Analgesia, Sedation, Paralytics, Delirium, and Iatrogenic Withdrawal

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KEYWORDS

• Sedation • Analgesia • Critical care pediatrics • Paralytics • Delirium • Withdrawal

KEY POINTS

- Critically ill children have age-related differences in pharmacokinetics/pharmacodynamics that must be considered.
- A complex association exists between pain management and sedation in critically ill children.
- Over-sedation has the potential to mask and lead to under-treatment of pain.
- When neuromuscular blocking agents are required, adequate analgosedation must be ensured. Continued use of neuromuscular blockade should be evaluated with the train of 4 monitoring, provision of a paralytic holiday, or both.
- Prolonged pain and sedation management can lead to tolerance and potential withdrawal.
- Tools to measure withdrawal and delirium should be used regularly as part of a protocol to identify at-risk patients and inform appropriate therapies.

PHARMACOLOGIC PRINCIPLES IN CRITICALLY ILL CHILDREN

It is important to distinguish age-related differences in pharmacology for infants and young children compared with older children and adults. In the first year of life, pharmacokinetic changes occur in absorption, distribution, metabolism, and excretion. Neonates and infants have distinct differences in drug metabolism that include[1]: a relative absence of hydrochloric acid in gastric secretions that lead to a decreased absorption of acidic drugs (eg, phenobarbital).[2] increased concentrations of active unbound drug due to decreased plasma protein binding from lower levels of albumin and α1-acid glycoprotein.[3] Immaturity of hepatic (cytochrome P-450) enzymes and low glucuronidation activity,[4] Reduced glomerular filtration and renal tubular secretion

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in the first weeks of life. These differences in renal and hepatic function can lead to prolonged drug elimination. For example, appropriate administration of morphine in this population should include less drug and less frequent dosing intervals to prevent drug accumulation and toxicity.

Analgesia

Pain management in critically ill children is complicated as pain can be multifactorial and subjective. There are 2 distinct types of pain, nociceptive and neuropathic. Nociceptive pain occurs from tissue damage or inflammation, whereas neuropathic pain results from nerve cell dysfunction. Some children may experience a mixed type of pain due to the underlying condition (eg, trauma or burns). Pain is also classified based on duration as acute or chronic. Acute pain is short lived and the goal in treatment is to get the patient through the episode. Chronic pain is continuous or recurrent and the goal in management is to allow function. Appropriate categorization of pain is important to allow for different treatment approaches, of which there are nonpharmacologic and pharmacologic treatments available.

Following categorization, objective measurement tools should be used to assess, document, and provide appropriate treatment of pain. Several pediatric pain assessment tools are available based on the patient's age, clinical condition, and developmental level. The Joint Commission has provided standardization for self-assessment and observational tools for the measurement of pediatric pain.[1] Assessments should occur regularly as pain can change over time and frequent assessments can help determine the efficacy of the intervention/treatment. Common indicators of acute pain may include crying, inconsolability, and facial expressions. Chronic pain can present with behaviors such as abnormal posturing, increased irritability, sleep disruption, and changes in appetite.[2] Documentation of pain can include severity level, location, patient characteristics, onset, and duration. Following a complete pain assessment, the appropriate therapy can be initiated, continued, or modified as applicable.

Pain management should include both nonpharmacological and pharmacologic methods. Nonpharmacologic interventions include a range of diversion techniques appropriate for age. Diversion techniques for infants include pacifiers, swaddling, rocking, and holding. For older children, diversion techniques might differ and can consist of familiar toys, video games, and television. Other nonpharmacologic interventions can include music or art therapy, a calm and low-stimulation environment, and cognitive behavioral therapy. The utilization of nonpharmacologic therapies should always be considered and intertwined with pharmacologic therapy.

