PICU Pharmacology

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KEYWORDS

• Pharmacology • Critical care pediatrics • Inotropy • Diuretics • Antibiotics
• Extracorporeal membranous oxygenation • Continuous renal replacement therapy

KEY POINTS

- Critically ill children have age-related differences in pharmacokinetics and pharmacodynamics that must be considered when selecting and administering medications.
- Inotropic agents should be selected based on anatomic and physiologic considerations.
- Proper identification of the source and location of respiratory failure dictates therapeutic interventions; lower airway obstructive lesions require different management strategies than the extrathoracic airway obstruction.
- Preservation of renal function is paramount when administering nephrotoxic medications, especially in the presence of acute kidney injury.
- Extracorporeal circuits alter the pharmacokinetics and pharmacodynamics of medications.

PHARMACOLOGY IN PEDIATRIC CRITICAL ILLNESS

Pediatrics does not deal with miniature men and women, with reduced doses and the same class of disease in smaller bodies, but… has its own independent range and horizon...

-Abraham Jacobi, on Pediatrics

Pharmacokinetics and pharmacodynamics are parts of pharmacology related to how drugs move through the body and the response resulting from the drug at the site of action. Critical illness and child development add an additional layer of complexity by altering kinetics and pathophysiology. Pharmacokinetics includes absorption, distribution, metabolism, and excretion/elimination of drugs. In each of these pharmacokinetic phases, there are age-related factors that may change how a drug is affected.[1] Critical illness plays a role and affects each phase differently, resulting in the need to adjust medication dosing, frequency, route of administration, or in the

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selection of alternative agents. It is important to understand pediatric pharmacologic principles to increase drug efficacy while limiting adverse and toxic effects.

Absorption

Absorption is the phase that includes the rate and extent to which the drugs move from the administration site into circulation. There are age-related changes in enteral absorption throughout development that should first be considered. The absence of hydrochloric acid in gastric secretions in neonates leads to an increase in the absorption of basic drugs such as penicillin G and a decrease in the absorption of acidic drugs such as phenobarbital. Neonates also have a decreased absorption of lipophilic drugs due to low intraduodenal levels of bile salts. Gastric emptying is decreased during the first 6 months of life and does not reach adult values until approximately 6 to 8 months of life.[2,3] Overall, the rate of absorption is slower in neonates and the effect on age and enteral absorption is not uniform and unpredictable.

The rate and extent to which a drug is absorbed when administered enterally is dependent on drug-specific properties such as particle size, solubility, lipophilicity, ionization, and dissociation rate constant. In addition, patient-specific factors will also influence absorption, and include gastric pH, regional blood flow, surface area, motility, and nutritional intake status. Enteral absorption can be reduced significantly in critical illness. For example, children in a state of shock, or who are on vasopressor therapy may have decreased gastrointestinal perfusion.[3,4] Disease states including trauma, sepsis, and surgery can result in reduced motility and gastric emptying time. Children with heart failure may have impaired drug absorption due to edema and higher drug plasma concentrations due to hepatic dysfunction resulting from congestion.[5] To provide adequate absorption, alternate routes of administration may have to be considered during critical illness.[6] Intravenous drug delivery can provide complete absorption or 100% bioavailability.[7]

Distribution

The distribution phase follows absorption. There are age-dependent changes in body composition throughout development. Infants have greater extracellular and total body water compared with children and adults. In addition, neonates have a higher level of fetal albumin, and both neonates and infants have reduced levels of total plasma proteins.[2,8]

The physiologic factors that affect drug distribution include cardiac output, regional blood flow, capillary permeability, and tissue volume. Drug factors such as protein binding, lipid solubility, changes in acid–base balance, and permeability of cell membranes also affect the extent of drug distribution. The volume of distribution (Vd) is the apparent volume into which the drug is distributed to provide the same concentration as it is in the blood plasma. Disease states that increase Vd includes sepsis, capillary leak, prolonged cardiac bypass time, renal failure, mechanical ventilation, ECMO, and burns.[2,9] Hydrophilic drugs have a small Vd and may therefore require a loading dose for efficacy, compared with lipophilic drugs, which have a large Vd. Drugs with higher protein binding have reduced Vd compared with drugs that are tissue bound.

Metabolism

Metabolism is the phase that results in drug elimination and terminates the pharmacologic activity. The liver is the main organ responsible for drug metabolism. Lipophilic drugs undergo extensive metabolism via phase I to phase III reactions. Phase I reactions are primarily catalyzed by enzymes of the cytochrome P450 system, predominantly CYP3A4.[10] Drugs commonly metabolized by this enzyme include midazolam

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and methadone. Enzyme activity is substantially reduced in neonates and many of the CYP450 enzymes do not reach adult values until 1 year of life. Disease states that can alter enzyme activity include burns and hypothermia. In addition, alterations in protein binding can result in a larger amount of free drugs available for metabolism.

Elimination

Elimination is the final pharmacokinetic phase resulting in drug removal from the body. The liver and the kidney are the main organs responsible for drug elimination. Glomerular filtration rate has age-related differences in development.[1,11] While the glomerular filtration rate rapidly increases in the first 2 weeks of life, it is lower in a premature neonate compared with a term neonate. Elimination via the hepatic system can be through 2 pathways, active secretion from bile into enterocytes or reabsorption via enterohepatic recycling. In the first few weeks of life, the transport proteins responsible for biliary excretion are decreased.

Drug elimination can be altered in critical illness in a variety of mechanisms. Hepatic and renal dysfunction can slow clearance and drug elimination and increase half-life while renal replacement modalities such as CRRT and ECMO can increase drug clearance.

