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Review Article

Review of delirium in the pediatric intensive care unit

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Abstract. Delirium is an acute neuropsychiatric syndrome reflecting serious cerebral dysfunction. The characteristic core symptoms of delirium include the inability to direct, focus, sustain, and shift attention; abnormalities of the sleep-wake cycle; impaired consciousness and awareness; disturbance of thought processes; and behavioral dyscontrol. Delirium is particularly prevalent in critically ill and post-operative patients in the intensive care unit, and may result from hypoxia or infection. It is most likely in the most severely ill, and length of stay is prolonged, and morbidity and mortality and higher with delirium.
A variety of clinical instruments have been developed to facilitate the diagnosis of delirium. The Delirium Rating Scale, and its 1998 revision (DRS and DRS-R98) are for psychiatrists to use and are based on DSM criteria. The Pediatric Confusion Assessment Method, adapted for pediatric patients in the ICU (pCAM-ICU), is designed for non-psychiatrists and nurses in the intensive care unit. The Pediatric Anesthesia Emergence Delirium scale (PAED) is the basis for the Cornell Assessment of Pediatric Delirium (CAP-D), and both are for nurses and doctors in the pediatric ICU to use to identify delirium in their patients.
Delirium is typically multifactorial and its pathogenesis reflects neurotransmitter changes associated with metabolic and inflammatory processes. Benzodiazepines and anticholinergic drugs, including opioids and antihistamines, are widely used in the pediatric ICU and may precipitate or exacerbate delirium. Benzodiazepines especially are best used sparingly, in the lowest dose possible, if at all.
The treatment of delirium is predicated on detecting and addressing its underlying cause, which usually results in its rapid resolution. Environmental interventions may ameliorate the risk for delirium, and drugs which may precipitate or worsen delirium should be avoided. Antipsychotics can provide benefit in managing agitation, perceptual disturbances, sleep-wake cycle abnormalities, and behavioral dyscontrol. Atypical antipsychotics, including olanzapine, risperidone, and quetiapine, have largely replaced haloperidol in newer approaches to management because of lower risk for adverse side effects.
The risk for delirium may be mitigated by vigilance, and awareness of its presentation, pathogenesis, and management. Its prevention will be of significant benefit in reducing morbidity, improving outcome, and providing comfort to these very ill and fragile children.

Keywords: Delirium, management, antipsychotic, pediatric, intensive care

1. Introduction

Delirium is an acute neuropsychiatric syndrome reflecting serious cerebral dysfunction [1]. Unfortunately, critical care clinicians in routine practice often fail to recognize delirium in their patients [2], yet one third of pediatric patients with delirium are cared for in the intensive care unit (ICU) [1,3]. Delirium has been linked to increased length of stay and morbidity, and may adversely affect long term outcome [4]. Patients with delirium are very ill and length of hospitalization is typically prolonged [5]. Delirium is an independent risk

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factor for increased mortality [6], and mortality is about 20% in pediatric patients [5]. Cognitive impairment may persist [7], and the risk of long term cognitive impairment increases the longer delirium lasts [8]. The Diagnostic and Statistical Manual of the American Psychiatric Association (DSM) -5 [9] criteria for delirium are essentially unchanged from DSM-IV [10], but with increased emphasis on impaired attention [9]. The criteria are applicable to pediatric as well as adult patients [5]. The characteristic core symptoms of delirium are recognizable in any age and include inability to direct, focus, sustain, and shift attention; abnormalities of the sleep-wake cycle; impaired consciousness and awareness; disturbance of thought processes; and behavioral dyscontrol [11].