Pain management may be different for every child. Patient-specific regimens should be implemented and adapted to meet the needs of each individual. There are 3 pharmacologic analgesic therapies: nonopioid, opioid, and miscellaneous drugs. Nonopioid medications are used for mild to moderate pain and inflammation and include acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). Opioid analgesics are typically used for moderate to severe pain. The intravenous route of administration is preferred for the treatment of acute pain and the enteral route for chronic pain when feasible. Unlike nonopioid medications, opioid analgesics do not have a ceiling dose limit for prolonged or chronic use. Combination therapy with nonopioid and opioid analgesics is beneficial as the utilization of nonopioid analgesics can reduce the requirement for opioids and associated adverse effects. Miscellaneous therapies include medications for adjunct or chronic, cancer, or neuropathic pain. Classes of medications include anti-epileptics, anti-depressants, and skeletal muscle relaxants (**Tables 1–3**).

Table 1
Nonopioid analgesics[a]

Drug	Acetaminophen	Ibuprofen	Naproxen	Ketorolac
Mechanism of Action	Activation of descending serotonergic inhibitory pathways in the CNS	Reversibly inhibits cyclooxygenase 1 and 2 enzymes; decreased formation of prostaglandin precursors		
Dosing	10–15 mg/kg/dose PO every 4–6 h	4–10 mg/kg/dose PO every 6–8 h	5–6 mg/kg/dose PO every 12 h	0.5 mg/kg/dose IV every 6–8 h
Adverse Effects	Skin rash Ceiling effect	Hepatotoxicity Nephrotoxicity Gastritis		

Abbreviations: IV, intravenous; PO, orals.
[a] Data from Lexi-Comp Online, Pediatric Lexi-Drugs Online.[11]

Nonopioid Analgesics

Acetaminophen

Acetaminophen is the most common nonopioid analgesic used in children. It is primarily used for the treatment of mild to moderate pain alone or in combination with opioid analgesics. The analgesic effects of acetaminophen are due to the activation of serotonergic inhibitory pathways in the CNS but other nociceptive systems (ie, periphery) may be affected. It lacks anti-inflammatory properties. Acetaminophen is available in many dosage forms including tablet, capsule, chewable, suspension, suppository, and parenteral. This drug is unique in that it is metabolized via sulfation in infants and by glucuronidation in adults.[3] Intravenous dosing is 15 mg/kg every 6 hours (max. dose 1 g) for children who are unable to tolerate oral intake. Oral dosing for infants, children, and adolescents is 10 to 15 mg/kg/dose every 4 to 6 hours. To avoid the risk of hepatotoxicity, dosing limits should not be exceeded. The daily dose should be limited to 75 mg/kg/d, not to exceed 4000 mg per day regardless of route of administration.

Nonsteroidal Anti-inflammatory Drugs

NSAIDs are used for the treatment of mild to moderate pain alone, or in combination with opioid analgesics for moderate to severe pain. One of the biggest differences between NSAIDs and acetaminophen is the additional anti-inflammatory effect provided by NSAIDs, but studies evaluating the analgesic effects of NSAIDs compared with acetaminophen show conflicting results as to whether NSAIDs provide a greater analgesic response.[4–6] The mechanism of action of NSAIDS is reversible inhibition of cyclooxygenase-1 and 2 enzymes that result in the inhibition of prostaglandin synthesis. NSAIDs are available in many dosage forms including tablets, capsules, suspension, and parenteral. Common oral forms of NSAIDs used in children include ibuprofen and naproxen. Ketorolac is an NSAID that is primarily administered in parenteral form. An important distinction is that intravenous NSAIDs do not provide more analgesia compared with enteral options.[7] The utilization of NSAIDs may be limited due to adverse effects such as gastrointestinal bleeding and increased platelet aggregation. This class of medications should also be used with caution in the neonatal population due to limited safety data.[8] In addition, caution should be used in patients with decreased intravascular volume, renal or hepatic insufficiency.

