; Bunney, BS., et al. Schizophrenia. Psychopharmacology: the fourth generation of progress. New York: Raven Press; 1995. p. 1171-1286.
90. Flacker JM, Cummings V, Mach JR Jr, Bettin K, Kiely DK, Wei J. The association of serum anticholinergic activity with delirium in elderly medical patients. *Am J Geriatr Psychiatry* 1998;6(1):31–41. [PubMed: 9469212]
91. Tune LE, Egeli S. Acetylcholine and delirium. *Dement Geriatr Cogn Disord* 1999;10:342–10344.
92. Tune LE, Strauss ME, Lew MF, Breitlinger E, Coyle JT. Serum levels of anticholinergic drugs and impaired recent memory in chronic schizophrenic patients. *Am J Psychiatry* 1982;139(11):1460–1462. [PubMed: 6127957]
93. Han L, McCusker J, Cole M, Abrahamowicz M, Primeau F, Elie M. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. *Arch Intern Med* 2001;161(8):1099–1105. [PubMed: 11322844]
94. Basarsky TA, Feighan D, MacVicar BA. Glutamate release through volume-activated channels during spreading depression. *J Neurosci* 1999;19(15):6439–6445. [PubMed: 10414972]
95. Somjen GG, Aitken PG, Balestrino M, Crain BJ, Czeh G, Kawasaki K, et al. Extracellular ions, hypoxic irreversible loss of function and delayed post ischemic neuron degeneration studied in vitro. *Acta Physiol Scand Suppl* 1989;582:58.
96. Busto R, Globus MY, Dietrich WD, Martinez E, Valdes I, Ginsberg MD. Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. *Stroke* 1989;20(7):904–910. [PubMed: 2568705]
97. Globus MY, Alonso O, Dietrich WD, Busto R, Ginsberg MD. Glutamate release and free radical production following brain injury: effects of posttraumatic hypothermia. *J Neurochem* 1995;65(4):1704–1711. [PubMed: 7561868]
98. Globus MY, Busto R, Dietrich WD, Martinez E, Valdes I, Ginsberg MD. Effect of ischemia on the in vivo release of striatal dopamine, glutamate, and gamma-aminobutyric acid studied by intracerebral microdialysis. *J Neurochem* 1988;51(5):1455–1464. [PubMed: 2902196]
99. Globus MY, Busto R, Martinez E, Valdes I, Dietrich WD. Ischemia induces release of glutamate in regions spared from histopathologic damage in the rat. *Stroke* 1990;21:III43–III46. [PubMed: 2237984]
100. Takagi K, Ginsberg MD, Globus MY, Martinez E, Busto R. Effect of hyperthermia on glutamate release in ischemic penumbra after middle cerebral artery occlusion in rats. *Am J Physiol* 1994;267(5 Pt 2):H1770–H1776. [PubMed: 7977807]
101. Marshall JC. Inflammation, coagulopathy, and the pathogenesis of multiple organ dysfunction syndrome. *Crit Care Med* 2001;29:S99–S106. [PubMed: 11445742]
102. Wheeler AP, Bernard GR. Treating patients with severe sepsis. *N Engl J Med* 1999;340(3):207–214. [PubMed: 9895401]
103. Papadopoulos MC, Lamb FJ, Moss RF, Davies DC, Tighe D, Bennett ED. Faecal peritonitis causes oedema and neuronal injury in pig cerebral cortex. *Clin Sci (Lond)* 1999;96(5):461–466. [PubMed: 10209077]
104. Huynh HK, Dorovini-Zis K. Effects of interferon-gamma on primary cultures of human brain microvessel endothelial cells. *Am J Pathol* 1993;142(4):1265–1278. [PubMed: 8475997]
105. Krueger JM, Walter J, Dinarello CA, Wolff SM, Chedid L. Sleep-promoting effects of endogenous pyrogen (interleukin-1). *Am J Physiol* 1984;246(6 Pt 2):R994–R999. [PubMed: 6611091]
106. Engel GL, Romano J. Delirium, a syndrome of cerebral insufficiency. *J Chronic Dis* 1959;9(3):260–277. [PubMed: 13631039]
107. Fink MP, Evans TW. Mechanisms of organ dysfunction in critical illness: report from a Round Table Conference held in Brussels. *Intensive Care Med* 2002;28(3):369–375. [PubMed: 11904670]
108. Girard TD, Shintani A, Thompson JL, Pun BT, Jackson JC, Canonico AE, et al. Biomarkers of inflammation and coagulopathy predict the duration of acute brain dysfunction in critically ill patients. *Crit Care Med* 2006;34:A19.
109. Wilson LM. Intensive care delirium. The effect of outside deprivation in a windowless unit. *Arch Intern Med* 1972;130(2):225–226. [PubMed: 5050558]