Antimicrobials

Antimicrobials are one of the most prescribed medication classes in the PICU. Safe administration of antibiotics to critically ill children can be challenging in the presence of changing pharmacokinetic properties resulting from critical illness. Furthermore, inappropriate antibiotic selection and use may occur in the treatment of critically ill children. Decision algorithms can aid in optimizing antibiotic choice, timing as well as de-escalation for critically ill children whereby a diagnosis other than an infection is likely.[12,13]

Characteristics of critically ill children can lead to the increase of the Vd of hydrophilic agents and decrease the concentration of hydrophilic antibiotics. Antimicrobials such as tobramycin are concentration-dependent, and a higher dose may be needed to sustain appropriate concentrations and efficacy. Conversely, acute kidney injury (AKI) decreases the clearance of hydrophilic agents, increases the concentration of hydrophilic antimicrobials, and may require a longer dosing interval. Hepatic injury affects lipophilic agents by decreasing the clearance that leads to increased concentrations of lipophilic antimicrobials. Extracorporeal modalities alter Vd and clearance of antibiotics often leading to subtherapeutic concentrations.[14] **Table 1** shows ECMO and CRRT associated variables to consider when prescribing common PICU antimicrobials.[15,16] When possible, serum levels should be obtained to guide dosing and therapy, and adjustments made with the alteration of extracorporeal parameters.

Cardiovascular

Acute cardiovascular dysfunction is common in critically ill children. Drugs can be used to improve the basic components of cardiac output that include preload, afterload, and contractility. The underlying diagnoses and physical examination findings must be taken into consideration. For example, therapy for dehydration is completely different from that of heart failure although both may present with similar symptoms that include malaise, tachypnea/hyperpnea, hypotension, and tachycardia.

Preload

Augmenting preload with crystalloids such as 0.9% saline or Lactated Ringer's solution is a relatively common intervention for hypovolemia. Colloids, such as 5% albumin

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Table 1
Extracorporeal effects on antimicrobial pharmacokinetics[14–16]

Drug	CRRT Effects
Vancomycin	Clearance t ½ drops after the initiation of CRRT but accumulation can occur. Follow serum levels
Meropenem	Increased clearance yielding need for increased doses/ frequency
Cefepime	Increased clearance yielding need for increased doses/ frequency
Ambisome	No dose adjustment needed
Micafungin	No dose adjustment needed
Drug	**ECMO Effects**
Acyclovir	No dose adjustment needed
Aminoglycoside	Increased Vd and decreased clearance. Monitor serum levels
Ambisome	No dose adjustment needed
Azithromycin	No dose adjustment needed
Cefepime	Increased Vd, possibly decreased clearance in infants
Fluconazole	Loading dose required and higher doses needed for efficacy
Meropenem	Sequestered with increased clearance. Consider loading dose and continuous infusion
Micafungin	Increased dosing for neonates
Piperacillin/Tazobactam	Decreased AUC in adults
Vancomycin	Increased Vd and decreased clearance. Monitor serum levels

may also be used. Volume administration of 10 to 20 mL/kg should be used and repeated as necessary for intravascular expansion. Other agents as starches and dextrans have been used (more commonly in adults). The benefits of crystalloids versus colloids have not been established.[17]

In conditions of hypervolemia or excess preload such as renal failure or congestive heart failure, diuretic therapy may be appropriate. Loop diuretics and thiazides are commonly used. Furosemide, bumetanide, and torsemide inhibit the Na/K/Cl cotransporter in the loop of Henle. Furosemide at 0.5 to 1 mg/kg every 6 to 8 hours is the diuretic most used in children with hypervolemia. For critically ill children with cardiovascular dysfunction, a continuous infusion of furosemide (0.05–0.2 mg/kg/h) prevents peaks and valleys of drug levels with less hemodynamic instability as compared with intermittent bolus dosing.[18] Of note, appropriate administration of intravenous furosemide (maximum rate of 0.5 mg/kg/min) can reduce/eliminate the risk of hearing loss.[19] Bumetanide (0.015–0.05 mg/kg PO or IV every 12–24 hours) is up to 40 times more potent than furosemide. Torsemide is a loop diuretic with the benefit of higher enteral absorption and is more commonly used in children with heart failure.

Thiazide diuretics inhibit sodium transport in the distal tubule and can be used to provide a synergistic effect with a loop diuretic to augment the distal delivery of sodium and water, resulting in improved diuresis. Chlorothiazide (10–20 mg/kg PO every 12 hours or 2–5 mg/kg IV every 12 hours) and hydrochlorothiazide (0.5–1 mg/kg PO every 12–24 hours) are commonly used in critically ill children. Metolazone is a thiazide-like diuretic that inhibits sodium reabsorption.

Mineralocorticoid receptor antagonists, such as spironolactone (1–3 mg/kg/d PO) have minimal diuretic effects but can be combined with loop or thiazide diuretics for

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its potassium-sparing effect. The use of diuretics should include the monitoring of serum electrolytes, especially when combination loop-thiazide therapy is used.

Afterload

Vasoactive agents include vasoconstricting and vasodilating agents. Several medications have dose-dependent properties that result in both vasoconstriction and vasodilation. Drugs that induce vasoconstriction of the vessels (vasopressors) increase afterload. Medications with primary vasoconstrictor function should be used with caution in patients with poor myocardial function. Examples of these vasopressors include norepinephrine (NE), vasopressin, and phenylephrine. Medications that induce peripheral vascular vasodilation decrease resistance or afterload to the systemic ventricle. Examples include sodium nitroprusside, calcium channel blockers (CCBs) (such as nicardipine), and ACE inhibitors.