Table 2
Opioid analgesics [a]

IV Drug	Fentanyl	Hydromorphone	Methadone	Morphine
Dosing INT	1–2 mCg/kg/dose IV every 1–2 h	0.005-0.015 mg/kg/dose IV every 3–6 h	0.025–0.1 mg/kg/dose IV every 4–8 h	0.05 mg/kg/dose IV every 2–4 h
CI	1–5 mCg/kg/h	0.003–0.05 mg/kg/h	NA	0.01–0.2 mg/kg/h
Adverse Effects	Tachyphylaxis Chest wall rigidity	Histamine release	QTc prolongation	Histamine release
Pharmacokinetics Onset	Immediate	5 min	10–20 min	5–10 min
T ½	2–36 h	2–3 h	4–62 h	2–10 h
Duration	0.5–1 h	3–4 h	22–48 h (repeat doses)	3–5 h
Metabolism	CYP3A4	Glucuronidation	CYP3A4, CYP2B6, CYP2C19, CYP2C9, and CYP2D6	

PO Drug	Hydrocodone/ Acetaminophen	Methadone	Morphine	Oxycodone
Dosing	0.1–0.2 mg/kg/dose PO every 4–6 h	0.1–0.2 mg/kg/dose PO every 6–8 h	0.1–0.2 mg/kg/dose PO every 3–4 h	0.025–0.1 mg/kg/dose PO every 4–6 h
Adverse Effects	Bradycardia Nephrotoxicity	QTc prolongation	Drowsiness Headache Nausea Constipation	
Pharmacokinetics Onset	10–20 min	0.5–1 h	30 min	10–15 min
T ½	4 h	4–62 h	4–13 h	3–4 h
Duration	4–8 h	22–48 h (repeat doses)	3–5 h	3–6 h
Metabolism	CYP2D6, CYP3A4	CYP3A4, CYP2B6, CYP2C19, CYP2C9, and CYP2D6	Hepatic via conjugation	CYP3A4, CYP2D6

Abbreviations: CI, continuous infusion; INT, intermittent; IV, intravenous; NA, not applicable; PO, oral; T ½, half-life.
[a] Data from Lexi-Comp Online, Pediatric Lexi-Drugs Online.[11]

Table 3
Miscellaneous analgesics [a]

Drug	Gabapentin	Pregabalin	Amitriptyline	Duloxetine
Dosing	5 mg/kg/dose PO every 8 h	3–5 mg/kg/dose PO every 12 h	0.1–0.5 mg/kg/dose PO every 24 h	30 mg PO every 24 h
Adverse Effects	Drowsiness Fatigue Peripheral edema	Weight gain, peripheral edema	Fatigue, cardiac arrhythmia	Weight loss, abdominal pain, nausea and vomiting, and drowsiness
Pharmacokinetics T ½	4–5 h	3–6 h	13–36 h	10–12 h
Metabolism	Not metabolized and excreted as unchanged drug	Excreted as 90% unchanged drug	Hepatic demethylation to active metabolite	CYP1A2, CYP2D6

Abbreviations: PO, oral; T ½, half-life.
[a] Data from Lexi-Comp Online, Pediatric Lexi-Drugs Online.[11]

Opioid Analgesics

Opioid analgesics should be reserved for moderate to severe pain. Opioids bind to G-protein-coupled receptors, mu, delta, or kappa, located in the brain and spinal cord to modulate nociception. These medications can be used intermittently or by continuous infusion. Intermittent dosing is useful for the treatment of acute pain while continuous infusion may be indicated for other conditions such as postoperative pain, providing consistent and sustained analgesia that is especially helpful for patients on mechanical ventilation. The utilization of opioid analgesics in children should be individualized. There are pharmacokinetic differences based on age that should influence the choice of opioid and dosage. Neonates and infants have immature hepatic and renal systems that can result in inadequate metabolism and slower elimination. Many of the opioid analgesics are available in a variety of intravenous and enteral dosage forms suitable for various ages (see **Table 2**). The most used opioid analgesics in critically ill children for intermittent and continuous infusion are fentanyl, morphine, and hydromorphone.

