Infant Delirium in Pediatric Critical Care Settings

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Pediatric delirium is a common though underrecognized and understudied phenomenon in pediatric critical care. The unique combination of the vulnerability and resiliency of children's developing brains makes it imperative that research on prevention, evaluation, treatment, and follow-up of this complication of pediatric medical illness and treatment be vigorously pursued. Although antipsychotics are rarely used for treatment, a small but growing body of research supports the efficacy and short-term safety of using both conventional and atypical antipsychotics. Further understanding of the complex neurophysiology of delirium may lead to more refined treatments. Developmentally valid screening tools will make the assessment and treatment of pediatric delirium more feasible when expert consultation is not available.

The DSM-IV diagnostic criteria for delirium are 1) an acute onset and often fluctuating course of 2) disturbances in arousal and 3) cognition, in the presence of 4) an underlying general medical condition triggering the syndrome (1). Children have been found to have a pattern of symptoms similar to that seen in adults (2).

Clinical subtypes of delirium, recognized in both adult and pediatric patients, are characterized by disturbances in arousal: hyperactive, hypoactive, and mixed delirium (3–5). Hypoactive delirium is underrecognized and has low referral rates because of its less disruptive clinical picture (5–7).

Associated symptoms of delirium include impairments in arousal, attention (thought to be a core symptom), cognition, thought (delusions), language, memory, orientation, perception (hallucinations), sleep-wake cycle, behavior, mood, and affect. Pediatric and adult delirium have similar high rates of impaired alertness, orientation, anxiety, and hallucinations (2). However, pediatric and particularly infant delirium may have subtle developmentally specific symptoms and signs not yet accounted for in available screening measures.

Adult delirium is associated with more self-extubations, longer requirement of mechanical ventilation, inadvertent removal of catheters, prolonged hospital stay, higher health care costs, and increased mortality (6). Adult survivors of delirium have been shown to be at risk for long-term cognitive impairment and posttraumatic stress disorder (PTSD) (6). Children have reported delusional memories of intensive care unit (ICU) experiences, which can become a basis for PTSD later.

Pathophysiology

Children, like elderly patients, have an elevated vulnerability to delirium (7). The "delirium cascade" can originate in any number of pathways associated with systemic illness or iatrogenic intervention: oxygen deprivation, inflammatory cytokine release, modification of blood-brain barrier permeability, sick euthyroid syndrome, up-regulation of the hypothalamic-pituitary-adrenal axis, and disruption of intracellular second messenger systems (6, 8). Dysregulation of multiple neurotransmitter systems, particularly of acetylcholine and dopamine, probably plays a role in symptom generation. From research in traumatic brain injury, epilepsy, and meningitis, it is clear that the immature brain has different responses to oxygen deprivation and cytokine release compared to the adult brain (9). Because delirium may represent "end organ damage" of the brain in critical illness, long-term neurocognitive outcome studies in child survivors of untreated delirium are needed.

Evaluation of Delirium in the PICU

Clinical Evaluation

Psychiatric evaluation of the patient in the pediatric intensive care unit (PICU) includes review of the medical history and hospital course, with special attention to the current medication history, pain, itching, and other disturbing medical symptoms; corroborative history, including from multidisciplinary staff and caregivers; and examination of the child.

Screening Instruments

There is a need for screening instruments that could help identify patients with delirium and the subset who need treatment. Some experts have recommended that screening be done during each shift in the PICU, because of the fluctuating course of delirium and the potential for prevention and reversal when treated (10).

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A 7.5-month-old girl undergoing chemotherapy for neuroblastoma with extensive metastatic disease develops agitation and delirium.