Clinically, delirium first presents with problems focusing and sustaining attention, which leads to disorientation of time, then place, and finally person [12]. Disturbed sleep, with brief naps during the day and fragmented sleep at night is almost universal. Impaired cognition, concentration, and confusion are reflected in disordered behavior and speech. Waxing and waning symptoms and fluctuations of consciousness are characteristic [9,10]. Auditory alone or auditory and visual hallucinations are recognized less frequently in younger patients than adults [5]. The commonest cause of delirium is infection, usually with central nervous system involvement, followed by anti-cholinergic medication, autoimmune disorders, following transplant, after surgery or serious trauma, malignancy, or organ failure [5]. Delirium's prevalence in medical and surgical settings has been documented to range between 10% and 50%, but can be as much as 80% in intubated, [13], critically ill and post-operative patients in the ICU [4]. Illness severity predicts risk for delirium in the pediatric ICU [14], and delirium predicts longer length of stay [13]. High severity of illness, respiratory disease, need for mechanical ventilation, number of infusing medications, elevated inflammatory biomarkers, anemia, hypotension, infection and sepsis, fever, and metabolic disturbances all increase risk for delirium [15]. Risk for delirium is greatest in critically ill patients with multiple medical problems or multiple medications [13,16].

2. Instruments for Diagnosis of Delirium in the Pediatric ICU

A variety of clinical instruments have been developed to facilitate the diagnosis of delirium based on DSM criteria (Table 1). The Delirium Rating Scale (DRS) and its 1998 revision (DRS-R-98) have been the most tested, have excellent reliability and very good validity, and are the most widely used diagnostic instruments [17]. They can be used to confirm the diagnosis and allow monitoring of response to medications [17]. Although developed for adults, they have been validated in children and are applicable to pediatric patients [18]. The DRS appears to be more useful for infants and toddlers [19], and the DRS-R98, with more specific cognitive items, for older children [1]. The DRS and DRS-R98 are more detailed than other instruments, require familiarity with psychiatric terminology, are usually scored by psychiatrists, and used for research purposes [17].

The Confusion Assessment Method (CAM) was developed to detect delirium in adults, and the CAM-ICU was derived from it for use by ICU nurses and physicians. The CAM-ICU consists of four criteria: acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness. It is the basis of the pCAM-ICU for evaluation of critically ill children at least 5-years-old in the pediatric ICU [20]. The Pediatric Anesthesia Emergence Delirium scale has been useful for recognizing delirium in the pediatric ICU [21]. The Cornell Assessment of Pediatric Delirium was derived from the Pediatric Anesthesia Emergence Delirium scale [22].

Table 1
Instruments used for pediatric patients in intensive care unit

	Purpose	Staff use	Patients >5 years	Patients <5 years
DRS [17,18,19]	Diagnosis	Psychiatrist	Yes	Yes
DRS-R98 [17,18]	Diagnosis and research	Psychiatrist	Yes	Possibly
pCAM-ICU [20]	Screen	Intensivist and RN	Yes	No
PAED [21]	Emerging from anesthesia	Anesthesiologist	Yes	Possibly
CAP-D [22]	Screen	Intensivist and RN	Yes	Yes
WAS-1 [61]	Opioid withdrawal	RN	Yes	Yes
RASS [62]	Agitation scale	RN	Yes	Yes

It is applicable for younger and nonverbal children, an advantage over the pCAM-ICU. The Cornell Assessment of Pediatric Delirium was also designed for use by nurses and non-psychiatric physicians [22].

3. Pathogenesis of Delirium

The symptoms of delirium are related to alterations in multiple neurotransmitters that can occur in seriously ill patients of any age. Some causes of delirium alter neurotransmitters via general metabolic changes, and other etiologies interfere with specific receptors or neurotransmitters. Inflammation and release of cytokines [23], hypoxia, and impaired oxidative metabolism [24] are implicated in the pathogenesis of delirium. The cholinergic system is particularly vulnerable to metabolic insults such as hypoxia or hypoglycemia and to inflammation [25]. Changes in the cholinergic system appear to predict the magnitude of the inflammatory response in delirium, and there is a shift to a more pro-inflammatory response with lower plasma levels of cholinergic activity [25]. Decreased acetylcholine and excess dopamine may be the underlying pathogenic mechanism of delirium [26], and its "final common pathway" [27].

The clinical presentation of delirium is associated with decreased cholinergic, serotonergic, and noradrenergic function; and excess release of dopamine, glutamate, and gamma amino butryric acid (GABA). Dopamine, norepinephrine, and serotonin are implicated in the regulation of the sleep-wake cycle and arousal, and additionally serotonin has a role in modulating behavior, mood, and motor activity. Increased dopamine levels are linked to psychosis and agitation [28]. These proposed changes in neurotransmitter levels provide clues to the effective pharmacologic management of delirium [27].