Fentanyl

The pharmacokinetics of fentanyl (see **Table 2**) make this agent ideal for short procedures such as intubation. Fentanyl is a lipophilic drug, and the pharmacokinetics may be altered in patients on extracorporeal support such as extracorporeal membrane oxygenation (ECMO) or continuous renal replacement therapy (CRRT). Approximately 70% of the drug is lost in the circuit, reducing efficacy that leads to higher drug requirements.[9] Fentanyl differs from the other opioids in that it can cause tachyphylaxis within approximately 5 days of use. In addition, a major adverse effect of fentanyl is chest wall rigidity, occurring when given rapidly in less than 3 minutes and with higher doses of 3 to 5 mCg/kg[10] for the induction phase of intubation or line placement. Accepted treatments for chest wall rigidity are reversal with naloxone or neuromuscular blockade with mechanical ventilatory support.

Morphine

Morphine is a commonly used opioid in pediatrics as intermittent dosing or continuous infusion. It should be used with caution in patients with renal dysfunction as morphine is eliminated by the kidneys and can accumulate, causing toxic effects. Morphine undergoes hepatic metabolism to morphine 6- and 3-glucuronide. Morphine-6-glucuronide is the active metabolite responsible for the analgesic effects of the drug but both metabolites undergo renal excretion. Dosing should be individualized as the half-life is variable based on age.[11] Hypotension can be common in patients who have hemodynamic instability and results from a combination of mechanisms including histamine-mediated vasodilation, direct inhibition of sympathetic nerve activity leading to negative chronotropic and inotropic effects, and reduction in baroreceptor mediated reflex responses.

Hydromorphone

Hydromorphone is an opioid that should be considered in patients that require a longer duration of analgesia and as an alternative to morphine in patients with renal failure. Although hydromorphone is like morphine, it is important to note that hydromorphone is 5 times more potent than morphine.

While maintaining appropriate pain control is crucial for patient care, the utilization of opioids can result in several adverse effects. The most common include respiratory depression, constipation, nausea and vomiting, sedation, and pruritis. Adverse effects such as respiratory depression or sedation can be minimized by reducing the dose

when possible. Other adverse effects such as constipation and pruritis may require additional treatment or a change in opioids to mitigate the effect. Patients may have a higher opioid dosing requirement following prolonged use and those who develop tolerance or a reduction in sensitivity to the opioid, may require higher doses to sustain the same response. A strategy to alleviate tolerance is to provide opioid rotation, using different opioids to prevent associated adverse effects from dose escalation, particularly in patients requiring long-term pain control.

Some opioid analgesics have fallen out of favor due to the lack of efficacy and significant adverse effect profile. Meperidine can have severe adverse effects including cardiac arrest and seizures especially with multiple dosing. Codeine and tramadol have an FDA warning that the use in children is contraindicated due to the serious risk of respiratory depression and death.[12,13]

If pain is not adequately controlled with a nonopioid, with or without an opioid, there are other pharmacologic classes that can be used as an adjunct therapy. These include anti-epileptics, anti-depressants, and skeletal muscle relaxants (see **Table 3**). Pain management is not a one size fits all and may need to be modified throughout the course of treatment.

Sedation

Historically, sedation practices used sedative medications alone, but subsequently, analgesics were added as needed as we believed that children required both sedation and analgesia to facilitate critical care. Sedation needs often occur concurrently with pain management in critically ill children. Analgosedation is the process of treating pain and leveraging the properties of analgesics with the intent of mitigating exposure to multiple drug classes and avoiding the side effects of polypharmacy. Sedative agents should be carefully selected and used only when needed. Over-sedation can result in the inability to accurately measure pain potentially resulting in inadequate analgesia and nonrestorative sleep patterns.[14] In addition to neurodevelopmental concerns of using sedative agents in newborns,[15,16] literature supports an association between benzodiazepines and pediatric delirium.[17] Standardized sedation scales should be used to provide an objective assessment of the patient and determine appropriate pharmacotherapy regardless of medication regimen. There are several pharmacologic therapies for children based on the indication for sedation and patient clinical status (**Table 4**).

