January

Question: 1

A 2-month-old, ex-36-week late preterm infant is intubated with a 3.5-cuffed endotracheal tube for rhinovirus bronchiolitis. She did not require the neonatal intensive care unit after birth and has had no prior hospitalizations. She has required reintubation twice after unplanned extubations. On day 10 of the illness, she does well on a pressure support trial but is found to have no air leak around the endotracheal tube in the early morning. She requires an FiO_2 of 0.30 and is very alert. She has been receiving dexmedetomidine 0.8 μg/kg per hour and fentanyl 2 μg/kg per hour for the past 3 days. The team makes rounds on the patient and decides to give intravenous dexamethasone 4 mg every 4 hours × 2 doses before extubation. Sedation infusions are cut in half. Eight hours later, she is noted to have an air leak around the endotracheal tube, the sedation is stopped, and she undergoes extubation to high-flow, high-humidity nasal cannula. She has no stridor immediately after extubation. However, 3 hours later, she is noted to have biphasic stridor, moderately severe subcostal retractions, and agitation with a brief response to racemic epinephrine before the recurrence of stridor. Two more doses of dexamethasone are ordered. She is placed on a helium/oxygen mixture via high-flow nasal cannula circuit with some improvement in her respiratory effort and stridor. Two days later, she requires reintubation for severe stridor and hypoxemia.

Of the following, the BEST next course of action is to

- **A.** order rigid laryngoscopy and bronchoscopy
- **B.** reintubate with a smaller endotracheal tube
- **C.** start methadone and clonidine
- **D.** treat with a proton-pump inhibitor

The infant in this vignette has postextubation upper airway obstruction presenting as stridor and respiratory distress due to prolonged intubation for rhinovirus bronchiolitis. Her risk factors for extubation failure caused by upper airway obstruction are young age, infection, multiple intubations, and possibly the use of a cuffed endotracheal tube (ETT)

especially if cuff pressures are not monitored consistently. A rigid laryngoscopy and bronchoscopy will allow characterization of her lesion and debridement of granulation tissue, most commonly located in the posterior glottis or subglottic regions. This granulation tissue can be excised using a microdebrider or carbon dioxide laser depending on surgeon preference. Balloon dilation is also often used for more mature stenosis.

It is estimated that postextubation upper airway obstruction explains one-third of all extubation failures. Acquired subglottic edema and stenosis are particularly common in infants and young children. In a single-center prospective study of children receiving mechanical ventilation, risk factors for subglottic upper airway obstruction in children with cuffed ETTs were intubation for upper airway obstruction, smaller absolute ETT size, absence of pre-extubation ETT leak, higher pre-extubation leak pressure, cuff kept deflated on the day of extubation, and lower cuff leak volume. Additional studies have identified other risk factors leading to laryngeal injury such as young age, traumatic intubation, intubation on the scene (ie, outside the hospital), use of cuffed ETTs, inappropriate tube size, duration of intubation, multiple intubations, and infection.

The most common location for ETT-related laryngeal injury in pediatric patients is the posterior glottis due to the location of the ETT. The pressure from the ETT and/or the ETT cuff causes edema and local ischemia to the epithelial tissue of the trachea, particularly at the level of the cricoid cartilage, the narrowest portion of the pediatric airway. Laryngeal injury can result in the development of subglottic stenosis. Subglottic stenosis is traditionally graded according to the Meyer-Cotton Scale (**Table**).

Depending on the grade of subglottic stenosis, the patient may require airway interventions such as balloon dilation, tracheal reconstruction, or tracheotomy.

Reintubation with a smaller ETT would alleviate acute upper airway obstruction in this patient but not treat the underlying lesion and result in more use of sedating medications. Moreover, the patient's lung disease has resolved, and so further mechanical ventilation puts the patient at risk for complications such as ventilator-associated pneumonia.

Although this patient did require pharmacologic sedation and pain control to facilitate mechanical ventilation, she is currently not showing signs and symptoms of α-agonist or opiate withdrawal. Therefore, loading with clonidine and methadone is not recommended.

Although gastroesophageal reflux may certainly exacerbate upper airway inflammation, treatment with a proton-pump inhibitor alone will not treat the laryngeal injury causing the patient's stridor and respiratory distress.

PREP Pearls

- Infants with bronchiolitis are at particularly high risk for laryngeal injury and postextubation upper airway obstruction when intubated.

- Postextubation upper airway obstruction may be treated with racemic epinephrine, steroids, and an inhaled helium/oxygen mixture in the acute phase but may require laryngoscopy/bronchoscopy and surgical intervention to definitively alleviate obstruction.

ABP Content Specifications(s)/Content Area

- Know the complications resulting from mechanical ventilation

Suggested Readings

Jefferson ND, Cohen AP, Rutter MJ. Subglottic stenosis. *Semin Pediatr Surg*. 2016;25(3):138-143. doi:10.1053/j.sempedsurg.2016.02.006

Veder LL, Joosten KFM, Schlink K, Timmerman MK, Hoeve LJ, van der Schroeff MP, Pullens B. Post-extubation stridor after prolonged intubation in the pediatric intensive care unit (PICU): a prospective observational cohort study. *Eur Arch Otorhinolaryngol*. 2020;277(6):1725-1731. doi:10.1007/s00405-020-05877-0

Table. Myer-Cotton Staging for Subglottic Stenosis.

Grade	% Obstruction of Airway
I	0-50%
II	51%-70%
II	71%-99%
IV	100%

Courtesy of E. Reade

January

Question: 2

A 16-year-old adolescent boy with a history of depression and insulin-dependent diabetes is seen at the emergency department with diabetic ketoacidosis (DKA). He has a 1-day history of vomiting and did not take his insulin yesterday because he had an argument with his girlfriend. He reports no illicit drug use. He smokes cigarettes on occasion and says that he drank 4 beers yesterday. His toxicology screen is positive for tetrahydrocannabinol. His medications include insulin and amoxapine. On examination, the patient is awake, alert, and oriented, and he responds appropriately to questions. His neurologic examination findings are unremarkable.

Laboratory data are shown:

Laboratory Test	**Result**
Complete blood cell count	
White blood cells	18,200/μL (18.2×10^9/L)
Hemoglobin	13 g/dL (130 g/L)
Hematocrit	38%
Electrolytes	
Sodium	132 mEq/L (132 mmol/L)
Potassium	4.7 mEq/L (4.7 mmol/L)
Chloride	102 mEq/L (102 mmol/L)

Carbon dioxide	12 mEq/L
Blood urea nitrogen	24 mg/dL (8.6 mmol/L)
Creatinine	1.5 mg/dL (132.6 μmol/L)
Glucose	535 mg/dL (29.7 mmol/L)
Magnesium (reference, 1.8-3.0 mg/dL)	1.1 mg/dL (0.45 mmol/L)
Phosphorus (reference, 2.5-4.5 mg/dL)	5.7 mg/dL (1.8 mmol/L)
Calcium (reference, 8.5-10.3 mg/dL)	7.2 mg/dL (1.8 mmol/L)
Albumin (reference, 3.4-5.4 g/dL)	3.0 g/dL (30 g/L)
Serum osmolarity	302 mOsm/kg (302 mmol/kg)

Of the following, hyponatremia is MOST likely related to

- **A.** excessive water intake
- **B.** hypoalbuminemia
- **C.** hyperglycemia
- **D.** metabolic acidosis

Electrolyte disturbances are frequently encountered in patients who are admitted to the intensive care unit. This is especially true in patients with hyperglycemia, where a spurious low serum sodium concentration is observed and referred to as *pseudohyponatremia*. Electrolyte disturbances related to hyperglycemia can result in osmotic fluid shifts and total body water deficits caused by an osmotic diuresis. Elevated plasma glucose concentration causes fluid shifts to the extracellular space, diluting serum sodium concentration and

resulting in a hypertonic hyponatremia. A correction factor of 1.6 mEq/L for each 100 mg/dL change in glucose above 100 mg/dL compensates for this dilutional effect of glucose, making hyperglycemia the correct response choice. Hyperlipidemia and hyperproteinemia from hypergammaglobulinemia or intravenous immunoglobulin administration can also cause a falsely low serum sodium level. Certain medications such as tricyclic antidepressants stimulate the release of vasopressin, causing true hyponatremia. Insulin is known to stimulate the vasopressin-dependent expression of aquaporin-2 in the kidney, which may explain hospital-acquired hyponatremia and insulin use in patients with diabetes. Serum osmolarity should be measured in the evaluation of hyponatremia. Hypoalbuminemia can affect circulating volume by stimulating antidiuretic hormone secretion with resultant hyponatremia and similar to excessive water intake results in a low serum osmolarity making these responses incorrect based on the laboratory values.

Disturbances in potassium are frequently encountered and can occur because of changes in pH, plasma insulin concentrations, and catecholamine levels. Potassium can shift from the extracellular to the intracellular compartment after administration of insulin, correction of hypertonicity, or by stimulation of β_2-adrenergic receptors. Hypokalemia is also common with diuretic therapy. Other causes of hypokalemia include hypomagnesemia, antibiotics such as penicillins and gentamicin, Bartter syndrome, leukemia, and chronic ingestion of licorice. Licorice contains glycyrrhizic acid, which has mineralocorticoid properties that can cause potassium wasting. Hyperkalemia is caused by redistribution of potassium as a result of hypertonicity, insulin deficiency, and acidosis in patients with diabetes and diabetic ketoacidosis (DKA). Hyperkalemia can occur after α-adrenergic receptor stimulation. Renal tubular acidosis impairs renal excretion of potassium, also resulting in hyperkalemia. Drugs such as trimethoprim-sulfamethoxazole, ketorolac tromethamine, and heparin are known to cause hyperkalemia. Heparin suppresses aldosterone, natriuresis, and potassium excretion. Familial pseudohyperkalemia is a rare inherited autosomal dominant condition wherein red blood cell permeability is abnormal, resulting in excessive leakage of potassium, which in turn leads to hyperkalemia. Falsely elevated potassium levels can be seen in patients with leukocytosis and thrombocytosis. Measured serum potassium levels will increase by 0.15 mEq/L for every 100,000 μL increase in the platelet count. Pseudohyperkalemia most commonly occurs from hemolysis after venipuncture.

Insulin deficiency and metabolic acidosis can increase serum magnesium levels, whereas poor glycemic control with a resultant osmotic diuresis can lead to renal wasting of magnesium. Treatment with insulin and correction of the acidosis will shift magnesium into the intracellular compartment, resulting in hypomagnesemia. Proton pump inhibitors also affect gastrointestinal absorption of magnesium, resulting in low magnesium levels. Hypomagnesemia can affect the release of parathyroid hormone, resulting in hypocalcemia. Administration of phosphate is commonly employed in treating a patient with DKA and can result in hypomagnesemia and hypocalcemia. Phosphate derangements

commonly occur in patients with DKA. Osmotic diuresis results in increased urinary phosphate loss. Hypophosphatemia occurs with insulin administration and correction of the metabolic acidosis, shifting phosphate to the intracellular space.

PREP Pearls

- Falsely low serum sodium levels can be seen with hyperglycemia. A correction factor of 1.6 mEq/L (1.6 mmol/L) for each 100 mg/dL (5.5 mmol/L) change in glucose above 100 mg/dL compensates for this dilutional effect of glucose.
- Hyperlipidemia and hyperproteinemia can cause a falsely low serum sodium level.
- Falsely elevated potassium levels can be seen in patients with leukocytosis and thrombocytosis. Measured serum potassium levels will increase by 0.15 mEq/L (0.15 mmol/L) for every 100,000/µL (100×10^9/L) increase in the platelet count.

ABP Content Specifications(s)/Content Area

- Interpret serum electrolyte concentrations and identify sources of error

Suggested Readings

Biff F. Palmer MD, Clegg DJ. Electrolyte and Acid–Base Disturbances in Patients with Diabetes Mellitus. *N Engl J Med* 2015; 373:548-559. doi: 10.1056/NEJMra1503102.

Liamis G, Liberopoulos E, Barkas F, Elisaf M. Spurious electrolyte disorder: A diagnostic challenge for clinicians. *Am J Nephrol* 2013;38:50-57. doi: 10.1159/000351804.

Mandal AK. Hypokalemia and Hyperkalemia *Med Clinics North America.* 1997;3:611-639. doi: 10.1016/s0025-7125(05)70536-8.

January

Question: 3

A 3-month-old infant who was born at 33 weeks' gestation is admitted to the pediatric intensive care unit for cough and difficulty breathing. On examination, the infant is afebrile but has respiratory distress. His vital signs are shown:

Blood pressure	78/35 mm Hg
Heart rate	177 beats/min
Respiratory rate	67 breaths/min
Oxygen saturation	93% on FiO_2 of 0.75

The precordium is hyperdynamic with an ejection systolic murmur over the left upper sternal border. There are scattered rhonchi bilaterally, the abdomen is soft, and the posterior tibial pulses are bounding. While echocardiography is being performed the technician shows the cardiologist the **Video**.

Of the following, the MOST likely diagnosis is

- **A.** aortic coarctation
- **B.** patent ductus arteriosus
- **C.** pulmonary atresia
- **D.** ventricular septal defect

Patent ductus arteriosus (PDA) is persistence of the fetal ductus arteriosus between the pulmonary artery and the aorta. The usual site of communication is between the descending aorta and the pulmonary trunk. Patent ductus arteriosus can be associated

with other congenital cardiac defects or occur as an isolated abnormality.

In the fetus the ductus arteriosus is open and the vast majority of the blood that is ejected from the right ventricle into the pulmonary artery is shunted through the ductus arteriosus into the descending aorta. This occurs because the lungs are not functioning as a gas exchange organ in utero, and the pulmonary vascular resistance is high. Thus, the blood takes the path of least resistance and is shunted into the descending aorta where it contributes to systemic blood flow.

The fetal ductus arteriosus at birth is a muscular artery with internal elastic lamina and media that consists of circularly arranged smooth muscles. Mucoid lakes are also seen within the wall of the ductus arteriosus. After birth, as the lungs expand and normal respiration is established, the pulmonary vascular resistance decreases dramatically. Therefore, the vast majority of blood ejected from the right ventricle goes into the pulmonary artery and pulmonary circulation. The ductus arteriosus functionally closes within 24 hours after birth as the pulmonary vascular resistance drops precipitously during this time. In the first several hours after birth, the smooth muscles within the ductus arteriosus contract. This leads to shortening of the ductus and protrusion of the intimal layer and the mucoid lakes into the lumen, thus narrowing the lumen. The pulmonary artery pressure further drops over the next few days after birth and enfolding of the endothelium along with intimal proliferation leads to anatomic closure of the ductus arteriosus. The ductus arteriosus becomes a fibrous band known as ligamentous arteriosus in most infants.

Isolated PDA can be seen in approximately 1 in 2,500 live births and represents approximately 10% of all congenital cardiac defects. However, PDA is also seen in association with other congenital cardiac defects. Exposure to rubella infection in the first trimester of pregnancy is well known to be associated with PDA. In this setting, the cardiovascular system is affected in up to 60% of fetuses, and the PDA is usually associated with other anomalies including renal artery stenosis and peripheral pulmonic stenosis. Patent ductus arteriosus is more common in preterm infants and may occur in up to 30% of preterm neonates. The diagnosis of PDA is based on physical examination findings of an ejection systolic murmur in the left upper sternal border possibly associated with a diastolic murmur. Widening of pulse pressure and bounding pulses may be noted in neonates and infants with a large PDA. If the PDA is large, with a large left-to-right shunt, the infant may have signs of congestive heart failure, including tachypnea, sweating, poor feeding, hepatomegaly, and failure to gain weight.

The diagnosis of PDA is confirmed with a two-dimensional transthoracic echocardiography with Doppler flow studies as seen in the **Video**. The video shows the main pulmonary artery dividing into the right and left pulmonary arteries (towards your right as you watch the

video on the screen). The homogenous blue in the color Doppler (**Video**) represents the blood flow from the right ventricle across the pulmonary valve into the pulmonary artery and then into the right and left pulmonary arteries, while the red flow represents the flow of blood into the pulmonary from the descending aorta through the PDA.

The red flow is the characteristic finding on the transthoracic echocardiography that confirms the presence of PDA. Transthoracic Doppler echocardiography can also assist in understanding if the PDA is restrictive or not and whether the PDA is hemodynamically significant. If the diastolic flow across the PDA is 50% or more greater than the systolic flow, the PDA is categorized as restrictive. If the diameter of the left atrium is greater than the diameter of the left atrium by 1.5 or higher, the PDA is considered to be hemodynamically significant.

The pulmonary valve is seen proximal to the blood flow (red) from the aorta into the pulmonary artery, it appears structurally normal and the valve opens and closes normally, thus ruling out the diagnosis of pulmonary atresia. Atrial septal defects are best demonstrated in the subcostal view and muscular ventricular septal defects are seen in the parasternal long access view or the apical 4-chamber views. The size of the PDA may be measured using a measurement scale. Alternatively, the size and clinical significance of a PDA may be assessed using colored Doppler imaging of the direction and the velocity of the flow of blood. In this case, the flow is from left to right (from the aorta to the pulmonary artery).

Administration of inhibitors of prostaglandins such as nonsteroidal anti-inflammatory medications may facilitate PDA closure in symptomatic infants. When medical therapy fails, percutaneous transcatheters using occlusion devices can achieve PDA closure. Other infants require surgical closure of PDA via a left posterolateral thoracotomy with application of a ligature or a titanium clip to close the PDA. Postoperative complications of surgical closure of a PDA include gastric distention, ileus, phrenic nerve, recurrent laryngeal nerve palsies, and chest wall abnormalities. Percutaneous transcatheter closure of PDA using occlusion devices is likely to reduce the rate of complications.

PREP Pearls

- Percutaneous transcatheter closure of patent ductus arteriosus may be successfully performed in infants with good outcome.

- Long-term complications of surgical closure of patent ductus arteriosus include rib abnormalities and chest wall abnormalities.

ABP Content Specifications(s)/Content Area

- Know the signs and findings of right-to-left shunt lesions

Suggested Readings

Paudel G, Joshi V. Echocardiography of the patent ductus arteriosus in premature infants. *Congenit Heart Dis*. 2019;14(1):42-45. doi:10.1111/chd.12703

Semberova J, Sirc J, Miletin J, et al. Spontaneous closure of patent ductus arteriosus in infants <1500 g. *Pediatrics*. 2017;140(2):e20164258. doi:10.1542/peds.2016-4258

Sorantin E, Heinzl B. What every radiologist should know about pediatric echocardiography. *Eur J Radiol.* 2014;83(9):1519-1528. doi:10.1016/j.ejrad.2014.05.030

January

Question: 4

An 8-year-old girl is admitted to the pediatric intensive care unit (PICU) for hypotension. She was seen in the emergency department with a 1-day history of fever and a rash on her left arm. She received ~50 mL/kg normal saline boluses and was transferred to the PICU for further management. Further history revealed that the patient had visited her pediatrician 2 weeks ago for edema of her face and around her eyelids. At that time, a referral was made to a nephrologist after finding high urinary protein on her urinalysis and a low serum albumin, but that appointment has not yet been made.

On examination, the patient is febrile, tachycardic, tachypneic, with capillary refill ~3 seconds, and cool extremities. The patient's blood pressure is 90/40 mm Hg. Her lungs are clear to auscultation, and no gallop or murmur is heard. Her oxygen saturation while breathing room air is 96%. Her abdomen is soft and nondistended, and there is no organomegaly. Her neurologic examination findings are normal. There is some edema of the face. A diffuse erythematous lesion (warm to touch) with elevated and sharply demarcated borders is seen on her left arm as shown in the

Of the following, the therapy, if started early in her prehospital course, that could have PREVENTED the lesion in the child's arm is

- **A.** antibiotics
- **B.** diuretics
- **C.** pneumococcal vaccine
- **D.** steroids

The patient in the vignette with facial edema, urinary protein loss, and hypoalbuminemia has cellulitis of her arm. She is most likely to have nephrotic syndrome. The hallmark of nephrotic syndrome includes edema, proteinuria, hypoalbuminemia, and hyperlipidemia.

Most children with nephrotic syndrome are between 1 and 8 years of age and have minimal change nephrotic syndrome, which is very responsive to steroids. Minimal change nephrotic syndrome does not require renal biopsy for diagnosis, provided the patient has no hematuria, hypertension, acute kidney injury, abnormal complement levels, or is younger than 1 year. About 80% to 90% of children with minimal change nephrotic syndrome are steroid-responsive within 2 weeks of therapy. Early initiation of steroids results in a lower relapse rate.

If the patient is not treated with steroids, urinary loss of proteins such as immunoglobulins, properdin factor B (involved in alternate complement pathway), predisposes patients to infections. Spontaneous bacterial peritonitis, sepsis, cellulitis, pneumonia, and urinary tract infection may be seen in patients with nephrotic syndrome. Infections with *Streptococcus pneumoniae*, *Escherichia coli*, β-hemolytic *Streptococcus*, and *Haemophilus* are common. The girl in the vignette most likely has cellulitis resulting from β-hemolytic *Streptococcus*. Although antibiotics are now indicated for sepsis and cellulitis, early use of antibiotics would not have prevented this infection. The lesion does not appear to be caused by varicella, however, the varicella vaccine is highly recommended, especially in patients with negative varicella titers. The patient should also be given pneumococcal and influenza vaccines.

For mild asymptomatic edema, the role of diuretics is unclear. If a child has symptomatic edema, pericardial, pleural effusions, or swelling of the scrotum, diuretics should be used under close supervision, and the patient should be admitted to the hospital. A concern with diuretic use is the increased risk for thromboembolic events. Patients with nephrotic syndrome are at increased risk for arterial as well as venous thrombosis. Renal vein thrombosis, sagittal sinus thrombosis, and pulmonary embolism may be seen in ~5% of patients. Due to loss of urinary protein, there is an increase in the prothrombotic factors (eg, fibrinogen) and decreased fibrinolytic factors (eg, protein C, protein S, and antithrombin III). Additionally, elevated platelet count, dehydration, and immobilization can further increase the risk of thrombosis. Although patients may have cholesterol synthesis issues leading to elevated serum cholesterol and triglyceride levels, the risk of atherosclerosis leading to myocardial infarction is extremely low.

In addition to complications of nephrotic syndrome, health care providers should be aware of complications resulting from treatments such as prolonged steroid and immunosuppressant use (eg, hyperglycemia, infections, osteoporosis, gastritis/peptic ulcers, cataracts, hypertension, and behavior changes). Atypical infections, reactivation of cytomegalovirus, Epstein-Barr virus, tuberculosis, bone marrow suppression, and electrolyte issues can result from immunosuppressive agents (eg, tacrolimus, cyclosporine,

cyclophosphamide, etc). Complications of nephrotic syndrome and its therapy are summarized in the **Table**.

PREP Pearls

- Early recognition and management of nephrotic syndrome with steroids can prevent relapse as well as complications associated with protein loss.
- Loss of immunoglobulins may result in predisposition to infections in patients with nephrotic syndrome.
- A decrease in fibrinolytic factors (eg, protein C, protein S, and antithrombin III) and an increase in prothrombotic factors such as fibrinogen predisposes patients with nephrotic syndrome to venous as well as arterial thrombosis.

ABP Content Specifications(s)/Content Area

- Plan treatment for the life-threatening complications of nephrotic syndrome

Suggested Readings

Andolino TP, Reid-Adam J. Nephrotic syndrome. *Pediatr Rev.* 2015;36(3):117-25; quiz 126,129. doi:10.1542/pir.36-3-117

Downie ML, Gallibois C, Parekh RS, Noone DG. Nephrotic syndrome in infants and children: pathophysiology and management. *Paediatr Int Child Health.* 2017;37(4):248-258. doi:10.1080/20469047.2017.1374003

Wang CS, Greenbaum LA. Nephrotic syndrome. *Pediatr Clin North Am*. 2019;66(1):73-85. doi:10.1016/j.pcl.2018.08.006

Table. Complications of Nephrotic Syndrome.

Due to Nephrotic Syndrome	Due to Steroids/Immunosuppression Therapy
Infections Sepsis, cellulitis, pneumonia, spontaneous bacterial peritonitis	Infection with atypical organisms Reactivation of CMV, hepatitis B
Thromboembolism of veins/arteries Renal vein thrombosis, pulmonary embolus, sagittal venous thrombosis	Hypertension
Fluid overload: Pleural effusion, pericardial effusion	Osteoporosis
Acute kidney injury	Bone marrow suppression
Electrolyte issues	Hyperglycemia
Anemia	Gastric/peptic ulcers
Hypertension	Behavior problems

Abbreviation: CMV, cytomegalovirus.

Courtesy of P. Kamat

January

Question: 5

A 7-year-old boy is being treated for pneumococcal septic shock and meningitis. Since admission 10 days ago, his condition has continued to deteriorate. He remains intubated and mechanically ventilated. He developed acute respiratory distress syndrome that required high ventilator pressures with escalation to high-frequency oscillatory ventilation. Multisystem organ dysfunction has ensued. He remains acidotic despite improved hemodynamics with volume resuscitation and an infusion of norepinephrine. Continuous renal replacement therapy has been initiated for acute kidney injury. He has significant elevation in his transaminase levels and an abnormal coagulation profile. Carbamazepine continues to be administered for his seizure disorder. Sedation is being achieved with continuous infusions of midazolam, fentanyl, and dexmedetomidine. Despite aggressive temperature management, he remains febrile. He is receiving a continuous infusion of cisatracurium for neuromuscular blockade.

Of the following, prolongation of neuromuscular blockade will MOST likely be caused by

- **A.** acidosis
- **B.** alkalosis
- **C.** hyperthermia
- **D.** renal failure

Cisatracurium is a nondepolarizing benzylisoquinolinium neuromuscular–blocking (NMB) agent. Cisatracurium is a more potent stereoisomer of atracurium. Cisatracurium produces neuromuscular blockade by competing with acetylcholine binding at postsynaptic nicotinic receptors on the motor end plate. Acetylcholinesterase inhibitors such as neostigmine reverse neuromuscular blockade.

Cisatracurium is 3 times more potent than atracurium. Unlike atracurium, dose-related histamine release is not encountered with cisatracurium, resulting in fewer hemodynamic changes even with administration of larger bolus doses and continuous infusion of this NMB agent. Cisatracurium is degraded in the plasma by ester hydrolysis and non-

enzymatic, organ-independent Hofmann elimination. Hofmann degradation is pH and temperature dependent. Acidotic and hypothermic patients receiving cisatracurium will have a longer elimination half-life of this drug because of decreased Hofmann degradation. Conversely, the patient with alkalosis or fever will require increased dosing. Cisatracurium elimination is not dependent on hepatic degradation, renal excretion, or plasma cholinesterase activity. This makes cisatracurium an ideal agent to provide neuromuscular blockade as a single dose or continuous infusion for patients with end-organ dysfunction. Cisatracurium is considered an intermediate-acting NMB agent. The onset of action for the benzylisoquinolinium group of neuromuscular-blocking agents is slower than aminosteroids such as rocuronium and vecuronium, or the depolarizing agent succinylcholine. Cisatracurium is not a preferred or recommended NMB agent for rapid-sequence endotracheal intubation because of its slower onset of action. Duration of action is similar to vecuronium. Adult and pediatric studies performed in the intensive care unit have compared patients receiving continuous vecuronium and cisatracurium infusions and shown faster recovery from NMB in the cisatracurium group. Increased dosing requirements have been described in infants compared with older children and adults. Increased dosing may also be related to tachyphylaxis and non-accumulation of cisatracurium compared with other NMB agents. Patients receiving chronic anticonvulsants such as carbamazepine or phenytoin can develop a moderate resistance to the action of cisatracurium.

Laudanosine is a tertiary amine analog of morphine and a metabolite of cisatracurium. Laudanosine has no NMB activity. This epileptogenic metabolite can accumulate with repeated dosing or during continuous infusion of cisatracurium. Laudanosine can cause transient hypotension and, in higher doses, seizures have occurred when administered to animals. Data to determine whether or not laudanosine contributes to seizures in intensive care unit (ICU) patients is insufficient. Rare reports of seizures have occurred with atracurium. However, many of these patients receiving atracurium had significant comorbidities that could have contributed to seizure activity. Laudanosine formation is potency dependent. The greater potency of cisatracurium, (3 times more potent than atracurium), results in less laudanosine formation. Laudanosine undergoes renal excretion, and this metabolite may increase in patients with renal insufficiency/failure.

The combination of neuromuscular-blocking agents and corticosteroids contributing to a polyneuropathy with prolonged muscle weakness or ICU-acquired weakness has been reported in the literature. This phenomenon has been described with aminosteroid (pancuronium, vecuronium, rocuronium) and benzylisoquinolinium NMB agents when used in combination with corticosteroids. The reader is reminded to be aware of prolonged muscle weakness following use of nondepolarizing NMB agents and corticosteroids.

Neuromuscular-blocking agents have no analgesia or sedative properties. The use of NMB agents must be combined with sedatives and analgesics when patients are chemically paralyzed. Additionally, whenever using continuous infusions of NMB agents, neuromuscular monitoring is recommended. Cisatracurium has not been studied in patients susceptible to malignant hyperthermia. Malignant hyperthermia can develop in the absence of established triggering agents. One should be prepared to recognize and treat malignant hyperthermia.

Commonly used drugs in the ICU may prolong the action of nondepolarizing NMB agents. These include antibiotics such as aminoglycosides, tetracyclines, bacitracin, polymyxin, and clindamycin. Magnesium salts, lithium, local anesthetics, procainamide, and quinidine can also prolong the action of neuromuscular blockade. Specifically, the effects of hemofiltration, hemodialysis, and hemoperfusion affecting plasma levels of cisatracurium and its metabolites are unknown. Patients receiving chronic anticonvulsant therapy with carbamazepine or phenytoin may require higher doses of cisatracurium to maintain NMB. Cisatracurium should be refrigerated to preserve potency of this NMB agent.

PREP Pearls

- Cisatracurium has minimal hemodynamic effects and does not stimulate histamine release.
- Cisatracurium undergoes organ-independent Hofmann degradation. Hofmann degradation is pH- and temperature-dependent. Acidosis and hypothermia will decrease activity and prolong the duration of action of cisatracurium
- Many commonly used drugs in the intensive care unit can prolong the duration of action of nondepolarizing benzylisoquinolinium neuromuscular-blocking agents.
- Chronic use of carbamazepine or phenytoin can reduce the action of cisatracurium requiring higher doses to maintain nondepolarizing benzylisoquinolinium neuromuscular blockers.
- Aminosteroids and nondepolarizing benzylisoquinolinium neuromuscular blockers combined with corticosteroids can contribute to a polyneuropathy with prolonged muscle weakness or intensive care unit–acquired weakness.

ABP Content Specifications(s)/Content Area

- Know that the hemodynamic effects of cisatracurium are minimal
- Know that cisatracurium is eliminated by Hoffman degradation
- Know that cisatracurium clearance is not dependent on liver or renal function

Suggested Readings

deBacker J, Hart N, Fan E. Neuromuscular blockade in the 21st century: management of the critically ill patient. *Chest*. 2017;151(3):697-706. doi:10.1016/j.chest.2016.10.040

Szakmany T, Woodhouse T. Use of cisatracurium in critical care: a review of the literature. *Minerva Anestesiol*. 2015;81(4):450-460. https://pubmed.ncbi.nlm.nih.gov/24721895/

Zuppa AF, Curley MAQ. Sedation analgesia and neuromuscular blockade in pediatric critical care: overview and current landscape. *Pediatr Clin North Am*. 2017;64(5):1103-1116. doi:10.1016/j.pcl.2017.06.013

January

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 6

A 2-year-old girl with no significant medical history is admitted to the intensive care unit with 3 days of fever, decreased oral intake, lethargy, and increased work of breathing. The patient was given a presumed diagnosis of bronchiolitis in the emergency department and placed on a high-flow nasal cannula, with minimal improvement. Her vital signs on arrival to the intensive care unit are as follows:

Heart rate	160 beats/min
Respiratory rate	42 breaths/min
Oxygen saturation	91% on 0.40 fraction of inspired oxygen
Blood pressure	70/35 mm Hg
Temperature	39°C

The physical examination is significant for the following:

- General appearance: lethargic, pale, difficult to arouse, grunting
- Chest: diffuse bilateral crackles, no wheezing
- Cardiovascular: muffled heart sounds, no murmur, audible gallop
- Abdomen: soft, nondistended, with liver edge palpable 3 cm below the right costal margin
- Extremities: cool, capillary refill approximately 5 seconds, weak peripheral and central pulses bilaterally

The results of an arterial blood gas test performed in the emergency department are pH, 7.10; partial pressure of carbon dioxide, 30 mm Hg; partial pressure of oxygen, 55 mm Hg; and serum lactate level, 13 mmol/L.

Of the following, the next BEST step in management is likely

- **A.** administration of 60 mL/kg of intravenous normal saline
- **B.** initiation of β-blocker treatment
- **C.** initiation of an epinephrine infusion
- **D.** initiation of a norepinephrine infusion

The patient in the vignette is displaying clinical signs of hypodynamic, cold shock. In healthy patients, the oxygen supply is equal to or greater than the demand. Any condition that disrupts this equilibrium (ie, decreases oxygen delivery or increases oxygen demand out of proportion to supply can result in shock).