Vasopressors

Norepinephrine (NE) acts primarily on the α-adrenergic receptors and is a potent vasoconstrictor. It is useful in vasodilatory shock states such as septic shock.[20,21] NE also stimulates the beta-adrenergic receptor resulting in inotropic and chronotropic effects and augments blood pressure and coronary blood flow. It is mainly used as a vasopressor in children.

Vasopressin acts on the V1 receptors in the vascular smooth muscles mediating vasoconstriction and has predominant systemic vasoconstrictor effects at the V1 receptor with pulmonary, cerebral, and coronary vasodilation.[22] Vasopressin is used to treat diabetes insipidus and at a lower dose (1–5 milliunits/kg/h) engages V2 receptors in the collecting duct resulting in the insertion of aquaporin channels with the reabsorption of free water and a decrease in urine volume. When administered at a higher dose for shock states (0.5–3 milliunits/kg/min), vasopressin results in an overall increase in cardiac output and increased renal blood flow resulting in a "paradoxic" increase in urine output.[23]

Phenylephrine acts at the alpha-adrenergic receptor as a pure vasoconstrictor. It can be used intravenously at 10 mCg/kg intermittently, or as an infusion of 0.5 to 5 mCg/kg/min in conditions when an immediate increase in systemic blood pressure is needed. Phenylephrine can be used for the management of hypercyanotic spells associated with Tetralogy of Fallot and as secondary pharmacologic support for other clinical states.[24]

Vasodilators

Vasodilators are used in children when a reduction in afterload is required to augment cardiac output by relieving the pressure against which the systemic ventricle must work. Common indications include myocardial dysfunction due to myocarditis or cardiomyopathy, after heart surgery, or in dilated cardiomyopathy and systemic hypertension.

Nitroglycerin and nitroprusside act as venodilators and arterial vasodilators, and increase venous capacitance and decrease vascular afterload. To avoid hypotension, nitroglycerin and nitroprusside dosing should be approached cautiously by starting with the lowest effective dose, and increasing the dose slowly as needed. Nitroprusside causes greater reduction in systemic pressure than nitroglycerin. It has a rapid onset of action and can be used for the treatment of hypertensive emergencies. It is used as a continuous intravenous infusion titrated to effect at 0.5 to 10 mCg/kg/min. Sodium thiosulfate is often reconstituted with nitroprusside during the

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preparation of the infusion to minimize the potential for cyanide toxicity resulting from nitroprusside metabolism.

CCBs inhibit calcium entry into cells with resultant decreased vascular or myocardial contractility. Nicardipine is used as an infusion (0.5–5 mCg/kg/min) to treat hypertensive emergencies and is useful after cardiac surgery as the dihydropyridine CCBs act mainly on peripheral vasculature.[25–27]

Angiotensin is a potent vasoconstrictor. ACE inhibitors inhibit the conversion to functional angiotensin 2. Captopril is given orally 0.3 to 1.5 mg/kg per day, divided into every 8 hours dosing; enalapril is given orally 0.1 to 0.5 mg/kg per day, as a single dose or divided into 2 doses daily. ACE inhibitors should be started at lower doses to prevent hypotension, hyperkalemia, and renal failure. Special care should be taken when administering ACE inhibitors to neonates who are at an increased risk for nephrotoxicity and AKI.[28,29]

Contractility

Epinephrine has dose-dependent effects at the receptor level. In lower doses of 0.02 to 0.03 mCg/kg/min, epinephrine acts predominantly on beta-adrenergic receptors, increasing contractility and therefore increases oxygen consumption. Epinephrine concomitantly enhances coronary blood flow by improving cardiac output. At lower doses, epinephrine results in vasodilation, but at higher doses (0.05 mCg/kg/min and greater), epinephrine stimulates the alpha-adrenergic receptors resulting in vasoconstriction.

Dopamine has a similar effect profile and dose-dependent receptor engagement as epinephrine. At lower doses (2–5 mCg/kg/min) dopamine affects the β-adrenergic receptors, resulting in an increase in myocardial contractility and chronotropy. At higher doses (5–10 mCg/kg/min), dopamine engages the alpha-adrenergic receptors resulting in peripheral vasoconstriction.

Dobutamine is a synthetic catecholamine delivered by infusion at rates of 2 to 10 mCg/kg/min and is predominantly an inotrope and vasodilator stimulating the beta-receptors, increasing myocardial contractility and afterload reduction.

Epinephrine, dobutamine, and dopamine have relatively short half-lives and duration of action and can therefore be titrated to effect quickly. Neonates have a relatively underdeveloped sympathetic nervous system and higher infusion rates (10–20 mCg/kg/min) of dopamine and dobutamine may be necessary in this population.

Milrinone is a phosphodiesterase 3 (PDE-III) inhibitor that prevents the metabolism of cAMP to AMP. The accumulation of intracellular cAMP leads to improved calcium cycling in the myocardium resulting in increased myocardial contractility and improved myocardial relaxation. In the peripheral vasculature, the increase in intracellular cAMP leads to cellular relaxation and vasodilation.[30] Milrinone administered by continuous infusion (0.25 mCg/kg/min-0.75 mCg/kg/min) is useful for improving cardiovascular system function in patients with cardiomyopathy and has been shown to decrease the risk of low cardiac output syndrome in children after repair of congenital heart disease.[31] Milrinone undergoes renal clearance and therefore should be used with caution in patients with AKI, and premature neonates.[32]

Anti-arrhythmic Agents

Arrhythmias are relatively common in critically ill children and can affect preload and cardiac contractility and limit cardiac output. Supraventricular tachycardia (SVT) is the most common arrhythmia in infants. Management principles should begin with pediatric advanced life support protocol.[33] Adenosine is a rapid-acting medication that interrupts electrical flow through the A-V node causing a transient heart block. It

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activates the A1 receptor in myocardial cells and can be used to interrupt certain types of SVT or can be used to unmask the underlying etiology for others (eg, atrial flutter). Adenosine has a half-life of 10 seconds due to rapid deamination by adenosine deaminase in the red blood cells. Initial dosing is 0.1 mg/kg by rapid IV push followed by a saline flush to hasten delivery before deamination. The dose can be increased to 0.2 mg/kg up to a maximum of 12 mg in older children and adults.