Alpha-2 Adrenergic Agonists

Dexmedetomidine is an alpha-2 adrenergic receptor agonist with 100 times the potency at central receptors when compared with clonidine. Continuous intravenous infusion results in sedative effects and mild analgesic properties with minimal respiratory depression. Ninety-three percent of dexmedetomidine is protein bound and it has a long half-life. Dexmedetomidine was marketed for sedation in patients 24 to 48 hours before extubation, but studies have reported longer use for sedation in children of up to several weeks, with minimal adverse effects.[18] Dexmedetomidine has been shown to decrease postoperative opioid requirements for up to 7 days without dose-dependent analgesic effect. It has been shown to provide short term neuroprotection in neonates exposed to anesthetics; however, further studies are required to evaluate long-term outcomes.[19]

Clonidine is also an alpha-2 adrenergic agonist administered as intermittent enteral doses or a transdermal patch for the prevention of dexmedetomidine withdrawal. The use of clonidine is limited by the side effects that include bradycardia and rebound hypertension if the drug is discontinued too quickly after prolonged use.

Table 4
Sedation medications [a]

Drug	Dexmedetomidine	Midazolam	Lorazepam	Propofol	Clonidine	Ketamine
Dosing INT	NA	0.025–0.1 mg/kg/dose IV once	0.025–0.1 mg/kg/dose IV once	1–2 mg/kg/dose IV once	1–5 mCg/kg/dose PO every 6–8 h	0.5–2 mg/kg/dose IV once
CI	0.2–1 mCg/kg/h	0.03–0.12 mg/kg/h	NA	20–100 mCg/kg/min	NA	0.3–1 mg/kg/h
Adverse Effects	Bradycardia, hypotension	Hypotension, respiratory depression		Bradycardia, hypotension, propofol infusion syndrome	Bradycardia, hypotension	Hypertension, tachycardia, emergence delirium
Pharmacokinetics Onset	5–10 min	1–5 min	15–20 min	30 s	Unknown	30 s
T ½	2–10 h	2–12 h	6–73 h	Initial 40 min	6 h	10–15 min
Duration	60–120 min	< 2 h	6–8 h	3–10 min	6–8 h	5–10 min
Metabolism	Glucuronidation	CYP450 enzymes	Hepatic via conjugation	Glucuronidation	Hepatic via enterohepatic recirculation	Hepatic via several pathways

Abbreviations: CI, continuous infusion; INT, intermittent; IV, intravenous; NA, not applicable; PO, oral; T ½, half-life.
[a] Data from Lexi-Comp Online, Pediatric Lexi-Drugs Online.[11]

Benzodiazepines

Benzodiazepines are sedative agents that do not have analgesic activity and are used intermittently for procedural sedation or as a continuous infusion when more constant sedation is needed. Preparations include intravenous and enteral dosage forms. For critically ill patients requiring a continuous infusion, midazolam is the benzodiazepine of choice. Of note, midazolam is a lipophilic agent, therefore, higher doses may be required, or an alternative sedative should be selected for patients on ECMO or CRRT. The relatively large surface area of the extracorporeal circuit tubing and filters leads to drug sequestration and decreased availability of lipophilic medications over time.

Lorazepam is a benzodiazepine with a longer half-life compared with midazolam and can, therefore, be administered intermittently. Respiratory depression is an adverse effect especially when used in conjunction with opioid analgesics. Patients on lorazepam require close monitoring, and the lowest effective dose is used whenever possible.

Propofol

Propofol is an agent that has sedative and amnestic effects. It is a general anesthetic that acts as a GABA agonist and blocks the NMDA receptor causing total CNS depression. This medication has a short half-life and can be used for procedural sedation or by continuous intravenous infusion if longer period of sedation is required. The drug is in a lipid emulsion and prolonged use requires monitoring of nutrition and total fat intake. In addition, propofol can result in propofol-related infusion syndrome (PRIS), with metabolic acidosis, hypotension, rhabdomyolysis, cardiac and renal failure, and death. Due to the risk of PRIS, propofol is not desirable for prolonged use in children.