When treating a patient with shock, the practitioner must understand the mechanisms of oxygen delivery and its basic equation to help reverse the process. Oxygen delivery is typically represented as follows:

$DO_2 = CO \times CaO_2$

which can further be represented as

$DO_2 = (HR \times SV) \times \{(Hbg \times 1.34 \times SaO_2) + (0.003 \times PaO_2)\}$

(DO_2 = oxygen delivery, CO = cardiac output, CaO_2 = arterial oxygen content, HR = heart rate, SV = stroke volume, Hbg = hemoglobin, SaO_2 = arterial oxygen saturation, PaO_2 = partial pressure of oxygen in the arteries)

As can be seen from this equation, any decrease in the blood oxygen–carrying capacity, oxygen tension, or decrease in normal circulatory function and cardiac output can result in shock. Insufficient cardiac output can be improved by ensuring optimal preload, afterload, and contractility (ie, improving the stroke volume) and in some cases by increasing the heart rate.

Shock can be classified based on the particular etiology; however, a complete discussion of all classifications is beyond the scope of this critique. The patient in the vignette is exhibiting clinical signs of significantly decreased oxygen delivery and cardiac output and evidence of cardiogenic shock. The physical examination findings of diffuse bilateral crackles, liver edge palpable below the right costal margin, decreased pulses, and significant tachycardia suggest severe cardiac failure. The hallmark of cardiogenic shock is a significant decrease in cardiac output. Myocardial dysfunction is the most common cause; however, abnormalities in heart rate caused by ventricular and atrial arrhythmias as well as heart block can also result in decreased cardiac output and subsequent cardiogenic shock. The underlying cause of the myocardial dysfunction often varies and can include familial cardiomyopathies, infectious myocarditis, sepsis, autoimmune diseases, acidosis, impaired coronary perfusion, recent cardiopulmonary bypass, and hypoxic-ischemic events.

Shock is a dynamic process that must be recognized early to prevent irreversible damage. As the stage of shock progresses, the risk of mortality increases. Shock can be characterized in 3 phases: compensated, uncompensated, and irreversible. The ability of children and infants to increase contractility and stroke volume is limited because of the insufficient muscle mass and stiffness of the young myocardium compared to the adult heart; therefore, they are more dependent on increases in heart rate to maintain cardiac output. Systemic vascular resistance can increase significantly in pediatric patients, and blood pressure may remain reassuring. Given these robust compensatory mechanisms, shock should not be thought of as a hypotensive state. Hypotension is a late and concerning finding in pediatric patients. Tachycardia and tachypnea may be the first warning signs of shock in a pediatric patient and must be recognized early.

The etiology of this patient's symptoms is unclear; however, it is likely secondary to a form of infectious myocarditis given that she has no known significant history of heart disease and had fever and lethargy of several days' duration on presentation. Further workup would likely demonstrate cardiomegaly on chest radiography and a significantly decreased ejection fraction on echocardiography given the severity of her symptoms and elevated lactate level. Because of the likely severe decrease in cardiac function, initiation of inotropic support with an epinephrine infusion would be useful as it would increase both the heart rate and contractility. Given the known α-agonist effect of norepinephrine, the significantly increased afterload to the failing left ventricle might cause the patient's condition to worsen. Although β-blockade may be useful in a patient with chronic heart failure, the decrease in heart rate and hypotension it would cause are detrimental. In addition, the patient likely has an element of dehydration from decreased oral intake and increased insensible losses from tachypnea. However, fluid resuscitation should be done judicially in patients with severe cardiac dysfunction; it is usually given in aliquots of 10 mL/kg to avoid worsening pulmonary edema and respiratory failure.

PREP Pearls

- Tachycardia is the first and early warning sign of shock in pediatric patients.
- Hypotension is a late finding of shock in pediatric patients.
- Fluid resuscitation of patients with cardiogenic shock should be done cautiously.

ABP Content Specifications(s)/Content Area

- Understand the pathophysiology of cardiogenic shock

Suggested Readings

Brissaud O, Botte A, Cambonie G, et al. Experts' recommendations for the management of cardiogenic shock in children. *Ann Intensive Care*. 2016;6(1):14. doi:10.1186/s13613-016-0111-2

McKiernan CA, Lieberman SA. Circulatory shock in children: an overview. *Pediatr Rev*. 2005;26(12):451-460. doi:10.1542/pir.26-12-451

February

Question: 1

A 13-year-old, unvaccinated, adolescent girl with a history of mild intermittent asthma has respiratory distress and a generalized rash. The patient is currently on 3 L/min via low-flow nasal cannula. The rash is present on the scalp, face, and trunk with multiple lesions (~250), some of which appear as erythematous macules, papules, clear, fluid-filled vesicles as well as some lesions, which are crusted (**Figure 1**). The cornea is not involved. A few ulcerated lesions are seen on the oropharynx. The patient is tachypneic for her age with normal work of breathing and normal bilateral breath sounds. She is tachycardic and her blood pressure is normal. She had a fever earlier during the day but is now afebrile. The patient's chest radiograph is nonspecific and does not show any consolidation. The patient is not taking any long-term medications or inhaled steroids.

Of the following, the patient who would most likely worsen and require admission to the pediatric intensive care unit is a

- **A.** teenager who chews smokeless tobacco
- **B.** teenager receiving chemotherapy with absolute lymphocyte count >1,500 cells/μL
- **C.** teenager with oculocutaneous albinism and leukocyte defect
- **D.** teenager receiving peritoneal dialysis awaiting renal transplantation

An unvaccinated teenager who is seen with a low-grade fever and a generalized rash in various stages of development, as seen in the vignette (eg, macules, papules, vesicular, etc), should be considered to have varicella (chickenpox) unless proven otherwise (**Figure 1**, **Figure 2**, and **Figure 3**). The varicella zoster virus (VZV) causes varicella, is a member of the herpesviridae family, and is highly contagious. Person-to-person transmission occurs either from direct contact with VZV lesions from varicella or herpes zoster or via airborne spread. Other modes of transmission include transplacental and via respiratory secretions (less common). The VZV can rapidly spread inside the hospital and affect multiple pediatric units

if patients are not quickly isolated and placed under airborne and contact precautions. In pediatric floors with no negative air-flow rooms, patients are admitted to the pediatric intensive care units (PICUs).

It is imperative that the pediatric critical care medicine physicians are well versed with the diagnosis and management of patients with varicella as more cases are encountered due to a lack of immunization. The World Health Organization has mentioned that the global antivaccine movement is one of the greatest threats to health care gains. Diseases that were eradicated (such as measles, varicella, and polio) now have the potential for resurgence, leading to community outbreaks due to misinformation about vaccine safety and the mistrust of the medical community.

The pulmonary and critical care medicine physicians must be aware that varicella can lead to severe disease (termed progressive varicella) in specific patient populations requiring intensive care management in the PICU. Patients can have bacterial sepsis, pneumonia, central nervous system complications such as encephalitis, stroke, and cerebellar ataxia. Reye syndrome (hepatic dysfunction with encephalopathy) is associated with the use of salicylates in patients with VZV. Patients with severe VZV infection can have thrombocytopenia, coagulopathy leading to hemorrhagic vesicles, hematuria, gastrointestinal bleeding, or rarely, hemorrhagic encephalitis. The VZV is a risk factor for severe invasive group A *Streptococcus* (varicella gangrenosum, necrotizing fasciitis, myocarditis, etc), which can be fatal.

Such complications are more common in patients who are immunocompromised. Although the patient in the vignette does not appear to have primary varicella pneumonia (uncommon in immunocompetent children), it is one of the most common complications seen in adults. Varicella infections are most severe in infants, teenagers, and adults.

Patients who are immunocompromised will present with multiple lesions (which could be hemorrhagic), high fevers, and the complications mentioned before. Children with congenital or acquired T-cell mediated immune deficiencies (including leukemia and lymphomas), HIV infection, high-dose steroids, immunosuppressive agents, long-term salicylate therapy, and chronic cutaneous or pulmonary disorders can have severe disease and even die of VZV. Of the options listed, the teenager with oculocutaneous albinism with leukocyte adhesion defect (Chediak-Higashi syndrome) is most likely to have a severe complicated course with VZV and hence should be admitted to the PICU. Cigarette smoking is a significant risk factor for developing varicella pneumonia in adults, though such an association is not seen with tobacco chewing. The patient awaiting renal transplantation is not at increased risk, provided the patient is not taking long-term steroids or immunosuppressive agents. Patients receiving chemotherapy are at risk if the lymphocyte count is less than 500/µL.

The diagnosis of VZV is made on clinical grounds. Laboratory testing for isolation purposes or when the diagnosis is unclear includes direct fluorescence assay of cells from skin lesions and polymerase chain reaction tests. A 4-fold increase of VZV IgG antibodies is also considered indicative of acute infection. The management of VZV involves symptomatic care (avoidance of salicylates), antipruritics, and prevention of secondary bacterial infection (cut nails short, frequent bathing). Oral acyclovir is indicated (ie, should be started within 72 hours to be effective) in high-risk patients with uncomplicated VZV. Severe VZV infection requires therapy with intravenous acyclovir. Varicella vaccine is administered within 3 to 5 days for postexposure prophylaxis for those without evidence of immunity to VZV. Passive immunoprophylaxis using VZV immunoglobulin within 10 days of exposure should be given to immunocompromised children exposed with no history of varicella or vaccination and unknown or negative serologic test results.

ABP Content Specifications(s)/Content Area

- Recognition and management of varicella infection

Suggested Readings

Centers for Disease Control and Prevention. Immunization of health-care personnel: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011;60(RR-7):1-45. https://pubmed.ncbi.nlm.nih.gov/22108587/

Ford L, Waksman J. Necrotizing fasciitis during primary varicella. *Pediatrics*. 2000;105(6) 1372-1375. doi:https://doi.org/10.1542/peds.105.6.1372

Jean-Philippe P, Freedman A, Philip S, Borkowsky W. Severe varicella caused by varicella-vaccine strain in a child with significant T-cell dysfunction. *Pediatrics*. 2007;120(5):e1345-9. doi:10.1542/peds.2004-1681

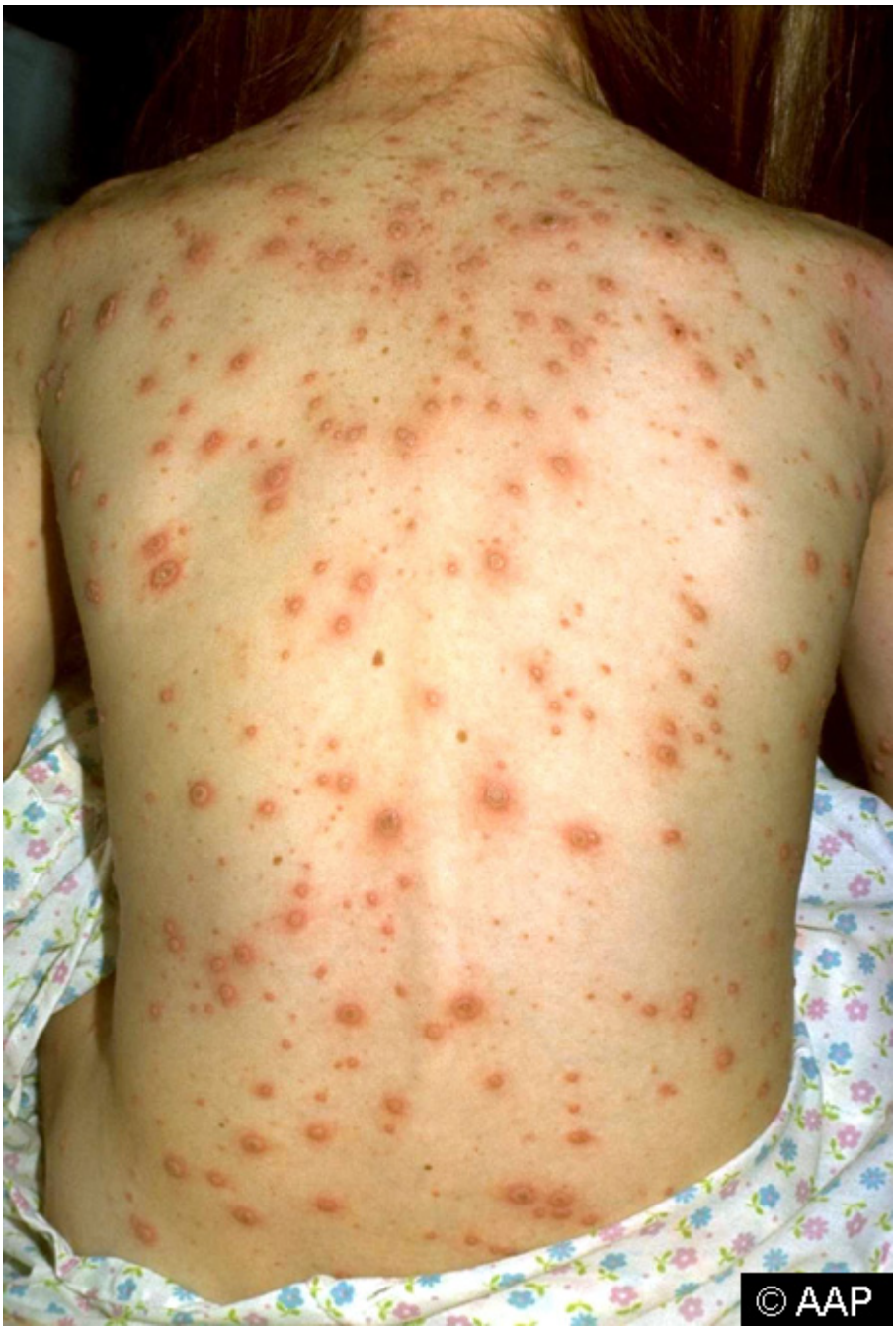

Figure 1: Patient in vignette

Reprinted with permission from Kimberlin DW, et al, eds. *Red Book Online*. Itasca, IL: American Academy of Pediatrics; 2019.

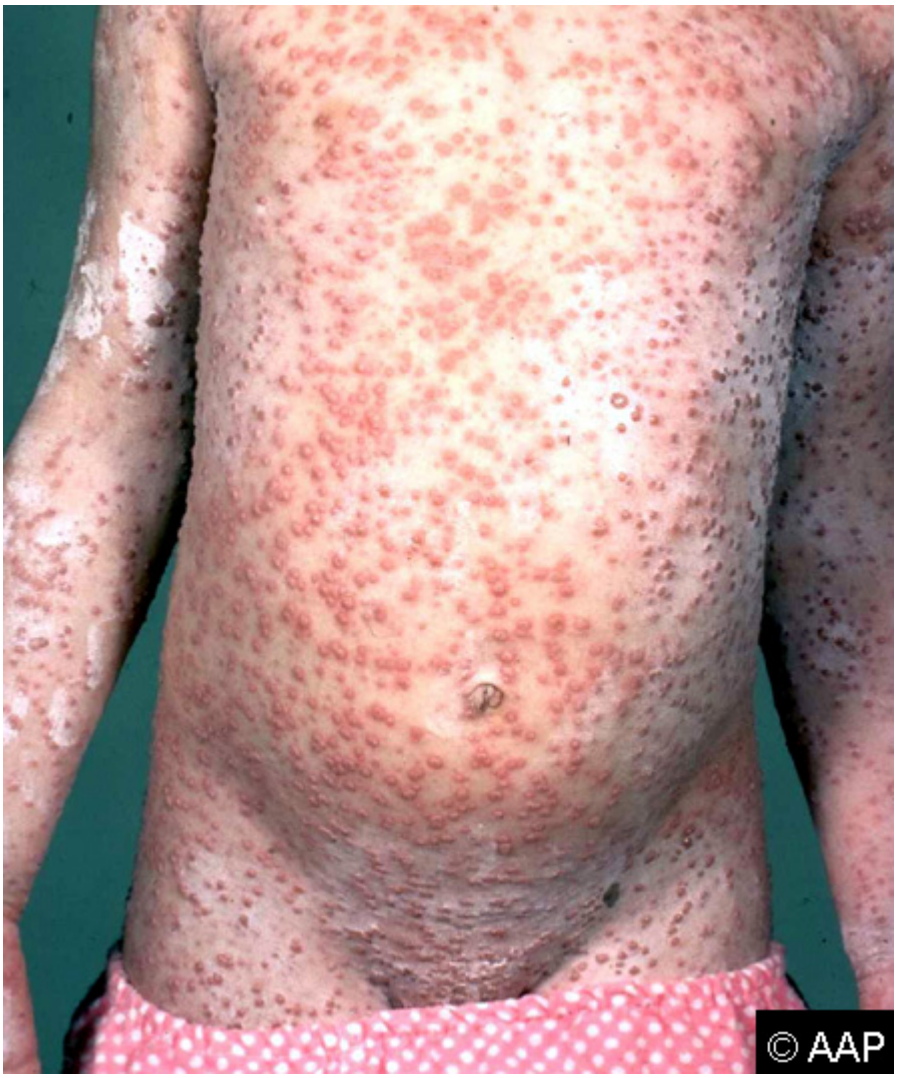

Figure 2: Varicella lesions in various stages of development.

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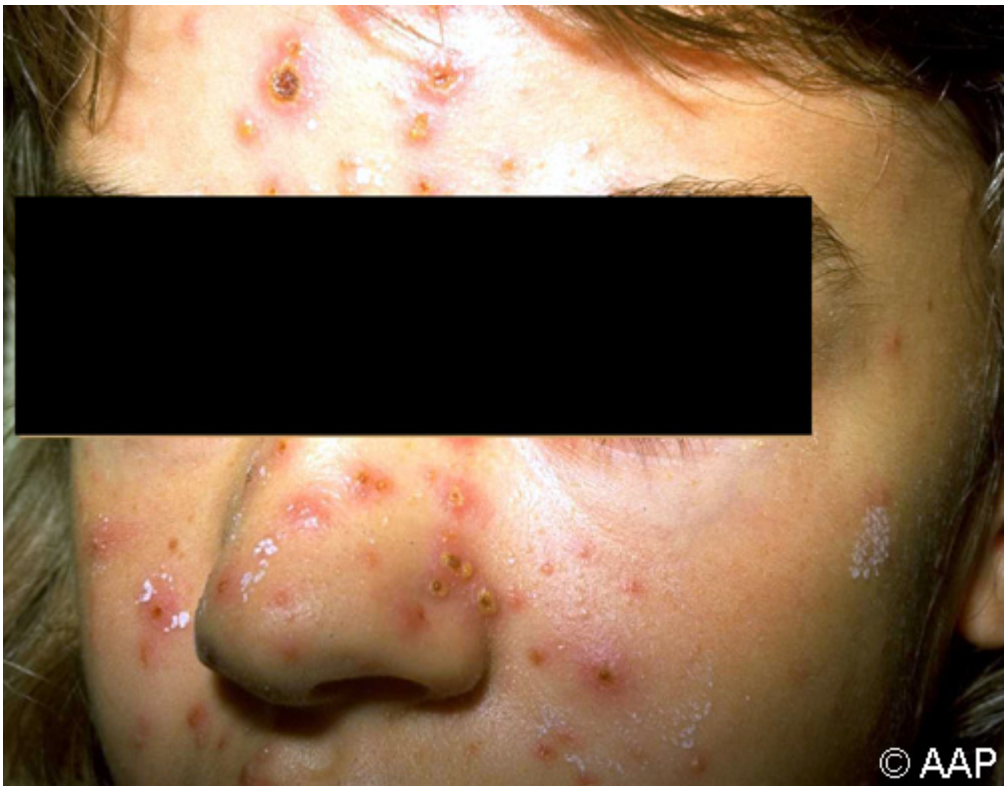


Figure 3: Varicella lesions in various stages of development.

Reprinted with permission from Kimberlin DW, et al, eds. *Red Book Online.* Itasca, IL: American Academy of Pediatrics; 2019.

February

Question: 2

A 7-year-old boy is admitted to the pediatric intensive care unit for frequent seizures leading to hypoventilation with the need for tracheal intubation. Vital signs are shown:

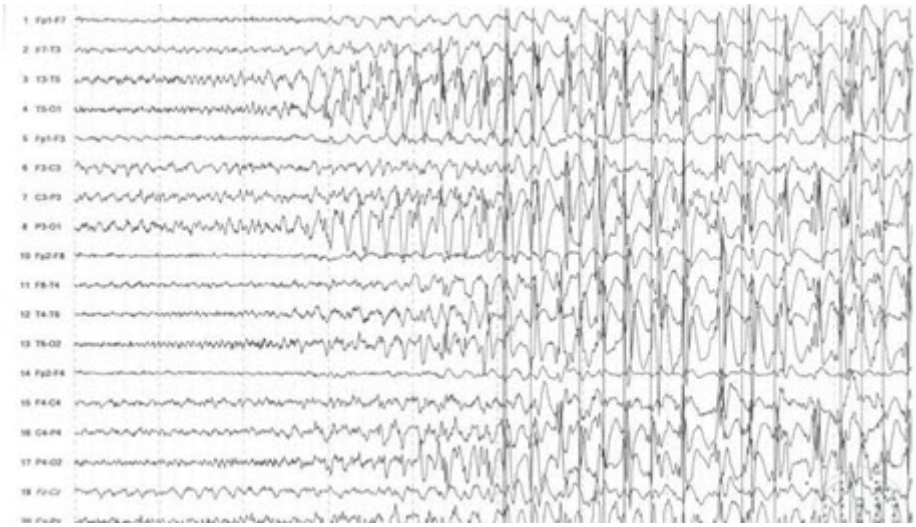
Temperature	37.9°C
Heart rate	156 beats/min
Respiratory rate	20 breaths/min
Blood pressure	110/75 mm Hg

Oxyhemoglobin is 99% on FiO_2 of 0.35 with an end-tidal carbon dioxide of 37 mm Hg.

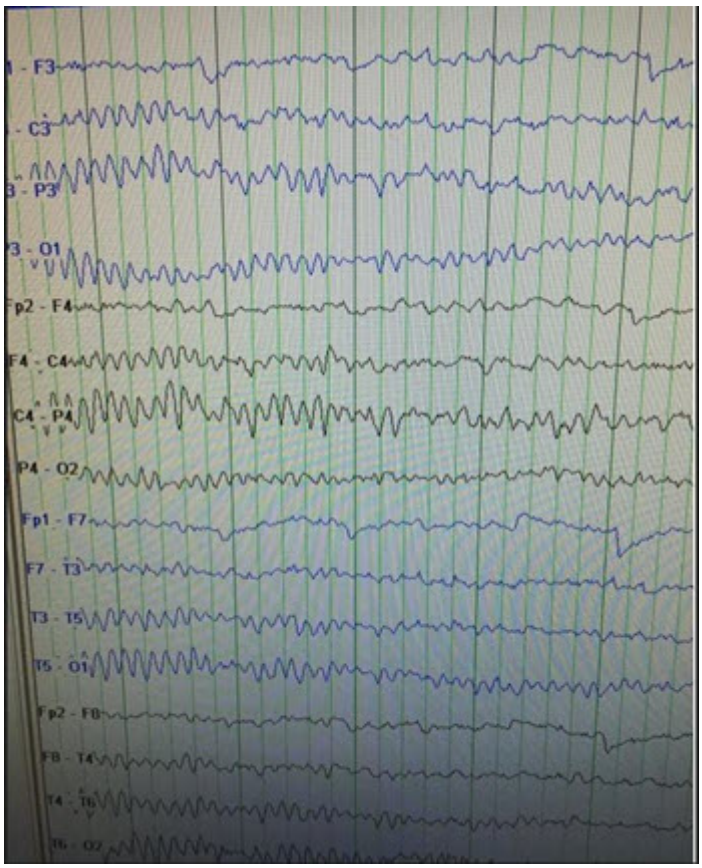
Despite treatment with phenobarbital, phenytoin, levetiracetam, and midazolam, he still exhibits intermittent tachycardia and fluttering of the eyes. His continuous electroencephalography shows frequent seizures. In conjunction with the pediatric neurologist, the intensive care unit specialist has made the decision to initiate pentobarbital infusion to control the seizure.

Of the following, as the dose of this medication is escalated, the GOAL should be to achieve which electroencephalographic tracing?

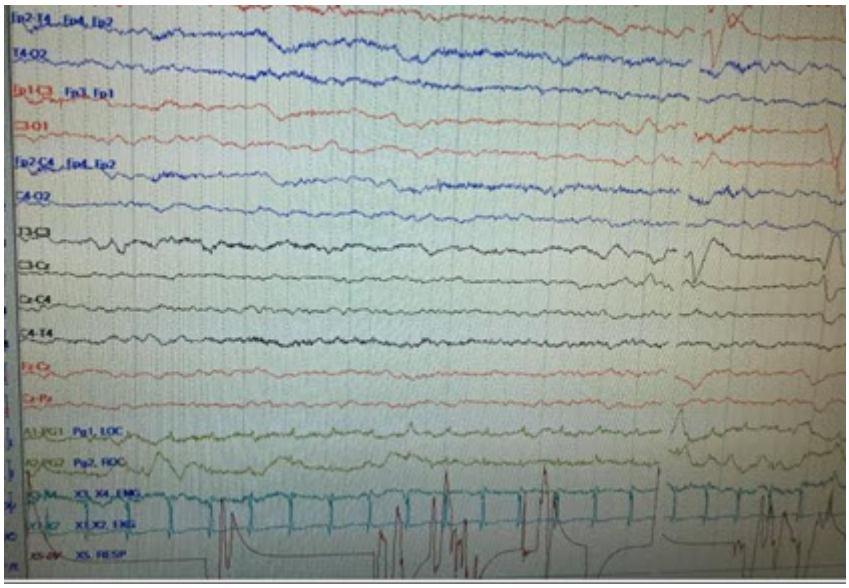
A. Response Choice A.



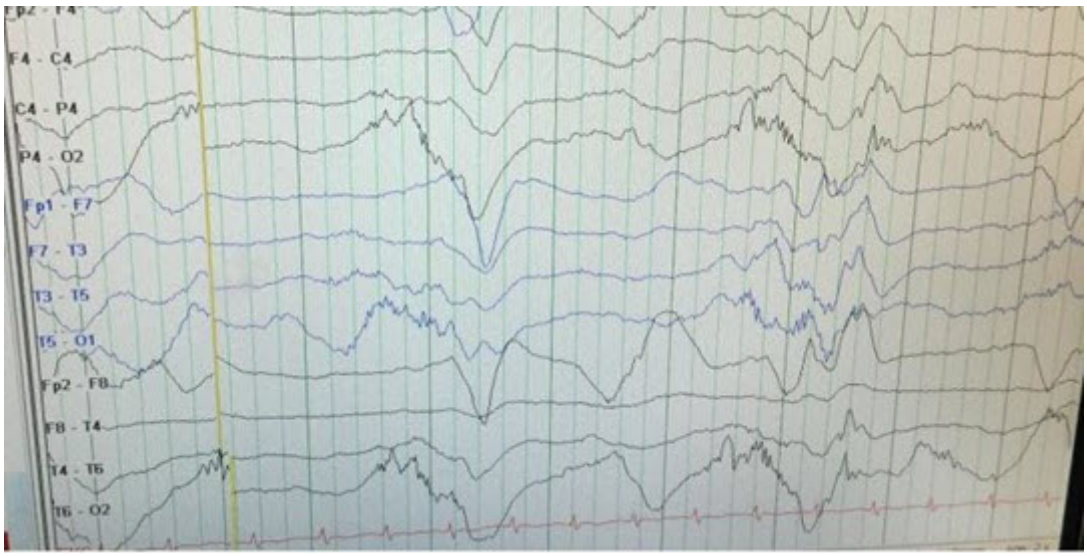
B. Response Choice B.



C. Response Choice C.



D. Response Choice D.



Status epilepticus is the occurrence of continuous seizures for longer than 30 minutes or the occurrence of frequent seizures without gaining consciousness between the separate seizure events. Generalized status epilepticus may be associated with tonic-clonic activities involving various parts of the body in a bilateral fashion, may have other subtle clinical features, or it may be subclinical and associated with only electroencephalographic (EEG) abnormalities. The characteristic EEG findings in status epilepticus include the presence of high-voltage waves that occur in a continuous and rhythmic manner with evolution over time. The seizures may start in one location in the brain with progression to the entire brain in a generalized manner.

The EEG is a recording of the electrical activities from the superficial surface of the cerebral cortex and is reflected as waveforms in the EEG that reflects the activities of groups of neurons that emit electrical activities at the same time. The EEG reflects primarily postsynaptic potentials of large groups of neurons and not individual neurons, using the principle of differential amplifier, in which the difference between the electrical activity detected by 2 electrodes are recorded as waveforms; this is often referred to as a channel. The EEG recording demonstrates waveforms of various shapes, amplitude, and frequency.

The international standard for recording the EEG is referred to as the 10-20 method. In this method, the electrodes are placed on the surface of the scalp from the front to back starting with a frontal area, the central area followed by the parietal area, and then the occipital area of the skull. The electrodes are placed 10% and 20% from each other on the surface of the scalp, thus the term 10-20 system (**Figure 5**). The nasion and anion are the reference points and the total distance is measured. The first electrode is placed on the scalp 10% from the nasion, and the subsequent electrodes are placed 20% (of the total distance measured) from each other. The last electrode is placed 10% from the anion. By convention, the electrodes on the right side of the head are referred to by even numbers and those on the left side with odd numbers. The electrodes also carry the first letter of the region of the skull. Frontal electrodes are labelled with the letter F, temporal electrodes with the letter T, parietal with P, and occipital with O. Thus, the electrodes on the right are: F2, F8, T8, P8, and O2, forming a “montage,” which is a logical, orderly arrangement of EEG derivations or channels created to display activity over the entire head and to provide lateralizing and localizing information. The electrical activities are recorded by referencing one electrode to the next, and this recording produces the various waves of the EEG that are named based on their shape, amplitude, and frequency as follows:

1. Beta waves are low amplitude and occur in the 12-14 Hz range.
2. Alpha waves have slightly higher amplitude and are in the 9-12 Hz range; alpha waves are seen on the EEG during wakefulness and are most prominent when the eyes are closed.
3. Theta waves are larger amplitude waves with 4-7 Hz and are observed primarily in children less than 5 years of age.
4. Delta waves are also larger amplitude (up to 200 μV) waves with 1- 3 Hz and are seen in adolescents and adults only during sleep. Waveforms slower than 1-3 Hz are rarely seen under normal circumstances.

In the awake state, the waveforms are primarily in the beta range (**Figure 3, Response Choice C**), which has a frequency of 12-14 Hz, but can be as high as 30 Hz. As the person becomes more drowsy the waveform frequency decreases, and alpha waves become

increasingly prevalent. During sleep there is also the appearance of the so-called sleep spindles (**Figure 2, Response Choice B**). Sleep spindles are seen primarily in the central electrodes of the electroencephalogram.

There are various clinical applications of EEG in the pediatric intensive care unit including the diagnosis of events such as seizures, response to therapy for intractable seizures such as status epilepticus, management of intracranial hypertension, and as a corroborative test in the diagnosis of brain death. The appearance of spike-and-wave activities on the EEG suggests that the brain is prone to initiating seizures, and therefore these waveforms are referred to as epileptiform discharges.

Initiation and progression of seizures on the EEG appear as rhythmic high-amplitude waveforms that accelerate in frequency in one montage and spread to other surrounding montages and may progress to involve all the montages. Status epilepticus manifests as rhythmic high amplitude waves that may start in one montage and then spread to all other montages on the EEG as seen in **Figure 1 (Response choice A)**.

When treating patients with status epilepticus that is resistant to multiple anticonvulsants, clinicians may resort to continuous administration of barbiturates. In pediatrics, pentobarbital infusion with escalation of therapy to induce suppression of electrical activities of the brain is occasionally required. As the dose of the pentobarbital is escalated, there is generalized slowing of the brain activity as reflected by waveforms in the theta and delta waveforms. Further escalation of the dose leads to periods of electrocerebral silence on the EEG followed by periods of high amplitude slow waveforms. This pattern is referred to as burst-suppression (**Figure 4, Response choice D**).

The goal of therapy with pentobarbital coma for status epilepticus is to induce burst suppression of various intervals and to keep the patient in this range for several hours. Subsequently, the medication is slowly weaned so that the burst suppression disappears from the EEG with the goal of controlling the seizures.

PREP Pearls

- Burst suppression appears on the electroencephalogram as periods of flat line interspersed with episodic high-amplitude slow waves.
- The goal of management of intractable status epilepticus with pentobarbital is to establish burst suppression on the electroencephalogram.
- Once burst suppression is established, it is usually maintained for 12 to 24 hours and then the pentobarbital is slowly weaned to allow the patient to emerge from burst suppression.

ABP Content Specifications(s)/Content Area

- Understand the basic principles of electroencephalography
- Recognize the appearance of a normal electroencephalography
- Recognize some of the unique patterns of abnormal EEGs in children in the pediatric ICU

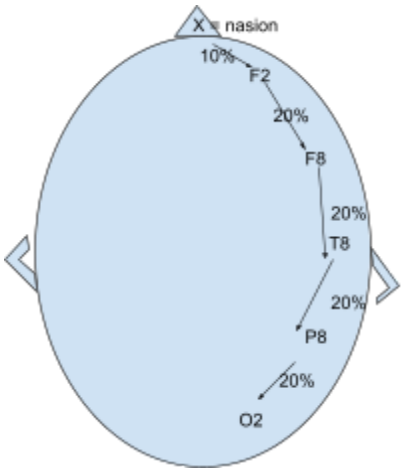
Suggested Readings

Henry JC. Electroencephalography: Basic principles, clinical applications, and related fields, fifth edition. 2006; 67(11). https://doi.org/10.1212/01.wnl.0000243257.85592.9a

Hirsch LJ, Brenner RP. In: Hirsch L, Brenner R, eds. *Atlas of EEG in Critical Care.* Hoboken, NJ: John Wiley and Sons; 2011;30:187-216.