Esmolol is a selective beta-1 adrenergic blocking agent (class II antiarrhythmic) that slows the A-V node refractory period and can be used for rate control or chemical cardioversion with a bolus of 100 to 500 mCg/kg infused over 1 minute is followed by an infusion of 25 mCg/kg/min. The dose can be increased in increments of 25 to 50 mCg/kg/min depending on the rate response.[34] Side effects include hypotension, negative inotropy, bradycardia, and hypoglycemia in infants and newborns.

Procainamide is a class 1a sodium channel blocking agent with a rapid onset (5–10 minutes) when administered intravenously. It is metabolized in the liver to an active metabolite, N-acetylprocainamide (NAPA). Procainamide dosing should be adjusted using therapeutic drug monitoring, particularly in patients with renal impairment or prematurity who may have abnormal drug accumulation. Loading dose is based on age: neonates 5 to 10 mg/kg; infants and older children 10 to 15 mg/kg over 30 to 60 minutes followed by an infusion of 20 to 80 mCg/kg/min titrated by effect and serum level.[35]

Amiodarone is a versatile agent with effects at multiple levels of the cardiac conduction system.[36] However, it has significant side effects that include hypotension due to myocardial depression, bradycardia, and heart block. Amiodarone has a long half-life and onset of action. It is administered by intravenous infusion of 5 to 15 mCg/kg/min.[36] Bolus dosing should be given as slowly as the clinical situation allows. In ventricular tachycardia, 5 mg/kg can be administered according to PALS guidelines.[33] For tachyarrhythmias that are not immediately life-threatening, a loading dose of 1 to 2 mg/kg over 30 to 60 minutes, up to a total of 5 mg/kg may be considered.

Lidocaine is a class 1b agent that slows conduction in the Purkinje fibers and is used for the treatment of ventricular tachycardia. An IV bolus of 1 mg/kg per dose and an infusion rate of 20 to 50 mCg/kg/min can be used. Lidocaine is metabolized in the liver and may require dose adjustment in patients with hepatic failure.

Magnesium sulfate has a specific role in tachyarrhythmias. Torsade de pointes is a polymorphic ventricular tachycardia that can be treated with IV magnesium sulfate at 25 to 50 mg/kg by IV push. Magnesium sulfate administration can result in hypermagnesemia and hypotension.[37]

CCBs in the nondihydropyridine class (verapamil and diltiazem) affect nodal conduction and can be used in children,[38] but with caution in those under 1 year of age due to the risk of cardiovascular collapse with nondihydropyridine CCBs.[39] The dihydropyridine CCBs have no role in the treatment of tachyarrhythmia. **Table 2** shows suggested strategies for the management of pediatric tachyarrhythmias.[37]

Ductal-dependent Heart Disease

The differential diagnosis of shock in neonates includes ductal-dependent heart disease. Prostaglandin E−1 (PGE-1) maintains ductus arteriosus patency and is important in the treatment of ductal-dependent congenital heart defects. Initiating PGE-1 infusion in a newborn with unexplained shock is imperative. In neonates with ductal-dependent systemic blood flow lesions such as hypoplastic left heart syndrome, interrupted aortic arch, or critical coarctation, patency of ductus arteriosus is necessary to maintain blood flow through the aorta. In neonates with ductal-dependent pulmonary blood flow lesions such as pulmonary atresia, PGE-1 maintains

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Table 2
Suggested pharmacotherapy for tachyarrhythmias

Arrhythmia	First-Line Medication	Second-Line Medication
Reentrant SVT	IV: adenosine, esmolol, procainamide Oral: propranolol, digoxin	IV: amiodarone Oral: sotalol, amiodarone, flecainide
Ectopic atrial tachycardia	IV: esmolol, procainamide Oral: propranolol	IV: amiodarone Oral: sotalol, amiodarone, flecainide
Intraatrial reentrant tachycardia	IV: esmolol, procainamide Oral: propranolol, digoxin	IV: amiodarone Oral: metoprolol, atenolol, sotalol
Permanent junctional reciprocating tachycardia	IV: esmolol Oral: propranolol, atenolol, metoprolol	IV: amiodarone Oral: flecainide, sotalol
Junctional ectopic tachycardia	IV: amiodarone	IV: esmolol, digoxin, procainamide
Ventricular tachycardia	IV: esmolol, procainamide, lidocaine	IV: amiodarone Oral: metoprolol, atenolol, sotalol
Ventricular fibrillation	IV: amiodarone, procainamide	IV: lidocaine
Torsades de Pointes	IV: magnesium sulfate	IV: amiodarone, procainamide, lidocaine

Adapted from Moffett B, Salvin J, Kim J. Pediatric Cardiac Intensive Care Society 2014 Consensus Statement: Pharmacotherapies in Cardiac Critical Care Antiarrhythmics. Ped Crit Care Med 2016;3:S49-S58.

blood flow to the lungs. PGE-1 is administered as a continuous intravenous infusion of 0.05 to 0.2 mCg/kg/min. After ductal patency is ensured, the dose can be decreased to 0.03 mCg/kg/min as less drug is required to maintain patency compared with that needed to open a closed ductus arteriosus. Lowering the effective infusion dose mitigates side effects of hypotension, apnea, and fever.