Ketamine

Ketamine is a sedative agent that has analgesic properties with opioid-sparing effects. It differs from other sedatives in that it is not associated with respiratory depression and hypotension, and therefore may be used as an alternative to benzodiazepines. The mechanism of action of ketamine is NMDA antagonism with direct action on the cortex and limbic system creating a state of dissociation of surroundings.[20] With its analgesic and sedative effects, ketamine is commonly used for procedural sedation and the lack of respiratory depression makes it especially useful in the emergency department. Lower doses of ketamine produce analgesic effects and aid in hyperalgesia and opioid tolerance. Adverse effects include tachycardia, hypertension, excessive salivation, hallucinations, and emergence delirium.

Analgesia and sedation can be a challenge in critically ill child. It is important to assess and monitor every patient with standardized, individualized assessment tools to determine their need for analgosedation according to clinical status. Careful drug selection and considerations for dosing should include age, weight, pharmacokinetic changes, renal and hepatic function.

NEUROMUSCULAR BLOCKING AGENTS

Critically ill patients may require NMBAs to facilitate mechanical ventilation, invasive procedures, and to minimize movements in patients with unstable airways or craniofacial/thoracic trauma or surgery. The addition of NMBAs can improve respiratory system compliance by reducing patient-ventilator dyssynchrony, but analgosedation must be optimized to avoid ongoing paralysis of a patient who is awake and in pain.

Nondepolarizing Agents

The nondepolarizing class of NMBAs includes vecuronium, pancuronium, rocuronium, atracurium, and cis-atracurium (**Table 5**). These drugs are competitive antagonists

Table 5
Neuromuscular blocking agents[a]

Drug	Rocuronium	Vecuronium	Cisatracurium
Intermittent	0.6–1.2 mg/kg IV	0.1 mg/kg IV	0.1–0.15 mg/kg IV
Continuous infusion	0.4–0.7 mg/kg/h	0.05–0.15 mg/kg/h	0.06–0.24 mg/kg/h
Onset	30–60 s	1–3 min	2–3 min
Duration	30–40 min	30–60 min	30–45 min
Adverse Effects	Hypertension Hypotension Tachycardia	Hypertension Hypotension Tachycardia	Bradycardia Bronchospasm Hypotension
Uses	Intubation Skeletal muscle relaxation		

[a] Data from Lexi-Comp Online, Pediatric Lexi-Drugs Online.[11]

and block acetylcholine binding to receptors on the motor endplate, thereby inhibiting depolarization. Neuromuscular blocking agents (NMBAs) have differing elimination and characteristics. For example, cis-atracurium is eliminated by Hoffman degradation and not dependent on renal or hepatic function.[21]

Depolarizing Agents

Succinylcholine is a membrane depolarizing agent that has a rapid onset of action and a short half-life.[22] It acts as a molecular receptor analog to acetylcholine and induces membrane depolarization. Administration of succinylcholine results in initial fasciculations resulting from active membrane depolarization, followed by flaccid paralysis. The recommended dose in children is 1 mg/kg/dose IV. The onset of paralysis occurs within 1 minute after injection and dissipates within 4 to 6 minutes as the drug is rapidly metabolized by plasma pseudocholinesterase. Succinylcholine is contraindicated in patients with increased intracranial pressure, spinal cord injuries, muscular dystrophy, concurrent hyperkalemia, rhabdomyolysis, or an individual or family history of malignant hyperthermia.

In patients requiring continuous neuromuscular blockade, the train of 4 (TOF) is useful in judging the effect of continuous neuromuscular blockade.[23] Monitoring the TOF in patients who are receiving a continuous infusion or numerous intermittent doses of NMBAs helps prevent overexposure to the paralytic. A paralytic "holiday" whereby the NMBA infusion is interrupted at a predetermined time to evaluate the degree of the neuromuscular blockade can be used concomitantly with TOF monitoring. This allows neuromuscular junction function recovery before the reinstitution of NMBAs. **Fig. 1** shows an example of a paralytic holiday schedule.