Marcuse LV, Fields MC, Yoo JJ. *Rowan's Primer of EEG.* 2nd edition. Philadelphia, PA: Elsevier; 2016.

Figure 5. A schematic diagram of the 10-20 system for application of EEG leads.



Courtesy of R. Hasan

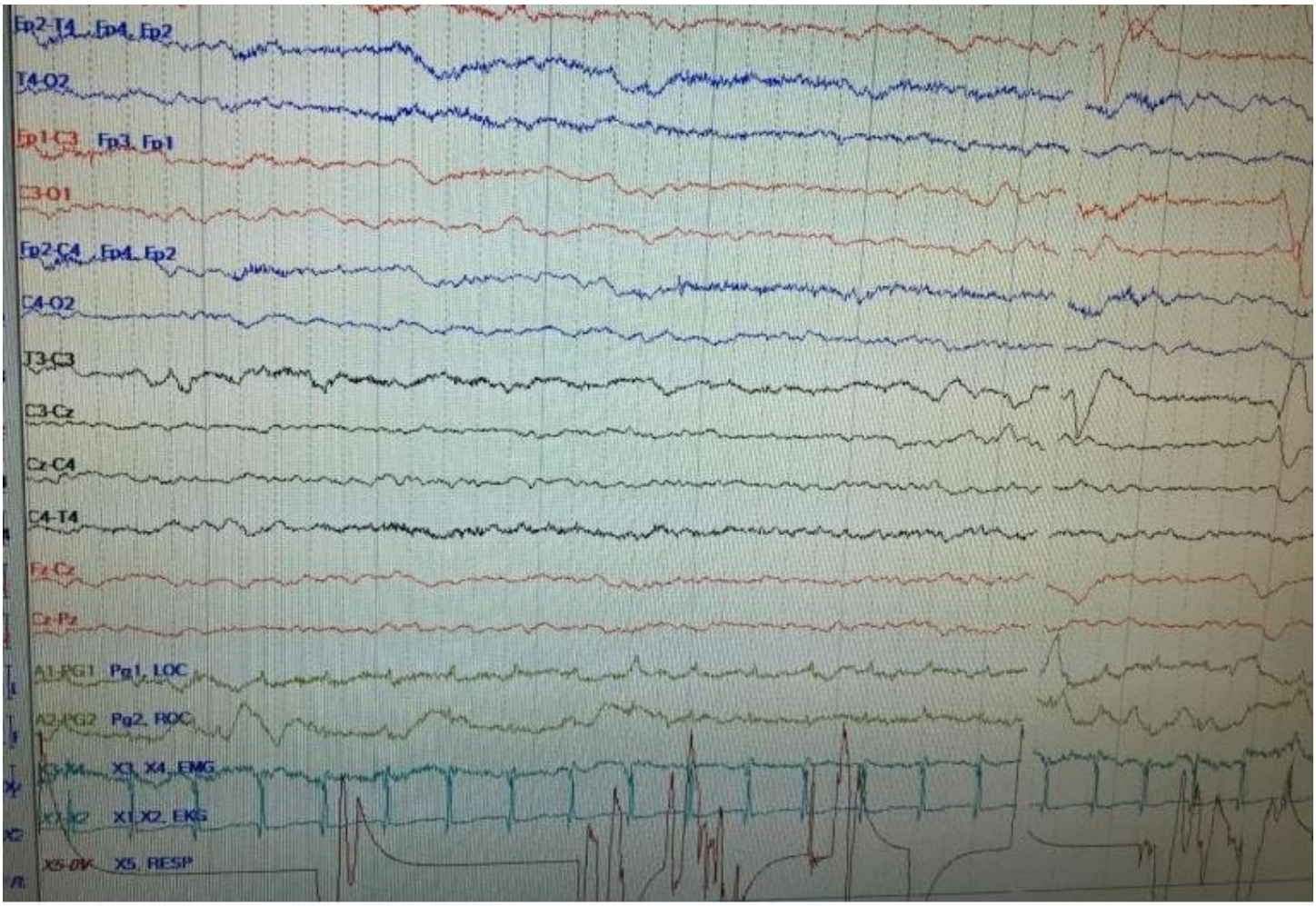


Figure 3: Electroencephalogram of a child in the awake state.

Courtesy of R. Hasan

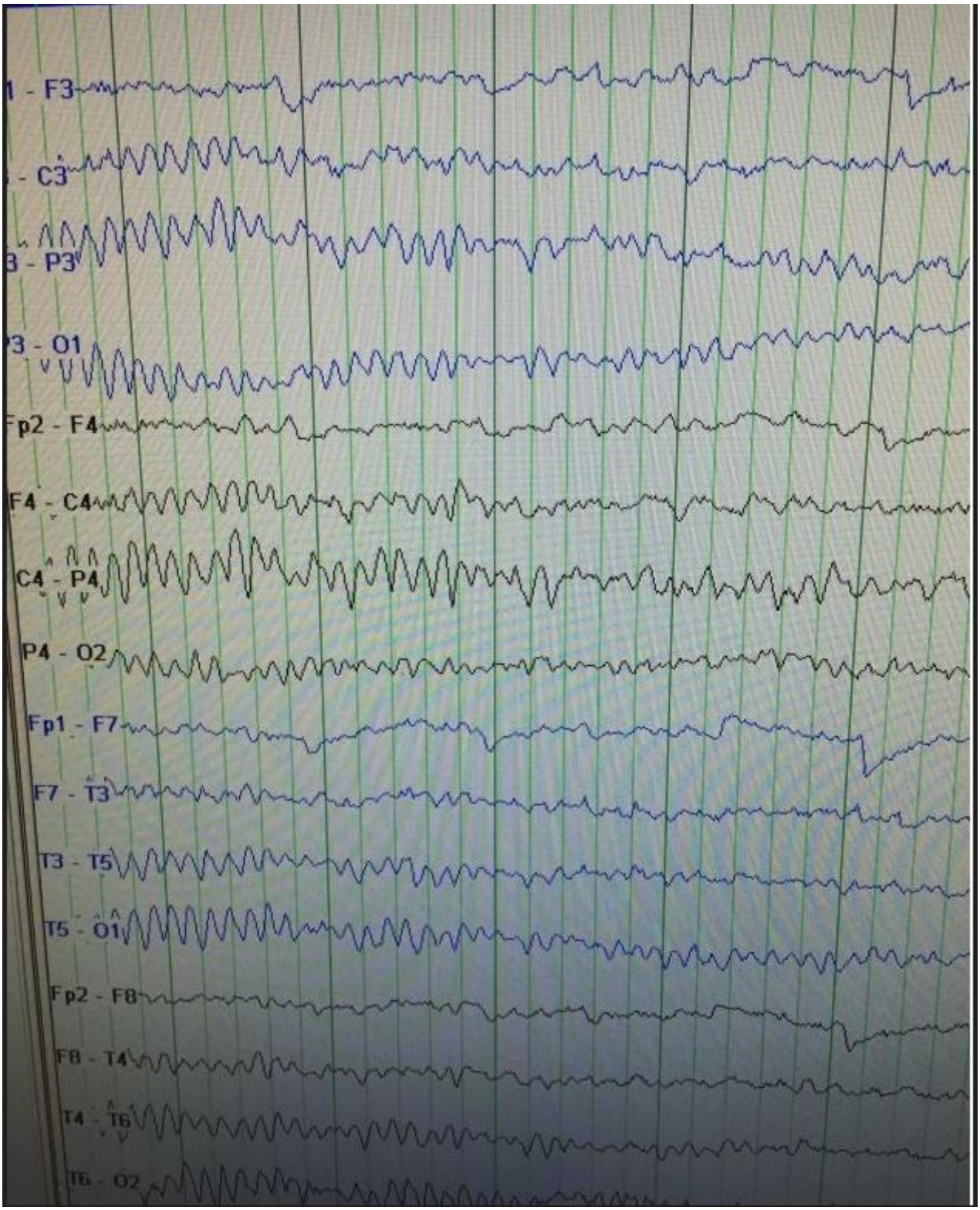


Figure 2: Sleep spindles on electroencephalogram

Courtesy of R. Hasan

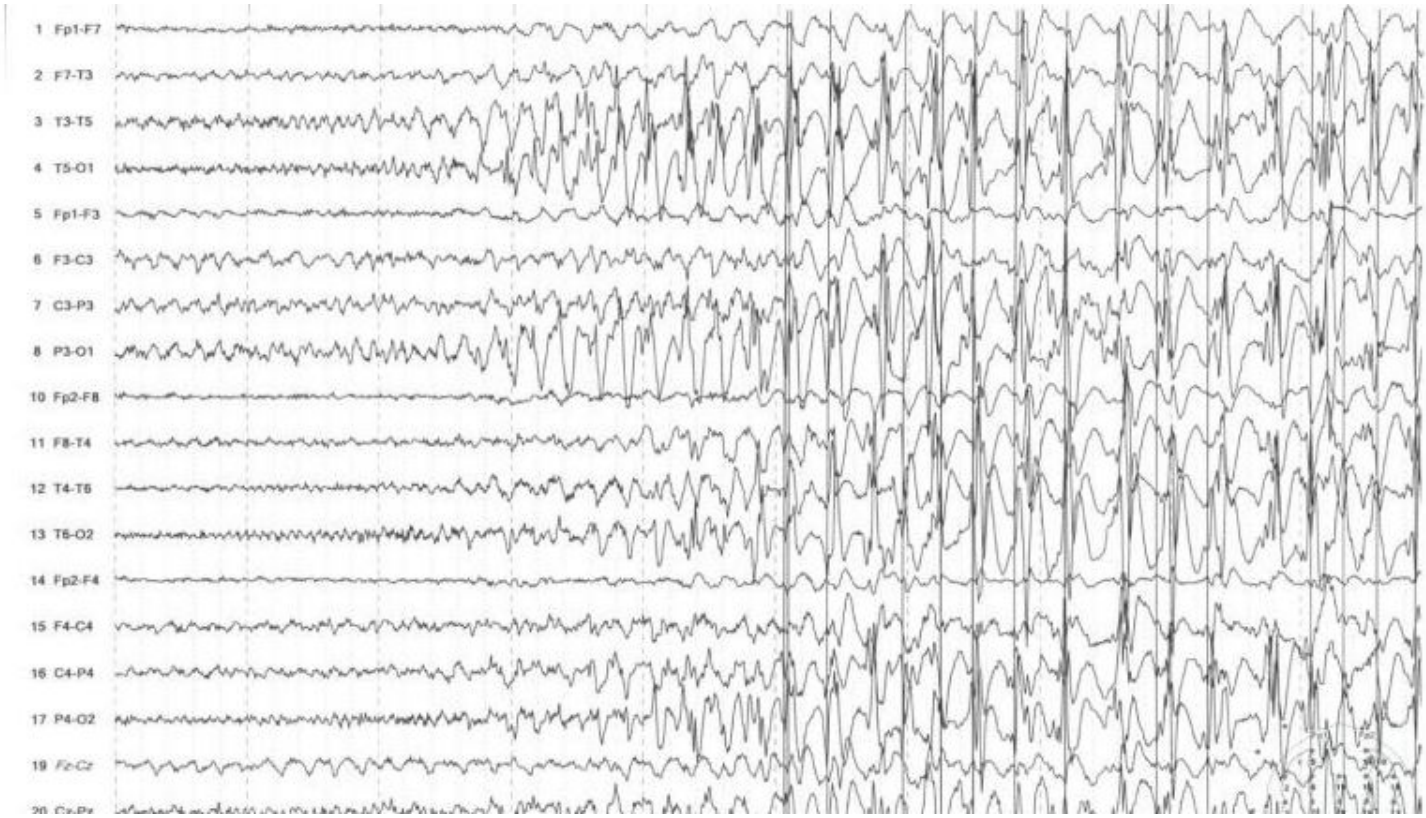


Figure 1: Electroencephalogram of a patient in generalized status epilepticus with diffuse high voltage rapid waves in all montages.

Courtesy of R. Hasan

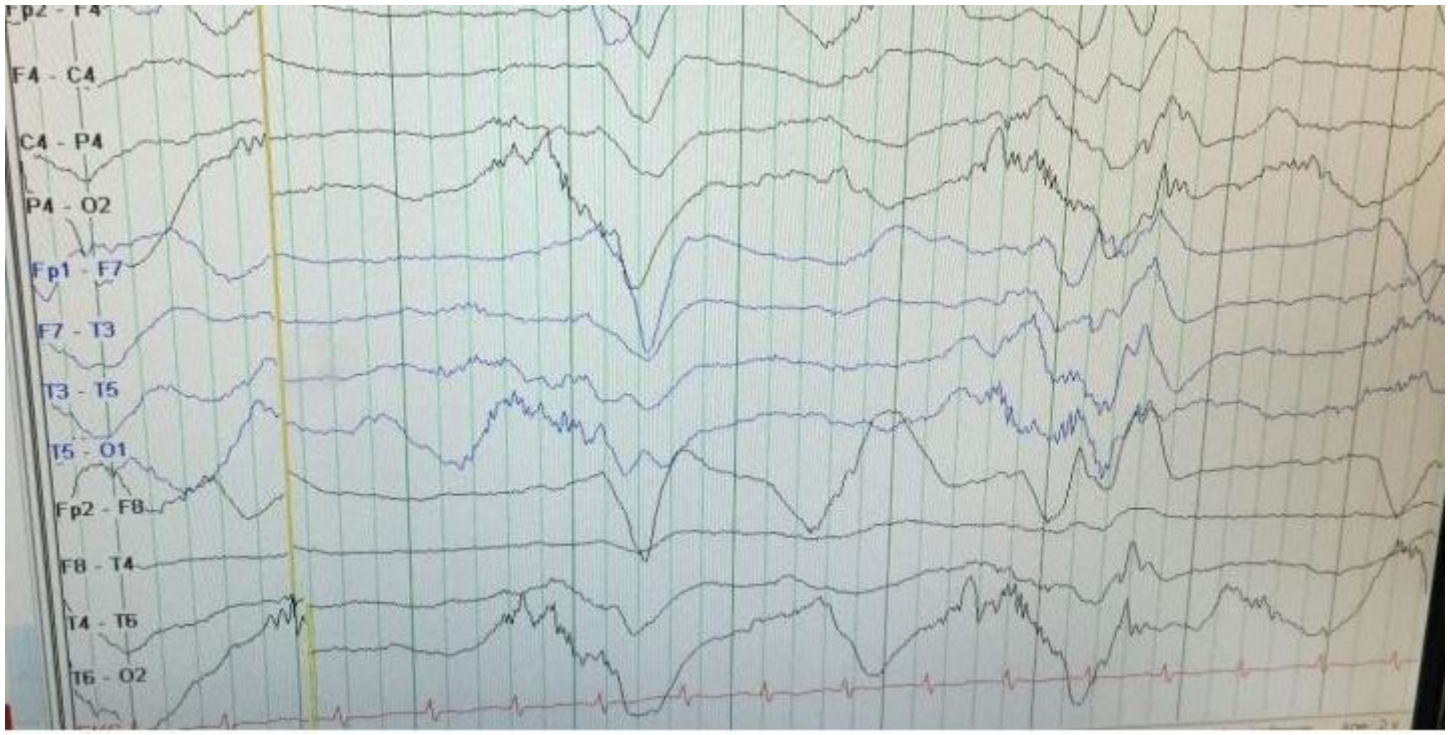


Figure 4: Burst-suppression pattern on electroencephalography.

Courtesy of R. Hasan

February

Question: 3

A 16-year-old male adolescent is admitted to the PICU for unresponsiveness. He had been on a camping trip with friends. He awoke today complaining of a severe headache and visual disturbances, and had 2 bouts of nonbilious emesis. His friends called for paramedics when he became confused and then passed out. Once in the emergency department, computed tomography shows no intracranial hemorrhage or mass lesion and normal ventricular size. His electrocardiography and echocardiography findings are normal and troponin is not elevated. The comprehensive metabolic panel and complete blood cell count are normal. A urine toxicology screen is positive for cocaine. Vital signs on arrival at the PICU are a heart rate of 135 beats/min, blood pressure 180/110 mm Hg, spontaneous respiratory rate 18 breaths/min (ventilator rate of 15), and pulse oximetry saturation 98% in room air. Physical examination reveals no murmur, abdominal bruit, or signs suggestive of hyperthyroidism. The pupils are dilated but reactive to light; funduscopic examination reveals papilledema, but no retinal hemorrhages. An arterial catheter is placed for invasive blood pressure monitoring.

Of the following, the MOST appropriate next therapeutic step is

- **A.** infusion of esmolol
- **B.** infusion of nicardipine
- **C.** infusion of nitroglycerin
- **D.** intermittent hydralazine boluses

The patient in the vignette has ingested cocaine, resulting in a hypertensive emergency (hypertensive encephalopathy). Classic presentations include headache, vomiting, confusion, seizure, altered mental status, and even death.

The term *hypertensive emergency* (previously called *hypertensive crisis* or *malignant hypertension*) is used when there are life-threatening symptoms of an end organ at risk for injury because of severe uncontrolled hypertension. Hypertensive urgency refers to an acute increase in blood pressure without target organ damage. As opposed to adults, most

hypertensive emergencies in pediatrics are due to a secondary cause of hypertension (renovascular or endocrine disease). In adults, most hypertensive emergencies are caused by long-standing unrecognized or untreated primary hypertension. The **Table** shows causes of hypertensive emergencies based on age. Uncontrolled severe hypertension induces vascular remodeling as well as myogenic vascular constriction, resulting in local hypoperfusion. Vasoactive hormones (norepinephrine, endothelin, renin-angiotensin) are then released to maintain normal tone, leading to further increase in peripheral resistance and increase in blood pressure and resulting in a vicious cycle (**Figure**).

In addition, prolonged high blood pressure will lead to endothelial damage, decreased nitric oxide production, fibrinoid necrosis, and ultimately, tissue ischemia. The risk factors for a hypertensive emergency are:

- Renovascular hypertension
- Untreated long-standing hypertension
- Head trauma
- Cocaine ingestion
- Eclampsia
- Coarctation
- Pheochromocytoma

Posterior reversible encephalopathy (PRES) especially in transplant recipients who are taking cyclosporine or tacrolimus and high-dose steroids can manifest as a hypertensive emergency. Acute coronary symptoms such as myocardial infarction and aortic dissection are rare in children.

The immediate goal for the patient in the vignette should be to lower his blood pressure at least 25% in the first 8 hours to prevent a stroke or intracranial hemorrhage. Cerebral autoregulation involves the arteries and arterioles, which constrict or dilate in response to the blood pressure. When systemic blood pressure is severely elevated, as seen in the patient in the vignette, autoregulation is no longer protective, resulting in edema of the vessel wall, hypoperfusion, and endothelial dysfunction, manifesting as papilledema, bleeding, or infarct. The first step in this patient is to start a titratable antihypertensive such as nicardipine. Nicardipine has an excellent safety profile and is widely used in pediatrics. It has replaced nitroprusside as the first-line agent for hypertensive emergencies.

The patient does not have an acute coronary event (which can be seen in cocaine ingestion resulting from coronary vasospasm); hence, nitroglycerin is not indicated. Esmolol is contraindicated in acute cocaine ingestion because of the unopposed α-adrenergic action of cocaine, which can worsen blood pressure. Hydralazine can be used once the acute hypertensive emergency is resolved. It is a short-acting agent that would require repeated bolus doses in this patient.

PREP Pearls

- *Hypertensive* emergency is a term used for severe acute elevation in blood pressure that threatens life or an end organ.
- In a hypertensive emergency, blood pressure should be decreased by 25% in the first 8 hours to prevent hypoperfusion and stroke.
- Titratable intravenous agents like nicardipine are becoming the first-line agents in pediatric hypertensive emergencies.

ABP Content Specifications(s)/Content Area

- Recognize the manifestations and life-threatening complications of acute hypertension

Suggested Readings

Adebayo O, Rogers RL. Hypertensive emergencies in the emergency department. *Emerg Med Clin North Am*. 2015;33(3):539-551. doi: 10.1016/j.emc.2015.04.005

Brathwaite L, Reif M. Hypertensive emergencies: a review of common presentations and treatment options. *Cardiol Clin*. 2019;37(3):275-286. doi: 10.1016/j.ccl.2019.04.003.

Weaver DJ. Hypertension in children and adolescents. *Pediatr Rev.* 2017;38(8):369-382. doi: 10.1542/pir.2016-0106.

Table. Causes of Hypertensive Emergencies in Children

Age	Cause
Infant	Coarctation of the aorta
	Renal parenchymal disease
	Renovascular causes
Young child	Renal parenchymal disease
	Renovascular causes
	Endocrine causes (eg, thyrotoxicosis)
	Coarctation of the aorta
School age	Renal parenchymal disease (eg, hemolytic uremic syndrome, Henoch-Schönlein purpura, acute poststreptococcal glomerulonephritis)
	Renovascular causes
	Endocrine causes
	Coarctation of the aorta
Adolescent	Renal parenchymal disease
	Renovascular causes
	Endocrine causes
	Medication and recreational substances

Reprinted with permission from Weaver DJ. Hypertension in children and adolescents. *Pediatr Rev*. 2017;38(8):379.

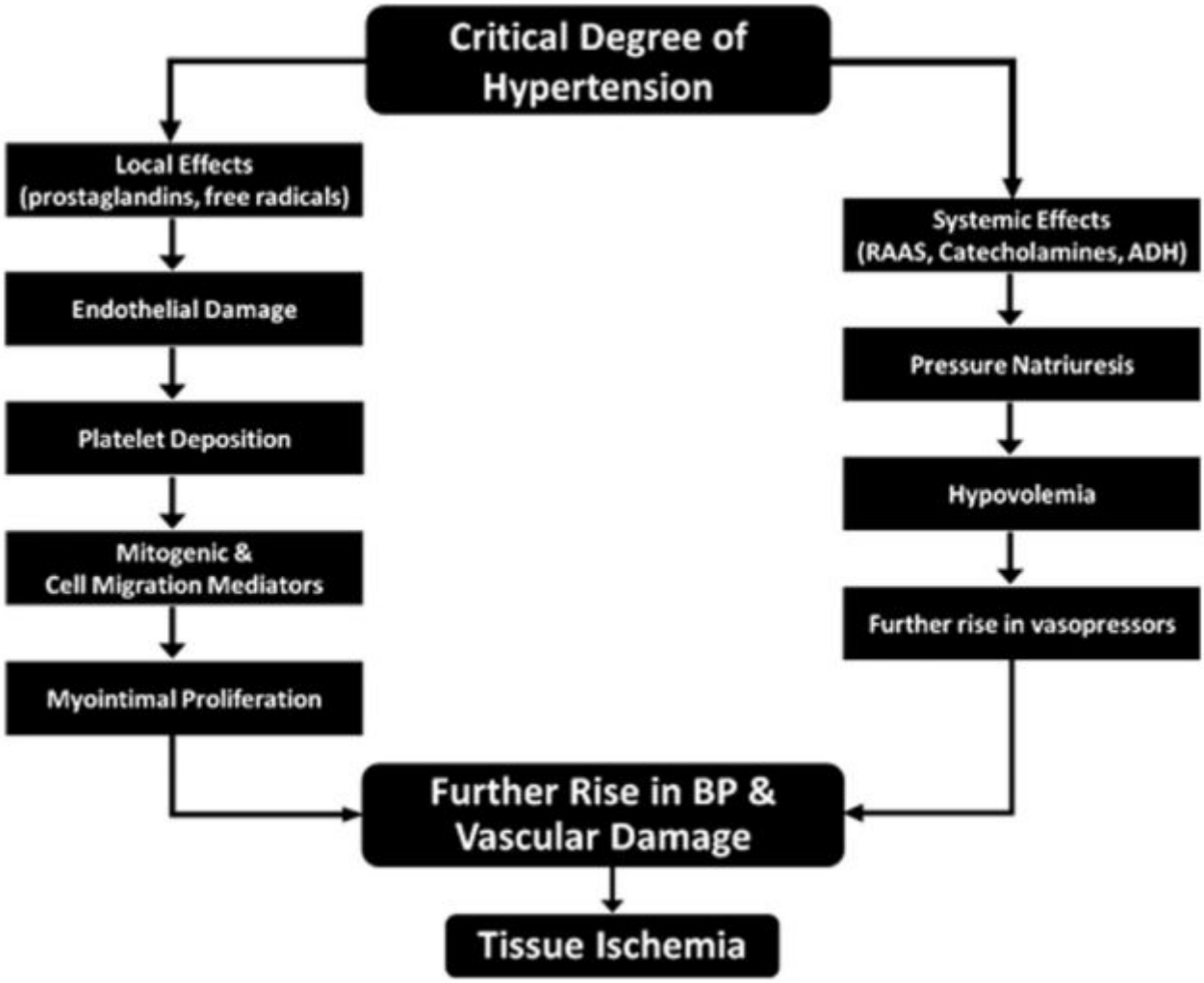


Figure: Pathogenesis of hypertensive emergency.

Reprinted with permission from Brathwaite L, Reif M. Hypertensive Emergencies: A Review of Common Presentations and Treatment Options. *Cardiol Clin*. 2019 Aug;37(3):276.

February

Question: 4

A 16-year-old adolescent boy is admitted to the pediatric intensive care unit after intubation for respiratory failure due to status asthmaticus. In addition to steroids and aggressive bronchodilator therapy, the patient is placed on continuous sedation to facilitate mechanical ventilation. The pediatric resident enters an order for ketamine at 1 mg/kg/h. Later in the shift, the patient becomes increasingly restless and self-extubates. He is eventually re-intubated but suffers some degree of hypoxic-ischemic encephalopathy.

The case is reviewed by the hospital's significant event committee. A comprehensive systems analysis finds the patient had 1:2 nurse staffing in the unit that day, the resident was post-call, and the hospital pumps were programmed to deliver ketamine in μg/kg/min dosing.

Of the following, the factor type that likely had the GREATEST contribution to this adverse medication event is

- **A.** individual
- **B.** information-related
- **C.** organizational
- **D.** work-related

Medication errors are common. Children are at significant risk for medication errors due to weight-based dosing, the frequent need for dilution of stock solutions, and the inability to warn clinicians about possible mistakes in medication administration. Compared to adults, children are twice as likely to suffer harm as a result of medication errors. In the past several decades, adverse drug events have become an increasing focus of research and national quality improvement initiatives.

In one of the first studies of medication errors in an inpatient pediatric population, Kaushal et al noted a medication error rate of 5.7%. The authors found the rate of adverse drug events was most frequent in the neonatal intensive care unit (NICU) at a rate of 91 per 100

admissions. Most medication errors were due to inappropriate dosing, followed by route of administration. Preventable adverse drug events were also higher in the NICU (2.8 per 100 orders vs 0.78 for medical wards and 1.3 for pediatric intensive care units (PICU). A 2010 study focusing on American PICUs showed an adverse drug event rate of almost 5 per 100 patient days. In a recent 5-year retrospective analysis of 16 pediatric hospitals, an adverse event rate of greater than 19 per 1,000 patient days was observed. They noted that teaching hospitals had a significantly higher adverse event rate than non-teaching hospitals (26.2 vs 5.1 per 1,000 patient days). Ten percent of these events were classified as life-threatening, 1.2% as resulting in permanent harm, and 0.7% as contributing to a patient's death. Despite the introduction of electronic medical records (EMR) into many of these facilities, the authors noted no significant changes in adverse event rates over the 5-year study period.

Before the advent of the EMR, orders were believed to be a major source of medication error, primarily due to illegible handwriting and misinterpretation. However, even in a post-EMR era, communication-related factors continue to be a major cause of medication errors. The causes include inappropriate documentation, misinformation during clinical handover, misinterpretation or missed orders, or decimal point/unit of measure errors.

It is estimated that 30 subtasks must be performed in order for a prescription in the PICU to be executed correctly. These tasks can be divided into 6 broad categories:

1. Planning
2. Information entry
3. Information retrieval
4. Selection
5. Calculation
6. Checking

A number of factors have been shown to disrupt this flow of information. These include individual, organizational, task-related, team-related, and work-related (**Table**). For example, a physician may not have the experience or supervision to understand correct dosing (ie, individual and team-related factors), or be tired from being on-call and used to protocols from other units (ie, work-related). In the vignette, the hospital EMR allows a drug to be ordered in mg/kg/h, but the hospital-programmed pumps are set to deliver the same medication in µg/kg/min. At a hospital organizational level, both the ordering and delivery of a medication should be identical. It is likely that most medication errors involve an overlap of multiple factors (ie, "Swiss cheese" model of medical errors).

Sutherland and colleagues examined the roles of hospital personnel and contributing factors in medication errors within the PICU. A survey of pediatric intensivists, staff, and residents showed that cognitive demands were most frequently identified as the main contributing factor to medication errors. Further, distractions and interruptions of workflow and fatigue play a significant role. The authors note a complex interplay of both subtasks and contributing factors, suggesting that a single intervention is unlikely to be effective in decreasing medication errors in the PICU.

Medication error prevention in the PICU is the focus of many quality improvement initiatives. Historically, the emphasis has been on “self” (a personal understanding of what is safe). Recently, this emphasis has shifted to cultural (group expectations of safe behavior) and administrative (increasing the role of rules, policies, and procedures). Standardization of medication infusions has been shown to significantly decrease prescribing errors in the PICU by reducing reliance on team experience or personal recall. Thus, while multiple contributing factors were identified by the significant event analysis in this vignette, it is likely that a hospital-based (organizational) component has the biggest impact in this medication error.

PREP Pearls

- Medication errors are common in the pediatric intensive care unit, with approximately 12% classified as life threatening or causing harm or death.
- In a pediatric intensive care unit, approximately 30 subtasks must be performed in order for a prescription to be executed correctly.
- Cognitive demands, fatigue and work interruptions are often cited as causes for prescribing errors in the pediatric intensive care unit.

ABP Content Specifications(s)/Content Area

- Hospital-associated medication errors

Suggested Readings

Agarwal S, Classen R, Larsen G et al. Prevalence of adverse events in pediatric intensive care units in the United States. *Pediatr Crit Care Med*. 2010; 11(5): 568-78. doi: 10.1097/PCC.0b013e3181d8e405.

Hermanspann T, van der Linden E, Schoberer M et al. Evaluation to improve the quality of medication preparation and administration in pediatric and adult intensive car units. *Drug, Healthcare and Patient Safety*. 2019; 11: 11-18. doi: 10.2147/DHPS.S184479.

Kaushal R, Bates DW, Landrigan C et al. Medication errors and adverse drug events in pediatric inpatients. *JAMA*. 2001; 285: 2114-20. doi: 10.1001/jama.285.16.2114.

Stockwell DC, Landrigan CP, Toomey SL et al. Adverse events in hospitalized pediatric patients. *Pediatrics*. 2018; 142(2): e20173360. doi: https://doi.org/10.1542/peds.2017-3360.

Sutherland A, Ashcroft DM and Phipps DL. Exploring the human factors of prescribing errors in the paediatric intensive care unit. *Arch Dis Child*. 2019; 104: 588-95.

Table. Factors Associated with Medication Errors.

Factors	Vulnerability	Hospital-based Examples
Organizational	• Divergent systems • Conflicting priorities	Bedside medication pumps programmed differently then EMR order
Work	• Distraction • Patient load • Repetition	Nurse asked to enter complex medication order while providing patient care
Task	• Complexity • Ambiguous information • Reliance on experience	Inability to located medication administration guidelines on hospital intranet
Team	• Support • Recognition of deficiency • Communication	Lack of medication information handover at shift change
Individual	• Inexperience • Fund of knowledge • Lack of skill	Non-pediatric residents writing weight-based medication dosing

Courtesy of M.Rowin

February

Question: 5

A 10-year-old boy is admitted to the pediatric intensive care unit for respiratory distress from a left lung empyema and small pneumothorax. He requires 2 L/min oxygen via nasal cannula to maintain oxygen saturation greater than 90%. The physical examination reveals mild tachypnea and decreased breath sounds on the left side. The patient's blood pressure, heart rate, and the remainder of physical examination findings are normal. Because of persistent fever, a thoracostomy tube is inserted for drainage of the empyema. The attending physician supervising the procedural sedation for the chest tube placement requests the respiratory therapist to have end-tidal monitoring during the sedation. Fentanyl and propofol are used to provide deep sedation. A medical student is intrigued by the end-tidal waveform and the end-tidal partial pressure of carbon dioxide ($PETCO_2$) reading (currently 40). She asks about condition(s) that could lead to increases in the $PETCO_2$ of this patient.

Of the following, the condition MOST likely to increase $PETCO_2$ rapidly in this patient is

- **A.** addition of dexmedetomidine
- **B.** bolus of sodium bicarbonate
- **C.** cardiac arrest
- **D.** tension pneumothorax

The patient in the vignette has an empyema with a small pneumothorax requiring chest tube placement. The American Academy of Pediatrics 2019 sedation guidelines have capnography as a "required" item for monitoring during deep procedural sedation. Various capnography devices (such as nasal cannulae) are available, which allow for simultaneous delivery of oxygen and the trending of end-tidal carbon dioxide ($ETCO_2$). The presence of a good waveform suggests that air exchange (ie, ventilation and oxygenation) is occurring and the patient has a cardiac output.