RESPIRATORY

Extrathoracic Airway Obstruction

Viral laryngotracheobronchitis (croup) is a relatively common childhood viral disease. Symptoms include a barky cough but may progress to significant airway compromise requiring intensive care monitoring or intervention. Inhaled racemic epinephrine results in the vasoconstriction of the airway soft tissues and can relieve obstructive symptoms when administered by facemask or high flow devices. If racemic epinephrine is given, children should be monitored for rebound extrathoracic airway obstruction as the effects of the inhaled racemic epinephrine wanes. Steroids may be used depending on the severity of symptoms. Dexamethasone reduces inflammation and edema and is recommended as first-line therapy. It has good bioavailability and can be used in enteral or parenteral form. Budesonide is a form of inhaled corticosteroid and has been shown to have similar effectiveness as dexamethasone. Glucocorticoid treatment reduces hospital length of stay and has been shown to improve symptoms within 2 hours of administration.[40]

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Intrathoracic Airway Obstruction

Status asthmaticus is a clinical condition with 3 hallmark processes that include inflammation, bronchospasm, and increased mucous production.[41] It is a common cause of admission to the PICU. Studies suggest that there is a trend toward increasing PICU admission rates for severe asthma potentially related to racial and regional health care disparities, and poor compliance with controller medications in patients with a severe asthma.[42,43] Pharmacotherapy is directed at maintaining adequate oxygenation and reversing airway obstruction, by reducing airway inflammation and bronchospasm. Hypoxemia should be treated with supplemental oxygen to maintain SpO2 more than 92%. Noninvasive modes of ventilation such as bimodal positive airway pressure (BiPAP) and high flow nasal cannula are increasingly being used to avoid more invasive respiratory support such as intubation and mechanical ventilation. However, despite the increasing use of noninvasive support, outcomes such as the need for invasive mechanical ventilation and hospital length of stay remain unchanged.[44–48]

Steroid therapy aimed at reducing inflammation is the main therapy for status asthmaticus. Early corticosteroid therapy is beneficial, and is recommended for children with status asthmaticus, with evidence that early administration minimizes potential time lag to effect.[49] Patients who require PICU admission should be given methylprednisolone IV at a dose of 1 mg/kg every 6 to 12 hours (maximum dose of 60 mg/d) and continued until symptoms are under control.[50] Once symptomatic control of status asthmaticus is achieved, enteral steroids should be started, and continued for 5 to 10 days after symptom onset.

Short-acting, inhaled beta-2 adrenergic agonists such as albuterol are the primary agents used for bronchodilation. Activation of beta-2 adrenergic receptors results in the relaxation of the airway smooth muscle. Continuous nebulization of albuterol may be administered by facemask 0.15 to 0.5 mg/kg/h (maximum 20 mg/h). Beta-2 agonist therapy results in tachycardia and the dose should be decreased as symptoms improve. Using a standardized treatment pathway has been shown to optimize therapy, reduce variation in care and potentially decrease ICU and hospital length of stay.[51–53]

Ipratropium bromide is an inhaled anticholinergic muscarinic antagonist that produces bronchodilation.[54] It is given as adjunctive therapy with inhaled beta-agonists. Studies in critically ill patients are limited, but for those with severe status asthmaticus who present to the emergency department, ipratropium bromide has been shown to decrease the need for hospitalization.[55]

The treatment of status asthmaticus with magnesium sulfate has increased over the last decade.[56] Magnesium antagonizes calcium channels, resulting in smooth muscle relaxation. Studies have suggested the benefits of intravenous administration of magnesium sulfate at a dose of 25 to 50 mg/kg (maximum of 2 g) given over 15 to 20 minutes. Repeated dosing and continuous infusion can result in hypermagnesemia with muscle weakness and respiratory depression; therefore, the measurement of serum magnesium levels is essential.[57]

Parenteral beta-2 agonists may be used in patients with severe bronchoconstriction when delivery of inhaled beta-2 agonists to the intrathoracic airway is difficult. Terbutaline is a selective beta-2 agonist that has the potential advantage of less tachycardia compared with nonselective IV beta-agonists. Initial dose is 5 mCg/kg bolus followed by a continuous infusion of 0.2 to 0.3 mCg/kg/min (maximum of 5 mCg/kg/min). Side effects include tachycardia, jitteriness, and chest pain. There are limited studies comparing the benefits of parenteral versus inhaled beta-agonists.

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The most common methylxanthine used for the treatment of asthma is aminophylline. An older medication class with bronchodilator and diuretic properties, aminophylline is administered as a bolus dose of 5 to 6 mg/kg and may be followed by continuous intravenous infusion. Aminophylline is metabolized in the liver and its half-life is prolonged in patients with hepatic dysfunction and heart failure. Side effects include tachycardia, nausea, and seizures. Aminophylline elimination has age-specific properties and should be adjusted accordingly. Initial continuous infusion rates should be at 0.5 to 0.7 mg/kg/h for infants, 1 to 1.2 mg/kg/h for children ages 1 to 9 years, and 0.7 to 0.9 mg/kg/h for older children and adults, adjusted to maintain serum concentrations between 10 and 20 mCg/mL. Monitoring of serum levels is imperative, especially when using more than one bolus dose or with continuous infusions. Due to the narrow therapeutic window of aminophylline, beta-agonists are recommended instead of methylxanthines.[50]

CENTRAL NERVOUS SYSTEM

Intracranial Injury

Children with intracranial pathology are admitted to the ICU with trauma, infection, or hypoxemic/ischemic brain injury. The primary injury can be exacerbated by ongoing intracranial hypertension with progressive secondary injury. Due to the properties of the cranial vault and the blood–brain barrier, certain entities are amenable to therapy to reduce intracranial hypertension, but others are not. Osmotherapeutic agents and medications aimed at reducing brain metabolism can mitigate intracranial pathology.