A 7.5-month-old, 9.4-kg girl was hospitalized for treatment of stage IV neuroblastoma. She had an abdominal mass, metastases in bone marrow, liver, and lungs, and extensive cranial bone involvement. Her neuroblastoma had favorable biological prognostic markers, giving her a 90% chance of 5-year survival. Her first cycle of chemotherapy was complicated by severe mucositis, respiratory compromise, and constant agitation. She was sedated with fentanyl, hydromorphone, diphenhydramine, and lorazepam. Because of worsening agitation and apneic episodes, she was intubated and had trials of sedation with propofol, phenobarbital, and pentobarbital, which brought no improvement. She remained inconsolable, pulling out intravenous lines and fighting the ventilator whenever sedation was decreased. She was maintained on the ventilator for 9 days on a combination of sedatives. Her mucositis was healing, and she was due to start her second round of chemotherapy. The Department of Child Psychiatry was consulted on the patient's 11th day in the pediatric intensive care unit (PICU) to assist in treating the agitation so that she could be extubated and given her next round of chemotherapy. On examination she was normotensive, persistently tachycardic (heart rate ranging from 160 to 200), on ventilator support, with significant facial edema. The mother described the patient as screaming, wiggling inconsolably, persistently arching her back, attempting and sometimes succeeding in self-extubating and pulling out lines. She said that her child did not seem to recognize her or to be comforted by any of the usual methods, including the parents' touch or voices. No difference was noted in the severity and quality of agitation or wakefulness during the day or night. On psychiatric examination the patient was struggling, moaning, and in respiratory distress. After a bolus dose of pentobarbital, she was deeply sedated and her percentage oxygen saturation was in the 70s. Her score on the Pediatric Anesthesia Emergence Delirium Scale, rated in retrospect, was 19 (this instrument consists of five 4-point questions; a score ≥10 indicates delirium).

The patient's laboratory results were significant for thrombocytopenia (a platelet count of 29,000) and mildly elevated liver enzymes. EEG showed no seizure activity. Cranial MR imaging and venography showed extensive metastatic disease invading the sinuses, orbits, and skull base; bilateral subdural collections; and generalized parenchymal volume loss, particularly within the left frontal and temporal bones.

A diagnosis was made of multifactorial delirium secondary to underlying disease, hypoxia, toxic effects of medications, pain, sensory deprivation, and trauma. A trial of intravenous haloperidol at 0.25 mg (0.025 mg × 10 kg) every 6 hours was recommended to immediately achieve safe airway management (including facilitation of successful extubation), reduce distress, and facilitate reduction of potential offending agents, such as the lorazepam, pentobarbital, and opioids. The dosage was determined on the basis of guidelines for children over 3 years of age, which recommend using 0.05–0.15 mg per kilogram of body weight, divided into two or three doses per day; the recommendations include using the lowest effective dose. Antipsychotic dosage recommendations have not been devised for children under age 3 for any reason or for the treatment of delirium in children of any age.

Within 24 hours, the patient's agitation and delirium had improved such that she began to have periods during which she rested comfortably. The pentobarbital was steadily decreased, and the patient was extubated on the third day after initiation of haloperidol. Her parents described her as "seeming to recognize us and being able to be soothed for the first time" since admission. The second cycle of chemotherapy was initiated and progressed successfully.

On day 5 of haloperidol treatment, the patient developed episodes of "repetitive movements," which were witnessed only by the PICU and junior neurology staff. The differential diagnosis included seizure, benzodiazepine or opiate withdrawal dyskinesia, and extrapyramidal symptoms. EEG was again negative for seizure. The psychiatric recommendation was to continue observation with the same or a 50% reduction of the haloperidol dosage, but the PICU team was uncomfortable with the possibility of extrapyramidal symptoms in an infant and discontinued the haloperidol. The Department of Child Psychiatry was consulted again, this time for a medication recommendation for delirium with a lower risk of extrapyramidal symptoms. Haloperidol was cross-tapered over three days to quetiapine at 6 mg b.i.d. Pediatric dosing guidelines for quetiapine exist only for children over age 13, for whom the usual starting dose is 25–50 mg b.i.d.; 6 mg is thus equivalent to about one-quarter of the starting dose of a 40 kg child. The patient still exhibited day-night reversal but was tolerating her chemotherapy and oral feedings and was more consolable and interactive despite some fussy episodes.

The patient improved neurologically and medically over the next week and started physical and occupational therapies. She tolerated her next two cycles of chemotherapy. The sedative taper was continued slowly over 1 month after the patient was transferred to Department of Oncology. Quetiapine was continued throughout the sedation tapers, and 6 weeks after it was started, it was decreased to 6 mg nightly for 2 nights, then discontinued, with no adverse events. Since this hospitalization, the baby is developing as expected and undergoing physical and occupational therapies to address ongoing obstacles to her development from her illness and treatment.

The Delirium Rating Scale, the most comprehensive scale used to date, has been shown to have cutoff scores for a pediatric cohort comparable to those for adults (11). However, this scale includes questions that are not applicable to younger children, including self-report of symptoms such as hallucinations and delusions. No validation studies for the Delirium Rating Scale have been conducted with pediatric samples.