A typical $ETCO_2$ waveform is shown in the **Figure**. As seen, there are 4 phases to a normal capnogram.

- Phase I: Ascending phase. The CO_2 concentration is zero (dead space gas with minimal CO_2 is exhaled out first).
- Phase II: Alveolar plateau. The rapid increase in CO_2 from alveolar gas.
- Phase III: Inspiratory limb. Mostly a constant steady detection of CO_2 from alveolar gas. The highest point is the $ETCO_2$.
- Phase IV: Dead space ventilation. Exhalation starts, and fresh gas with no CO_2 enters the airway.

The waveform's width corresponds with expiration time, and the height (amplitude) is determined by $ETCO_2$ concentration. The $ETCO_2$ waveform, as well as the $PETCO_2$, can provide important information during procedural sedation. For example, a sudden loss of waveform suggests apnea or complete airway obstruction (ie, laryngospasm) much before a change in pulse oximetry (lag of pulse oximetry). Studies have shown the use of capnography decreases hypoventilation episodes and hypoxia during procedural sedation in the emergency department. Usually, the blood $PaCO_2$ is slightly higher than $PETCO_2$ and this gradient (Pa-PET) CO_2 is lower than 5 mm Hg. An increase in this gradient suggests increasing dead space ventilation. While a single $PETCO_2$ number may not be the most useful during procedural sedation, a trend indeed provides valuable information.

Sedation providers must be aware of 2 types of drug-induced hypoventilation patterns seen during procedural sedation.

1. Bradypneic hypoventilation (type I): Here, the tidal volume does not change, but the respiratory rate does. Both the $PaCO_2$ and the $PETCO_2$ increase. This pattern is commonly seen with opioids.
2. Hypopneic hypoventilation (type II): The tidal volume is low with minimal change in the respiratory rate. It is characterized by a normal decrease in $PETCO_2$ and increased $PaCO_2$.

If the patient in the vignette has a sudden increase in the pneumothorax during the procedure, resulting in a tension pneumothorax physiology, the $PETCO_2$ will decrease. The decrease in $PETCO_2$ is caused by obstruction of pulmonary blood flow to the heart (ie, reduction of cardiac output). Similarly, if the patient experiences a cardiac arrest, the patient will not have a cardiac output, bringing CO_2-rich blood to the lungs. Hence, the $PETCO_2$ will decrease. Waveform capnography allows providers to monitor cardiopulmonary resuscitation (CPR) quality, optimize chest compressions, and detect return of spontaneous circulation (ROSC) during chest compressions, and it is becoming

standard of care during CPR. An increase in metabolic rate (eg, malignant hyperthermia) will increase CO_2 production and increase $PETCO_2$. The patient in the vignette is sedated using propofol and fentanyl, and addition of dexmedetomidine should not increase the $PETCO_2$.

Of the options listed, only the intravenous administration of sodium bicarbonate, which forms excess CO_2, will result in an immediate increase in $ETCO_2$ tension.

PREP Pearls

- Capnography is an important tool to monitor patients undergoing procedural sedation.
- End-tidal carbon dioxide monitoring waveform suggests a presence to a cardiac output. Loss of end-tidal waveform should alert providers to check pulses in a patient who has no airway obstruction or apnea.
- End-tidal capnography can detect apnea or complete airway obstruction earlier than a change in pulse oximetry can during procedural sedation.

ABP Content Specifications(s)/Content Area

- Interpret capnography waveforms during procedural sedation

Suggested Readings

Kodali BS. Capnography. www.capnography.com

Krauss B, Hess DR. Capnography for procedural sedation and analgesia in the emergency department. *Ann Emerg Med*. 2007;50(2):172-181. doi:10.1016/j.annemergmed.2006.10.016

Long B, Koyfman A, Vivirito MA. Capnography in the emergency department: a review of uses, waveforms, and limitations. *J Emerg Med*. 2017;53(6):829-842. doi:10.1016/j.jemermed.2017.08.026

Sandroni C, De Santis P, D'Arrigo S. Capnography during cardiac arrest. *Resuscitation*. 2018;132:73-77. doi:10.1016/j.resuscitation.2018.08.018

February

✓ **CONGRATULATIONS**

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PREP Pearls

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ABP Content Specifications(s)/Content Area

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Sandroni C, De Santis P, D'Arrigo S. Capnography during cardiac arrest. *Resuscitation*. 2018;132:73-77. doi:10.1016/j.resuscitation.2018.08.018

February

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 6

A 2-year-old boy is seen at the emergency department for bloody emesis at home after he ingested unknown amounts of medications from the family medicine cabinet. On arrival, he appears pale, diaphoretic, confused, and agitated.

Laboratory data are shown:

Laboratory Test	Result
Serum glucose	290 mg/dL (16 mmol/L)
Serum bicarbonate	12 mEq/L (12 mmol/L)
Anion gap	21 mEq/L (21 mmol/L)

The patient is admitted to the pediatric intensive care unit and develops a generalized tonic-clonic seizure. His parents are asked about the medications he may have ingested. His older brother has attention-deficit/hyperactivity disorder and seizures for which he takes amphetamine and phenobarbital. His grandmother has chronic arthritis in her knee for which she applies a salicylate-containing oil, and she also takes amitriptyline for depression.

Vital signs are shown:

Temperature	Afebrile
Blood pressure	100/60 mm Hg

Heart rate	142 beats/min
Respiratory rate	40 breaths/min
Oxygen saturation	100% in room air

He is not in any respiratory distress, and his physical examination findings are normal.

Of the following, the BEST intervention to increase renal excretion of the drug most likely to be responsible for the patient's symptoms is

- **A.** albumin infusion
- **B.** intralipid infusion
- **C.** urine acidification
- **D.** urine alkalinization

The patient in the vignette is exhibiting several signs and symptoms (confusion, agitation, tachypnea, hyperglycemia, anion gap acidosis, seizures) consistent with severe salicylate poisoning. Topical medications may contain high concentrations of salicylate. Oil of wintergreen contains 98% methyl salicylate and is extremely dangerous for young children if even a small amount is ingested. Five mL of oil of wintergreen is approximately equal to 7,000 mg of salicylate, or twenty-two 325 mg aspirin pills and can result in life-threatening toxicity. Ingestion of greater than 300 mg/kg salicylate can be fatal. Increasing urinary excretion of salicylate compounds through alkalinization is an important component of treatment for salicylate poisoning. Though salicylates are highly protein bound, additional albumin infusion does not play a role in therapy. Other targeted therapy includes administration of activated charcoal, and hemodialysis if severe electrolyte or acid base abnormalities persist despite forced alkaline diuresis.

The metabolism and excretion pathways for the majority of the drugs involve the liver, kidney, or both organs. Drug excretion by the kidney is affected by glomerular filtration, active tubular secretion, and passive tubular absorption. Urine and blood pH, as well as the size and protein binding of the drug molecule affect whether the drug is excreted in the urine or remains in circulation. Glomerular filtration passively removes small molecules

(generally less than 66 kDA, the size of albumin). Drugs that are highly protein bound are not filtered; however, small molecule drugs that are not protein bound can be cleared rapidly. Unchanged drugs or their metabolites may be excreted into the urine if they are water soluble. Polar compounds, which account for most drug metabolites, cannot diffuse back into the circulation and are excreted unless a specific transport mechanism exists for their reabsorption (eg, as for glucose, B vitamins). Urine pH, which varies from 4.5-8.0, may markedly affect drug reabsorption and excretion because urine pH determines the ionization state of a weak acid or base. The pH affects ion trapping and passive resorption of the drug. Lipid soluble drugs are not readily removed by the kidneys and require hepatic metabolism (eg, phase I and phase II biotransformation reactions) to increase their water solubility.

Urinary pH can be manipulated to decrease tubular reabsorption of weak non-polar acids and bases, thereby increasing their excretion. The ionized form of the drug is not reabsorbed well from the glomerular ultrafiltrate and gets excreted. An increase in the ionized form of the drug decreases reabsorption and enhances renal elimination. Weakly acidic drugs such as phenobarbital or salicylates are unlikely to give up hydrogen ions if the urine pH is low. The drug remains relatively nonpolar (uncharged) and will get mostly reabsorbed through the nonpolar tubular membranes. Achieving a higher urine pH through alkalinization enables a greater proportion of a weakly acidic drug to remain in the ionized form, effectively trapping it in the tubular space. This property can be used to enhance the excretion of weakly acidic drugs such as salicylates and phenobarbital. Similarly, acidifying urine can enhance excretion of basic drugs and can be achieved by administering arginine hydrochloride or ammonium chloride. However, urinary acidification is not used clinically for poisoning with weak bases such as amphetamines, quinine, quinidine, and procainamide because potential complications include myoglobinuria, acute renal failure, and hyperkalemia. The renal elimination of weak acids is increased in alkaline urine if the ionization constant (pKa) of the drug lies between 3.0-6.5; for weak bases, elimination is increased in acid urine if the pKa of the drug lies between 7.5-10.5.

Because the ionization constant (pKa) is a logarithmic function, a small change in urine pH has a disproportionately larger effect on salicylate clearance. The elimination of salicylates (pKa of 3.5) increases four-fold with each unit rise in urine pH. In patients with intact renal function, urine alkalinization (goal urinary pH 7.5-8.5) can be achieved by adding sodium bicarbonate to intravenous fluids. Urine output should be about 2 to 5 mL/kg/h. Usually an infusion at 1.5 × maintenance fluid rate, and about 0.25−0.5 mEq/kg/h of sodium bicarbonate is needed to achieve forced alkaline diuresis. Urine alkalinization does present certain risks, including hypernatremia, hypokalemia, and fluid overload. Though acetazolamide also alkalinizes the urine, in salicylate poisoning it should be avoided, as it worsens systemic acidosis, which can enhance salicylate toxicity. It is crucial to provide

potassium in the intravenous fluids to avoid hypokalemia, and to treat hypokalemia if it occurs. A low serum potassium promotes secretion of hydrogen ions (instead of potassium secretion), thereby counteracting attempts at alkalinization.

PREP Pearls

- Drug excretion by the kidney is affected by glomerular filtration, active tubular secretion, and passive tubular absorption.
- A drug molecule's size, protein binding, polarity, and lipid solubility affect its renal excretion.
- Urine pH determines the drug's ionization state, making forced alkaline diuresis an effective strategy to enhance excretion of weakly acidic drugs such as salicylates.
- Increase in pH by 1 increases salicylate elimination 4-fold.

ABP Content Specifications(s)/Content Area

- Identify the factors that alter renal drug excretion

Suggested Readings

Chan TYK, The risk of severe salicylate poisoning following the ingestion of topical medicaments or aspirin. *Postgrad Med J.* 1996; 72:109-112. doi:10.1136/pgmj.72.844.109

Chyka PA, Erdman AR, Christianson G, et al. Salicylate poisoning: An evidence-based consensus guideline for out-of-hospital management. *Clinical Toxicology.* 2007;45:95-131. doi: 10.1080/15563650600907140

Nares MA, Cantwell GP and Weisman RS. Poisoning. In: Nichols DG and Shaffner DH, eds. *Rogers Textbook of Pediatric Intensive Care*. 5th ed. Wolters Kluwer; 2016:476-498.

Vale JA. Reviews in medicine: clinical toxicology. *Postgrad Med J* 1993;69:19-32. doi:10.1136/pgmj.69.807.19

March

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 1

A 15-year-old adolescent boy sustained a head injury when he was ejected from a vehicle that collided with a pole while the vehicle was traveling at 65 miles per hour. He was unconscious at the scene, and intubation and mechanical ventilation were initiated. A computed tomographic scan of the head is obtained (**Figure 1**).

Of the following, the MOST likely diagnosis is

- **A.** epidural hematoma
- **B.** intraventricular hematoma
- **C.** subarachnoid hematoma
- **D.** subdural hematoma

Trauma is the leading cause of death in children and young adults, and head injury makes the highest contribution to mortality in patients with trauma. In clinical practice, most cases of head injury involve a combination of multiple forces that the skull and brain sustain. As a result, there are usually more than one type of intracranial hemorrhage in patients who have sustained severe head injury. The types of intracranial hemorrhages that can be seen in the setting of head injury include epidural hematoma, subdural hematoma, intraparenchymal hemorrhage, and intraventricular hemorrhage.

Epidural hematoma is blood accumulation between the skull and the dura mater. The dura is adherent to the inner surface of the skull, particularly close to suture lines. Epidural hematoma generally can be considered a vascular injury rather than injury to brain parenchyma. Damage to an artery results in bleeding that separates the dura from its

adherence to the skull and expands the space between the inner aspect of the skull and the dura, displacing the dura and the adjacent brain tissue. The expansion of the hematoma is usually limited by the suture line. The epidural blood accumulation forms a biconvex or lenslike shape that is characteristic of epidural bleeding (**Figure 2**).

The classical clinical history associated with epidural hematoma is trauma to the head with brief initial alteration in mental status such that it may be perceived as a minor head injury. This trauma is followed by what is called a “lucid interval,” during which the patient appears normal, with subsequent neurological deterioration within 12 to 24 hours after the initial injury. This lucid interval has been reported to occur in up to 60% of adult patients but in a substantially lower proportion of children. The vast majority of infants do not exhibit alterations in mental status immediately after the injury. As the hematoma expands, the patient will progress from having headache and nuchal rigidity to ipsilateral pupillary dilation and contralateral hemiparesis and then progression into coma. If an epidural hematoma is not recognized and promptly treated, rapid deterioration with herniation and death may ensue. The vast majority of epidural hematomas are treated with surgical drainage of the hematoma with minimal operative complications.

Subdural hematoma is a collection of blood on the surface of the brain underneath the dura. Acute subdural hematomas are almost always associated with some form of trauma, and significant force is necessary to produce a subdural hematoma. With subdural hematomas, there are often underlying cortical injuries, and there may be associated injuries to bridging veins and cortical arteries.

The clinical manifestations of acute subdural hematoma are neurological deterioration without a lucid interval after the injury; the clinical features range from seizures, focal neurological signs, and clinical features of increased intracranial pressure. Initial management should be directed at controlling seizures and increased intracranial pressure. Neurosurgical drainage may be necessary for larger subdural hematomas that produce mass effects.

Intracerebral hematomas are blood clots within the substance of the brain. They are infrequent in children in association with trauma but tend to have a poor prognosis because of the associated injuries to the underlying brain tissue. Sometimes, intracerebral hematomas are located in silent areas of the brain and produce minimal or no symptoms. The primary management of intracerebral hematoma is control of intracranial pressure. Surgical evacuation is indicated for lesions that are superficial or in silent areas of the brain, as well as in cases in which medical management to control intracranial pressure has failed.

Most intraventricular hemorrhages resolve spontaneously; however, when there is significant bleeding, obstructive hydrocephalus can result at the level of the foramen of Monro or at the level of the aqueduct of Sylvius. Acutely, these issues may require ventricular drainage, and a ventriculoperitoneal shunt may be required on a long-term basis.

PREP Pearls

- Epidural hematomas usually do not cross suture lines.
- Epidural hematomas usually need surgical drainage
- Most intraventricular hemorrhages resolve spontaneously.

ABP Content Specifications(s)/Content Area

- Understand the pathogenesis and pathophysiology of traumatic intracranial hemorrhage
- Assess the severity of neurologic dysfunction after head trauma

Suggested Readings

Champagne P-O, He KX, Mercier C, Weil AG, Crevier L. Conservative management of large traumatic supratentorial epidural hematoma in the pediatric population. *Pediatr Neurosurg*. 2017;52(3):168-172. doi:10.1159/000455925

Gutowski P, Meier U, Rohde V, Lemcke J, von der Brelie C. Clinical outcome of epidural hematoma treated surgically in the era of modern resuscitation and trauma care. *World Neurosurg.* 2018;118:e166-e174. doi:10.1016/j.wneu.2018.06.147

Ozturk S, Ozturk Y, Ocal O. The first case of Kernohan-Woltman notch phenomenon caused by epidural hematoma in a pediatric patient. *Pediatr Neurosurg.* 2017;52(3):181-184. doi:10.1159/000474945

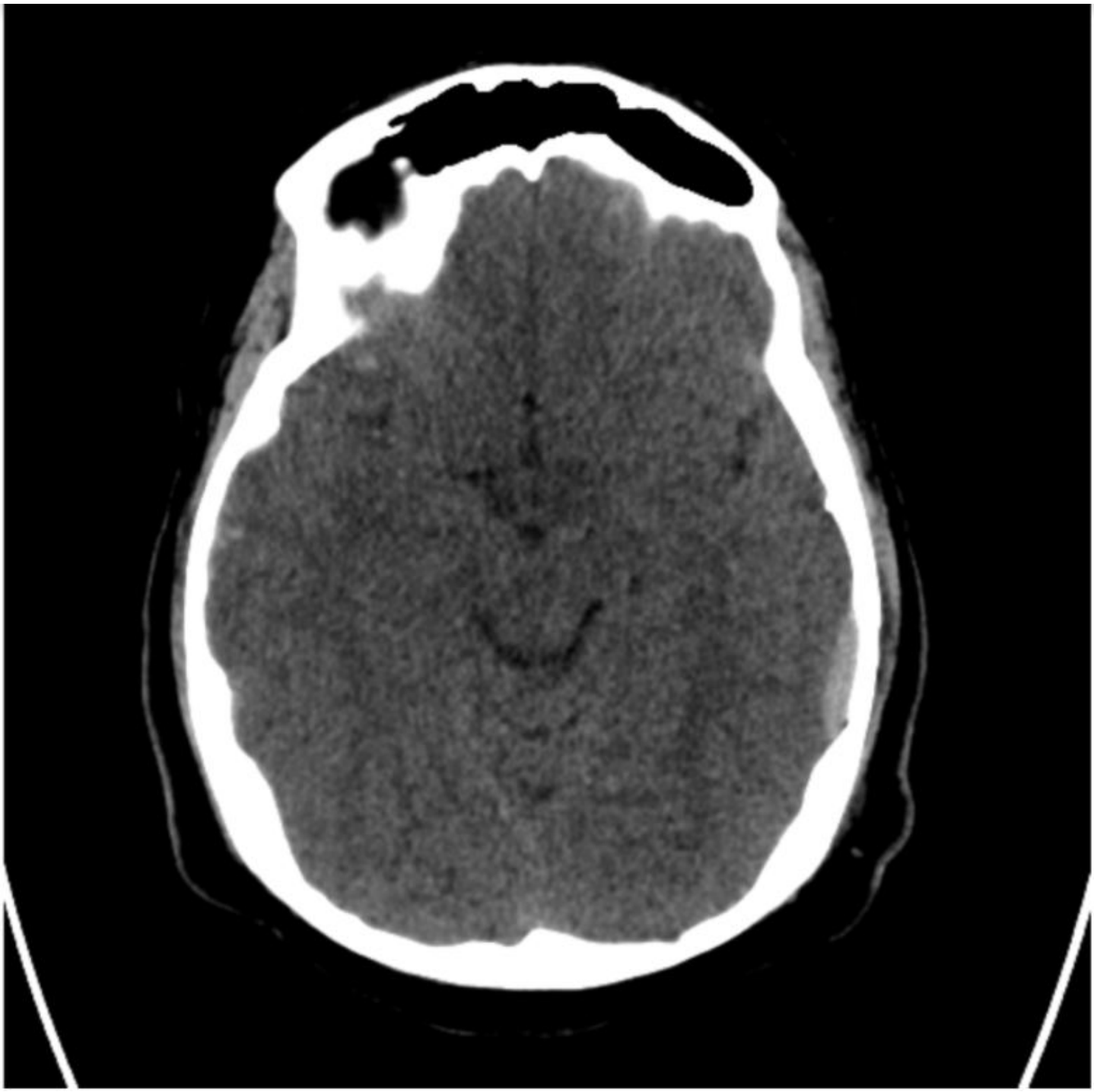

Figure 1:
Computed tomographic scan of the patient's head.

Courtesy of R. Hasan

March

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 2

A 10-year-old boy is admitted to the pediatric intensive care unit with lethargy, shortness of breath, and profound weakness. He has been able to stand and walk only with assistance for the past 3 years. His physical examination shows an S3 gallop, rales in the pulmonary bases, hepatomegaly, and calf hypertrophy. His hip and shoulder muscles do not appear to be atrophied. Laboratory analysis shows significant elevation of B-type natriuretic peptide and creatine kinase levels. An echocardiogram is obtained (**Video**).

Of the following, the abnormality that is MOST likely to be associated with this disease is

- **A.** absent dystrophin expression
- **B.** altered sarcomere Z-band formation
- **C.** excessive cytosine, thymine, and guanine repeats
- **D.** increased mitochondrial iron deposition

Cardiomyopathies and conduction defects can be associated with genetic muscle disorders. Cardiac failure can be one of the early clinical manifestations. Cardiomyopathy phenotypes that can occur with hereditary muscle disorders include dilated, hypertrophic, and restrictive. The echocardiogram in this vignette demonstrates a classic dilated cardiomyopathy.

The most common genetic muscle disorders cause dilated and hypokinetic cardiomyopathies. These include Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), X-linked dilated cardiomyopathy, limb girdle muscular dystrophy, and Emery-Dreifuss muscular dystrophy. Duchenne muscular dystrophy, BMD, and X-linked

dilated cardiomyopathy are caused by altered dystrophin expression and are therefore commonly classified as dystrophinopathies. The dystrophin protein acts as a connection between the inner aspect of the muscle cell membrane and the intracellular actin filaments. Lack or reduction of dystrophin increases membrane fragility and muscle fiber injury with contractions. Thus, elevation in levels of serum creatine kinase, an intracellular enzyme in muscle cells, is universally noted in these disorders. Additionally, abnormal dystrophin may act as a binding site for viruses, thus increasing the risk of viral myocarditis in muscular dystrophy patients.

Duchenne muscular dystrophy is the most common genetic muscle disorder in children. It is an X-linked recessive disease characterized by proximal limb and pelvic weakness, calf hypertrophy, and progressive cardiomyopathy. It has a prevalence of 6 per 100,000 males. In DMD there is complete absence of dystrophin in the cardiac and skeletal myocyte sarcolemma. Dilated cardiomyopathy can begin in the first decade of life. Approximately 25% of patients with DMD under the age of 6 years will have dilated cardiomyopathy. Virtually all patients have cardiomyopathy by the second decade of life as injured myocytes are replaced by fibrotic tissue. Because of the advent of improved out-of-hospital pulmonary support, cardiomyopathy is now the main cause of death in DMD. Corticosteroids improve muscle strength and function and duration of ambulation, and they decrease onset of cardiomyopathy by approximately 4% for each year of treatment. Additionally, early use of angiotensin-converting enzyme inhibitors +/- β-blockers significantly improves mortality.

Dystrophin expression is decreased but not entirely absent in Becker muscular dystrophy. Thus, patients with BMD typically do not manifest cardiac and skeletal muscle issues until adulthood, and many of these patients have minimal symptoms. Prevalence is 2 per 100,000 males. Mortality in BMD depends on the degree of cardiac involvement.

X-linked dilated cardiomyopathy presents almost exclusively with cardiac involvement. Skeletal muscle involvement is rare. Males with this disorder typically present in the second decade of life with rapid progression of congestive heart failure. Patients with X-linked dilated cardiomyopathy have little to no dystrophin in cardiac muscle tissue but near-normal levels in skeletal muscle.

Myotonic dystrophy is the third most common genetic muscle disorder. It tends to cause clinical symptoms typically in the second to fourth decade of life. Symptoms can include sustained myoclonus; weakness of the head, neck, and face muscles; difficulty swallowing; cataracts; and cardiac arrhythmias. Cardiomyopathy is rare in myotonic dystrophy. Myotonic dystrophy is caused by abnormal DNA expansion on the dystrophia myotonica

protein kinase (*DMPK*) gene. Myotonic dystrophy patients have hundreds to thousands of cytosine, thymine, and guanine (*CTG*) repeats. Non-affected patients have fewer than 30 *CTG* repeats. The number of repeats correlates with age of onset and disease severity.

Limb girdle muscular dystrophy is the fourth most common genetic muscle disorder. It causes weakness and atrophy of the proximal muscles around the hips and shoulders as well as dilated cardiomyopathy. It is divided into 2 major groups, type 1 (autosomal dominant) and type 2 (autosomal recessive). The genetic defects in Limb girdle muscular dystrophy are multiple and tend to affect sarcomere Z-band formation, molecular trafficking, and signal transduction. Limb girdle dystrophy can present in childhood, adolescence, or young adulthood. When initial presentation occurs in childhood, progression occurs faster, and cardiomyopathy is more common.

Emery-Dreifuss muscular dystrophy (EDMD) can cause dilated cardiomyopathy but is more frequently associated with atrial-ventricular conduction defects. Patients tend to present in early childhood with joint contractures (elbows, ankles, cervical spine) and, later, skeletal muscle weakness. Emery-Dreifuss muscular dystrophy is caused by mutations in genes (*EMD, FHL1*, *LMNA*) that encode nuclear envelope proteins such as emerin, lamin A and C, and nesprin.

Friedreich ataxia can cause both skeletal and cardiac muscle abnormalities. It is caused by a genetic alteration in frataxin production. Frataxin is a protein required for mitochondrial iron trafficking. Patients typically present in the first decade of life with ataxia, dysarthria, and neuro-sensory hearing loss. Later, hypertrophic cardiomyopathy develops in more than 90% of patients. Pathology reveals increased iron deposit in mitochondria and fibrosis of skeletal and cardiac muscles.

Myofibrillar myopathy may present with weakness, cardiac involvement, and elevated creatine kinase levels. It is caused by abnormal accumulations of protein-containing vacuoles within skeletal muscle and endomyocardial myofibrils, leading to disruption of the Z-disks. Patients present with progressive weakness of both proximal and distal skeletal muscles as well as a restrictive cardiomyopathy with impaired diastolic filling.

PREP Pearls

- Duchenne muscular dystrophy is caused by absence of the muscle protein dystrophin.
- Dystrophin connects the actin myofilament to the inner wall of the muscle cell membrane. Its absence increases membrane fragility and myofibril injury.
- Disorders of the dystrophin protein typically cause skeletal muscle weakness and dilated cardiomyopathy as injured cells are replaced with fibrotic tissue.

- Abnormal dystrophin may act as a binding site for viruses, thus increasing the risk of myocarditis in patients with muscular dystrophy.

ABP Content Specifications(s)/Content Area

- Recognize the muscular dystrophies associated with impaired myocardial function

Suggested Readings

Arbustini E, Di Toro A, Giuliani L, et al. Cardiac phenotypes in hereditary muscle disorders: JACC state-of-the-art review. *J Am Coll Cardiol*. 2018;72(20):2485-2506. doi:10.1016/j.jacc.2018.08.2182

Buddhe S, Cripe L, Friedland-Little J et al. Cardiac management of the patient with duchenne muscular dystrophy. *Pediatrics.* 2018;142(suppl 2):72-81. doi:10.1542/peds.2018-0333I

Mavrogeni S, Markousis-Mavrogenis G, Papavasiliou A, et al. Cardiac involvement in duchenne muscular dystrophy and related dystrophinopathies. *Methods Mol Biol.* 2018;1687:31-42. doi:10.1007/978-1-4939-7374-3_3

Van Westering TLE, Betts CA and Wood MJA. Current understanding of molecular pathology and treatment of cardiomyopathy in duchenne muscular dystrophy. *Molecules*. 2015;20(5):8823-8855. doi:10.3390/molecules20058823

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✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 3

A 5-year-boy with developmental delay and acute respiratory failure secondary to lobar pneumonia who required mechanical ventilation, including high frequency oscillatory ventilation for acute respiratory distress syndrome, for 5 days is now ready for extubation. The patient is currently on ceftriaxone for his pneumonia and is in the process of weaning infusions of dexmedetomidine and fentanyl. No steroids were used in this patient during this illness, however, he required furosemide for fluid overload (now resolved), and vecuronium for tolerance of high frequency oscillatory ventilation.

The patient's liver and renal function panels are normal, as are his arterial blood gas values, pH, and electrolytes. Additionally, his vital signs are normal with the exception of his temperature that is 34°C. The mother states that since his hypoxic-ischemic injury at birth, her son has issues regulating his temperature and is frequently on the "cooler side."

In considering extubation readiness, you note that the child has an air leak after deflation of the endotracheal tube cuff and is on low ventilator settings. The nurse and the respiratory therapist point out that despite discontinuing vecuronium 12 hours ago the patient currently exhibits no spontaneous movement and is breathing at the same rate as that set on the ventilator, although a few hours ago he seemed to have good effort. You suspect that the patient may have residual muscle paralysis. Train-of-four testing reveals only 1 twitch.

Of the following, the MOST likely reason for the patient's current state is:

- **A.** active metabolite of vecuronium
- **B.** hypokalemia due to furosemide use
- **C.** hypothermia

D. respiratory acidosis

Neuromuscular blocking agents (NMBAs) are required in the pediatric intensive care unit to facilitate intubation, mechanical ventilation, and procedures. Adult studies have shown that specific disease processes such as acute respiratory distress syndrome (ARDS), raised intracranial pressure, and management of abdominal compartment syndrome may benefit from the short-term use of NMBAs, and this strategy is frequently used in children with such conditions.

The most commonly used NMBAs infusions in the PICU include the aminosteroid compounds such as vecuronium, rocuronium, and pancuronium. The aminosteroid compounds are nondepolarizing agents that act as competitive inhibitors of the nicotinic receptors, preventing the action of acetylcholine at the neuromuscular junction. All of the aminosteroid compounds are metabolized by the liver and excreted by the kidneys. In patients with acute kidney injury, vecuronium produces an active metabolite, 3-desacetyl-vecuronium, which retains 50% to 75% of the parent activity giving rise to prolonged neuromuscular blocking effect. In patients with renal or hepatic failure, the benzylisoquinolines such as mivacurium, cisatracurium, and atracurium are preferred as these agents undergo Hoffman (a nonenzymatic, pH and temperature dependent) degradation which does not lead to the development of active metabolites.

The pharmacokinetics of NMBAs are complex and certain conditions such as age, the volume of distribution, or use of other medications can affect the duration of action. Neonates have increased total body water and volume of distribution leading to decreased half-life of NMBAs compared to older children or adults who have smaller volume of distribution. An important consideration in NMBAs elimination and prolongation of their duration of action is temperature. Patients who are hypothermic may have the duration of action of NMBAs doubled for every 2°C drop in the temperature below 36.5°C. The exact mechanism of hypothermia prolonging the duration of action of NMBAs remains unknown. It is possible that low temperature alters the sensitivity of the neuromuscular junction to the drug or its active metabolite. Hypothermia can also decrease the rate at which acetylcholine attaches to the nicotinic receptors, as well as the excretion by the liver and the kidneys. Hepatic enzyme function is suboptimal when body temperature is low resulting in the inability to efficiently metabolize drugs such as NMBAs. Additionally, hypothermia can diminish muscle contractility by its action on weakening the function of the contractile elements and their response to acetylcholine. Temperature changes can affect Hoffman elimination of NMBAs prolonging their duration of action. Other factors that can extend the duration of action of NMBAs in critically ill patients include disturbances in electrolytes. Examples include:

1. hypocalcemia will decrease the release of acetylcholine at the neuromuscular junction prolonging muscle weakness;
2. hypermagnesemia acts by impeding the calcium channels in the presynaptic region thus indirectly decreasing acetylcholine release;
3. hypokalemia can lead to changes in the membrane action potential (makes resting membrane potential more negative) due to the failure of the sodium-potassium exchange pump. As sodium cannot be exchanged for potassium, the action potential across the cell membrane is delayed resulting in muscle weakness and prolonged neuromuscular blockade. Hypokalemia can thus further prolong muscle weakness and recovery even after the NMBAs are stopped.

It is unclear how respiratory acidosis or alkalosis prolongs the duration of action of the NMBAs. Various drugs used in the critically ill patients, such as phenytoin and ranitidine, can cause resistance to NMBA action. Antibiotics such as aminoglycosides, tetracyclines, clindamycin, and vancomycin can prolong neuromuscular blockade.

The patient in the vignette has prolonged muscle weakness despite discontinuation of the NMBA 12 hours before the decision to extubate. Given there is no hepatic or renal dysfunction this continued weakness is unlikely due to the accumulation of an active metabolite of vecuronium. The patient in the vignette has normal serum potassium so hypokalemia is an unlikely cause of his prolonged muscle weakness. The patient in the vignette also has a normal blood gas with no respiratory acidosis. Given the patient's temperature is 34°C, this is the most likely reason for his prolonged muscle weakness despite stopping the vecuronium. Although peripheral nerve stimulators can be used to titrate and monitor NMBA response, one needs to note that hypothermia can dampen the stimulator twitch response resulting in an inaccurate interpretation of the train-of-four response. Passive and active warming strategies may be required in this patient to increase his body temperature to at least 36.5°C before extubation. The short duration of NMBA use in this patient, and lack of the steroids use argues against intensive care unit-acquired skeletal muscle weakness as a cause for prolonged muscle weakness. Although NMBA use has been implicated, no study has confirmed this association due to a multitude of confounding factors in critically ill patients.