Osmotherapy can be used for situations whereby cellular edema and cellular fluid can be reduced in the presence of an intact blood–brain barrier. Osmotherapeutic agents include hypertonic saline and mannitol. The use of hypertonic saline has increased relative to mannitol despite few studies supporting the superiority of one therapy over the other.[58] The aim of osmotherapy is to reduce intracranial content without inducing hypovolemia. It is important to monitor serum electrolytes, osmolality, and cardiovascular status. The recommended dose of hypertonic saline is 1 to 3 mL/kg (3% saline), up to a maximum dose of 250 mL.[59] Continuous intravenous infusion of hypertonic saline has also been used for control of ICP. The dose of hypertonic saline should be adjusted to maintain the minimum serum osmolality needed to result in the desired ICP, maintaining serum sodium less than 160 mEq/L, and osmolality less than 360 mOsm/kg.[59]

The effects of mannitol result from the creation of osmotic differences on cerebral tissue and subsequent diuresis. The dose is 0.5 g to 1 g/kg given more than 10 minutes with osmotic effects occurring within 15 to 30 minutes. The dose can be repeated based on clinical response and/or ICP levels, if available. Mannitol is rapidly eliminated and should be given intermittently to achieve maximum osmotic effects and to avoid accumulation and renal injury.

Sedatives are generally indicated in the management of patients with intracranial hypertension. The beneficial effects of barbiturates for refractory intracranial hypertension result from the decrease in cerebral metabolic rate and its antioxidant properties. Pentobarbital can be used to induce an anesthetized state with an IV bolus of 5 mg/kg followed by the continuous infusion of 1 to 2 mg/kg/h. The infusion rate may be titrated to achieve the desired ICP. In refractory intracranial hypertension, or if used concomitantly for the treatment of status epilepticus, a higher infusion rate may be needed to achieve burst suppression or seizure control. The potential for neuronal apoptosis from the use of benzodiazepines and barbiturates warrants more research.[60] Barbiturate therapy is associated with significant hypotension and myocardial depression,

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and many patients require simultaneous administration of inotropic agents to maintain hemodynamic stability.[61]

Status Epilepticus

Status epilepticus is defined as continuous or repeated convulsive or nonconvulsive seizures lasting 30 minutes or longer. The neuronal hyperactivity leads to an increase in cerebral metabolism which can deprive the brain of oxygen and glucose. Status epilepticus should be considered an emergency that requires the immediate institution of time-based, targeted therapy (**Table 3**).

On the completion of initial evaluation to ascertain the adequacy of airway and circulation, pharmacologic therapy should be started and directed toward the symptoms and underlying etiology. Imaging and testing including lumbar puncture should be considered when the patient's condition allows. Status epilepticus in children is frequently due to subtherapeutic medication levels in those receiving anticonvulsant therapy for underlying seizure disorder, but may also result from infection, trauma, toxic ingestion, hyponatremia, hypoglycemia, and tumors.

Seizures in infants can be due to metabolic derangements that do not respond to antiepileptic medications. Hypoglycemia should be treated with 2 to 4 mL/kg of 10% or 25% dextrose. Hyponatremic seizures can result from the inappropriate preparation of formula or excessive water ingestion. Hyponatremia should be suspected in infants with status epilepticus who are otherwise healthy, and initial assessment should include a detailed history of formula preparation and supplemental water feeds. The goal of treatment with hypertonic saline is not to immediately restore serum sodium levels to normal but to increase serum sodium enough to raise the transmembrane potential to stop seizure activity. Rare causes of status epilepticus, such as pyridoxine deficiency should be considered in the differential diagnosis of refractory infantile seizures.

Benzodiazepines are a family of drugs with good bioavailability regardless of route of administration. These drugs bind to γ-aminobutyric acid (GABA) receptors altering transmembrane potential and reducing neuronal transmission (**Table 2** for first- and second-line medications for the treatment of status epilepticus). Benzodiazepines are recommended for the initial therapy of status epilepticus.[62] Lorazepam is the recommended first-line drug for the treatment of status epilepticus because it can be injected rapidly and has an onset of action of 2 to 3 minutes. Respiratory depression is a potential side effect. Continuous infusion of lorazepam is not recommended due to potential side effects resulting from the accumulation of the diluent propylene glycol.

Intravenous, intramuscular, or transmucosal midazolam is also used as a treatment of status epilepticus. An intravenous infusion of midazolam (0.2–0.6 mg/kg/h) can be used for the treatment of status epilepticus refractory to intermittent dosing. Continuous EEG and cardiovascular monitoring are recommended for continuous infusion therapy.

Diazepam can be administered through the rectal route and is recommended for the treatment of status epilepticus in patients without IV access.

Levetiracetam and fosphenytoin are recommended as second-line therapy for status epilepticus.[63] Levetiracetam is effective and has a good safety profile that includes the absence of respiratory depressive effects often seen with benzodiazepines.