110. Levkoff SE, Evans DA, Liptzin B, Cleary PD, Lipsitz LA, Wetle TT, et al. Delirium. The occurrence and persistence of symptoms among elderly hospitalized patients. *Arch Intern Med* 1992;152(2): 334–340. [PubMed: 1739363]
111. Francis J, Kapoor WN. Delirium in hospitalized elderly. *J Gen Intern Med* 1990;565–579.
112. Williams-Russo P, Urquhart BL, Sharrock NE, Charlson ME. Post-operative delirium: predictors and prognosis in elderly orthopedic patients. *J Am Geriatr Soc* 1992;40(8):759–767. [PubMed: 1634718]
113. Marcantonio ER, Juarez G, Goldman L, Mangione CM, Ludwig LE, Lind L, et al. The relationship of postoperative delirium with psychoactive medications. *JAMA* 1994;272(19):1518–1522. [PubMed: 7966844]
114. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA* 1996;275(11):852–857. [PubMed: 8596223]
115. Aldemir M, Ozen S, Kara IH, Sir A, Bac B. Predisposing factors for delirium in the surgical intensive care unit. *Crit Care* 2001;5(5):265–270. [PubMed: 11737901]
116. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006;104(1):21–26. [PubMed: 16394685]
117. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993;261(5123):921–923. [PubMed: 8346443]
118. Laskowitz DT, Sheng H, Bart RD, Joyner KA, Roses AD, Warner DS. Apolipoprotein E-deficient mice have increased susceptibility to focal cerebral ischemia. *J Cereb Blood Flow Metab* 1997;17(7):753–758. [PubMed: 9270492]
119. Lynch JR, Pineda JA, Morgan D, Zhang L, Warner DS, Benveniste H, et al. Apolipoprotein E affects the central nervous system response to injury and the development of cerebral edema. *Ann Neurol* 2002;51(1):113–117. [PubMed: 11782990]
120. Ely EW, Girard TD, Shintani AK, Jackson JC, Gordon SM, Thomason JW, et al. Apolipoprotein E4 polymorphism as a genetic predisposition to delirium in critically ill patients. *Crit Care Med* 2007;35(1):112–117. [PubMed: 17133176]
121. Leung JM, Sands LP, Wang Y, Poon A, Kwok PY, Kane JP, et al. Apolipoprotein E e4 Allele Increases the Risk of Early Postoperative Delirium in Older Patients Undergoing Noncardiac Surgery. *Anesthesiology* 2007;107(3):406–411. [PubMed: 17721242]
122. Schor JD, Levkoff SE, Lipsitz LA, Reilly CH, Cleary PD, Rowe JW, et al. Risk factors for delirium in hospitalized elderly. *JAMA* 1992;267(6):827–831. [PubMed: 1732655]
123. Aurell J, Elmqvist D. Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care. *Br Med J (Clin Res Ed)* 1985;290(6474):1029–1032.
124. Gabor JY, Cooper AB, Crombach SA, Lee B, Kadikar N, Bettger HE, et al. Contribution of the intensive care unit environment to sleep disruption in mechanically ventilated patients and healthy subjects. *Am J Respir Crit Care Med* 2003;167(5):708–715. [PubMed: 12598213]
125. Chevron V, Menard J, Richard J, Girault C, Leroy J, Bonomarchand G. Unplanned extubation: risk factors of development and predictive criteria for reintubation. *Crit Care Med* 1998;26:1049–261053.
126. Marx CM, Smith PG, Lowrie LH, Hamlett KW, Ambuel B, Yamashita TS, et al. Optimal sedation of mechanically ventilated pediatric critical care patients. *Crit Care Med* 1994;22:163–22170.
127. Brook AD, Ahrens TS, Schaiff R, Prentice D, Sherman G, Shannon W, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med* 1999;27(12):2609–2615. [PubMed: 10628598]
128. Kollef M, Pittet D, Sanchez GM, Chastre J, Fagon JY, Bonten M, et al. A Randomized Double-Blind Trial of Iseganan in Prevention of Ventilator-associated Pneumonia. *Am J Respir Crit Care Med* 2006;173(1):91–97. [PubMed: 16192451]

129. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000;342(20):1471–1477. [PubMed: 10816184]
130. Randolph AG, Wypij D, Venkataraman ST, Hanson JH, Gedeit RG, Meert KL, et al. Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized controlled trial. *JAMA* 2002;288(20):2561–2568. [PubMed: 12444863]
131. Francis J. Drug-induced delirium: diagnosis and treatment. *CNS Drugs* 1996;5103–5114.
132. Twite MD, Rashid A, Zuk J, Friesen RH. Sedation, analgesia, and neuromuscular blockade in the pediatric intensive care unit: survey of fellowship training programs. *Pediatr Crit Care Med* 2004;5(6):521–532. [PubMed: 15530187]
133. Rhoney DH, Parker D. Use of sedative and analgesic agents in neurotrauma patients: effects on cerebral physiology. *Neurol Res* 2001;2–3:237–259.
134. Inouye SK, Bogardus ST Jr, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med* 1999;340(9):669–676. [PubMed: 10053175]
135. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *J Am Geriatr Soc* 2001;49(5):516–522. [PubMed: 11380742]
136. Lundstrom M, Edlund A, Karlsson S, Brannstrom B, Bucht G, Gustafson Y. A multifactorial intervention program reduces the duration of delirium, length of hospitalization, and mortality in delirious patients. *J Am Geriatr Soc* 2005;53(4):622–628. [PubMed: 15817008]
137. Maldonado JR, van der Starre PJ, Wysong A. Post-operative sedation and the incidence of ICU delirium in cardiac surgery patients. *Anesthesiology* 2003;99:A465.
138. Morrison RS, Magaziner J, Gilbert M, Koval KJ, McLaughlin MA, Orosz G, et al. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. *J Gerontol A Biol Sci Med Sci* 2003;58(1):76–81. [PubMed: 12560416]
139. Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. *Chest* 1998;114(2):541–548. [PubMed: 9726743]
140. Ely EW, Stephens RK, Jackson JC, Thomason JW, Truman B, Gordon S, et al. Current opinions regarding the importance, diagnosis, and management of delirium in the intensive care unit: a survey of 912 healthcare professionals. *Crit Care Med* 2004;32(1):106–112. [PubMed: 14707567]
141. Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting. *Intensive Care Med* 2004;30(3):444–449. [PubMed: 14685663]
142. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007;298(22):2644–2653. [PubMed: 18073360]
143. Ibacache ME, Munoz HR, Brandes V, Morales AL. Single-dose dexmedetomidine reduces agitation after sevoflurane anesthesia in children. *Anesth Analg* 2004;98(1):60–63. [PubMed: 14693585]

Figure 1.
Abbreviated schematic of the pCAM-ICU.

^aCourtesy of Heidi AB Smith, MD and Jenny Boyd, MD, Nashville, TN

Figure 2.
The Attention Screening Exam (ASE) pictures used for assessment of “Feature 2: Inattention” for the pCAM-ICU are adapted for pediatrics with use of bold colors and child-friendly images.
^aCourtesy of Heidi AB Smith, MD and Jenny Boyd, MD, Nashville, TN

Table 1**Terms used in the Diagnosis of Delirium^{ab}**

Alertness: A level of consciousness where a person is spontaneously and fully aware of their environment with appropriate interactions.

Mental Status: The current state of mind, which can be evaluated using domains of appearance, attitude, behavior, mood and affect, speech, thought process, thought content, perception, cognition, insight, and judgment.

Comatose: A state of a lack of consciousness where the patient is unarouseable and unaware of their surroundings. A comatose patient may have acute brain dysfunction or delirium.

Consciousness: A type of mental state, a way of perceiving, particularly the perception of a relationship between self and other. In practical terms, it denotes being awake and responsive to the environment, in contrast to being asleep or in a coma.