PREP Pearls

- The pharmacokinetics of neuromuscular blocking agents can be affected in critically ill children.
- Hypokalemia, hypermagnesemia, and hypocalcemia can prolong muscle weakness in patients on neuromuscular blocking agents.
- Commonly used drugs such as antibiotics, immunosuppressive agents, and β-blockers action prolong the action of neuromuscular blocking agents.

- Patients who are hypothermic may have the neuromuscular blocking agents duration of action doubled for every 2°C drop in the temperature below 36.5 °C.

ABP Content Specifications(s)/Content Area

- Recognize that a patient may have no residual muscle blockade but can become paralyzed again if hypokalemic, hypomagnesemic, cold, or poorly perfused

Suggested Readings

DeBacker J, Hart N, Fan E. Neuromuscular blockade in the 21st century. Management of the critically ill patient. *Chest*. 2017;151(3):697-706. doi: 10.1016/j.chest.2016.10.040

Greenberg SB, Vender J. The use of neuromuscular blocking agents in the ICU: Where are we now? *Crit Care Med*. 2013;41(5):1332-1344. doi: 10.1097/CCM.0b013e31828ce07c

Price D, Kenyon N, Stollenwerk N. A fresh look at paralytics in the critically ill: real promise and real concern. *Ann Intensive Care.* 2012;2(1):43. doi: 10.1186/2110-5820-2-43

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✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 4

A 15-year-old adolescent patient who was diagnosed with acute myelogenous leukemia 2 weeks ago and is receiving chemotherapy is admitted to the pediatric intensive care unit with acute respiratory failure requiring mechanical ventilatory support. Chest radiography demonstrates bilateral diffuse infiltrates with a small pleural effusion. Echocardiography shows normal cardiac function.The blood and urine cultures have yielded negative results.

Of the following, the MOST appropriate diagnostic procedure for this patient is

- **A.** bronchoscopy with bronchoalveolar lavage
- **B.** computed tomography–guided thoracentesis
- **C.** magnetic resonance imaging of the chest
- **D.** serum galactomannan antigen testing

The patient in the vignette is immunocompromised by the underlying diagnosis of acute leukemia and a recent course of chemotherapy. He has bilateral diffuse pneumonia with a small pleural effusion. Considering the timeline of his underlying diagnosis and clinical course, the most likely microbiologic agent is a bacterial pathogen. He has not been immunocompromised long enough to be at risk for fungal infections such as aspergillosis, for which serum galactomannan antigen testing may have a role in the diagnosis. The small amount of pleural effusion seen on chest radiography at this time in the clinical course likely represents a sympathetic effusion, and the diagnostic yield from this fluid is very low. Magnetic resonance imaging of the chest will likely identify the presence of pneumonia and

pleural effusion but will not contribute to identifying a microbiologic agent in this patient. Therefore, the most prudent approach in this patient at this time is flexible fiberoptic bronchoscopy with bronchoalveolar lavage (BAL).

Bronchoscopy may be performed using a rigid or flexible bronchoscope. In the pediatric population, the rigid bronchoscope is used primarily to remove foreign bodies from the airways in the clinical setting of foreign body aspiration. The flexible bronchoscope is more portable (particularly the battery-operated varieties) and more practical for clinical use in the pediatric intensive care unit (PICU).

Flexible fiberoptic bronchoscopy may be performed in a patient who is not intubated by passing the scope through the nose or in patients who are intubated as seen in the vignette. For patients who are intubated, after administration of appropriate doses of sedation and analgesia, the appropriately sized flexible bronchoscope is passed through the endotracheal tube and slowly advanced past the tip of the endotracheal tube. The operator inspects the trachea, the trachea-carina, the main bronchi, on the right side (right main bronchus, right upper bronchus, bronchus intermedius, and right lower lobe bronchus) and on the left side (left upper and the left lower bronchus) for abnormalities such as inflammation, ingested foreign body, or airway narrowing.

The procedure to obtain a BAL sample is as follows: the flexible bronchoscope is carefully and gently advanced into the lower airway until the tip of the bronchoscope is wedged into one of the lower airways. At this point, the bronchoscope is withdrawn slightly and 5 to 10 mL (depending on the age and weight of the patient) of saline is injected through the proximal channel of the bronchoscope by an assistant. The saline is allowed to settle for several seconds, and then suctioned into a sterile container connected to the suction port of the bronchoscope. The sample that is collected represents the BAL sample and is submitted for various types of staining (eg, Gram stain and staining for acid-fast bacilli) and aerobic and anaerobic cultures.

Flexible fiberoptic bronchoscopy with BAL is a recognized diagnostic modality for the diagnosis of respiratory pathogens in children with respiratory failure in the PICU and in experienced hands is associated with minimal complications. When practical, flexible bronchoscopy should be considered for diagnostic purposes in children with pneumonia who are admitted to the PICU with acute respiratory failure to tailor the antimicrobial therapy to the specific agents.

PREP Pearls

- Flexible fiberoptic bronchoscopy is a useful tool for diagnosing upper and lower airway diseases in children.

- Flexible fiberoptic bronchoscopy may be performed in the pediatric intensive care unit with the child sedated.
- Bronchoalveolar lavage collected from the lower airway and alveoli during fiberoptic bronchoscopy is useful in identifying microbiologic agents in children with pneumonia.

ABP Content Specifications(s)/Content Area

- Know the indications for bronchoscopy with bronchoalveolar lavage

Suggested Readings

Boesch RP, Baughn JM, Cofer SA, Balakrishnan K. Trans-nasal flexible bronchoscopy in wheezing children: diagnostic yield, impact on therapy, and prevalence of laryngeal cleft. *Pediatr Pulmonol*. 2018;53(3):310-315. doi:10.1002/ppul.23829

Hasan RA, Reddy R. Sedation with propofol for flexible bronchoscopy in children. *Pediatr Pulmonol*. 2009;44(4):373-378. doi:10.1002/ppul.2101

Hysinger E, Friedman N, Jensen E, et al. Bronchoscopy in neonates with severe bronchopulmonary dysplasia in the NICU. *J Perinatol*. 2019;39(2):263-268. doi:10.1038/s41372-018-0280-y

March

✓ **CONGRATULATIONS**

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Question: 5

A 1-week-old female neonate is brought to the emergency department after being found unresponsive by her parents. She is pulseless and apneic upon arrival. A cardiac rhythm is reestablished after 20 minutes of cardiopulmonary resuscitation. Initial laboratory studies demonstrate disseminated intravascular coagulation, hypoglycemia, and severe metabolic acidosis. The neonate was born via vaginal delivery after an uneventful pregnancy.

The patient is admitted to the pediatric intensive care unit and treated with mechanical ventilation, volume resuscitation, inotropic medications, antibiotics, and blood product administration for correction of coagulopathy. Despite aggressive treatment, the patient's shock state worsens, and she dies on hospital day 2. Gross autopsy findings show extensive hepatic necrosis and severe interstitial edema of the pulmonary and cerebral parenchyma.

Of the following, the organism MOST likely to be isolated on viral culture or polymerase chain reaction is

- **A.** cytomegalovirus
- **B.** herpes simplex virus type 2
- **C.** human herpesvirus 6
- **D.** Zika virus

Herpes simplex virus (HSV) is a member of the *Herpesviridae* family. Members of the *Herpesviridae* family have a worldwide distribution, with humans as the only reservoir. Herpes simplex virus types 1 and 2 are most frequently associated with human disease, ranging from localized blister formation to disseminated organ involvement and shock.

Globally, World Health Organization data suggest almost 600 million people are infected with HSV. Worldwide, the incidence of neonatal HSV disease ranges from 1 in 3,000 to 20,000 live births. In one study, approximately 1,500 cases of neonatal HSV infections were reported in the United States with a mortality rate of 0.8 deaths per 100,000 live births. However, the true US incidence and prevalence is unknown because neonatal HSV is not a reportable disease in most states.

The seroprevalence of HSV type 1 in the United States in 2005-2010 was 54%, while the seroprevalence of HSV type 2 was 15.7%. Interestingly, although less prevalent than HSV 1, HSV 2 accounts for 75% of neonatal infections. This may in part be due to increased viral shedding with HSV 2 compared to HSV 1, thereby increasing the chance of viral transmission to the neonate. Neonatal HSV acquisition occurs via perinatal transmission in a majority of cases, although approximately 10% of cases occur through postnatal transmission and 5% occur via an intrauterine route. Expectant mothers are often unaware of HSV genital infections, with over 60% of women stating they were asymptomatic. Risk of transmission increases to greater than 60% if the mother has a primary HSV infection at the time of delivery. By comparison, recurrent HSV infection has a transmission rate of 2%.

Neonatal HSV is classified into 3 main disease manifestations:

- Localized skin, eye, and mouth (SEM)
- Central nervous system (CNS) involvement with or without SEM
- Disseminated disease

Localized SEM disease accounts for 45% of neonatal HSV. It usually presents as clear-appearing vesicles on erythematous bases (**Figure**). Vesicles appear most often in the first 6 weeks after birth. Prognosis for infants with only SEM manifestations of HSV is excellent, with a mortality rate of less than 1%. However, if left untreated, 75% of infants with SEM disease will progress to HSV meningoencephalitis.

Central nervous system HSV presentation accounts for 33% of neonatal HSV disease. Many of the neonates with CNS HSV disease also have skin vesicles. Infants with CNS involvement typically demonstrate lethargy, irritability, tremors, poor feeding, temperature instability, and focal or generalized seizures. Infection is likely due to inoculation at birth with subsequent retrograde intraneuronal transport of the virus. Mortality rate for CNS HSV disease is 15%, but more than half of infants with CNS HSV infection suffer persistent neurologic adverse sequelae. Neurodevelopmental outcome is improved however when patients are placed on long-term suppressive antiviral therapy.

Disseminated HSV disease causes approximately 25% of infections. It tends to predominate in younger neonates, typically in the first or second weeks after birth. Herpes simplex virus disseminated disease involves multiple organs, often including the brain, liver, lungs,

adrenals, skin, eyes, and aero-digestive tract. Central nervous system involvement is noted in a majority of cases with disseminated disease, likely from hematogenous spread. Acute necrotizing hepatitis progressing to liver failure is reported in fewer than 10% of cases. Neonates with disseminated HSV can present with nonspecific clinical signs, such as temperature instability, apnea, irritability, lethargy, respiratory distress, abdominal distension, and ascites. Disseminated HSV disease has a mortality rate of greater than 85% without treatment.

Diagnosis is confirmed by viral culture, or, increasingly, through the use of polymerase chain reaction for the presence of HSV DNA in blood, cerebrospinal fluid, or vesicular fluid. Initial treatment for neonates with active HSV disease includes supportive measures, such as fluid maintenance, nutrition, correction of hypoglycemia, and management of coagulopathy, shock, and seizure activity. Acyclovir is the antiviral drug of choice for neonatal HSV infections. The dose is 60 mg/kg/day divided every 8 hours. Localized skin, eye, and mouth disease should be treated for a minimum of 14 days. Disseminated and CNS disease should be treated for a minimum of 21 days. After aggressive acyclovir therapy, infants with disseminated or CNS disease should remain on suppressive dose acyclovir (900 mg/m2/day) for 6 months. Despite aggressive therapy, the 1-year mortality rate for disseminated disease is 29%. Severe hepatitis, acute liver failure, coma, disseminated intravascular coagulation, prematurity, and pneumonitis are associated with worse prognosis.

Cytomegalovirus (CMV) is the most frequent cause of congenital infections worldwide. It is a DNA virus that belongs to the herpesvirus family. The clinical spectrum of congenital CMV varies, with 85% of infected infants appearing asymptomatic. Symptomatic infants typically show hepatosplenomegaly, microcephaly, and hearing loss. Congenital CMV has a mortality rate of less than 10%. Human herpesvirus 6 is closely related to CMV. It is generally acquired after 6 months of age and typically presents as an acute febrile illness. Ten percent of patients may develop seizures and CNS involvement. Human Zika virus is classified as an arbovirus and has been associated with microcephaly, developmental delay, and retinal lesions in neonates.

PREP Pearls

- The seroprevalence of herpes simplex virus type 2 in the United States is approximately 15%, but it accounts for 75% of neonatal herpes simplex virus infections.
- Disseminated neonatal herpes simplex virus disease tends to present earlier in life than central nervous system involvement alone, typically in the first 10 days.
- Central nervous system herpes simplex virus disease can cause significant long-term neurologic morbidity. Use of acyclovir suppressive therapy for 6 months can significantly improve neurodevelopmental outcomes.

ABP Content Specifications(s)/Content Area

- Understand the pathogenesis and pathophysiology of disseminated viral infection with shock
- Recognize the clinical manifestations of disseminated viral infection with shock
- Differentiate among the disseminated viral infections that cause shock in infants and children
- Recognize the life-threatening complications of disseminated viral infection with shock

Suggested Readings

Basinger JM, Fiester SE, Fulcher JW. Mortality from neonatal herpes simplex viremia causing severe hepatitis. *Forensic Sci Med Pathol.* 2019;15:663-666. doi:10.1007/s12024-019-00147-w

Harris JB, Holmes AP. Neonatal herpes simplex viral infections and acyclovir: an update. *J Pediatr Pharmacol.* 2017; 22(2): 88-93.doi: 10.5863/1551-6776-22.2.88

Pinninti SG, Kimberlin DW. Neonatal herpes simplex virus. *Semin Perinatol.* 2018;42(3):168-75. doi:10.1053/j.semperi.2018.02.004

Sampath A, Maduro G, Schillinger JS. Infant deaths due to herpes simplex virus, congenital syphilis and HIV in New York City. *Pediatrics.* 2016;137(4):e20152387. doi:10.1542/peds.2015-2387

Wang A, Wohrley J, Rosebush J. Herpes simplex virus in the neonate. *Pediatr Ann.* 2017; 46(2):42-46. doi:10.3928/19382359-20170112-01

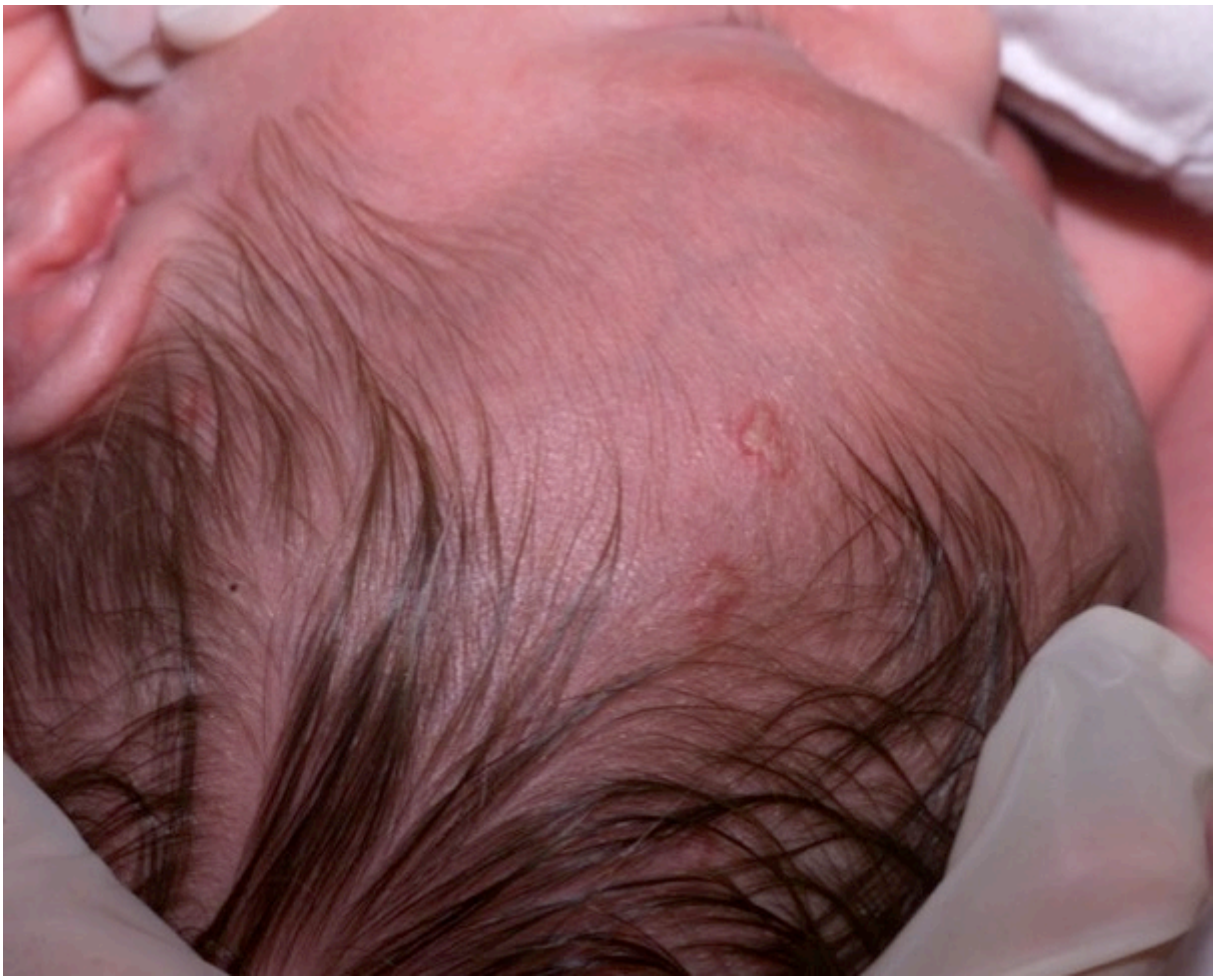

Figure:
Vesicles from herpes simplex virus (HSV), type 2 infection in a neonate.

Courtesy of M. Rowin

March

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 6

A 2-year-old girl is evaluated in the emergency department for altered mental status. She has a history of a ventricular-peritoneal shunt placed due to hydrocephalus secondary to Arnold-Chiari malformation, type 2. She was sent to the emergency department by her pediatrician after several hours of nonbloody, nonbilious vomiting. The vomiting was not abated by several doses of ondansetron. The child is lethargic. She responds to the insertion of an intravenous catheter by moaning. Pupils are in mid-position and sluggishly reactive to light. She is afebrile; her respiratory rate is 45 breaths/min and shallow, heart rate is 60 beats/min, and blood pressure is 155/65 mm Hg. Her eyes are not sunken and tears are present with painful stimuli. Her capillary refill time is less than 2 seconds. The mother states that her daughter has had no urine output today. A head/brain computed tomography scan is read as normal. The emergency department attending physician orders a 20 mL/kg normal saline bolus and begins intravenous fluids with half normal saline at 1.5 times maintenance rate. She is now admitted to the pediatric intensive care unit.

Of the following, the MOST appropriate next step in the care of this child is to

- **A.** administer another 20 mL/kg bolus of normal saline
- **B.** administer intravenous fosphenytoin
- **C.** start intravenous vancomycin and fluconazole
- **D.** tap the ventricular peritoneal shunt

Children with cerebrospinal shunts placed for hydrocephalus are frequently brought to the emergency department with signs and symptoms of a shunt malfunction as a result of partial or complete obstruction, infection, or rarely, bowel perforation. The most common

cause is obstruction of the shunt. As increased intracranial pressure (ICP) develops, typical signs are headache, vomiting, lethargy or behavioral changes, pupillary changes, and irritability. Elevated ICP can result in development of the Cushing triad. This consists of hypertension with widened pulse pressure, bradycardia, and abnormal respiratory pattern, including apnea, which may reflect the occurrence of herniation. The child in this vignette clearly has elevated ICP. When history and physical examination findings are suggestive of a shunt malfunction and intracranial hypertension, a CT scan of the head/brain should be obtained immediately. Ideally, a previous study is available for comparison of ventricular size, loss of grey-white matter differentiation, and signs of mass volume effects. Studies demonstrate that 13% to 30% of children with a shunt malfunction can have a negative CT scan. When the symptoms of a shunt malfunction are present but the radiographic images show no evidence of elevated ICP or malfunction, the next and possibly life-saving step is to tap the shunt, measure the opening pressure, obtain a cerebrospinal fluid (CSF) specimen for culture, and if the patient is *in extremis*, remove sufficient CSF until the child's mental status improves. In the event that no CSF can be withdrawn, this would indicate a proximal shunt malfunction and require urgent neurosurgical intervention.

The child described in the vignette may indeed be dehydrated from her vomiting and lack of oral intake, therefore ongoing fluid administration is warranted but the risk of cerebral herniation is greater. Likewise, infection of the shunt is also a common cause of shunt malfunction, therefore, obtaining a CSF specimen for culture and analysis as well as starting appropriate antibiotics are prudent steps, but do not supersede tapping the shunt. Starting prophylactic antiseizure medications such as fosphenytoin immediately is not necessary.

PREP Pearls

- Children with signs and symptoms of a shunt malfunction and subsequent increased intracranial pressure require a computed tomographic or magnetic resonance imaging scan of the head/brain.
- Scans may not show evidence of increased intracranial pressure (ICP); in these cases, the shunts should be tapped if the history and physical examination findings are suggestive of elevated ICP.

ABP Content Specifications(s)/Content Area

- Management of ventricular shunt malfunctions

Suggested Readings

Iskandar B, McLaughlin R, Mapstone T, Oakes J. Pitfalls in the diagnosis of ventricular shunt dysfunctions: radiologic reports and ventricular size. *Pediatrics.* 1998;101(6):1031-1036. doi:10.1542/peds.101.6.1031

Paff M, Alexandru-Abrams D, Muhonen M, Loudon W. Ventriculoperitoneal shunt complications: a review. *Interdiscip Neurosurg.* 2018;13:66-70. doi:10.1016/j.inat.2018.04.004

April

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 1

A previously healthy, 10-year-old boy is admitted to the general pediatric floor with 5 days of high fever, right ocular pain, and eyelid swelling. He was admitted to the hospital 2 days ago, at which time he was found to have an orbital cellulitis and a positive blood culture result for methicillin-resistant *Staphylococcus aureus*, sensitive to clindamycin. He remains in the hospital, receiving intravenous clindamycin, but continues to experience persistent, intermittent fever. He has developed progressively worsening confusion and altered mental status over the course of the day, and his mother noticed that he has been breathing fast since yesterday. On examination, he is moaning and demonstrating only minimal response to noxious stimuli.

His vital signs are shown:

Temperature	40°C
Blood pressure	130/70 mm Hg
Heart rate	60 beats/min
Respiratory rate	14 breaths/min
Oxygen saturation	95% in room air

Of the following, the MOST appropriate next intervention is to

- **A.** administer hyperosmolar therapy
- **B.** administer a rapid 20-mL/kg bolus of crystalloid
- **C.** immediately arrange for a computed tomographic scan of the brain
- **D.** start epinephrine infusion at 0.1 µg/kg/min

The patient in this vignette is likely experiencing an intracranial abscess secondary to intracranial extension and spread of bacteria. The most frequent organisms associated with these brain abscesses are *Streptococcus* and *Staphylococcus* species; among these species, *Streptococcus viridans* and *Staphylococcus aureus* are the most common. In the case in the vignette, a blood culture was positive for methicillin-resistant *Staphylococcus aureus* sensitive to clindamycin. However, clindamycin lacks the ability to effectively cross the blood–brain barrier in high concentrations. If an intracranial abscess is untreated, it can expand and create a large mass. In addition, the vasogenic edema surrounding an abscess may also contribute to significant mass effect. As one can surmise from the Monro-Kellie doctrine, an enlarging space-occupying mass can ultimately lead to displacement of the other intracranial contents, resulting in one of the cerebral herniation syndromes.

As the Monro-Kellie doctrine indicates, the intracranial vault has a fixed volume that contains three basic constituents: brain (80%), blood (10%), and cerebrospinal fluid (CSF) (10%). These components exist within the thick, inelastic dura mater and the semirigid cranium. The brain, blood, and CSF are always in a state of volume-pressure equilibrium, meaning that if one component increases in volume, another must decrease. For example, if a patient has an intracranial mass that causes an increase in “brain” volume, the patient may compensate by hyperventilating because a reduction in partial pressure of carbon dioxide ($PaCO_2$) will cause a reduction in cerebral blood flow (CBF). Cerebral blood flow is affected by brain metabolism, blood pressure, $PaCO_2$, and partial pressure of oxygen (PaO_2). The CBF is affected by changes in arteriolar tone; decreasing $PaCO_2$ by hyperventilation will increase arteriolar tone and thereby decrease CBF and cerebral blood volume and vice versa.

Treatment of increased intracranial pressure (ICP) should first focus on maintaining adequate respiratory and circulatory functions. Focus should then be paid to positioning the neck midline and elevating the head of the bed to 30 degrees to optimize venous drainage. If seizures or fever are present, these should be treated to reduce cerebral metabolism and, thus, the need for high CBF. Immediate hyperventilation can be used to emergently reduce $PaCO_2$, thereby reducing cerebral blood flow temporarily. In the case in

the vignette, it is appropriate to immediately initiate hyperosmolar therapy, then consider imaging and a neurosurgical evaluation. Mannitol can be used for treatment of increased ICP, because it is known to decrease brain and CSF volume by reducing the brain's overall water content, altering CBF via cerebral vasoconstriction, and improving cerebral perfusion by decreasing blood viscosity. It has a rapid onset of action and can maintain its effect for hours. Administration of hypertonic saline can be used to acutely raise serum osmolality with a similar effect. Elective intubation should be considered.

In the vignette, the patient's signs and symptoms do not reflect the classic progression of sepsis. An inotropic infusion will increase the patient's heart rate and blood pressure, but the patient in the vignette does not yet require vasopressor support.

PREP Pearls

- Increases in intracranial pressure may produce only subtle findings (such as papilledema and headache), and thus a full neurological examination (motor/sensory) is necessary.
- Concern about elevated intracranial pressure and impending herniation should trigger the immediate initiation of hyperosmolar therapy.
- Immediate hyperventilation via bag mask ventilation can be used to reduce the partial pressure of carbon dioxide, thereby emergently reducing cerebral blood flow.

ABP Content Specifications(s)/Content Area

- Understand the effects of blood carbon dioxide concentration on cerebral vascular resistance and cerebral blood flow regulation
- Understand cerebral autoregulation

Suggested Readings

Kochanek PM, Carney N, Adelson PD, et al; American Academy of Pediatrics—Section on Neurological Surgery; American Association of Neurological Surgeons/Congress of Neurological Surgeons; Child Neurology Society; European Society of Pediatric and Neonatal Intensive Care; Neurocritical Care Society; Pediatric Neurocritical Care Research Group; Society of Critical Care Medicine; Paediatric Intensive Care Society UK; Society for Neuroscience in Anesthesiology and Critical Care; World Federation of Pediatric Intensive and Critical Care Societies. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents—second edition. *Pediatr Crit Care Med.* 2012;13(suppl 1):S1-S82. doi:10.1097/PCC.0b013e31823f435c

Tasker RC, Adelson PD. Head and spinal cord trauma. In: Nichols DG, Shaffner DH, eds. *Rogers' Textbook of Pediatric Intensive Care.* 5th ed. Wolters Kluwer; 2015:951-981.

April

Question: 2

A 4-year-old boy with status asthmaticus is intubated in an outlying emergency department for respiratory failure. The transport team arrives and notes that the patient is mechanically ventilated with peak pressures of 34 cm H_2O and 5 cm H_2O of positive end-expiratory pressure. He has poor chest rise and minimal breath sounds. He is intubated with a 4.5-mm uncuffed endotracheal tube. His FiO_2 is 1.0 and saturations are 85%. The results from an arterial blood gas analysis are shown:

Laboratory Test	**Result**
pH	7.19
Partial pressure of carbon dioxide	74 mm Hg
Partial pressure of oxygen	82 mm Hg

Of the following, the BEST treatment option to improve ventilation in this patient is to

- **A.** change the endotracheal tube to a 4.5-mm cuffed tube
- **B.** change the endotracheal tube to a 6.5-mm uncuffed tube
- **C.** increase end-expiratory pressure to 8 cm H_2O
- **D.** increase peak inspiratory pressure to 40 cm H_2O

Selecting the appropriate size of endotracheal tube (ETT) is necessary to reduce airway trauma and appropriately treat a patient with respiratory failure secondary to airway compromise or pulmonary disease. An endotracheal tube (ETT) that is too small can result in insufficient ventilation and affect reliability of end-tidal carbon dioxide monitoring. This is exacerbated if lung compliance is poor or high airway resistance is present that can be manifested by a large air leak with decreased exhaled volumes noted on the ventilator. Additionally, an increased risk of aspiration, and dispersion of anesthetic gas into the surrounding environment can occur. An ETT that is too large can cause excessive tracheal wall pressure and cause local ischemia creating upper airway damage, tracheal edema, local ulceration, and scar formation that can result in subglottic stenosis.

Selecting the appropriate size ETT may be determined by an age-based formula. Pediatric advanced life support (PALS) guidelines use the following formula:

Uncuffed ETT (age/4) + 4

Cuffed ETT (age/4) + 3.5

According to this formula, the calculated size for the patient in the vignette should be a 4.5-mm cuffed ETT. The reader is reminded that the ETT size is a measurement of the internal diameter of the tube. This age-based formula has limitations if the child's age is unknown. The use of length-based resuscitation tapes can be helpful in identifying the correct ETT size for children up to approximately 35 kg in weight. Additionally, the length-based resuscitation tape provides additional information, such as drug dosing for resuscitation of a pediatric patient. The size of the patient's little finger has been used as an estimation of ETT size; however, this method may be unreliable and difficult in an emergency situation.

Cuffed ETTs are commonly used in infants and children in the pediatric intensive care unit. Cuffed ETTs are now mainly low-pressure tubes and are as safe as uncuffed tubes in pediatric patients, provided the proper-sized ETT and cuff inflation pressure are selected. The choice of a cuffed or uncuffed ETT should be based on the disease process and the reason for intubation. A cuffed ETT should be considered for children who are critically ill, have poor lung compliance, or are undergoing certain surgical procedures in which occluding the airway and allowing higher ventilation pressures may be necessary. An important factor in choosing a cuffed ETT is downsizing by one-half the calculated tube size to compensate for the cuff. This avoids intubation with too large an ETT, which may result in airway injury. Although the ETT is smaller, any leakage from around the tube can be

resolved in most instances by adding air to the cuff. Increased airway resistance from a smaller ETT can be overcome with modern ventilators. The clinician should be aware that ETT cuff pressures can increase with altitude during air transport.

A cuffed ETT offers several advantages:

- Improved protection against aspiration
- Avoidance of unnecessary ETT changes that can result in additional trauma if the initial tube selected is too small
- Allowance of higher ventilation pressures in patients with poor pulmonary compliance
- More precise delivery of tidal volume and monitoring of ventilation
- Less loss of anesthetic gases

Cuffed tubes have disadvantages as well:

- Smaller tubes have greater airway resistance to breathing.
- The smaller ETT lumen can result in challenges with airway clearance.

PREP Pearls

- Selecting the appropriate size of endotracheal tube is necessary to reduce airway trauma and treat a patient with respiratory failure secondary to airway compromise or pulmonary disease.
- When choosing a cuffed endotracheal tube, it is important to downsize by one-half the calculated uncuffed endotracheal tube size to compensate for the cuff.
- The appropriate size of endotracheal tube may be determined according to an age-based formula provided the patient's age is known.
- The use of length-based resuscitation tapes can be helpful in identifying the correct endotracheal tube size for children up to approximately 35 kg.
- Endotracheal tube cuff pressures can increase with altitude during air transport.

ABP Content Specifications(s)/Content Area

- Know the reasons to use a cuffed endotracheal tube

Suggested Readings

Chambers NA, Ramgolam A, Somerfield D, et al. Cuffed vs. uncuffed tracheal tubes in children: a randomised controlled trial comparing leak, tidal volume and complications. *Anaesthesia*. 2018;73(2):160-168. doi:10.1111/anae.14113

Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. Part 10: pediatric advanced life support. The American Heart Association in collaboration

with the International Liaison Committee on Resuscitation. *Circulation*. 2000;102(8 suppl):I291-I342. https://pubmed.ncbi.nlm.nih.gov/10966679/

Long MT, Cvijanovich NZ, McCalla GP, Flori HR. Changes in pediatric-sized endotracheal tube cuff pressure with elevation gain: observations in ex vivo simulation and in vivo air medical transport. *Pediatr Emerg Care*. 2018;34(8):570-573. doi:10.1097/PEC.0000000000000755

April

Question: 3

A 2-year-old, full-term boy with a history of exploratory laparotomy 2 days after birth and parental exposure to COVID-19 one month ago, is brought to the emergency department with a 4-day history of vomiting followed by diarrhea and fever. His vomiting and diarrhea have stopped, but he now seems tired and does not want to eat.

His vital signs are shown:

Temperature	39.1°C
Heart rate	138 beats/min
Respiratory rate	24 breaths/min
Blood pressure	102/74 mm Hg

He has a blood specimen drawn for laboratory studies, and is given 20 mL/kg normal saline bolus. His initial lactate value is 119.8 mg/dL (13.3 mmol/L), which improves to 30.6 mg/dL (3.4 mmol/L) after 3 boluses of normal saline are given. Chest radiography performed on arrival for evaluation of fever demonstrated small perihilar infiltrate with normal cardiac silhouette and otherwise clear lung fields.