Fosphenytoin is a prodrug of phenytoin. Phenytoin or fosphenytoin should be infused slowly over 20 minutes, as bradycardia and cardiovascular collapse are associated with a rapid infusion. Fosphenytoin can also be administered intramuscularly in patients without IV access. With significant variability in phenytoin metabolism in infants, serum concentrations should be monitored. There are no clear data to support the superiority of fosphenytoin over levetiracetam.

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Table 3
Pathway-based management for status epilepticus

Convulsive Status Epilepticus Management Guidelines

Phase	Time	Management	Notes
Stabilization	0–5 min	1. Evaluate and address ABC's and place on monitors 2. Note time of seizure onset 3. Obtain finger stick glucose A. Treat <60 with 2 mL/kg D25 W 4. Obtain IV access 5. Treat identified reversible causes	*Labs to consider*: • Electrolytes • Infectious work up • Anti-epileptic drug levels • Toxicology
Primary intervention (Benzodiazepine)	5–15 min	• IV Access ○ IV lorazepam (0.1 mg/kg, max 4 mg per dose, up to 2 doses) • No IV Access ○ IM midazolam (0.2 mg/kg max 10) ○ Intranasal midazolam (0.2 mg/kg max 10 mg) ○ PR diazepam acceptable if other options not available	Consider imaging and antibiotics early
Secondary intervention	> 15 min	Choose one: • IV levetiracetam (30–60 mg/kg, max 3000 mg) • IV fosphenytoin (20 mg PE/kg, max 1500 mg). May repeat with 10 mg PE/kg, max 750 mg • Continued seizure despite secondary therapy = admit to ICU and consult neurology	For neonates, may use: • IV phenobarbital (20 mg/kg)
Refractory status epilepticus		Admit to ICU for continuous anti-epileptic drip • Midazolam – load 0.2 mg/kg (max 10 mg), infusion 0.2–0.6 mg/kg/h • Pentobarbital – load 5–15 mg/kg, infusion 1–5 mg/kg/h	Neurotelemetry to be initiated Repeat loading dose with escalations in drip rate to get to steady state quicker

Barbiturates such as phenobarbital or pentobarbital can be used for the treatment of refractory status epilepticus. Adverse effects include respiratory depression and negative inotropy which can result in hypotension. Inotropic support is often required with multiple doses or continuous infusion of barbiturates to counteract the

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cardiovascular effects. Serum drug levels should be monitored to achieve a level of 20 mCg/mL, but higher levels may sometimes be necessary for the treatment of refractory status epilepticus in neonates whereby clearance is influenced by birth weight and postnatal age.[64] Pentobarbital may be administered by intravenous bolus and continuous infusion for the treatment of status epilepticus unresponsive to first and second lines of therapy.

Table 4 shows first- and second-line medications to treat status epilepticus. Other agents have been used for the management of status epilepticus unresponsive to the drugs listed above. These include: valproic acid, propofol, ketamine, inhaled anesthetics, as well as therapeutic hypothermia.[65]

HEMATOLOGY

Anticoagulation

Pediatric venous thromboembolism can occur in critically ill children and is associated with complications including pulmonary embolism, cerebrovascular events, and death.[66] Early detection, prompt treatment, and prophylaxis can help avoid these complications and to manage long term consequences. Pediatric risk factors for developing venous thrombosis including the presence of an indwelling central venous catheter, surgery, immobilization, dehydration (especially with hyperosmolar-hyperglycemic states), malignancy, infectious and inflammatory conditions. The use of anticoagulants for the treatment of venous thromboembolism is associated with an increased risk of bleeding; therefore, monitoring is recommended. Guidelines for anticoagulation are provided by the American Society of Hematology.[67]

Unfractionated heparin (UFH) is a parenteral anticoagulant that inhibits coagulation factors by binding to antithrombin and augmenting antithrombin activity. Heparin can be used for prophylaxis and treatment. Side effects include potential for bleeding, and in addition, it is associated with heparin-induced thrombocytopenia (HIT), an immune-mediated, prothrombotic state.[68] Benefits of heparin include the ability to monitor drug activity levels by the measurement of activated partial thromboplastin time (aPTT) or anti-Xa levels. In addition, the anticoagulant effects of UFH can be reversed with the administration of protamine.

Low-molecular-weight heparin (LMWH) has similar actions as UFH, and effects can be monitored by the measurement of anti-Xa levels at less frequent intervals than required for UFH. Subcutaneous administration is an added benefit in patients without IV access.

Warfarin is an oral anticoagulant used for prophylaxis and treatment of thromboembolic disease. Warfarin inhibits the synthesis of vitamin K-dependent coagulation factors II, VII, IX, and X and anticoagulant proteins C and S. Warfarin has a narrow therapeutic window and increases the risk of bleeding; therefore the measurement of prothrombin time (PT) and international normalized ratio (INR) are required to monitor effects. To avoid the prothrombotic potential of warfarin during the early stages of administration, therapy should be initiated with concomitant anticoagulation with UFH, which can then be discontinued several days after warfarin therapy is initiated and the INR is at the desired level. Warfarin effects can be reversed by administering vitamin K-dependent factors with fresh frozen plasma, prothrombin concentrates, or with vitamin K.