Confusion: A symptom of a pathologic condition such as delirium or acute brain dysfunction, which is characterized by a deficit in orientation (ability to place oneself correctly in the world by time, location, and personal identity), memory (ability to correctly recall previous events or learn new material), and executive functions.

Delirium: A disturbance of consciousness characterized by an acute onset and fluctuating course of impaired cognition. Delirium develops acutely, is usually reversible, and is caused by a general medical condition, substance intoxication or withdrawal, medication, or toxin exposure.

Lethargy: A level of consciousness where a person is drowsy but easily arouseable. Though this patient is unaware of certain elements within their environment, they become fully aware and can interact appropriately with minimal provocation.

Psychosis: A major mental disorder characterized by the inability to distinguish reality from fantasy, the presence of hallucinations or delusions, and the inability to maintain interpersonal relations which compromises daily functioning. A psychotic individual may be able to perform actions that require a high level of intellectual effort in clear consciousness, whereas a delirious individual will have impaired memory and cognitive function.

Stupor: A level of consciousness where a person is difficult to arouse, unaware of certain elements within their environment. A stuporous patient may become incompletely aware and interactive when provoked significantly.

^a Adapted from Ely, EW, Siegel MD, Inouye SK. Delirium in the Intensive Care Unit: An Under-Recognized Syndrome of Organ Dysfunction. *Sem Resp Crit Care Med* 2001;22(2):115–126.

^b See References 1:23.

Table 2**The Pediatric Anesthesia Emergence Delirium Scale³² (PAED)^{ab}**

Item A: The child makes eye contact with the caregiver.

Item B: The child's actions are purposeful.

Item C: The child is aware of his/her surroundings.

Item D: The child is restless.

Item E: The child is inconsolable.

^a Items A, B, and C are scored as follows: **4** - not at all, **3** - just a little, **2** - quite a bit, **1** - very much, **0** -extremely. Items D and E are scored as follows: **0** - not at all, **1** - just a little, **2** - quite a bit, **3** - very much, **4** - extremely. The scores of all items are summed to obtain a total PAED scale score. The degree of emergence delirium increases directly with the total score.³²

^b Adapted from Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. *Anesthesiology* 2004;100(5):1138–1145.

Table 3Richmond Agitation-Sedation Scale^{35;36} (RASS)^a

Scale	Label	Description
+ 4	COMBATIVE	Combative, violent, immediate danger to staff
+ 3	VERY AGITATED	Pulls to remove tubes or catheters: aggressive
+ 2	AGITATED	Frequent non-purposeful movement, fights ventilator
+ 1	RESTLESS	Anxious, apprehensive, movements not aggressive or violent
+ 0	ALERT & CALM	
− 1	DROWSY	Not fully alert, but has sustained awakening to voice (eye opening & contact >10 sec)
− 2	LIGHT SEDATION	Briefly awakens to voice (eye opening & contact <10 sec)
− 3	MODERATE SEDATION	Movement or eye opening to voice (but no eye contact)
− 4	DEEP SEDATION	No response to voice
− 5	UNAROUSEABLE	Movement or eye opening to physical stimulation No response to voice or physical stimulation

^a Patients are assessed for delirium with the pCAM-ICU if their level of consciousness is a RASS score of − 3 or higher. Patients who are comatose, RASS score of − 4 or − 5, are reassessed at a later time.

Table 4**Risk Factors for Delirium^a**

PREDISPOSING FACTORS		PRECIPITATING FACTORS	
Host	Factors of Critical Illness	Iatrogenic Factors	
Age	Acidosis	Few Social Interactions	
Apolipoprotein E4 polymorphism	Anemia	Frequent Nursing Care	
Cognitive Impairment	CNS pathology	Immobilization	
Depression	Electrolyte Disturbances	Medications	
Epilepsy	Endocrine Derangement	Over Sedation	
Stroke history	Fever	Poorly controlled Pain	
Vision/hearing impairment	Hepatic Failure	Sleep Disturbances	
	High Severity of Illness	Vascular Access Lines	
	Hypoperfusion		
	Hypotension		
	Hypothermia		
	Hypoxia/Anoxia		
	Intracranial Hemorrhage		
	Infection/Sepsis		
	Malnutrition		
	Metabolic Disturbances		
	Myocardial Failure		
	Poisoning		
	Respiratory Failure		
	Shock		
	Trauma		

^aSee References 2;6;37;43;81;108–123.