His laboratory data are shown:

Laboratory Test	**Result**

Complete blood cell count	
White blood cell count	19,500/μL (19.5 × 10^9/L)
Hemoglobin	14.5 g/dL (145 g/L)
Hematocrit	43%
Platelet count	433 × 10^3/ μL (433 × 10^9/L)
Initial electrolytes	
Sodium	134 mg/dL (134 mmol/L)
Chloride	96 mg/dL (96 mmol/L)
Potassium	3.4 mg/dL (3.4 mmol/L)
Bicarbonate	16 mg/dL (16 mmol/L)
Blood urea nitrogen	19 mg/dL (6.8 mmol/L)
Creatinine	0.58 mg/dL (51.3 μmol/L)
Glucose	106 mg/dL (5.9 mmol/L)

He remains tachycardic despite being afebrile after administration of acetaminophen. His capillary refill time had initially improved but is now 3 seconds, and he is requiring oxygen at 2 L/min to maintain his pulse oximetry reading over 92%.

His repeat vital signs are shown:

Temperature	37.2°C
Heart rate	168 beats/min
Respiratory rate	36 breaths/min
Blood pressure	76/34 mm Hg

Of the following, the diagnostic test that would BEST identify the cause of this child's deteriorating course would be

- **A.** brain natriuretic peptide
- **B.** echocardiography
- **C.** electrocardiography
- **D.** troponin I

This child's symptoms and signs suggest acute myocardial dysfunction as illustrated by tachycardia and hypotension without fever. Furthermore, his initial improvement after fluid boluses with subsequent deterioration are indicative of poor pump function. Echocardiography is the most sensitive first-line method to determine if a patient has heart failure due to myocarditis. Echocardiography can evaluate both the structure (ventricular dilatation, edema, and pericardial effusion) along with the functional effects (decreased ejection fraction) of this highly variable disease process. In addition, the portability and increased ability of both emergency physicians and intensivists to use this modality have increased its early use in diagnosis. Echocardiography can demonstrate both subtle and profound changes in ventricular function and determine if the left ventricle is enlarged.

More subtle findings include myocardium thickening that can occur due to edema, pericardial effusion, visualization of intracardiac thrombus, and whether valves are regurgitant. The specialized echocardiographic technique of speckle tracking imaging can help detect decreased longitudinal strain even when left ventricular function appears preserved. In patients where it remains unclear as to why the patient has ventricular dilatation, and is either poorly responding or unresponsive to treatment, cardiac magnetic resonance imaging is the gold standard for non-invasive methods. Cardiac MRI can detect edema, tissue injury, fibrosis and hyperemia that may not be seen on echocardiography but this imaging technique requires that the patient can tolerate sedation for several hours. Hence, echocardiography is the preferred modality for the diagnosis and management of myocarditis.

Brain natriuretic peptide (BNP) is secreted by ventricular myocytes in response to increased volume and pressure. Levels of BNP in the Pediatric Carvedilol Study were predictive of patients who had worse outcomes due to heart failure. Elevated levels of BNP could identify myocarditis as the cause for increased tachycardia and hypotension after fluid boluses were administered. But BNP is more useful as a marker for heart failure, as noted on trends over time to determine if therapy is improving the disease course. Similarly, both troponin I and T can be elevated in acute myocarditis but are nonspecific markers of cardiac injury that are not always elevated, even in biopsy-proven cases of myocarditis. Hence, a normal or only slightly elevated troponin might mislead the clinician into not pursuing myocarditis as the underlying cause further.

Electrocardiography has variable features in children (nonspecific ST-T wave change, T-wave inversions, ST segment elevation, atrioventricular conduction delays, low-voltage QRS complex). Although some findings such as new-onset third-degree heart block should raise suspicion of myocarditis, there is no single pattern that is specific for myocarditis. However, electrocardiography may also identify changes associated with pericarditis such as ST segment elevation and PR depression.

Historically, enteroviruses have been the most common cause of myocarditis but more recent surveys show an increasing number of cases with parvovirus and herpes virus as the cause. Two disease processes that overlap with myocarditis are Kawasaki disease (KD) and multi system-inflammatory syndrome in children (MIS-C). For the child in the vignette, KD should certainly be considered even though he did not have the classic 5 days of fever with 4 of the following: rash, cervical lymphadenopathy, conjunctival injection, mucosal changes, or peripheral extremity changes. Echocardiographic assessment of the coronary arteries for dilation and aneurysm, along with laboratory findings such as elevated C-reactive protein, would be needed to assess for inflammation. In addition, MIS-C would be a reasonable consideration because the parents had been exposed to COVID-19 and the child had fever and tachycardia. However, a review found that more than 61% of patients were hypotensive

on presentation, which was only seen in this patient after he received fluids. This same review found that 41% of the cases had parenchymal changes on initial chest radiography and that 59% of the echocardiograms had coronary aneurysm and/or pericardial effusions, thus reinforcing the usefulness of early echocardiography.

PREP Pearls

- Echocardiography should be performed early to diagnose myocarditis.
- Distinctive features of myocarditis overlap with those of Kawasaki disease and multi system-inflammatory syndrome in children.

ABP Content Specifications(s)/Content Area

- Know how to diagnose myocardial infection

Suggested Readings

Auerbach SR, Richmond ME, Lamour JM, et al. BNP levels predict outcome in pediatric heart failure patients: post hoc analysis of the Pediatric Carvedilol Trial. *Circ Heart Fail.* 2010;3:606-611. doi:10.1161/CIRCHEARTFAILURE.109.906875

Dasgupta S, Iannucci G, Mao C, Clabby M, Oster ME. Myocarditis in the pediatric population: a review. *Congenit Heart Dis*. 2019;14(5):868-877. doi:10.1111/chd.12835

Dionne A, Dahdah N. Myocarditis and Kawasaki disease. *Int J Rheum Dis.* 2018;21(1):45-49. doi:10.1111/1756-185X.13219

Law YM, Lal AK, Chen S, et al. Diagnosis and management of myocarditis in children:a scientific statement from the American Heart Association. *Circulation*. 2021;144(6):e123-e135. doi:10.1161/CIR.0000000000001001

Radia T, Williams N, Agrawal P, et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): a systematic review of clinical features and presentation. *Paediatr Respir Rev*. 2021;38:51-57. doi:10.1016/j.prrv.2020.08.001

April

Question: 4

A 12-year-old, 120-kg boy was admitted to the pediatric intensive care unit (PICU) 5 days ago after being thrown from the all-terrain vehicle that he was driving without a helmet. His injuries include multiple compression fractures of the lumbar and thoracic spine, ligamentous injury to the cervical spine, and diffuse axonal injury without extra-axial hemorrhage affecting the frontal, parietal, and occipital areas of the brain on magnetic resonance imaging (MRI). He is given fentanyl 100 μg/hour and dexmedetomidine 0.5 μg/kg/hour as infusions for 48 hours to facilitate mechanical ventilation. He undergoes successful extubation, but continues to undergo cervical spine immobilization with thoracic and lumbar bracing. Since extubation, he has been very agitated and intermittently confused. He is given clonidine for anxiolysis and risperidone for delirium. He has been responding to commands intermittently. His other medications include enoxaparin for deep vein thrombosis prophylaxis, levetiracetam for early posttraumatic seizure prophylaxis, and famotidine for gastrointestinal prophylaxis.

Overnight, he becomes increasingly agitated and removes his intravenous catheter as well as his cervical collar repeatedly. The PICU staff gives him 3 doses of haloperidol (2 mg intravenously) for these episodes. Six hours after the last dose of haloperidol he is poorly responsive with his head turned to the left and eyes deviated to the left. He will not follow commands and cannot participate in extraocular movement testing. Pupils are 4 mm and reactive. His nurse states that he is afebrile, mildly tachycardic, and hypertensive. He is maintaining his airway and has room air oxygen saturations of 99%. The nurse further notes that he is moving his left arm but keeping his right hand clenched in a fist, protruding his tongue, and intermittently moaning.

Of the following, the MOST appropriate next management step for this patient is to

- **A.** administer diphenhydramine
- **B.** administer lorazepam
- **C.** initiate rapid cooling
- **D.** perform repeat brain magnetic resonance imaging

The *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition,* defines delirium as an acute disturbance in attention, awareness, and cognition, which (1) develops over a short period of time (usually hours to a few days), (2) represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day, and (3) is not a direct physiologic consequence of another medical condition, substance intoxication, or withdrawal. It is categorized into 3 subtypes: hyperactive, hypoactive, and mixed. Delirium is very common and increasingly recognized with screening in the pediatric intensive care unit (PICU). Various studies have found an incidence of delirium in the PICU ranging from 15% to 60%. Treatment of delirium in children and adolescents with traumatic brain injury is challenging because of the difficulty in discerning whether behaviors and symptoms are due to the underlying injury or delirium.

The patient in this vignette exhibits signs of an acute dystonic reaction caused by the antipsychotic medication haloperidol. Acute dystonia is an unpredictable adverse effect of antipsychotic medications, characterized by abnormal and prolonged contraction of the muscles of the eyes (oculogyric crisis), head, neck (torticollis or retrocollis), limbs, or trunk, often developing within a few days of starting or raising the dosage of a medication (such as a neuroleptic). Dystonic reactions can occur at any time, even after the first dose of a medication. The dystonia is thought to result from nigrostriatal dopamine D_2 receptor blockade which then leads to an excess of striatal cholinergic output (imbalance of dopaminergic/cholinergic stimulation). Dystonic reactions are more likely with older, high-potency antipsychotics such as haloperidol and are also more common in male patients and younger age groups. However, they have also been reported in newer and less potent antipsychotics commonly used to treat delirium in the PICU.

Haloperidol is a butyrophenone antipsychotic that non-selectively blocks brain postsynaptic dopaminergic D_2 receptors. The half-life of intravenous (IV) haloperidol is 14 to 26 hours. Duration of action is dose dependent and ranges from 3 to 24 hours. Adult dosing guidelines are based on degree of agitation (mild 0.5-2.5 mg IV; moderate 2-5 mg IV; severe 10-20 mg IV). Studies of haloperidol in PICU patients suggest that haloperidol has a narrow therapeutic range to achieve an appropriate degree of D_2 receptor occupancy without resulting in adverse events.

In addition to discontinuation of the inciting medication, the appropriate treatment for acute dystonia is treatment with an anticholinergic agent. Of the choices listed, diphenhydramine (1 mg/kg IV or intramuscular) is the most appropriate medication and likely the easiest to obtain in the PICU setting. It may be given via the intravenous or enteral route depending on patient condition. Benztropine, a medication with both anticholinergic

and antihistaminic effects, is generally the gold standard for treating acute dystonic reactions, but may not be readily available in most PICUs. The dose is 0.02 to 0.05 mg/kg per dose up to adult dosing of 1 to 2 mg/dose. Benztropine is not recommended for use in children younger than 3 years. Repeat dosing may be required, as the half-life for antipsychotic medications may be longer than the half-life of benztropine or diphenhydramine.

The differential diagnosis for this patient's acute presentation includes neuroleptic malignant syndrome, seizure, stroke, delirium, sympathetic storm, and cerebral hemorrhage. Neuroleptic malignant syndrome is also associated with antipsychotic agents but is characterized by hyperthermia (temperature >38°C, often higher than 40°C), rigidity ("lead-pipe"), mental status changes, and dysautonomia. Extreme muscle rigidity can cause severe creatine kinase elevation and rhabdomyolysis. It is commonly seen with haloperidol and other first-generation antipsychotics. Neuroleptic malignant syndrome is a consideration in this case, but the patient is afebrile and only has some evidence of dysautonomia at this point. Seizure is less likely because the patient has been receiving seizure prophylaxis with levetiracetam. In addition, he is not demonstrating tonic clonic activity. If the patient did not respond to treatment of acute dystonia, it may be reasonable to evaluate for seizure activity with electroencephalography. Evaluating for stroke with repeat brain magnetic resonance imaging might be considered because he is receiving prophylactic dosing of enoxaparin and is at higher risk for central nervous system hemorrhage. However, this is less likely as neither extremity is flaccid, and the patient is only intermittently unresponsive. Sympathetic storm might also be considered due to tachycardia and hypertension, but is less likely as the patient did not have these symptoms before receiving antipsychotics, does not have any reported injury to deep brain structures, and is not hyperthermic or diaphoretic.

PREP Pearls

- Risk factors for acute dystonic reactions from antipsychotic medications include male sex, young age, and the use of high-potency D_2 receptor antagonists in high doses.
- Response to parenteral diphenhydramine or benztropine is often diagnostic as well as therapeutic in patients presenting with acute dystonic reaction.

ABP Content Specifications(s)/Content Area

- Treatment of acute dystonia

Suggested Readings

Siegel EJ, Traube C. Pediatric delirium: epidemiology and outcomes. *Curr Opin Pediatr.* 2020;32:743-749. doi:10.1097/MOP.0000000000000960

Sloof VD, van den Dungen DK, van Beusekom BS, et al. Monitoring haloperidol concentration and associated adverse events in critically ill children with delirium: first results of a clinical protocol aimed to monitor efficacy and safety. *Pediatr Crit Care Med.* 2018;19:e112-e119. doi:10.1097/PCC.0000000000001414

Tural Hesapcioglu S, Ceylan MF, Kandemir G, Kasak M, Sen CP, Correll CU. Frequency and correlates of acute dystonic reactions after antipsychotic initiation in 441 children and adolescents. *J Child Adolesc Psychopharmacol.* 2020;30(6):366-375. doi: 10.1089/cap.2019.0123

April

Question: 5

A 5-month-old girl is brought to the emergency department with lethargy and decreased activity. The parents first noticed that the infant was feeding poorly when she became constipated 1 week ago. They have noticed increased drooling, which they attributed to teething. They also noticed that her cry has become weaker. The infant had been developing normally until this illness. The neurological examination is significant for sluggishly reactive pupils, weak cry, drooling, and an expressionless face. She appears to have poor head control, hypotonia, and generalized weakness, all described by the family as new clinical findings over the past week. Anal sphincter tone and deep tendon reflexes are decreased. Analysis of cerebrospinal fluid and nerve conduction studies are normal.

Of the following, the therapy that is MOST most likely to be effective in this patient is

- **A.** intrathecal nusinersen
- **B.** intravenous botulism immune globulin
- **C.** intravenous immunoglobulin
- **D.** oral neostigmine

The patient in the vignette is exhibiting typical clinical features of infant botulism and should receive intravenous botulism immune globulin (BIG-IV) as soon as possible (without waiting for laboratory confirmation of the diagnosis). Infant botulism results from spores of *Clostridium botulinum* (or rarely, toxigenic *Clostridium butyricum* or *Clostridium baratii*) germinating in the large intestine and producing botulinum neurotoxin. The neurotoxin is absorbed into the bloodstream and affects peripheral cholinergic synapses. There it cleaves intracellular proteins needed for release of acetylcholine, blocking transmission to muscles and resulting in flaccid paralysis.

Botulism presents with a combination of clinical features including generalized weakness, hypotonia, decreased activity, poor feeding, constipation, cranial nerve palsy, hypoventilation with shallow rapid breaths, and occasionally, respiratory failure. There have

been some case reports of rapid progression of neuromuscular weakness with initial presentation as cardiopulmonary arrest or apparent sudden infant death syndrome. In botulism there is no fever, and the infant is the only ill family member. The presence of bulbar palsy, sluggish pupils, symmetric descending paralysis, and fatigability with repetitive stimulation of muscle contraction (elicitable clinically by repeatedly assessing the pupillary light reflex over 1 to 3 minutes) are some discriminating features of infant botulism. An enema with sterile, non-bacteriostatic water (not saline) is used to obtain a fecal specimen for a diagnostic botulinum toxin assay. Botulism immune globulin is the treatment of choice for infant botulism caused by toxin type A or B in patients less than 1 year of age. It shortens the hospital length of stay (LOS) and decreases associated costs. The greatest LOS reduction was achieved when BIG-IV was administered soon after hospital admission. For additional resources for procuring and administration of BIG-IV, please refer to https://infantbotulism.org.

Nusinersen is a survival motor neuron-2 (SMN2)-directed antisense oligonucleotide indicated for the treatment of spinal muscular atrophy. Due to a mutation in the *SMN1* gene, patients with spinal muscular atrophy (SMA) type 1 rely on the *SMN2* gene to produce functional SMN protein. Delivered intrathecally, nusinersen binds to a specific sequence in the *SMN2* gene and increases the production of functional SMN protein in the central nervous system. Spinal muscular atrophy type 1 also presents with generalized weakness in infants but unlike botulism, typically spares the extraocular muscles and sphincters. Unlike the more acute onset of botulism in the otherwise healthy infant in the vignette, patients with SMA often have a history of progressive weakness for weeks to months before diagnosis.

Intravenous immune globulin is indicated for the treatment of Guillain-Barré syndrome (GBS) which typically occurs in older children after a preceding viral illness. It is an autoimmune, post-infectious, demyelinating, peripheral neuropathy that presents with acute flaccid paraparesis or ascending quadriparesis. In contrast, over 99% of cases of infant botulism occur at age less than 1 year and present with a symmetric, descending paralysis. Pupillary abnormalities are rarely seen with GBS. Although cranial nerve palsies are seen in the Miller Fisher variant of GBS in infants, it can be distinguished from infant botulism by cerebrospinal fluid (CSF) analysis and nerve conduction studies. Guillain-Barré syndrome is associated with elevated protein concentration in CSF, whereas CSF is normal in infant botulism as in the case in the vignette.

Oral neostigmine has been used to improve dysphagia in patients with neonatal myasthenia gravis (MG). Neonatal MG is a temporary form of MG due to transplacental transmission of maternal autoantibodies that affect nicotinic acetylcholine receptors as well as the muscle-specific receptor tyrosine kinase. Neonatal MG is rare and occurs in only 10% to 15% of infants born to mothers with MG. However, in contrast to botulism, infants

become symptomatic within 72 hours of birth with a weak cry, poor suck, generalized hypotonia, respiratory distress, and facial diplegia. Outcome is excellent with respiratory and nutritional support needed for a few weeks until spontaneous remission occurs. Other immunomodulatory treatments used to treat MG in older children and adults such as plasmapheresis, intravenous immunoglobulins, and corticosteroids are rarely needed.

PREP Pearls

- A careful history and neurologic examination are essential for distinguishing infant botulism from its clinical mimics.
- Multiple symmetrical cranial nerve palsies (manifested as a weak cry, poor suck and gag reflex, ptosis, sluggish pupils, expressionless face) help distinguish infant botulism from other causes of subacute- to acute-onset generalized weakness.
- Fatigability with repetitive stimulation of muscle contraction, a hallmark of botulism, is elicitable clinically by repeatedly assessing the pupillary light reflex over 1 to 3 minutes.

ABP Content Specifications(s)/Content Area

- Botulism

Suggested Readings

Arnon SS. Infant botulism. In: Feigin RD, Cherry JD, Demmler GJ, Kaplan SL, eds. *Textbook of Pediatric Infectious Diseases*. 5th ed. Philadelphia, PA: WB Saunders; 2004:1758-1766.

Infant Botulism Treatment and Prevention Program. Accessed December 8, 2021. https://infantbotulism.org/

Payne JR, Khouri JM, Jewell NP, Arnon SS. Efficacy of human botulism immune globulin for the treatment of infant botulism: the first 12 years post licensure. *J Pediatr*. 2018;193:172-177. doi:10.1016/j.jpeds.2017.10.035

April

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 6

A 3-month-old male infant is admitted to the pediatric intensive care unit with respiratory distress resulting from viral bronchiolitis. The infant has a history of prematurity, respiratory distress syndrome, and bronchopulmonary dysplasia, and at home requires supplemental oxygen via nasal cannula to maintain his oxygen saturation above 92%. His home medications include bronchodilators, inhaled steroids, furosemide, and ranitidine. Over the past 24 hours the infant has developed poor oral intake, rapid breathing, and an increased supplemental oxygen requirement.

On admission, the infant is tachypneic, tachycardic, and hypotensive with weak pulses and prolonged capillary refill time. The infant is placed on non-invasive positive-pressure ventilation, intravenous access is secured, and 20 mL/kg isotonic fluid bolus is administered. Capillary blood gas values are shown:

Laboratory Test	Result
pH	7.51
PCO_2	47 mm Hg
HCO_3	39 mEq/L (39 mmol/L)

Of the following, the MOST likely cause of this infant's abnormal pH is

- **A.** diuretic therapy
- **B.** hyperventilation
- **C.** saline administration
- **D.** supplemental oxygen use

The patient's capillary blood gas values are consistent with metabolic alkalosis, a condition that commonly occurs in infants receiving chronic diuretic therapy. Metabolic alkalosis results when there is either a loss of hydrogen or an excess of bicarbonate in extracellular fluid. This acid-base disorder is classified based on urine chloride levels. Patients with metabolic alkalosis who have a urine chloride level less than 10 mEq/L are considered chloride responsive, while patients with a urine chloride level greater than 20 mEq/L are chloride resistant. In general, chloride-responsive metabolic alkalosis results from gastric or renal loss of chloride, often in combination with hydrogen. Chloride-resistant metabolic alkalosis results from bicarbonate excess, or from a shift of hydrogen from extracellular to intracellular space. The **Table** summarizes the causes of chloride-responsive and chloride-resistant metabolic alkalosis.

The most common type of metabolic alkalosis encountered in critically ill children is chloride responsive, which occurs in the following settings:

1. **Gastric loss of hydrogen:** Caused by gastric fluid loss from severe vomiting or nasogastric suctioning, which leads to the loss of hydrochloric acid.
2. **Contraction alkalosis:** Results from loss of water in the extracellular space, which triggers the renin-angiotensin-aldosterone system and stimulates renal excretion of hydrogen and chloride. Commonly seen with use of loop and thiazide diuretics.
3. **Post-hypercapnia syndrome:** Hypoventilation leads to hypercapnia and respiratory acidosis. Renal compensation results in the loss of hydrogen and bicarbonate retention, which may persist after carbon dioxide levels return to baseline.

Other causes of chloride-responsive metabolic alkalosis include cystic fibrosis, congenital chloride-losing enteropathy, and villous adenoma.

Chloride-resistant metabolic alkalosis is less common in children compared to chloride-responsive metabolic alkalosis, and it can be categorized into conditions associated with mineralocorticoid excess and those without mineralocorticoid excess. Examples of conditions with mineralocorticoid excess include hyperaldosteronism, renal artery stenosis, iatrogenic steroid use, Cushing syndrome, adrenal hyperplasia, Liddle syndrome, and

licorice ingestion. Examples of conditions not associated with mineralocorticoid excess include milk-alkali syndrome, exogenous buffer administration, Bartter syndrome, and hypokalemia.

The treatment for metabolic alkalosis is generally not an emergency and depends on the underlying disorder. Patients with mild or moderate alkalosis may not require any treatment. Those with severe metabolic alkalosis may require correction of hypovolemia, hypochloremia, and hypokalemia. Antiemetics and anti-reflux medications may be useful in patients with gastric losses resulting from vomiting. Causative agents such as antacids or buffers in intravenous fluids should be eliminated. Patients on diuretic therapy should reduce or discontinue use if possible. Those with chloride-responsive metabolic alkalosis may benefit from chloride supplementations such as sodium chloride, potassium chloride, ammonium chloride, or arginine hydrochloride. Acetazolamide, a carbonic anhydrase inhibitor that facilitates renal excretion of bicarbonate, may be useful in some patients with metabolic alkalosis.

The infant described has contraction alkalosis induced by the use of furosemide, a loop diuretic. Hyperventilation causes respiratory alkalosis, not metabolic alkalosis. Saline administration can cause metabolic acidosis in some situations, but it would not cause alkalosis. Supplemental oxygen use would not be expected to affect the acid-base status in this patient.

PREP Pearls

- Metabolic alkalosis occurs in the setting of excess bicarbonate or increased loss of acid, and is further classified based on urine chloride levels. Patients with a urine chloride level less than 10 mEq/L are chloride responsive, while those with a urine chloride level greater than 20 mEq/L are chloride resistant.
- Causes of chloride-responsive metabolic alkalosis include loss of gastric fluid, diuretic therapy, and post-hypercapnia syndrome; examples of chloride-resistant metabolic alkalosis include mineralocorticoid excess, exogenous buffer administration, and hypokalemia.
- Treatment of metabolic alkalosis is generally not an emergency but may include correction of hypovolemia, hypokalemia, and hypochloremia.

ABP Content Specifications(s)/Content Area

- Know how to treat metabolic alkalosis
- Know the causes of metabolic alkalosis

Suggested Readings

Bar A, Cies J, Stapleton K, Tauber D, Chopra A, Shore PM. Acetazolamide therapy for metabolic alkalosis in critically ill pediatric patients. *Pediatr Crit Care Med*. 2015:16(2);34-40. doi:10.1097/PCC.0000000000000313

Nitu M, Montgomery G, Eigen H. Acid-Base disorders. *Pediatr Rev*. 2011:32(6);240-251. doi:10.1542/pir.32-6-240

Sierra CM, Hernandez EA, Parbuoni KA. Use of arginine hydrochloride in the treatment of metabolic alkalosis or hypochloremia in pediatric patients. *J Pediatr Pharmacol Ther*. 2018:23(2);111-118. doi:10.5863/1551-6776-23.2.111

Table. Causes of Metabolic Alkalosis in Children

High urine chloride (chloride resistant)	Low urine chloride (chloride responsive)
Mineralocorticoid excess Renal artery stenosis Renin-secreting tumor Adrenal hyperplasia Liddle syndrome Cushing syndrome Iatrogenic steroid use 17α-hydroxylase/17,20-lyase deficiency 11-β-hydroxylase deficiency Licorice ingestion Bartter syndrome Gitelman syndrome Hypokalemia Hypomagnesemia Milk alkali syndrome Exogenous buffer administration	Gastrointestinal loss Vomiting Diarrhea Nasogastric suction Cystic fibrosis Villous adenoma Congenital chloride-losing enteropathy Post-hypercapnia syndrome Volume contraction from diuretic use

Courtesy of C. Preissig

May

Question: 1

A 2-month-old, full-term female infant is admitted to the pediatric intensive care unit (ICU) after presenting the day prior to the pediatric emergency department (ED) with several days of fever, lethargy, and poor feeding.

Vital signs and laboratory data obtained on arrival at the pediatric ICU were as follows:

Temperature	38.4°C
Heart rate	175 beats/min
Blood pressure	70/46 mm Hg
Respiratory rate	32 breaths/min
Oxygen saturation	100% in room air

Her laboratory data are as follows:

Laboratory Test	**Result**
Glucose	20 mg/dL (1.1 mmol/L)
Blood urea nitrogen	23 mg/dL (8.2 mmol/L)
Creatinine	0.9 mg/dL (79.6 µmol/L)
Aspartate aminotransferase	1,652 U/L

Alanine aminotransferase	1,268 U/L
Lactate	54.1 mg/dL (6 mmol/L)

Blood, urine, and cerebrospinal fluid cultures are obtained as well as herpes simplex virus polymerase chain reaction test (HSV PCR) results. A dextrose bolus is administered for hypoglycemia. She is started on vancomycin, ceftriaxone, and acyclovir and receives 40 mL/kg of intravenous 0.9% saline with improvement in her heart rate.

In the pediatric ICU over the next 24 hours, she continues to decompensate with progressive hemodynamic instability and rising blood lactate concentration requiring intubation and multiple vasoactive infusions.

Further laboratory data are shown:

Laboratory Test	**Result**
Aspartate aminotransferase	>6,000 U/L
Alanine aminotransferase	>6,000 U/L
Ammonia	346 µg/dL (247 µmol/L)
International normalized ratio	9.6
Fibrinogen	112 mg/dL (1.1 g/L)
White blood cell count	2,400/µL (2.4×10^9/L)
Platelet count	18 × 103/µL (18×10^9/L)
Ferritin	86,000 ng/mL (86,000 µg/L)

HSV PCR results are negative in the blood and cerebrospinal fluid, and bacterial cultures show no growth. She is started on continuous renal replacement therapy for severe metabolic acidosis and hyperammonemia as well as fluid overload.

Of the following, the finding that would MOST likely establish the suspected diagnosis is

- **A.** high NK cell activity
- **B.** low concentration of soluble interleukin 2 receptor
- **C.** perforin gene mutation
- **D.** SERPINA-1 gene mutation

Acute liver failure (ALF) is rare in the United States and most countries. The leading causes of ALF in infants are metabolic diseases. In older children, ALF results most commonly from viral etiologies (especially hepatitis A), drug-induced hepatotoxicity, and autoimmune hepatitis. However, for many children, the cause of ALF may never be identified.

Acute liver failure has been defined in adults as a severe liver injury in a patient without preexisting liver disease that progresses to hepatic encephalopathy within 8 weeks of the onset of symptoms (usually jaundice).

Pediatric hepatic encephalopathy (HE) may be difficult to identify or may present much later (if at all) in a patient's course of illness. Therefore, pediatric ALF is defined as a multisystem disorder with severely impaired liver function, with or without encephalopathy, in a patient with no history of liver disease. More specifically, biochemical evidence of liver dysfunction with an international normalized ratio (INR) ≥ 1.5 with HE or an INR ≥ 2 regardless of the presence of hepatic encephalopathy.

There are 7 main etiologic categories for pediatric ALF: metabolic/genetic, infectious, toxin- or drug-induced, autoimmune, malignancy-induced, vascular, and undetermined. For children younger than 1 year, the main causes are viral infections (usually enteroviruses) and inborn errors of metabolism. For children aged 1 year or older, most cases of ALF in which a cause is identified are drug-induced, autoimmune, and viral. Hepatitis A virus is the most common cause of ALF in endemic areas, but it is uncommon in North America and Europe. The diagnostic evaluation for pediatric ALF is oriented toward rapid identification of an underlying cause and assessment of disease severity.

Hemophagocytic lymphohistiocytosis (HLH) is a rare cause of neonatal liver failure, with an incidence of about 1 in 50,000 to 150,000. It is characterized by proliferation of macrophages in the tissues that leads to pathologic immune activation. It may be familial (fHLH) or occur secondary to a severe infection, rheumatoid disorder, or malignancy. Infections known to be associated with HLH include Epstein-Barr virus, parvovirus B19, cytomegalovirus, and bacterial or fungal infections. Neonatal cases, such as that seen in this patient, are usually primary. The most common gene mutations associated with fHLH affect the perforin gene (*PRF1*). Perforin is released by cytotoxic T cells and natural killer (NK) cells to perforate target cell membranes and initiate apoptotic cell death. When perforin is absent, these cells' activity is disrupted, and there is unregulated production of proinflammatory cytokines and activated macrophages.

The diagnosis of HLH can be made through a molecular diagnosis by identifying relevant gene mutations (perforin, hMUNC 13-4, and others) or through flow cytometry for perforin in NK and cytotoxic T cells. The diagnosis can also be established by the presence of certain clinical criteria; the patient must meet 5 of the 8 criteria listed in the **Table**.

This patient met 4 of 8 criteria with persistent fever, cytopenias, hypofibrinogenemia, and hyperferritinemia. Hemophagocytosis, low NK cell activity, or high concentration of soluble interleukin 2 receptor would have established the diagnosis by clinical criteria. Testing demonstrating a mutation in the perforin gene is also sufficient to establish the diagnosis.

The SERPINA-1 gene mutation is associated with α1-antitrypsin deficiency, the most common genetic cause of pediatric liver disease and the most frequent genetic indication for pediatric liver transplant. It is not, however, associated with HLH.

Pediatric ICU teams work closely with multidisciplinary liver transplant teams and oncology services to provide highly specialized care to infants with HLH. Allogeneic stem cell transplantation is the only cure for familial HLH, so initial management when the diagnosis is established should include an early search for an appropriate stem cell transplantation donor. Potential medical therapies include dexamethasone to decrease inflammation and suppress neutrophil migration and emapalumab, a monoclonal antibody that inhibits interferon gamma (which plays an important role in disease activity) and is the first drug for HLH approved by the U.S. Food and Drug Administration.

PREP Pearls

- Hemophagocytic lymphohistiocytosis is a rare cause of neonatal liver failure characterized by proliferation of histiocytes leading to a hyperinflammatory state.
- The diagnosis of hemophagocytic lymphohistiocytosis can be established through clinical criteria or by identifying causative genetic mutations.

- Stem cell transplantation is the only curative therapy for familial hemophagocytic lymphohistiocytosis.

ABP Content Specifications(s)/Content Area

- Understand the epidemiology of pediatric acute liver failure.
- Describe differences in etiologies of liver failure comparing neonates to older children.
- Describe the diagnostic criteria for hemophagocytic lymphohistiocytosis
- Know the most common genetic mutations associated with hemophagocytic lymphocytosis

Suggested Readings

McLean J, Katebian R, Suh E, Mirza K, Amin S. Neonatal hemophagocytic lymphohistiocytosis. *NeoReviews.* 2019;20(6):e316-e325. doi:10.1542/neo.20-6-e316

Molleran Lee S, Villanueva J, Sumegi J, et al. Characterisation of diverse PRF1 mutations leading to decreased natural killer cell activity in North American families with haemophagocytic lymphohistiocytosis. *J Med Genet.* 2004;41(2):137-144. doi:10.1136/jmg.2003.011528

Table. Diagnostic Criteria for Hemophagocytic Lymphohistiocytosis.