The Pediatric Confusion Assessment Method for the ICU (6) is the first validated screening instrument for critically ill children that can be used by staff for the rapid assessment of ventilated and nonventilated patients over age 5. Through the use of yes/no questions, pictures, and hand signals, this instrument allows the evaluation of a child's "inattention" and "disorganized thinking." Sensitivity and specificity are currently being evaluated in U.S. and European pilot studies.

The Pediatric Anesthesia Emergence Delirium Scale was developed in studies of emergence delirium, which occurs when children are awakening from anesthesia (6, 12). This instrument includes items about the child's eye contact with caregivers, awareness of surroundings, purposeful nature of movements, ability to be consoled, and restlessness. It is validated in children from 19 months to 6 years of age in postoperative settings and is being studied for use in PICU settings. As part of a pediatric delirium diagnostic algorithm, which includes caregiver and multidisciplinary team consensus, the Pediatric Anesthesia Emergence Delirium Scale's focus on neurobehavioral symptoms may make it a useful tool in this younger population and may guide us in developing tools for assessing delirium in the very youngest patients, in whom neurocognitive symptoms are difficult or impossible to assess (10).

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Treatment

Sedation in Pediatric Critical Care

Sedative and analgesic agents are integral to the care of critically ill children. Although nonpharmacologic methods, such as intervention by child life specialists and parental presence at the bedside, are routine in the PICU, medications are universally required for tolerance of mechanical ventilation and painful procedures. Fear and anxiety in this stressful environment are also addressed by medications. The medications routinely used in the PICU are presented in Table 1 (13, 14).

Treatment of Pediatric Delirium

When considering treatment for delirium, it is imperative that one consider the risks and benefits of intervention while evaluating 1) the underlying illnesses and treatments, 2) offending agents, such as medications, 3) environmental factors, and 4) indication for antipsychotics. Here we focus on the last three factors.

Potential offending agents include benzodiazepines, opioids, and steroids, as well as other sedatives, including propofol and ketamine. These agents have potentially neurotoxic effects. Recent biochemical research has shown that the toxicity is mediated through complex pathways that may have pro-apoptotic mechanisms as well as through the enhancement of γ-aminobutyric acid (15). These toxic effects have been found to be dependent on dose and duration of exposure, and there is evidence suggesting that they are minimized during exposure to noxious neurostimulation, such as surgery. PICU patients are often exposed to these agents for days, weeks, or months, raising concern about potential long-term neurocognitive harm despite the lack of long-term outcome studies in children (16). Timely dosage tapering minimizes withdrawal symptoms in patients exposed to benzodiazepines, barbiturates, and opioids. Research exploring the association between Akt phosphorylation and anti-apoptotic activity suggests that antipsychotics may be neuroprotective. Coupled with their enhancement of cellular glucose uptake and metabolism, the atypical antipsychotics may make cells more resistant to cellular stress and restore levels of nerve growth factor and brain-derived neurotrophic factor (17). Although this research is preliminary, the potential for neuroprotection and substantial clinical benefits further supports the consideration of antipsychotics.

Environmental stressors do not cause delirium but are an exacerbating factor. They can be minimized by having an active parental (or other familiar caregiver) present at bedside; having familiar, orienting objects in view, such as favorite toys and pictures of home and pets; limiting noxious noise and light; limiting room and staff changes; maintaining approximately normal diurnal schedules; and using one-on-one nursing observation as necessary (5, 18).

Pharmacologic Strategies

Pharmacotherapy may be used to resolve delirium; to reduce agitation, allowing removal of potentially offending agents and improving respiratory management; to limit the time the patient is delirious, decreasing any associated trauma, distress, and potential toxicity; and to reduce the length of hospital stay. The medications recommended are conventional and atypical antipsychotics, which are listed with dosage recommendations in Table 2 (3, 5, 6, 19, 20). There is a nascent pediatric delirium literature indicating safe and rapid resolution of delirium with these agents, even in very young children (2, 3, 5, 6, 21, 22). As in adults, a model of high dopamine for hyperactive delirium and low dopamine/cholinergic imbalance for hypoactive and mixed delirium may suggest the choice of antipsychotic (3). In the case of hyperactive delirium, haloperidol may be more effective because of its narrower targeting of the dopamine D_2 receptor. Because of their wider receptor effects, atypical antipsychotics may be more useful in mixed or hypoactive delirium and may lessen the cognitive side effects seen with conventional antipsychotics.