4. Management of Delirium

The treatment of delirium is predicated on detecting and addressing its underlying cause [29], which usually results in its rapid resolution [16]. Although delirium is typically multi-factorial, it is essential to attempt to identify etiology while addressing adverse effects of medications, infection, physiologic instability and respiratory dysfunction which contribute to delirium [1].

Adjusting the environment to help reassure and reorient the child with calendars, clocks, and pictures or familiar objects from home often helps maintain orientation and decrease anxiety. Providing bright daytime lighting and a dim night light will assist day-night discrimination [4]. Limiting changes in staff, minimizing noise levels, involving relatives in frequent and repeated re-orientation and reassurance, help decrease fear and confusion [30] and maintain the child's connection to the environment [31].

Most medications used in child psychiatry are used off-label, which means that special attention should be paid to providing information and obtaining consent from parents when recommending antipsychotic or other psychotropic medication [32]. Although antipsychotic medications are not approved by the Federal Drug Administration to manage delirium in adults or children [33–35] they are considered beneficial despite limited data [36]. The only double-blind randomized trials demonstrating the effectiveness of antipsychotic medication in managing delirium have been in adults [37]. These studies have demonstrated that low dose quetiapine is equivalent to haloperidol [38] and superior to placebo [39], and olanzapine and risperidone are equally effective [40,41]. Antipsychotics can provide benefit for agitation, perceptual disturbances, sleep-wake cycle abnormalities, and behavioral dyscontrol [1,25,31,36–48].

Haloperidol had been the preferred drug for many years [45], but atypical antipsychotics are becoming more widely used to manage the symptoms of delirium in pediatric patients, including in the ICU [1,19]. No significant difference in efficacy has been found between haloperidol, olanzapine, and risperidone in the management of delirium in adults [42], or between olanzapine, quetiapine, and risperidone in children and adolescents [1]. Delirium symptoms improve more with olanzapine than without medication in pediatric patients, and this effect remains significant even when controlling for severity [49]. Olanzapine, risperidone, and quetiapine have been useful in managing the symptoms of delirium in pediatric patients from infancy [19] through adolescence [1]. Antipsychotic use may facilitate lower sedative-hypnotic and narcotic use, providing an alternate option to address excessive agitation without exacerbating delirium [1].

Antipsychotics are sedating and starting with nightly dosing will usually address the sleep problems of delirium. (Table 2) Olanzapine's long half-life frequently helps control symptoms during the day as well. Quetiapine is also sedating but with a shorter half life. Risperidone is less sedating, and its liquid

Table 2
Atypical anti-psychotics to manage delirium [1,19]

	Risperidone	Olanzapine	Quetiapine
P450 metabolism	2D6	1A2 and 2D6	3A4
Half-life	3-21 h	20-40 h	6 h
Peak level	1-2 h	6 h	1-2 h
Starting dose	0.1-0.25 mg	0.625-2.5 mg	6.25-25 mg
Maximum dose	2 mg	10 mg	100 mg

concentrate makes it easier to give small doses to very young patients. Both risperidone and olanzapine have oral disintegrating tablet preparations which may make administration easier [1]. Aripiprazole is also available as an oral disintegrating tablet, but there is less data regarding its use in the treatment of pediatric delirium. We recommend consultation with a child psychiatrist when antipsychotic is considered, especially if higher doses are required (Table 2).

A limited number of the same or lower doses of antipsychotic may be given as needed in addition to control persistent hallucinations, confusion, insomnia, agitation, and potentially dangerous behavior. A daily dose can then be established based on the total amount to control symptoms. With improved clinical status, excess daytime sedation, or other side effects, antipsychotic dose should be tapered and discontinued as soon as possible [1]. Antipsychotic can usually be discontinued by the time the child is transferred from the ICU [5]. Monitoring for potential side effects from antipsychotic agents is intrinsic to their use [50]. While weight gain and metabolic effects are of concern for long term use of antipsychotics, especially olanzapine, their brief use in the pediatric ICU does not pose the same risk [50,51].