1	Persistent fever
2	Splenomegaly
3	Cytopenias (hemoglobin <9.0 g/dL [90 g/L], neutrophils <1,000/μL [$<1.0 \times 10^9$/L], platelets $<100 \times 10^3$/μL [$<100 \times 10^9$/L])
4	Hypofibrinogenemia (<150 mg/dL [1.5 g/L]) or hypertriglyceridemia (>265 mg/dL [>3.0 mmol/L])
5	Hyperferritinemia (>500 ng/mL [>500 μg/L])
6	Hemophagocytosis
7	Low natural killer cell activity
8	High concentration of soluble interleukin 2 receptor

Courtesy of K. Hoops

May

Question: 2

A 15-year-old adolescent boy arrives in the pediatric intensive care unit with severe status asthmaticus. He received continuous inhaled albuterol and systemic corticosteroids in the emergency department and is started on bilevel positive airway pressure in the pediatric ICU. Two hours later, he is somnolent and states that it is harder to breathe. He is intubated and placed on mechanical ventilation. He is sedated and has undergone neuromuscular blockade. His ventilator settings are as follows:

Mode	Synchronized intermittent mandatory ventilation
Limit	Pressure
Rate	12 breaths/min
Inspiratory time	1 second
Peak inspiratory pressure	40 cm H_2O
Exhaled tidal volume	9 mL/kg
Positive end expiratory pressure	3 cm H_2O
Pressure support	10 cm H_2O
FiO_2	0.55

Of the following, the NEXT step in providing the best estimate of the contribution of airway resistance to the overall peak inspiratory pressure is to

- **A.** change the inspiratory flow method
- **B.** evaluate the flow-volume loop
- **C.** perform an expiratory hold maneuver
- **D.** perform an inspiratory hold maneuver

Patients with severe bronchospasm (eg, asthma and chronic obstructive pulmonary disease) have significantly elevated airway resistance due to decreased airway radius. Despite multiple medical advances, hospitalizations and deaths in children due to asthma have been relatively unchanged over the past 20 years. The complex cardiopulmonary interactions in patients with severe asthma play a role in this.

The mainstay of ventilatory management in patients with lower airway obstruction is to minimize "air trapping" within the alveoli while maintaining oxygen saturation and $PaCO_2$ that is compatible with life (permissive hypoxemia and hypercapnia) as the medical treatment (eg, bronchodilators and corticosteroids) continues. This can be achieved by allowing for adequate expiratory time, primarily through ventilatory rate reduction, due to the increased time constant (amount of time to fill or empty a lung unit) in highly resistant lung units.

The instantaneous pressure within a closed respiratory system is the combination of the pressure to overcome airway resistance and the pressure to overcome the respiratory system elastance (ie, elastic recoil of the lung and chest wall). Thus, the peak inspiratory pressure (PIP) is the highest pressure during the inspiration cycle, as seen in the following (equation 1):

$$Paw = P_{airway\ resistance} + P_{lung+chest\ wall\ elastance} \quad \text{(Equation 1)}$$

Using Poiseuille's law for laminar flow through a tube and the static pressure-volume relationship in the lung and chest wall, the formula becomes as follows (equation 2):

$$Paw = \left[\frac{\partial V}{\partial t_i} \cdot \left(\frac{8\eta l}{\pi r^4}\right)\right] + VE \qquad \text{(Equation 2)}$$

where

$\frac{\partial V}{\partial t_i}$ = inspiratory flow rate
η = viscosity
l = airway length
r = airway radius
V = lung volume
E = lung and chest wall elastance

For most patients, the PIP is typically at the end of inspiration, because the pressure at end inspiration is much higher than the pressure to overcome airway resistance. However, in patients with severe airway obstruction (such as asthma), the pressure to overcome airway resistance (the dynamic component of respiratory system compliance) is much higher owing to the significantly elevated resistance (due to decreased airway radius). Thus, the PIP in these patients may not reflect the true alveolar pressure (P_{alv}; and the static compliance of the respiratory system).

To determine whether the PIP reflects the P_{alv}, it is necessary to separate the contribution of airway resistance from the respiratory system's static compliance. As seen in equation 2, the pressure to overcome airway resistance is the product of the inspiratory flow rate $(\frac{\partial V}{\partial t_i})$ and resistance. Therefore, if the $(\frac{\partial V}{\partial t_i})$ becomes zero, then the pressure due to airway resistance is also zero, and the Paw reflects the P_{alv}. This is termed the plateau pressure (P_{plat}). P_{plat} is a useful measure in both research and clinical settings as a way to adjust ventilator settings to minimize the risk of ventilator-associated lung injury (VALI). Although the term *barotrauma* has been used to describe VALI, it is actually volutrauma (excessive volume per alveolus) that participates in the majority of VALI (Gattinoni). This was illustrated in a study (Dreyfuss), in which rats with high volume but minimal P_{aw} (open chest) had significantly more lung injury than rats with low volume but high P_{aw} (strapped chest). P_{plat} is still a useful measure to follow since, for a given static compliance, alveolar volume increases as Pplat increases. Thus, P_{plat} can be a surrogate for alveolar volume, especially since we cannot direct where air is delivered once it leaves the endotracheal tube.

The inspiratory hold maneuver will bring $(\frac{\partial V}{\partial t_i})$ to zero to estimate Pplat. This allows for estimation of the contribution of airway resistance to overall PIP by the difference between PIP and P_{plat} (PIP - P_{plat}). This difference can then be followed to (a) ensure that the P_{plat} is not excessively high and (b) measure the effect of bronchodilators (PIP-P_{plat} will decrease as the airway radius increases). This method works only if the inspiratory flow rate is held constant, however. In most ventilators, pressure-limited breaths (pressure control) use a decelerating inspiratory flow ("ramp" waveform) (**Figure**). Because of this, the inspiratory flow rate is highest when the lung volume is lowest and decreases during inspiration. In a decelerating flow pattern, the inspiratory flow rate approaches zero at the end of inspiration. This leads to a situation in which the contribution of airway resistance is highest when the lungs are deflated and absent when the lungs are inflated (at end inspiration). Because the contributions of airway resistance and static compliance are continuously changing throughout inspiration (equation 2), it is difficult to interpret the relative contributions of airway resistance and static compliance in the PIP. Therefore, the PIP-P_{plat} may not truly reflect the contribution of airway resistance to overall dynamic compliance of the lung. Additionally, decelerating inspiratory flow patterns may have breath-to-breath variability in the peak inspiratory flow rate, making consistent comparisons difficult.

To more accurately use PIP-P_{plat} to determine the contribution of airway resistance to overall dynamic compliance, the inspiratory flow rate must be constant ("square" waveform). With a constant inspiratory flow rate, the pressure to overcome airway resistance is also held constant. Therefore, the PIP is the point at which the lungs are maximally inflated (in which static compliance is also constant). This allows for a more accurate and consistent measurement of PIP-P_{plat} to assess airway resistance. This can only be done in a volume-limited breath (volume control) in which a constant inspiratory flow rate and inspiratory time are set. Of note, most modern ventilators have combined modes that allow for volume-limited breaths using a decelerating inspiratory flow (eg, "autoflow," "volume control plus," "pressure-regulated volume control," etc). Once a patient is using a constant inspiratory flow, then the inspiratory hold maneuver can accurately depict PIP-P_{plat} as an estimate of the contribution of airway resistance to PIP. The expiratory hold maneuver is primarily used to assess auto (or intrinsic) positive end expiratory pressure. The flow-volume loop can help assess for both inspiratory and expiratory flow limitations.

PREP Pearls

- A constant ("square") inspiratory flow rate using volume control is necessary to accurately estimate the contribution of airway resistance to overall dynamic lung compliance.

- Excessive alveolar volume is significantly more damaging to the lungs than is increased alveolar pressure.

ABP Content Specifications(s)/Content Area

- Understand the principles and applications of the various modes of pressure-controlled mechanical ventilation
- Know the advantages and limitations of the various modes of volume-controlled mechanical ventilation
- Understand the effects of high airway resistance on mechanical ventilation

Suggested Readings

Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema: Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *Am Rev Respir Dis.* 1988;137(5):1159-1164. doi:10.1164/ajrccm/137.5.1159

Gattinoni L, Protti A, Caironi P, Carlessoa E. Ventilator-induced lung injury: The anatomical and physiological framework. *Crit Care Med.* 2010;38(suppl 10):S539-S548. doi:10.1097/CCM.0b013e3181f1fcf7

Henderson W, Paré PA, Ayas NT. Respiratory system mechanics and energetics. In: Broaddus VC, ed. *Murray & Nadel's Textbook of Respiratory Medicine*. 6th ed. Elsevier Saunders; 2016:76-91.

May

Question: 3

A 6-year-old, 15-kg female patient who has undergone heart transplantation is admitted for subacute rejection and heart failure. During her hospitalization she developed ventricular dysrhythmias, which required pharmacologic treatment with amiodarone. She is being maintained on milrinone, dopamine, and amiodarone infusions for her heart failure and dysrhythmia. She also developed seizure activity, which required treatment with carbamazepine. Her medications include furosemide, spironolactone, glucocorticoids, and tacrolimus.

Of the following, the drug that is LEAST likely to affect her thyroid hormone levels is

- **A.** amiodarone
- **B.** carbamazepine
- **C.** dopamine
- **D.** milrinone

Thyroid hormone plays an important role in regulation of cellular metabolism and energy expenditure. Excessive thyroid hormone levels increase metabolic rate while decreased thyroid hormone levels result in the opposite effect. Thyroid hormone acts systemically at the tissue level to modulate energy expenditure. At the tissue level, thyroxine (T_4) undergoes conversion to the active form, triiodothyronine (T_3). Thyroxine is converted to T_3 by type 1 and 2 deiodinase enzymes. Triiodothyronine is 10 times more biologically active than T_4. The circulating half-life of T_4 is 7 days compared to the 1-day half-life of T_3. Thyroid hormone release is stimulated by thyrotropin-releasing hormone (TRH) from the hypothalamus. Thyrotropin-releasing hormone stimulates the anterior pituitary to secrete thyroid-stimulating hormone (TSH) that in turn stimulates secretion of T_4 from the thyroid gland.

In addition to regulation of energy metabolism, thyroid hormone plays an important role in thermogenesis. Thyroid hormone also plays an active role in maintaining core body temperature. This occurs through activation of the β_3-adrenergic pathway that increases cellular metabolism through the action of type 2 deiodinase with stimulation of ATP production and generation of heat to maintain core temperature. The lack of thyroid hormone results in minimal heat production. Thyroid hormone increases metabolic rate and oxygen consumption. Metabolic rate increases glucose utilization and cellular glucose uptake with stimulation of gluconeogenesis and insulin clearance.

Thyroid hormone plays an important role in many organ systems. The systemic effects of thyroid hormone affect the cardiovascular, respiratory, and renal systems. Thyroid hormone exerts direct effects on the cardiovascular system by increasing inotropic and chronotropic actions that affect myocardial work and oxygen consumption. Additionally, thyroid hormone also causes lusitropy, relaxation of vascular smooth muscle, and increased sensitivity to α and β agonists. In addition to increased sensitivity to catecholamines, thyroid hormone has been attributed to increased catecholamine receptor numbers, cellular pump activity, and second messenger coupling. Thyroid hormone is involved in control of ventilation, increased surfactant production with reduced alveolar surface tension, and alveolar fluid clearance with enhanced water absorption. Thyroid hormone also stimulates release of renin and increases reabsorption of sodium and water in the proximal renal tubules. Additionally, T_3 stimulates natriuretic peptides, resulting in sodium and water excretion. Thyroid hormone is also involved in directly increasing phagocytic activity of immune cells, lymphocyte proliferation, and antibody production. Finally, synthesis of hepatic enzymes and increased gastrointestinal motility are enhanced with thyroid stimulation. Supplemental thyroid hormone administration has been used in the care of postoperative heart patients and organ donors.

When patients are critically ill, T_3 levels are known to decrease. It is unclear whether this is an adaptive response in an effort to conserve energy and limit metabolic demands or is a true pathologic state. Although T_3 and T_4 levels may decrease, thyrotropin typically remains in a normal range. This change during chronic or critical illness has been termed the sick euthyroid syndrome or low T_3 syndrome. The sick euthyroid state occurs for several reasons, including caloric intake, medications that affect thyroid function, and severity of the disease process. The level of thyroid hormone during the sick euthyroid syndrome is proportional to the severity of illness and occurs as a result of altered conversion of T_4 to T_3 by serum deiodinases. Studies have revealed that patients who died had persistently lower T_3 levels compared with survivors. Patients with lower cardiac output after cardiac surgery, major trauma including burns, and sepsis also have lower T_3 levels. Patients with sick euthyroid syndrome do not require treatment with thyroid hormone. Treatment should be focused on management of the underlying disease process.

Several classes of drugs can interfere with thyroid activity, including glucocorticoids, antiepileptic agents, catecholamines, and amiodarone. These drugs can affect the hypothalamic pituitary axis, thyroid hormone synthesis, or release of thyroid hormone. Milrinone has no effect on thyroid hormone levels, making it the correct response.

Pharmacologic agents such as glucocorticoids, dopamine agonists, and somatostatin can suppress TSH. Dopamine is known to suppress TSH in addition to affecting prolactin and growth hormone secretion. Drugs with excessive iodine concentrations—including iodinated contrast agents, amiodarone, and topical povidone-iodine preparations—can affect thyroid hormone production. The antiarrhythmic agent amiodarone is 37.3% iodine by weight. The excessive iodine in amiodarone can cause amiodarone-induced thyrotoxicosis, which is treated with antithyroid drugs. Hypothyroidism can also occur from amiodarone in addition to a destructive thyroiditis as a result of the direct cytotoxic effects of amiodarone on thyrocytes. The amiodarone-induced destructive thyroiditis is treated with glucocorticoids.

There are several classes of drugs that affect protein binding of thyroid hormone. Displacement of thyroid hormone from binding proteins can occur with some nonsteroidal anti-inflammatory drugs, high-dose furosemide, and heparin (including low-molecular-weight heparin preparations), carbamazepine, and phenytoin. Carbamazepine and phenytoin also enhance the metabolism of thyroid hormone. Drugs that inhibit conversion of T_4 to T_3 include glucocorticoids, high-dose propranolol, propylthiouracil, and amiodarone. Thyroid test results are altered with amiodarone, resulting in T_4 and TSH elevation and a decreased T_3 level.

PREP Pearls

- There are many pharmacologic agents that can interfere with stimulation, synthesis, and release of thyroid hormone. Commonly used agents in the pediatric ICU include dopamine, amiodarone, povidone iodide, carbamazepine, and phenytoin. Certain drugs, such as nonsteroidal anti-inflammatory drugs, high-dose furosemide, and heparin including low-molecular-weight heparin preparations, and antiepileptic agents, can displace thyroid hormone from binding proteins.
- Thyroid hormone is important for regulation of cellular metabolism, energy expenditure, and thermogenesis.
- The level of thyroid hormone during the sick euthyroid syndrome is proportional to the severity of illness. It is unclear if the sick euthyroid state is an adaptive response to conserve energy and limit metabolic demands or if this a true pathologic state. Patients with sick euthyroid syndrome do not require treatment with thyroid hormone. Treatment should be directed at management of the underlying disease process.

ABP Content Specifications(s)/Content Area

- Know the role of thyroid hormones in regulating energy metabolism
- Know the role of thyroid hormones in modulating catecholamine effects
- Know which drugs may interfere with the normal thyroid hormone axis
- Recognize the laboratory manifestations of sick euthyroid syndrome
- Know that thyroid supplementation is not indicated for patients with sick euthyroid syndrome

Suggested Readings

Burch BH. Drug effects on the thyroid. *New Engl J Med* 2019;381:749-761. doi:10.1056/NEJMra1901214

Fliers E, Bianco AC, Langouche L, et al. Endocrine and metabolic considerations in critically ill patients. *Lancet Diabetes Endocrinol.* 2015;3(10):816-825. doi:10.1016/S2213-8587(15)00225-9

Maiden MJ, Torpy DJ. Thyroid hormones in critical illness. *Crit Care Clin*. 2019;35:375-388. doi:10.1016/j.ccc.2018.11.012

Yavuz S, Salgado Nunez del Prado S, Celi FS. Thyroid hormone action and energy expenditure. *J Endocr Soc.* 2019;3(7):1345-1356. doi:10.1210/js.2018-00423

May

Question: 4

A 17-year-old adolescent boy with a history of anxiety and COVID-19 infection 7 months ago is evaluated for chest pain and tachycardia. In addition, he has mild nasal congestion, malaise, and a sore throat. Oxygen saturation in room air is 96%. He was given 2 L of normal saline in the emergency department but remains tachycardic. An electrocardiogram demonstrated sinus tachycardia with normal axis and intervals.

Laboratory data are shown:

Laboratory Test	**Result**
Troponin I	<0.01 ng/mL (<0.01 µg/L)
Brain-type natriuretic peptide	<10 pg/mL (<10 ng/L)
D-dimer	10 µg/mL (54.76 nmol/L)

He reports tenderness to palpation over the sternum and discomfort when supine or with cough. A chest radiograph shows a cardiac silhouette that is at the high end of normal without any pulmonary infiltrates. A rapid antigen test result for SARS-CoV-2 is positive.

Of the following, the disease process that is MOST likely causing this patient's symptoms is

- **A.** costochondritis
- **B.** myocarditis
- **C.** pericarditis
- **D.** pulmonary embolism

Pericarditis is a rarely encountered cause of chest pain in children, but the recent COVID-19 pandemic has been associated with increased reporting of this infrequent disease. This recent spike in infection-related cases reverses the trend of the last few decades, in which most cases of pericarditis were associated with postcardiotomy syndrome. Historically, patients who have undergone bone marrow transplant and children who have had surgical atrial septum repair are at the highest risk of experiencing pericarditis owing to noninfectious causes. The patient in the vignette has persistent tachycardia despite having received fluid boluses. The patient's electrocardiogram does not have the classic ST-segment elevation often associated with pericarditis. However, this finding is present in less than one-half of cases and is seen only during the most acute phase of the disease.

Although myocarditis should be considered in this presentation, the normal concentrations of brain-type natriuretic peptide and troponin indicate that myocardial inflammation is unlikely. An echocardiogram would be indicated in both disease processes to assess myocardial function and whether there is an effusion present that may need drainage.

D-Dimer is a sensitive test for pulmonary embolism when there is no evidence of pulmonary disease. However, D-dimer levels can be elevated in COVID-19 even when there is no thrombus present. It would be appropriate to obtain a ventilation-perfusion scan or computed tomographic scan of the chest with pulmonary angiography, but the lack of heart strain on electrocardiogram and relatively normal chest radiographic findings make this disease process unlikely. Lastly, the reproducible tenderness to palpation on the chest and pain with cough can be correlated with costochondritis, but the persistent tachycardia indicates that another disease process is present.

Finally, although the result of the rapid antigen test for SARS-CoV-2 was positive, this test is sensitive for COVID-19 only at the time of maximal viral shedding. Polymerase chain reaction testing is more sensitive, and its results can remain positive for a longer duration without active infection. Cases have been reported in which the patient screened antigen negative for COVID-19 but echocardiographic results suggested pericarditis. In these reports, the more sensitive polymerase chain reaction test revealed a positive result for SARS-CoV-2 and a cause for pericarditis was determined. In addition to association with COVID-19 infection, there have also been rare reports of pericarditis occurring after vaccination against COVID-19.

PREP Pearls

- Pericarditis should be considered whenever a patient remains persistently tachycardic and chest pain is present.

- A normal electrocardiographic finding does not rule out pericarditis, because classic ST-segment elevation occurs in only 40% to 50% of cases
- Patients who have undergone bone marrow transplant and children who have had surgical atrial septum repair are at the highest risk of experiencing pericarditis owing to noninfectious causes.

ABP Content Specifications(s)/Content Area

- Understand the difference between myocarditis and pericarditis.
- Identify the most common etiology of pericarditis

Suggested Readings

Bergmann KR, Kharbanda A, Haveman L. Myocarditis and pericarditis in the pediatric patient: validated management strategies. *Pediatr Emerg Med Pract.* 2015;12(7):1-22; quiz 23. https://pubmed.ncbi.nlm.nih.gov/26197653/

Dimopoulou D, Spyridis N, Dasoula F, et al. Pericarditis as the main clinical manifestation of COVID-19 in adolescents. *Pediatr Infect Dis J.* 2021;40(5):e197-e199. doi:10.1097/INF.0000000000003096

Raymond TT, Das A, Manzuri S, Ehrett S, Guleserian K, Brenes J. Pediatric COVID-19 and pericarditis presenting with acute pericardial tamponade. *World J Pediatr Congenit Heart Surg.* 2020;11(6):802-804. doi:10.1177/2150135120949455

May

Question: 5

A 5-year-old Black boy is seen in the emergency department with bruising, fatigue, and fever. He is diagnosed with acute lymphocytic leukemia on the basis of a blood smear and admitted to the pediatric ICU owing to leukocytosis and concern regarding tumor lysis syndrome.

Laboratory data obtained on admission are shown:

Laboratory Test	**Result**
Uric acid	9 mg/dL
Hemoglobin	10 g/dL (100 g/L)
White blood cell count	35,000/μL (35×10^9/L)
Platelet count	20×10^3/μL (20×10^9/L)
Potassium	5 mEq/L (5 mmol/L)
Blood urea nitrogen	40 mg/dL (15.3 mmol/L)
Creatinine	1 mg/dL (88.4 μmol/L)

Treatment with rasburicase is initiated, in addition to intravenous hydration and allopurinol. The following morning, he is noted to have new scleral icterus, elevated total and indirect bilirubin levels, as well as a drop in hemoglobin level to 8 g/dL (80 g/L) with no associated blood loss.

Of the following, the cause for the patient's new findings is MOST likely

A. antibody-mediated immune destruction of erythrocytes

B. increased erythrocyte destruction by the spleen

C. lymphocytic infiltrate of bone marrow

D. oxidative stress on erythrocytes

The patient in the vignette is undergoing treatment for tumor lysis syndrome. Tumor lysis syndrome results from massive cell lysis/cell turnover associated with certain oncologic diagnoses, including high-grade lymphomas and acute lymphoblastic leukemia, and typically is seen hours to days after initiation of chemotherapy. Tumor lysis syndrome presents with hyperkalemia, hyperphosphatemia, and hyperuricemia resulting from release and catabolism of nucleic acids. Tumor lysis syndrome is an oncologic emergency that requires close monitoring and intervention. Renal function, electrolytes (specifically potassium, phosphate, and calcium), and uric acid should be monitored regularly.

Patients are treated with aggressive hydration to improve glomerular filtration and renal perfusion. Patients with hyperuricemia are treated with allopurinol, which reduces the production of uric acid through inhibition of xanthine oxidase but does not act on uric acid that has already formed. Patients with elevated uric acid levels and disease that presents a high risk of tumor lysis syndrome should be treated with rasburicase in addition to allopurinol. Rasburicase reduces uric acid concentrations by catalyzing the oxidation of uric acid to allantoin (and is thus an oxidizing agent) and is shown to be effective in lowering the uric acid level.

Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are at risk of developing hemolytic anemia in the presence of oxidizing agents. G6PD is responsible for production of NADPH, which is required for regeneration of reduced glutathione. In turn, glutathione prevents erythrocytes from oxidative damage. In the presence of oxidative agents such as rasburicase, erythrocytes become depleted of glutathione leading to erythrocyte deformation and hemolysis. In patients with a high risk of G6PD deficiency (children of African and Mediterranean descent), testing for G6PD deficiency should be considered before administration of oxidative agents.

PREP Pearls

- Tumor lysis syndrome is the result of rapid cell turnover leading to hyperkalemia, hyperphosphatemia, and hyperuricemia.

- Rasburicase is indicated for high-risk patients with hyperuricemia because it helps with excretion of existing uric acid as opposed to allopurinol, which helps to prevent additional uric acid formation.
- Rasburicase, through its mechanism as an oxidative agent, can cause hemolytic anemia for patients with glucose-6-phosphate dehydrogenase deficiency.

ABP Content Specifications(s)/Content Area

- Recognize tumor lysis syndrome

Suggested Readings

Akande M, Audino AN, Tobias JD. Rasburicase-induced hemolytic anemia in an adolescent with unknown glucose-6-phosphate dehydrogenase deficiency. *J Pediatr Pharmacol Ther.* 2017;22(6):471-475. doi:10.5863/1551-6776-22.6.471

Cheuk DK, Chiang AK, Chan GC, Ha SY. Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer. *Cochrane Database Syst Rev.* 2017 8;3(3):CD006945. doi:10.1002/14651858.CD006945.pub4

Goldman SC, Holcenberg JS, Finklestein JZ, et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. *Blood*. 2001;97(10):2998-3003. doi:10.1182/blood.v97.10.2998

May

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 6

A 5-year-old boy is evaluated in the pediatric PICU for refractory status asthmaticus exacerbation. He has a history of severe asthma involving multiple previous admissions to the pediatric ICU. The patient is intubated for worsening hypercarbia and altered mental status. After intubation, he continues to experience hypercarbia despite receiving optimized multiple bronchodilator therapies and ventilator titration. The decision is made to start inhaled sevoflurane.

Of the following, the MOST likely complication associated with this treatment is

- **A.** hepatotoxicity
- **B.** hypotension
- **C.** loss of cerebral autoregulation
- **D.** nephrotoxicity

Several case studies/series have described the use of anesthetic gases for use in the pediatric ICU for indications such as sedation, status epilepticus, and refractory status asthmaticus. Isoflurane and sevoflurane are the best described. Sevoflurane is an excellent bronchodilator with little airway irritation, which may accompany other inhaled anesthetics. Hypotension is a common side effect of sevoflurane administration owing to vasodilatory effects and lowering of systemic vascular resistance, and thus use of an α-agonist such as norepinephrine is sometimes needed with sevoflurane administration. Sevoflurane preserves cerebral autoregulation, decreases the cerebral metabolic rate, and causes cerebral vasodilation. Sevoflurane can degrade to compound A when exposed to soda lime, an absorbent in the anesthesia machine. Compound A is nephrotoxic in rats and can cause proteinuria and glycosuria in humans. However, this effect does not seem to cause

concomitant increases in blood urea nitrogen and creatinine or long-term sequelae, and it does not seem to be clinically significant. There are few to no hepatotoxic effects with sevoflurane because, unlike isoflurane, it does not metabolize to trifluoroacetic acid. Trifluoroacetic acid causes an immune-mediated reaction, although transient elevation in liver enzyme levels is reported. Hepatic injury is most common with halothane.

Inhalational anesthetic use in the pediatric intensive care unit requires a special ventilator with the ability to scavenge exhaled gas, as well as specially trained staff. It is also associated with a high cost. Before initiation of inhaled anesthetic agents, screening for risks of malignant hyperthermia should be performed. Use of inhaled anesthetics for refractory status asthmaticus may be considered in the most refractory cases as a rescue therapy before initiation of more invasive therapies such as extracorporeal membrane oxygenation.

PREP Pearls

- The most common side effect associated with sevoflurane use is hypotension due to vasodilation.
- Sevoflurane is degraded to compound A, which is nephrotoxic in animal models but does not appear to be so in humans.
- Sevoflurane preserves cerebral autoregulation, decreases the cerebral metabolic rate, and causes cerebral vasodilation.
- Before initiation of inhaled anesthetic agents, screening for risks of malignant hyperthermia should be performed.

ABP Content Specifications(s)/Content Area

- Understand the respiratory effects of inhaled anesthetics

Suggested Readings

Ong Sio LCL, dela Cruz RGC, Bautista AF. Sevoflurane and renal function: a meta-analysis of randomized trials. *Med Gas Res*. 2017;7(3):186-193. doi:10.4103/2045-9912.215748

Rehder KJ. Adjunct therapies for refractory status asthmaticus in children. *Respir Care.* 2017;62(6):849-865. doi:10.4187/respcare.05174

Tobias JD. Therapeutic applications and uses of inhalation anesthesia in the pediatric intensive care unit. *Pediatr Crit Care Med*. 2008;9(2):169-179. doi:10.1097/PCC.0b013e31816688ef

June

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 1

A 16-year-old with a history of focal segmental glomerulosclerosis and end-stage renal disease is brought to the emergency department by his mother because of confusion. He receives hemodialysis every other day and is receiving multiple medications for hypertension, but the mother is not sure if the patient is compliant with use of his medications. Physical examination shows an obese adolescent who is cursing at everyone around him, appears disoriented, and is not cooperative with physical examination. His vital signs are a temperature of 37°C, heart rate 135 beats/min, blood pressure 225/140 mm Hg, respiratory rate 25 breaths/min, and oxygen saturation of 99% in ambient air.

Of the following, the MOST appropriate intervention for this patient is

- **A.** diazoxide infusion to lower blood pressure slowly to 120/80 mm Hg
- **B.** nicardipine infusion to lower blood pressure slowly to 170/90 mm Hg
- **C.** nitroglycerine infusion to rapidly lower blood pressure to 140/80 mm Hg
- **D.** nitroprusside infusion to rapidly lower blood pressure to 150/90 mm Hg

Blood pressure (BP) is the product of cardiac output and systemic vascular resistance. Blood pressure is regulated by the unique interaction of these 2 factors and is directly proportional to either of these factors. Hypertension in the pediatric population is defined as a BP that is greater than the 99th percentile for age and sex according to the National Heart, Lung, and Blood Institute's *Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.*

Hypertension can result from increased cardiac output, which can be the consequence of fluid overload. Fluid overload may occur in patients with end-stage renal disease if the patient does not adhere to fluid restriction. The other factor that can lead to hypertension is an increase in peripheral vascular resistance, which can be caused by various disorders that affect the endothelial function and muscle tone of the blood vessel wall. Dysregulation of neural and hormonal control have been implicated in the pathogenesis of hypertension; these include activation of the renin-angiotensin-aldosterone system and alterations in production and circulation of nitric oxide, endothelin, vasopressin, and catecholamine. All of these substances have been implicated in the pathogenesis of hypertension and hypertensive crises. Hypertension can be primary when there is no clearly defined etiology or secondary to underlying disorders such as chronic renal failure and end-stage renal disease (as seen in the vignette).

- Hypertensive urgency is defined as an acute severe elevation in BP without the presence of end-organ dysfunction or damage.
- Hypertensive emergency is characterized by severe and sudden elevation in BP that is complicated by acute end-organ dysfunction, including myocardial dysfunction, cerebral dysfunction, and retinopathy.
- Hypertensive encephalopathy is defined as an acute elevation in BP associated with cerebral dysfunction that is usually characterized by alterations in mental status; these can range from disorientation to seizures and may progress to coma and death. Other associated symptoms of hypertensive encephalopathy may include headache, nausea, vomiting, and blurred vision. The latter may progress to cortical blindness if the hypertension is not appropriately treated. Intracranial hemorrhage is possible.

Two physiologic mechanisms have been described in association with hypertensive encephalopathy. The first proposed mechanism, originally described by Oppenheimer and colleagues in the 1950s (on the basis of experiments in rats), was intense vasoconstriction that led to decreased cerebral blood flow to various regions of the brain, in turn leading to the clinical manifestations of hypertensive encephalopathy. More recently, a physiologic mechanism has been proposed indicating that hypertensive encephalopathy is secondary to loss of autoregulation, with various degrees of vasodilation in different parts of the brain that leads to the pathophysiology and clinical features of hypertensive encephalopathy. A radiographic abnormality referred to as “posterior reversible encephalopathy” may be seen in patients with hypertensive encephalopathy. It is characterized by white matter vasogenic edema in the posterior aspect (occipital and parietal regions) of the brain. These radiographic abnormalities are best seen on magnetic resonance imaging of the brain. The degree of the radiographic abnormalities is variable, but it is being increasingly recognized with the widespread availability of magnetic resonance imaging of the brain.

Under basal conditions, the cerebral blood flow is maintained over a wide range of mean arterial pressure (MAP), which in an adolescent, would be between 50 and 150 mm Hg (solid line in **Figure**). In patients with chronic hypertension, such as the adolescent in the

vignette, the graph shifts to the right (hatched line in **Figure**). Therefore, in these patients, treatment of hypertensive encephalopathy includes slow and gradual reduction in MAP by approximately 20% to 25% of the difference between the basal MAP and the current MAP in the first several hours of therapy, followed by further slow reduction in BP over the next 24 hours. The slow reduction of BP is essential because the cerebral autoregulation curve is shifted to the right, and a sudden and precipitous drop in BP is likely to lead to a dramatic drop in cerebral blood flow with consequent ischemia and permanent neurologic abnormalities and deficits. Therefore, initiation of an infusion of nicardipine and slow reduction in BP is the most prudent approach for a patient with hypertensive encephalopathy.

A number of medications may be used for the treatment of hypertensive urgency, hypertensive emergency, and hypertensive encephalopathy, including diazoxide, nitroglycerin, nitroprusside, calcium channel blockers, and vasodilators. Sodium nitroprusside would not be an appropriate medication for the patient in the vignette because of the potential for abrupt drop in BP, and accumulation of byproducts. These byproducts, such as cyanide and thiocyanate, are toxic and can accumulate in renovascular disease, leading to severe metabolic acidosis. Thiosulfate can be added to sodium nitroprusside to reduce the risk of toxicity. Diazoxide and nitroglycerin have fallen out of favor because of the availability of safer medications. Nicardipine is a calcium channel blocker with a short half-life and can be given as an infusion for the management of acute hypertension with gradual titration to effect. Nicardipine would be an appropriate agent for the patient in the vignette. It can be gradually titrated upward to reduce BP gradually over the next 24 hours or so.