REVERSAL AGENTS

Rapid reversal of neuromuscular blockade is sometimes necessary for patients in the ICU who have received nondepolarizing agents. Acetylcholine esterase inhibitors provide an increase in acetylcholine and can overcome the competitive antagonism of the nondepolarizing NMBAs. Neostigmine, 0.05 to 0.07 mg/kg IV (maximum of 5 mg) has a peak action within 5 to 8 minutes and can be used for this purpose. Atropine may have to be administered with neostigmine to counteract excessive muscarinic effects that include bradycardia, increased secretions, and bronchospasm. Sugammadex is a newer medication that encapsulates aminosteroid, nondepolarizing NMBAs (rocuronium and vecuronium), directly reversing their pharmacologic actions.[24]

Daily holiday timing: 8:00am or after shift-change (whichever is sooner) for patients receiving continuously infused neuromuscular blocking agents (rocuronium, vecuronium , or cisatricurium)

1. Patient assessment
   - Unsafe movement/severe hemodynamic instability: **do not proceed with holiday and skip to step #5**
   - Safe movement/immobility and hemodynamically stable: proceed with holiday (step #2)
2. Have available IV push paralytic/sedation/analgesia vials at bedside
3. Stop continuous paralytic infusion
4. Patient reassessment
   - Unsafe movement/hemodynamic instability
     - Give IV push paralytic/analgesic/sedative prior to restarting paralytic infusion
     - Restart continuous neuromuscular blockade infusion (follow infusion restart guideline below)
   - Safe movement and hemodynamically stable: OK to continue to hold continuous infusion and manage sedation/analgesia with PRN orders
5. Report back to rounding team; discuss ongoing need for paralytic infusion

Neuromuscular blockade infusion restart guideline

Timing of return to spontaneous movement	Resume dose at:	Calculation
<15 min	100% of previous dose	Resume previous dose
15 – 30 min	75% of previous dose	=previous dose x 0.75
31 – 60 min	50% of previous dose	=previous dose x 0.5
61 – 120 min	25% of previous dose	=previous dose x 0.25
>2 hr	Consult MD prior to restart	

Fig. 1. Paralytic holiday schedule.

There are several drugs frequently used in critically ill children that can potentiate the effects of NMBAs and result in prolonged paralysis or myopathy. These include aminoglycosides, beta-blocking agents, furosemide, and steroids. Electrolyte abnormalities and hypothermia can also result in prolonged paralysis from NMBAs. A persistent neuromyopathy can occur with prolonged use of NMBAs, especially when used in combination with corticosteroids, though the association may not be as strong as was once thought.[25] Regardless of the cause, critical illness neuromyopathy is associated with undesirable outcomes such as prolonged duration of mechanical ventilation, and prolonged ICU and hospital stay.[26]

DELIRIUM

The recognition of delirium is evolving. It was previously thought of as a phenomenon limited to adult patients but is increasingly recognized to also be a problem affecting children. Studies show that delirium occurs in 20% to 60% of critically ill children and is associated with prolonged ICU length of stay.[27–29] Routine use of validated screening tools for prompt recognition of delirium is supported by position statements since 2014.[30–33] Additionally, screening is an inexpensive intervention that raises awareness for the diagnosis of delirium which is often mistakenly thought to be agitation, pain, and other forms of cognitive disorders associated with critical illness.[29,34] The clinical diagnosis should be confirmed by clinicians with specific training in the

Table 6
Anti-psychotic agents[a]

Drug	Risperidone	Quetiapine	Olanzapine	Haloperidol
Dosing	0.01–0.04 mg/kg PO every 24 h	0.5 mg/kg/dose PO every 8 h	0.1 mg/kg PO Q24	0.025 mg/kg IV
Adverse Effects	Hypotension, EPS, NMS	EPS, NMS, QTc prolongation, hypotension	NMS, EPS, diabetes mellitus, hypotension	EPS, TD, dystonia, QTc prolongation, NMS
Pharmacokinetics T ½	20 h	6–7 h	21–54 h	21–24 h
Metabolism	CYP2D6, CYP3A4	CYP3A4	CYP1A2, CYP2D6; glucuronidation	CYP1A2, CYP2D6