TABLE 1. Medications Commonly Used for Sedation in the Pediatric Intensive Care Unit

Drug Class and Agents	Effects	Benefits	Adverse Effects
Opiates: fentanyl, morphine, hydromorphone	Analgesia, sedation, no amnesia	Fentanyl: minimal cardiovascular effects, decrease in sympathetic response, minimal pulmonary vascular resistance effects	Fentanyl: rigid chest; morphine: histamine release, hypotension
Benzodiazepines: midazolam, lorazepam, diazepam	Sedation, amnesia, anxiolysis, seizure control, no analgesia	Midazolam: short-acting; lorazepam and diazepam: seizure control	Lorazepam (continuous infusion): lactic acidosis, renal failure, rhabdomyolysis, mental status changes
Barbiturates: thiopental, methohexital, pentobarbital	Sedation, seizure control, intracranial pressure control	Seizure control, intracranial pressure control	Hypotension, apnea
General anesthetics: propofol	Sedation, anesthesia, seizure control, no analgesia	Short-acting, seizure control, intracranial pressure control	Hypotension, apnea, hypertriglyceridemia, propofol infusion syndrome[a]
Dissociative anesthetics: ketamine	Amnesia, analgesia	Maintains heart rate, blood pressure, and respirations; bronchodilation	Increases intracranial pressure, increase in intraocular pressure, negative inotropy, emergence reactions, increase in pulmonary vascular resistance
α_2 Adrenergic agonists: dexmedetomidine	Sedation, anxiolysis	Sedation, anxiolysis	Hypotension, hypertension, bradycardia, sinus arrest

[a]Propofol infusion syndrome is characterized by metabolic acidosis, dysrhythmias, rhabdomyolysis, and cardiac failure.

All antipsychotics carry the risk of QT prolongation, which can lead to torsade de pointes and ultimately sudden death (18, 23, 24). Children with medical illness may have electrolyte abnormalities, infection, hypoxia, or exposure to other cardiotoxic drugs, all of which can increase the likelihood of cardiac arrhythmias with antipsychotic treatment. These factors must be assessed and addressed before antipsychotics are introduced. While most children in PICU settings are already receiving continuous cardiac monitoring, the additional monitoring of QTc, electrolyte levels, and drug interactions during the introduction and course of antipsychotic treatment is prudent. Cessation of antipsychotic treatment must be considered if there is significant QTc prolongation, a QTc >500 msec, new T wave abnormalities, marked bradycardia, or a Brugada phenotype. Risks may increase with the addition of metabolic inhibitors or other drugs that prolong QTc. Intravenous haloperidol is associated with particular risk for cardiac arrhythmia and should be avoided in high-risk patients whenever possible (18). There are no established clinical guidelines for the use of antipsychotics for delirium in children with preexisting cardiac disease. Each case must be evaluated individually, perhaps with the guidance of pediatric cardiologists, to weigh the risk of arrhythmia against the risks of untreated delirium, such as respiratory compromise and brain anoxia, as in the case presented here.

If cardiac risk is low and the use of antipsychotics is desired, multiple factors may bear on specific drug choice. Intravenous haloperidol has many benefits in cases of reduced gastrointestinal absorption or acute psychomotor agitation threatening the safety of catheters and ventilatory support because it can be rapidly administered and absorbed. It also has minimal effects on blood pressure, respiration, and heart rate; a low sedative effect; and few anticholinergic side effects. In less acute situations and when oral medication is possible, atypical antipsychotics are preferred (5, 18). The choice of atypical agent can be based on side effect profile. The most serious side effects to consider are those of cardiac toxicity. Current limited data indicate that cardiac risks are similar across all atypical antipsychotics except that there may be less QTc prolongation with aripiprazole. Once the decision has been made to use an atypical agent, one can consider need for sedation, appetite stimulation/weight gain, nausea control, or glycemic control to identify the best drug. Table 2 describes drug profiles in detail.

Conclusions

The treatment of infants and young children with delirium is a new frontier in pediatrics and psychosomatic medicine, with limited information about assessment tools, best practices, and potential side effects of treatment. Clinical practitioners should be aware, however, that there are potential developmental consequences to untreated delirium in this population and consider intervention when appropriate.