All antipsychotic medications, both typical and atypical, may cause serious ventricular arrhythmia and sudden cardiac death by prolongation of the QTc interval, increasing potential risk for ventricular dysrhythmias and torsades de pointes [52]. Cardiovascular effects with antipsychotics have been reported less frequently in children and adolescents than in adults [50]. It is prudent to avoid agents associated with greater risk of arrhythmia when treating patients with cardiac dysfunction [50]. Zisprasidone has been reported to increase the QTc interval by 10 msec more than risperidone, olanzapine, or quetiapine in adults [52], and is usually avoided in pediatric patients with delirium. Although asymptomatic hepatic dysfunction may be seen with antipsychotic use, cytolytic and cholestatic changes are rare [53]. Cholestasis with elevated bilirubin and alkaline phosphatase is most common with low potency typical antipsychotics, and generally resolves after cessation of treatment [54]. Asymptomatic increases of serum hepatic transaminases with atypical antipsychotics may be common, but clinically significant increases are not [55]. Antipsychotic dosage may need to be modified to account for delayed metabolism in patients with hepatic dysfunction [50].

Modification of antipsychotic use for renal failure is generally not needed, but may be necessary for patients on hemodialysis or continuous venous-venous hemofiltration. All antipsychotics may induce mild, clinically insignificant leucopenia [50].

5. Reducing risk for Delirium in the Pediatric ICU

Awareness of risk factors and suspicion for its occurrence are essential in reducing risk for delirium in the pediatric ICU [2]. Benzodiazepines and anticholinergic opioids and antihistamines are widely used in the pediatric ICU and may precipitate or exacerbate delirium. Anticholinergic drugs can cross the blood brain barrier, and their use should be minimized to reduce the risk of delirium. When opioids are used to treat pain they can be protective against the development of delirium, but when used at higher doses for sedation, they increase its risk [15].

Children requiring mechanical ventilation in the ICU present a unique problem. Sedation and analgesia for children requiring mechanical ventilator support may require continuous infusions of opioids and/or benzodiazepines to keep these children comfortable. Controlling agitation in an intubated child is critical in preventing an unplanned extubation, which could significantly increase morbidity and mortality in fragile patients. Repetitive motion of the head and neck in an agitated child on mechanical ventilation can cause shifting of the endotracheal tube, traumatizing the airway and causing subglottic swelling, which

may prevent a successful extubation in the future. A variety of combinations of intermittent or continuous infusions of opioids and benzodiazepines have been investigated, along with adjunctive medications like dexmedetomidine, for mechanically ventilated infants and children [56–59]. With these consequences in mind, patients requiring intubation may be first sedated with continuous infusions of a short acting opioid and benzodiazepine [56], which are effective in the short term.

At our institution, an initial fentanyl infusion with intermittent midazolam dosing is most commonly used for mechanically ventilated patients. If the fentanyl infusion is required for longer than several days or no longer appears to be effective, it is changed to a hydromorphone infusion. The benzodiazepine regimen usually starts with midazolam as needed, then round-the-clock midazolam, and finally a lorazepam infusion also after several days. If the patient's pain or agitation is still not able to be controlled well, a dexmedetomidine infusion is instituted [56–59]. Opioid and benzodiazepine use for long term sedation leads to the development of tolerance and dose escalation [36]. Escalating doses, in turn, contribute to confusion and agitation and when increased further to control worsening symptoms, delirium results from both the underlying disorder and medications used to control its symptoms [46,60]. Additionally, continuous infusions of analgesic and sedation agents have been linked to longer duration of mechanical ventilation and extended length of stay in the ICU and hospital [61].

To minimize these risks, it is useful to document total daily dose of opioids and benzodiazepines. There is no standard opioid or benzodiazepine equivalent to use for comparing the total amount of opioid or benzodiazepine used for a given patient. Nevertheless, it is generally accepted that in order to compare the total opioid or benzodiazepine doses, possibly comprised of different agents within the same medication class for a given patient, a common currency of equivalent doses of medications must be established. It is the convention at our institution to use morphine and lorazepam equivalents. This provides a standard for monitoring dosing and recognizing when doses rapidly escalate and tolerance is developing. If long term analgesia from opioids is required, those with longer duration of action are preferable. Transition to enteral methadone may provide another option instead of parenteral agents [62].