Abbreviations: EPS, extrapyramidal symptoms; NMS neuroleptic malignant syndrome; PO, oral; T ½ , half-life; TD, tardive dyskinesia.
[a]Data from Lexi-Comp Online, Pediatric Lexi-Drugs Online.[11]

recognition of the 3 main subtypes: hyperactive, hypoactive, and mixed-type delirium. Minimization and avoidance/removal of agents that are associated with the development of delirium remain the best intervention. Despite the potential benefits of sedation, the least number of sedative agents needed to achieve sedative effects should be used to allow more accurate treatment of pain and mitigate factors that lead to delirium.

While recognition and appropriate diagnosis of delirium are important, prevention is paramount. Nonpharmacologic means of reducing delirium risk, such as maintaining a normal day–night circadian rhythm with exposure to sunlight and promotion of normal sleep, are low-cost methods available to everyone. The optimal prevention and management solutions for delirium in children remain unclear though some protocols are in use.[35] Pharmacologic management of delirium is often institution dependent and there are no widely accepted guidelines. Meta-analyses to evaluate antipsychotic medication use in adults with delirium have mixed results with respect to treatment of symptoms of hyperactive delirium and has not been shown to improve outcomes.[36–38]

There are presently no data supporting antipsychotic drug use for the prevention or treatment of delirium in children, or for the specific treatment of children with hypoactive delirium. The data are mixed with respect to patient outcomes but there are some studies that support the use of second-generation antipsychotic drugs for the pharmacologic reduction of hyperactive delirium symptoms in children.[39–43] See **Table 6** for antipsychotic medication dosing. There are currently no FDA-approved medications for the treatment of pediatric delirium. Use of these agents should be accompanied by monitoring for adverse drug events that include QTc prolongation, hypotension, over-sedation, extrapyramidal symptoms, and neuroleptic malignant syndrome.

WITHDRAWAL

Iatrogenic withdrawal syndrome (IWS) refers to a range of symptoms that occur after abrupt discontinuation or sudden reduction of the dose of sedative and analgesic medications in a health care environment. IWS results from prolonged use of sedative/analgesic medications and follows the spectrum of increased drug needs/

tolerance and dependence. Iatrogenic withdrawal can be prevented/mitigated by understanding the complex relationship between the duration of drug exposure and dosage. It is rare for patients to develop dependence and withdrawal when a sedative or analgesic has been given for less than 4 days, but treatment of more than 7 days significantly increases risk.[44–47] To avoid IWS, screening should be performed using validated scoring tools for pediatrics such as the Withdrawal Assessment Tool −1 or WAT-1.[48]

The prevention and/or treatment of IWS should be with a drug selected from the same family as the medication that led to withdrawal. For opioid dependence/IWS, methadone, morphine, and hydromorphone in tapering dosage are reasonable choices (see **Table 2** for opioid dosing). For benzodiazepine dependence/IWS, lorazepam is a reasonable choice (see **Table 4** for dosing). The duration of dose tapering should follow a standardized pathway but may need to be adjusted according to patient characteristics. A standardized approach to screening improves the ability to apply defined criteria and a protocol reduces the potential for unnecessary medication exposure. Studies show that using a weaning protocol reduces the duration and total dose of opioid administration.[49,50]

Comfort care for critically ill children must take into account the pharmacologic differences between children and adults. Adequate provision of analgesia is a key principle. With adequate pain control, the need for sedation can be better assessed. Clinicians should minimize or avoid medications that mask pain and promote delirium. Tools to measure withdrawal and delirium should be used to identify at-risk patients and inform appropriate, evidence-based therapies.

CLINICS CARE POINTS

- Analgosedation should be employed for patient comfort as needed with a focus on pain management and lighter sedation to lessen the potential for delirium generation and iatrogenic withdrawal.
- Each ICU patient should be screened for delirium each day with a focus on prevention.

DISCLOSURE

The authors have nothing to disclose.

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