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TABLE 2. Profiles of Medications Used in the Treatment of Pediatric Delirium[a]

Drug	Dosing	Forms Available	Frequencies of Adverse Effects[b]	Cardiac Effects[c]
Haloperidol	Age 3–12 years, 0.05–0.15 mg/kg per day divided into two or three doses; dosing interval, 2–12 hours	Oral (tablet, solution), intravenous, intramuscular (immediate release and depot), subcutaneous	>30%: extrapyramidal side effects; >10%: agitation, insomnia, weight gain, hyperglycemia; >2%: sedation, anticholinergic effects, hyperlipidemia, orthostasis; <2%: blood dyscrasias,[d] hepatic impairment, seizure, skin reaction; rare: neuroleptic malignant syndrome (highest potency antipsychotic, thus highest risk)	Abnormal ECG, <2%; QTc prolongation, >2%; tachycardia, <2%
Chlorpromazine	Oral: age 6 months–12 years, 2.5–6.0 mg/kg per day, with dosing every 4–6 hours; maximum dosage: age 6 months–5 years, 50 mg/day; age 5–12 years, 200 mg/day. Intramuscular: 2.5–4 mg/kg per day, with dosing every 6–8 hours; maximum, 40 mg/day	Oral, intravenous, intramuscular	>30%: sedation, anticholinergic effects, orthostasis, weight gain, hyperglycemia, hyperlipidemia, abnormal skin pigmentation; >10%: photosensitivity, other rashes; 2%–10%: extrapyramidal side effects; <2%: agitation, blood dyscrasias,[d] hepatic impairment, seizures	Abnormal ECG, >30%; QTc prolongation, >2%; tachycardia, >10%
Risperidone	Age 5–16 years, 0.5 mg–2.5 mg/day p.o., divided into two to four doses; maximum dosage: <20 kg, 1 mg/day, 20–45 kg, 2.5 mg/day, >45 kg, 3 mg/day	Oral (tablets, orally disintegrating tablets, solution), intramuscular (depot)	>30%: weight gain; >10%: sedation, agitation, extrapyramidal side effects (akathisia/parkinsonism > dystonia), anticholinergic effects, hyperglycemia, hyperlipidemia, orthostasis; <2%: skin reactions, blood dyscrasias,[d] seizures, hepatic impairment	Abnormal ECG, >2%; QTc prolongation, <2%; tachycardia, >10%
Olanzapine	Age 13–17 years, 2.5–10 mg/day; dosing every 12–24 hours; recommended maximum, 20 mg/day	Oral (tablets, orally disintegrating tablets), intramuscular	>30%: sedation, anticholinergic effects, weight gain, hyperlipidemia, hyperglycemia; >10%: insomnia, agitation; 2%–10%: extrapyramidal side effects (akathisia > dystonia/parkinsonism); >2%: orthostasis, hepatic impairment; <2%: skin reaction, blood dyscrasia, seizure	Abnormal ECG, <2%; QTc prolongation, <2%; tachycardia, <2%
Quetiapine	Age 10–17 years, 12.5–400 mg; dosing every 12–24 hours (usually 12 hours); recommended maximum, 750 mg/day	Oral (tablets; immediate release, extended release)	>30%: sedation, anticholinergic effects, hyperglycemia; >10%: agitation, orthostasis, weight gain, hyperlipidemia; >2%: extrapyramidal side effects (akathisia > parkinsonism/dystonia), hepatic impairment; <2%: seizure, skin reaction (no data for rate of blood dyscrasias with quetiapine[d])	Abnormal ECG, <2%; QTc prolongation, <2%; tachycardia, >2%
Ziprasidone	Adults, 5–100 mg/day, usually with dosing every 12 hours	Oral, intramuscular	>30%: agitation; >10%: sedation, anticholinergic effects, orthostasis; >2%: extrapyramidal side effects, weight gain, hyperglycemia; <2%: seizure, skin reaction; rare: priapism reported in adults	Abnormal ECG, >2%; QTc prolongation, <2%; tachycardia, >2%
Aripiprazole	Age 6–17 years, 2–15 mg/day; dosing interval, 12–24 hours	Oral (tablets, orally disintegrating tablets, solution), intramuscular	>10%: sedation, agitation; 2%–10%: extrapyramidal side effects (akathisia > parkinsonism/dystonia); >2%: anticholinergic effects, weight gain, rash; <2%: hyperglycemia, hyperlipidemia, blood dyscrasia, hepatic impairment (other: dopamine stabilizing, possibly good for hypoactive delirium)	Abnormal ECG, <2%; QTc prolongation, <2%; tachycardia, >2%

[a]All pediatric recommendations are off-label, not approved by the Food and Drug Administration.
[b]Data are for adults.
[c]Risk increases with dose.
[d]Because of the small risk of leukopenia, discontinue if absolute neutrophil count <1,000.

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