Prolonged benzodiazepines use particularly is not recommended [15], and benzodiazepine should be tapered and discontinued as soon as possible as continued use will exacerbate confusion, agitation, and disordered sleep. Lorazepam has been shown to be an independent risk factor for delirium in the ICU [63], and refractory agitation in the pediatric ICU is a marker for delirium and is related to benzodiazepine use [64]. It is important to prevent rapid escalation of dosing of analgesic and sedative agents, especially for mechanically ventilated patients. Sedation protocols are an effective strategy to promote consistency of care amongst caregivers and promote systematic drug administration. They effectively can reduce the total amount of sedation and analgesic medications given intubated patients, without increasing the risk for unplanned extubations, while reducing the duration of mechanical ventilator support and length of ICU and hospital stay [65–68].

As patients clinically stabilize and extubation is anticipated, weaning of sedative and opioid medication should begin. Early transition from short-acting to longer acting opioid and benzodiazepine agents will facilitate this process. Benzodiazepines and opiates may be tapered simultaneously on alternating days. It is very important to monitor for withdrawal symptoms as doses are tapered. Standardized scales such as the Withdrawal Assessment Tool-1 can be useful for monitoring for signs of opioid withdrawal [69], including tremor, agitation, increased heart rate, sweating, diarrhea, and nausea. Higher scores indicate symptoms of opioid withdrawal, and clarify agitation due to withdrawal from delirium. Withdrawal from benzodiazepines may result in agitation, anxiety, and, if high doses are weaned abruptly, induce seizures. The Richmond Agitation-Sedation Scale is useful in monitoring for level of sedation and agitation [70]. Other than rescue doses during weaning, discontinuing unscheduled prn doses and consolidating total drug received per day into routine dosing can facilitate a methodical weaning process. Weaning proceeds first by lowering total daily dose and then by increasing the interval between doses until the drug is discontinued. Typically, the doses of both opioid and benzodiazepine are alternatively decreased every 2 or 3 days by 10% to 20% of the last total daily dose before tapering began.

Alpha-2 adrenergic agonists, such as dexmedetomidine [71] and clonidine [72], may provide additional agents for addressing agitation and decreasing the risk for delirium in the pediatric ICU. As a continuous infusion, dexmedetomidine may decrease the need for benzodiazepines and blunt the sympathetic stress

response and endogenous catecholamine release [71]. If a dexmedetomidine infusion is found useful for augmenting sedation, it may be transitioned to a clonidine transdermal patch for continued, longer term alpha-2 agonist use. Clonidine may also be useful when opioids are weaned to ameliorate symptoms of opioid withdrawal [71–73]. Because disordered sleep is a characteristic symptom of delirium, a number of pharmacologic agents have been tried to improve sedation. Diphenhydramine is anticholinergic; chloral hydrate is metabolized to trichloroethanol, a CNS depressant, or to trichloroacetic acid, which is toxic [74]; and benzodiazepines are GABA-ergic. These common drugs are contraindicated because they may worsen delirium. Low dose sedating antipsychotics such as quetiapine may be more helpful in improving sleep. Melatonin is usually well tolerated with minimal side effects [75]. Melatonin and ramelteon, a synthetic selective melatonin receptor agonist, may be helpful in reducing risk for delirium [76,77], and melatonin given immediately post-operatively may decrease emergence delirium in children [78]. Melatonin may help reset the sleep/wake cycle to prevent delirium, or it may have a more direct role in the pathogenesis of delirium. Other pharmacologic agents have been tried, but none have been shown to be of help in reducing the risk of developing delirium [79].

In conclusion, patients in the pediatric ICU are at high risk for developing delirium, and the development of delirium in critically ill children may be enough to tip the balance to unfavorable morbidity and higher mortality. This risk may be mitigated by vigilance, and awareness of delirium's presentation, pathogenesis, and management. Its prevention will be of significant benefit in reducing morbidity, improving outcome, and providing comfort to these very ill and fragile children.

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