Argatroban and bivalirudin are parenteral direct thrombin inhibitors (DTIs) often used as alternatives to UFH for anticoagulation, in patients with circulatory devices or those who require anticoagulation but have a history of HIT.[69,70] Bivalirudin is eliminated via nonenzymatic proteolysis and is preferred in patients with hepatic insufficiency. The

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Table 4
Status epilepticus medications[a]

Drug	Lorazepam	Midazolam	Diazepam	Fosphenytoin	Levetiracetam
Dosing: Intermittent	0.1 mg/kg/dose IV	0.1–0.2 mg/kg/dose IV/ intranasal/buccal	0.5 mg/kg PR	20 mg PE/kg (max. 1500 mg PE)	30–60 mg/kg IV (max. 3000 mg)
Continuous infusion	NA	0.2–0.6 mg/kg/h	NA	NA	NA
Adverse Effects	Hypotension, respiratory depression			Bradycardia, hypotension	Bone marrow suppression, headache
Pharmacokinetics Onset	15–20 min	1–5 min	15 min	15 min	5–30 min
T ½	6–73 h	2–12 h	30–60 h	12–29 h	6–8 h
Duration	6–8 h	< 2 h	12 h	3 h	
Metabolism	Hepatic via conjugation	CYP450 enzymes	CYP450 enzymes	CYP450 enzymes	Not extensive-enzymatic hydrolysis

Abbreviation: T ½, half-life.
[a] Data from Lexi-Comp Online, Pediatric Lexi-Drugs Online.[74]

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Table 5
Anticoagulation

Anticoagulant	Dosing	Goal	Dose Adjustment	
Heparin		aXa 0.3–0.7	Anti-Xa	Rate Change
• Bolus	50–100 units/kg Bolus		<0.1	+5 units/kg/h + 50 units/kg bolus
• Infusion	28 units/kg/h (<1 y)		0.1–0.29	+2.5 units/kg/h
	20 units/kg/h (>1 y)		0.3–0.7	0 units/kg/h
			0.71–0.8	−2.5 units/kg/h
			0.81–1	−2.5 units/kg/h + hold 30 min
			>1	−5 units/kg/h + hold 60 min
Enoxaparin		aXa 0.1–0.5	*Anti-Xa*	*Dose change*
-prophylaxis	0.75 mg/kg SC q 12 h (<2 mo)	aXa 0.5–1	<0.1	Increase 25%
-treatment	0.5 mg/kg SC q 12 h (>2 mo)		0.1–0.5	no change
	1.5 mg/kg SC q 12 h (<2 mo)		0.51–1	decrease 20%
	1 mg/kg SC q 12 h (>2 mo)		>1	decrease 30%
			Anti-Xa	*Dose change*
			<0.35	increase 25%
			0.35–0.49	increase 10%
			0.5–1	no change
			1.1–1.5	Decrease 20%
			1.6–2	Decrease 30%
			>2	Hold until 0.5–1; decrease 40%
DTI		aPTT 50–80 s	*aPTT*	*Rate Change*
Argatroban	0.75 mCg/kg/min		<50 s	Increase dose by 20%
Bivalirudin	0.25 mCg/kg/min		50–80 s	No change
	(hepatic impairment)		81–95 s	aPTT 81–95 Decrease dose by 20%
	0.1–0.3 mg/kg/h		96–120 s	Hold infusion for 1 h then resume at 20% decrease from prior dose
			≥ 121 s	Hold infusion for 2 h then obtain aPTT every 2 h until <95 then resume

(*continued on next page*)

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Table 5 (*continued*)

Anticoagulant	Dosing	Goal	Dose Adjustment	
Warfarin	0.1–0.2 mg/kg PO q 24 h (max 5 mg)	INR 2–3	*Dose adjustment after day 3:*	
			INR	*Dose Change*
			1.1–1.4	increase 20%
			1.5–1.9	increase 10%
			2–3	no change
			3.1–3.5	decrease 10%
			>3.5	hold until INR <3.5, decrease 20%

Adapted and modified from Malec L, Young G. Treatment of Venous Thromboembolism in Pediatric Patients. Front Pediatr. 2017 Feb 28;5:26. LMWH, low-molecular-weight heparin; DTI, direct thrombin inhibitor; aPTT, activated partial thromboplastin time; aXa, anti Xa; INR, international normalized ratio; PT, prothrombin time.

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data for use of these drugs in children are limited and most of the information is extrapolated from studies in adults. Both medications require monitoring to achieve a goal of 1.5 to 2.5 times the baseline aPTT, to maintain aPTT less than 100s.[66] See **Table 5** for anticoagulation medications, monitoring, and adjustment parameters.

Thrombolytic Therapy

The use of recombinant tissue plasminogen activator (rTPA) results in clot lysis with the potential to spare tissues from a devastating injury. Thrombolytic therapy has a role in the treatment of hemodynamically significant PE, and more recently, is considered important in the treatment of pediatric stroke.[67,71,72] A regional stroke team should be involved in the decision to use thrombolytic therapy in this context. rTPA dosing for hemodynamically significant PE is a bolus of 0.5 to 0.7 mg/kg (up to 100 mg) followed by continuous IV infusion of 0.03 to 0.06 (max 2 mg/h) with a continuous heparin infusion of 4 to 10 units/kg/h. For thrombolytic therapy for stroke, the recommended dose is 0.9 mg/kg with the first 0.09 mg/kg given over 5 minutes followed by 0.81 mg/kg over the first hour.[71,73]

Pharmacologic therapy for critically ill children is a complex endeavor that requires knowledge of the developmental stage, drug interactions, end-organ function, and the risk to benefit ratio of a given therapy. While unavoidable, polypharmacy increases the risk of medication errors which account for a large burden of iatrogenic morbidity and mortality that can potentially be avoided with physiologic and laboratory monitoring and clinical assessment.

CLINICS CARE POINTS

- Pediatric dosing/adjustment of medications is frequently weight-dependent; additional care should be taken with certain medications (e.g. cardiovascular) that have differential dose-dependent effects.

DISCLOSURE

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