PREP Pearls

- Cerebral autoregulation is shifted to the right and upward in patients with chronic hypertension.
- Rapid and significant reduction in blood pressure is ill advised in patients with chronic hypertension.
- The most prudent approach in patients with chronic hypertension who exhibit hypertensive encephalopathy is to give an infusion of antihypertensive medication and lower the blood pressure slowly by 20% to 25% in the first 12 to 24 hours.

ABP Content Specifications(s)/Content Area

- Manage a patient with chronic hypertension.

Suggested Readings

National Institutes of Health; National Heart, Lung, and Blood Institute. *The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.* NIH Publication no. 05-5267. Bethesda, MD: National Institutes of Health; 2005..

Sunamak EÇ, Özdemir N, Celkan T. Posterior reversible encephalopathy syndrome in children with acute lymphoblastic leukemia: experience of a single center using BFM protocols. *Pediatr Blood Cancer.* 2019;66(6):e27711. doi:10.1002/pbc.27711

Tatsi C, Xekouki P, Nioti O, et al. A novel mutation in the glucocorticoid receptor gene as a cause of severe glucocorticoid resistance complicated by hypertensive encephalopathy. *J Hypertens.* 2019;37(7):1475-1481. doi:10.1097/HJH.0000000000002048

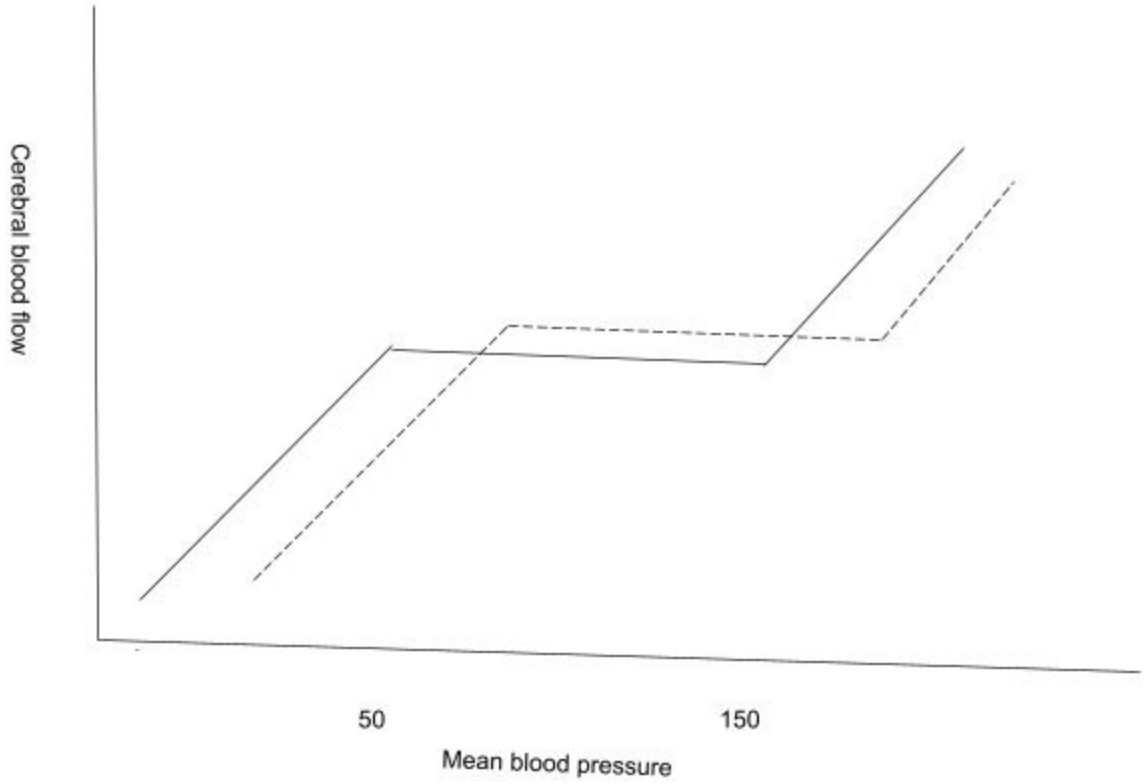

Figure: The relationship between cerebral blood flow and mean arterial blood pressure under normal conditions and in patients with chronic hypertension.

Courtesy of R. Hasan

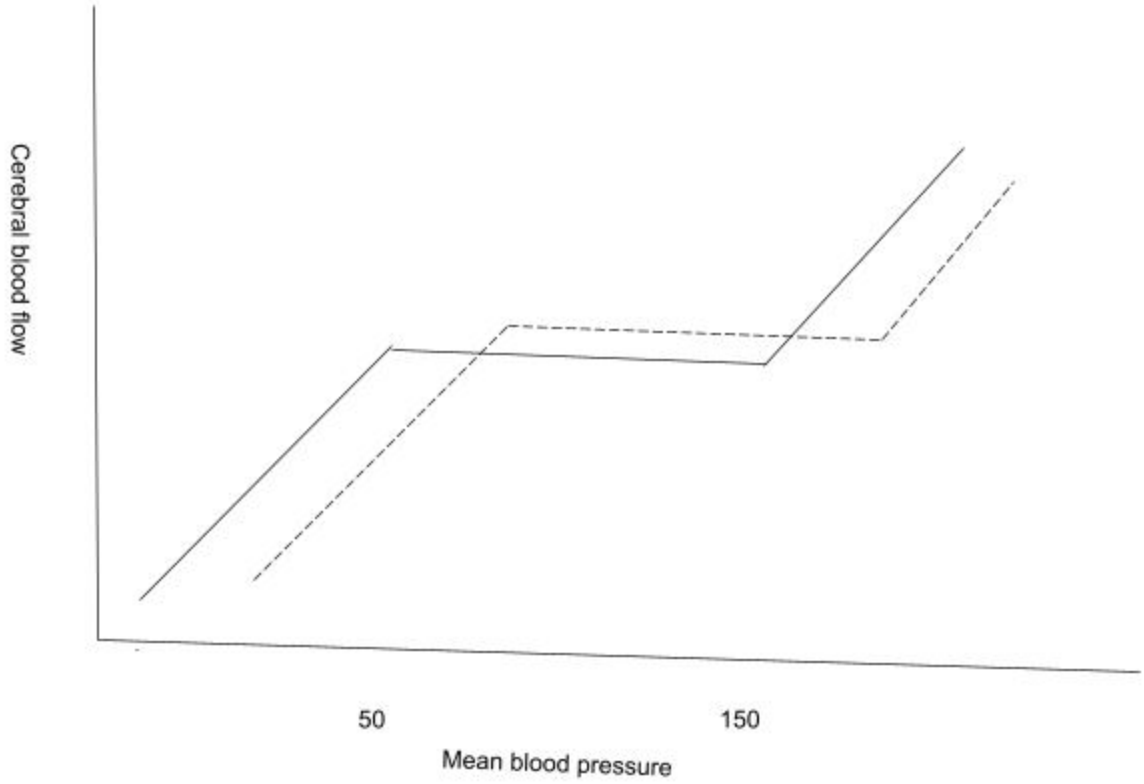

Figure: The relationship between cerebral blood flow and mean arterial blood pressure under normal conditions and in patients with chronic hypertension.

Courtesy of R. Hasan

June

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 2

A 4-year-old child who had a cardiac transplant because of complex congenital heart disease is admitted to the pediatric ICU with concerns regarding worsening cardiac function and rejection. The ejection fraction measured by echocardiography is 46%. Laboratory results reveal a serum creatinine concentration of 1.2 mg/dL (106.1 µmol/L) and a blood urea nitrogen concentration of 15 mg/dL (5.4 mmol/L). The cardiologist has recommended cardiac catheterization, but concern is raised about contrast-induced nephropathy.

Of the following, the drug that has shown the MOST promising results in decreasing contrast-induced acute kidney injury is

- **A.** acetazolamide
- **B.** dexmedetomidine
- **C.** enalapril
- **D.** sodium bicarbonate

Contrast-based diagnostic interventions and procedures carry the risk of contrast-induced acute kidney injury (CI AKI). These factors can be exacerbated with pre-existing conditions such as cardiac or renal disease. Additional comorbidities include increased age, diabetes mellitus, and nephrotoxic drugs that can impact AKI with contrast administration. The risk of the procedure with use of contrast must be weighed against the benefits of completing the procedure.

Direct tubular cytotoxicity and vasoconstriction are the 2 mechanisms primarily responsible for CI AKI. Cytotoxicity of contrast medium results in cell damage or cell death. Free iodine released from contrast results in a direct cytotoxic effect on endothelial cells. Contrast agents also have a direct nephrotoxic effect on the tubules, resulting in cell damage and cell death. The hyperosmolarity of contrast agents can create an osmotic nephrosis with altered oxygen delivery to the tissues and an osmotic diuresis. This can lead to increased viscosity, resulting in longer exposure of contrast in the tubular cells and causing more endothelial damage. Intravenous (IV) hydration may be beneficial by reducing viscosity and minimizing contrast exposure in the tubular cells. Contrast agents also affect the vascular endothelium-releasing vasoactive molecules (eg, adenosine and endothelin), which can reduce availability of vasodilators (eg, prostaglandin and nitric oxide), resulting in cellular injury from oxidative stress.

The Kidney Disease Improving Global Outcomes (KDIGO) updated definition of CI AKI is an increased creatinine concentration 0.3 mg/dL or more above baseline value within 48 hours of exposure to contrast media or at least 1.5 times the baseline value within 7 days without another cause for AKI. The actual incidence of CI AKI is unknown but has been estimated to be between 5.5% and 11%. The incidence of CI AKI has decreased and is likely multifactorial owing to increased awareness of contrast agents that potentially affect renal function, improved contrast agents, and less invasive procedures that do not require contrast.

Treatment strategies to prevent CI AKI include hydration, limiting the amount and using contrast agents with lower osmolarity, medications, and renal replacement therapies. Studies show conflicting data regarding the benefit or lack thereof of these treatment strategies. Studies have shown no difference between prophylactic hydration pre-procedure with or without sodium bicarbonate compared with no prophylactic hydration. Trials were small and included lower-risk procedures and patients with only moderate AKI. Whether isotonic or hypotonic fluid is the optimal choice continues to be debated. There are no well-designed randomized controlled clinical trials to address this specific issue. Forced urine output with hydration and diuretic therapy has also not shown significant benefit. Limiting the volume of contrast and using contrast agents with reduced osmolarity are factors that may lessen CI AKI. Despite convincing evidence, minimizing contrast administration and prophylactic pre-hydration remain commonly employed strategies in an attempt to reduce the risk or prevent CI AKI. The clinician must take into account pre-existing conditions that can be exacerbated with prophylactic pre-hydration. Some studies have demonstrated that the access site for catheterization procedures may influence development of CI AKI. Radial artery versus femoral artery catheterization for diagnostic procedures has shown a lower incidence of CI AKI in one study. The importance of controlling hemorrhage resulting in altered hemodynamics and contributing to AKI and a low perfusion state has been stressed.

Medications used to decrease CI AKI include *N*-acetylcysteine (NAC), urine alkalization, and statins. Randomized controlled trials of NAC as a scavenging agent have not demonstrated benefit in low- or high-risk patients. Urine alkalization using sodium bicarbonate, sodium citrate, or acetazolamide have been promoted as a strategy to reduce oxygen free radicals that can be generated with contrast agents leading to CI AKI. These studies have yielded conflicting conclusions as well. One study involving the use of Na+/K+ citrate showed patients with a urine pH greater than 6 demonstrated less AKI compared with those who had a urine pH less than 6. Another study in children compared acetazolamide with sodium bicarbonate and demonstrated less post-contrast AKI in the acetazolamide group. Statins have also been used for their anti-inflammatory and antioxidant properties. A study of adults with acute coronary syndrome treated with hydration and NAC concluded those who received statin therapy showed less CI AKI.

Dexmedetomidine is an α2-receptor agonist. This agent has shown renal protective effects in an animal model. A randomized controlled trial for children with congenital heart disease who underwent coronary angiography showed a decrease in CI AKI. The authors noted that 24 hours after angiography, neutrophil gelatinase-associated lipocalin (NGAL), a specific biomarker for AKI, and renin levels were significantly lower in the dexmedetomidine group. A lower incidence of postoperative AKI has been shown in adult cardiac surgery patients who received dexmedetomidine. Renal protection may occur by stabilization of the sympathetic nervous system that inhibits vasoconstriction; promotes renal blood flow and diuresis; and reduces inflammation, ischemia, and reperfusion. The protective renal effects with dexmedetomidine seem to be dose-dependent with minimal adverse effects including bradycardia. Dexmedetomidine is a promising agent to reduce CI AKI, making this the correct response.

PREP Pearls

- Contrast-induced acute kidney injury is defined as an increased creatinine level ≥0.3 mg/dL above baseline value within 48 hours of exposure to contrast media or at least 1.5 times the baseline value within 7 days without another source for AKI.
- Urinary alkalinization with sodium bicarbonate or acetazolamide, statins, and N-acetylcysteine has yielded mixed results for renal protection from administration of contrast agents.
- Dexmedetomidine may produce renal protection promoting renal blood flow and diuresis by stabilizing the sympathetic nervous system and reducing inflammation, ischemia, and reperfusion.

ABP Content Specifications(s)/Content Area

- Recognize and treat contrast induced nephropathy

Suggested Readings

Chandiramani R, Cao D, Nicolas J, Mehran R. Contrast-induced acute kidney injury. *Cardiovasc Interv Ther.* 2020;35(3):209-217. doi:10.1007/s12928-020-00660-8

Mehran R, Dangas GD, Weisbord SD. Contrast-associated acute kidney injury. *N Engl J Med*. 2019;380:2146-2155. doi:10.1056/NEJMra1805256

Morcos R, Kucharik M, Bansal P, et al. Contrast-induced acute kidney injury: Review and practical update. *Clin Med Insights Cardiol.* 2019;13:1-9. doi:10.1177/1179546819878680

Windpessl M, Kronbichler A. Contrast-associated acute kidney injury (CA-AKI) in children: Special considerations. *Child Kidney Dis*. 2019;23:77-85. https://doi.org/10.3339/jkspn.2019.23.2.77

June

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 3

A 15-year-old boy recently returned from the Ivory Coast after completing a church mission trip. He has a 1-week history of periodic fever, lethargy, malaise, and worsening headaches. On the day of admission, he developed new seizure activity and now remains unresponsive. Computed tomography of the brain shows no obvious intracranial masses or areas of contrast enhancement. Laboratory evaluation demonstrates the following:

Laboratory Test	Result
Complete blood count	
White blood cells	19,200/μL (19.2 ×10^9/L)
Hemoglobin	5.1 g/dL (51 g/L)
Hematocrit	18%
Platelet	200 × 10^3/μL (200 × 10^9/L)

Electrolytes	
Sodium (Na+)	131 mEq/L (131 mmol/L)
Potassium (K+)	3.8 mEq/L (3.8 mmol/L)
Chloride (Cl−)	105 mEq/L (105 mmol/L)
Carbon dioxide (CO_2)	11 mEq/L (11 mmol/L)
Blood urea nitrogen	32 mg/dL (11.42 mmol/L)
Creatinine	2.8 mg/dL(247.5 µmol/L)
Glucose	46 mg/dL (2.55 mmol/L)
Lactate	63 mg/dL (7.0 mmol/L)

Microscopic evaluation of a thin blood smear is shown in the **Figure**.

Of the following, the medications and routes for initial treatment of this disease SHOULD include

- **A.** artemether-lumefantrine (oral)
- **B.** primaquine (oral)
- **C.** quinidine gluconate (intravenous)
- **D.** rifampin (intravenous)

The thin blood smear in this patient demonstrates a number of malaria organisms within the red blood cells. Malaria is caused by infection with the parasite *Plasmodium* and is transmitted by the bite of the female *Anopheles* mosquito. It is the leading cause of death by parasitic disease in the world. Five species of *Plasmodium* cause disease in humans, and more than one-half of children worldwide live in malaria-endemic countries. In 2015, it was estimated that there were more than 200 million cases of malaria worldwide and about 429,000 deaths. *Plasmodium falciparum* is most prevalent in Africa, whereas *Plasmodium vivax* is the most prevalent malaria parasite outside of Africa. In the United States, *P*

falciparum is responsible for approximately 80% of cases of pediatric malaria because of travel from endemic areas. In the past few decades, the incidence of malaria has dropped almost 60%, largely because of efforts to eradicate mosquito populations worldwide.

The pathophysiology of malaria is well described. While feeding, the infected mosquito injects *Plasmodium* sporozoites. Sporozoites are the motile form of the parasite; on entering the bloodstream, they migrate to the liver, where they invade hepatocytes and multiply. Two species of *Plasmodium* (*P vivax* and *P ovale*) can develop dormant parasitic forms within the hepatocyte, known as hypnozoites. The hypnozoites may remain in the liver for years after the primary infection and are responsible for relapsing malaria and recurrent systemic illness. Eventually, infected hepatocytes rupture, releasing thousands of parasites (merozoites). Merozoites then invade red blood cells and begin a cycle of asexual replication (trophozoites production) or a sexual cycle with production of gametocytes. As parasite burden within the red cell increases, the cell membrane ruptures. Growth within the red blood cell typically takes 48 to 72 hours before rupture of membrane and release of schizonts (merozoites and gametocytes). Mosquitos ingest gametocytes during a blood meal, eventually producing the next generation of sporozoites.

Clinical symptoms from malaria can present within 7 days to 3 months of parasite exposure. Periodic fever, occurring every 23 days and coinciding with erythrocyte rupture, is a classic symptom. Initial symptoms are variable and can resemble influenza. Symptoms include chills, myalgia, lethargy, nausea, abdominal pain, headaches, and cough. Part of the malaria clinical presentation is due to release of cytokines from systemic macrophages. This is largely facilitated by hemozoin, a proinflammatory metabolite produced from parasitic digestion of heme and released on rupture of the red blood cell. Disease progression is related to worsening anemia as well as end-organ damage resulting from vascular adherence of infected erythrocytes with resultant capillary occlusion. Severe malaria can cause organ injury, including central nervous system (cerebral malaria), kidney (Blackwater fever), and lung (acute respiratory distress syndrome) involvement. Large parasite loads (>4% to 5% infected erythrocytes) significantly increase the risk of severe malaria and death. Children are at higher risk of developing severe malaria with end organ damage. Severe malaria most commonly is caused by *P falciparum*, likely because this organism reaches higher parasite levels than other species of *Plasmodium*. Pediatric mortality resulting from malaria ranges from 1% in mild cases to 30% in severe cases. Respiratory distress, metabolic acidosis, hypoglycemia, central nervous system involvement, malnutrition, and concurrent bacterial infections all increase mortality.

Diagnosis of malaria requires a high degree of clinical suspicion, especially for travelers returning from endemic areas. Travelers are also more likely than residents within endemic areas to present with severe malaria. Laboratory anomalies include anemia, hemoglobinuria, metabolic acidosis, and hypoglycemia. Microscopic examination of blood

films is still considered the criterion standard for laboratory confirmation of malaria. Thick blood films are helpful with *Plasmodium* detection, and thin blood films often allow speciation. Antigen detection rapid diagnostic tests for malaria were introduced in the past decade. These kits have a high sensitivity and specificity for *P falciparum*, but less so for *P ovale, P malariae*, *and P vivax*.

Treatment of malaria requires knowledge of the parasite's species, severity of symptoms, and the likelihood of drug resistance. Artemisinin-based combination therapies have largely replaced chloroquine or quinine as the treatment of choice for uncomplicated malaria. In the United States, uncomplicated *P falciparum* infections can be treated with a 3-day course of artemether-lumefantrine. Both components of this agent are schizontocides, inhibiting both parasitic nucleic acid and protein synthesis within the erythrocyte. Artemether-lumefantrine can be used in both adults and children, but is not intended as a chemoprophylaxis agent. In areas where chloroquine resistance is low, chloroquine can still be considered, although artemether-lumefantrine is preferred. Patients with *P vivax* or *P ovale* infections must also be treated with a 14-day course of primaquine to cover the latent liver stages.

In cases of severe malaria, treatment with intravenous artesunate, quinine, or quinidine gluconate (a d-isomer of quinine) is recommended. Direct comparison of these agents in adult trials favors artesunate. In the United States, intravenous quinine is not available. Intravenous artesunate is currently available only through the Centers for Disease Control and Prevention (CDC). The drug can be obtained by calling the CDC Malaria Hotline (1-770-488-7788), but it may not be readily available for a patient whose condition is rapidly deteriorating. Thus, intravenous quinidine is likely to be the first agent available for a patient in the pediatric ICU whose condition is rapidly deteriorating. Close cardiac monitoring is required during infusion because these agents may cause hypotension, QTc prolongation, and arrhythmias. If clinical improvement occurs, parasite density is less than 1%, and the patient can tolerate oral medications, treatment may be transitioned to artemisinin-based combination therapies after 24 hours. Treatment using exchange transfusion in severe cases remains controversial; the CDC no longer advocates its use, whereas the American Society for Apheresis states that the decision should be individualized.

Untreated *P falciparum* malaria can progress rapidly to life-threatening illness. Prompt recognition and treatment are essential. Artemisinin-based combination therapies might be considered in individuals who can tolerate oral medications, but in critically ill patients, parenteral treatment is indicated. Rifampin has no role in malaria management. Bacterial coinfections can occur in patients with malaria, but these organisms are most frequently gram-negative (often *Salmonellae species*) and best managed with a third-generation cephalosporin.

PREP Pearls

- Microscopic examination of blood films is still considered the criterion standard for laboratory confirmation of malaria.
- Current treatment recommendations for mild malaria include early treatment with artemisinin-based combination therapies.
- Severe malaria can involve the central nervous system, kidney, and lung. In the United States, treatments include intravenous quinidine or artesunate.
- As of 2020, intravenous artesunate was not readily available in the United States. It can be obtained by calling the Centers for Disease Control and Prevention Malaria Hotline (1-770-488-7788).

ABP Content Specifications(s)/Content Area

- Plan the treatment for a patient with parasitic infection

Suggested Readings

Cohee LM, Laufer MK. Malaria in children. *Pediatr Clin North Am.* 2017;64(4):851-866. doi:10.1016/j.pcl.2017.03.004

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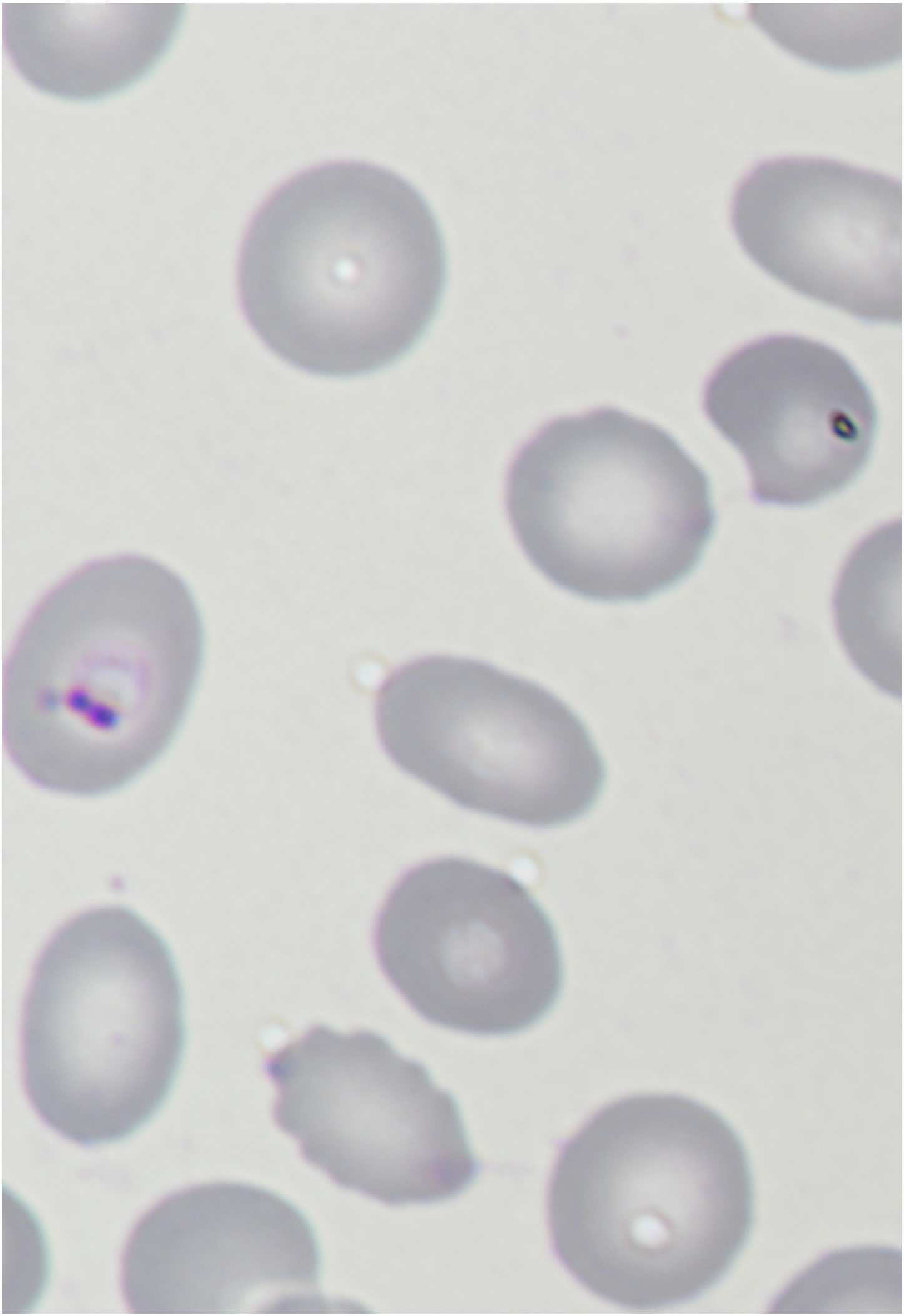

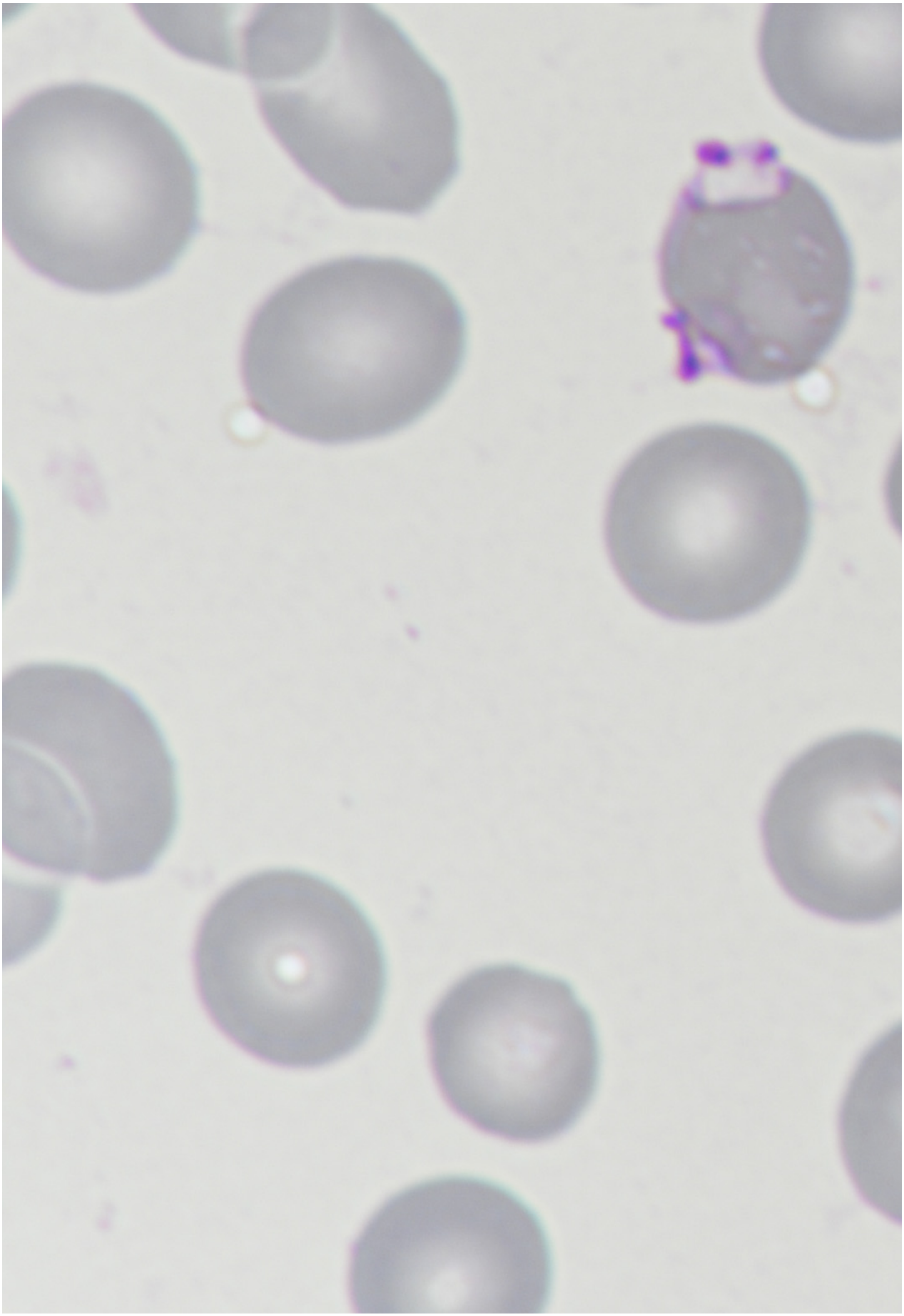

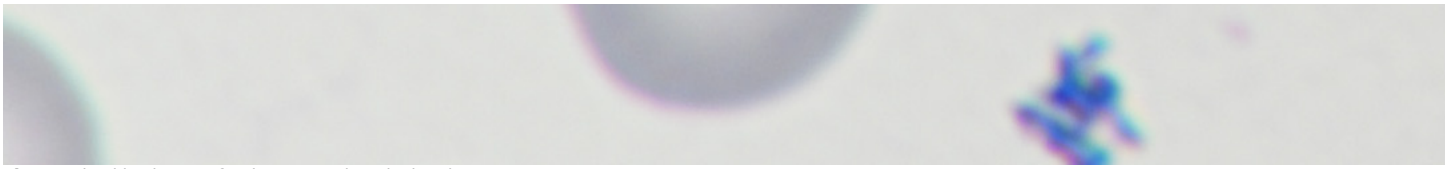

Figure: Thin blood smear for the patient described in the vignette.

Courtesy of M. Rowin

June

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 4

A 9-month-old female infant with lethargy, poor feeding, and diarrhea is transferred from the emergency department to the pediatric intensive care unit. Her symptoms began 3 days ago, and she has produced 1 wet diaper in the past 24 hours. A peripheral intravenous catheter was placed in the emergency department, and she received 40 mL/kg of 0.9% saline intravenously before being transferred. On admission to the pediatric intensive care unit, the infant is lethargic but arousable, with sunken eyes and anterior fontanelle as well as dry mucous membranes. The patient demonstrates no hepatomegaly. Her vital signs are a temperature of 36.4°C, a heart rate of 190 beats/min, a blood pressure of 65/36 mm Hg, a respiratory rate of 24 breaths/min, and an oxygen saturation of 97% in room air. Her capillary refill time is 4 seconds.

Of the following, the BEST next step in the care of this patient is to

- **A.** deliver another 20 mL/kg bolus of 0.9% saline intravenously
- **B.** initiate intravenous fluids containing dextrose, saline, and potassium at maintenance rate
- **C.** place a nasogastric tube and start oral rehydration therapy
- **D.** start an infusion of norepinephrine

Dehydration, or hypovolemia, is common in children, and early recognition and treatment are essential to prevent progression to hypovolemic shock and end-organ damage. Management depends on both the degree of hypovolemia and the type of dehydration. The degree of hypovolemia is best evaluated by means of history taking and physical examination and is categorized as mild, moderate, or severe.

- **Mild:** Volume depletion is 3% to 5%; associated with normal or minimally increased pulse rate, decreased urinary output, and otherwise normal physical examination findings
- **Moderate:** Volume depletion is 6% to 10%; associated with tachycardia, decreased urine output, decreased tears, dry mucous membranes, sunken fontanelle, irritability or lethargy, delayed capillary refill time, and mild skin tenting
- **Severe:** Volume depletion is greater than 10% to 15%; rapid, weak pulse; hypotension; minimal or no urine output; no tears; very dry mucous membranes; sunken eyes and fontanelle; lethargy; delayed capillary refill time; mottled, cool, pale skin; and significant skin tenting

Dehydration is further classified according to osmolarity. Three main types are isonatremic, hyponatremic, and hypernatremic.

- **Isonatremic (Isotonic):** Water and electrolytes are lost in equal proportion, and serum sodium levels are 130-150 mEq/L; most common causes in children include gastrointestinal losses, particularly vomiting, and diarrhea from gastroenteritis
- **Hyponatremic (Hypotonic):** Electrolyte loss is disproportionately greater than water loss, and serum sodium levels are less than 130 mEq/L; causes include cystic fibrosis, Addison disease, renal tubular acidosis, and certain diuretic therapies
- **Hypernatremic (Hypertonic):** Water loss is disproportionately greater than loss of electrolytes, and serum sodium levels are greater than 150 mEq/L; causes include excessive perspiration, fever, inadequate water intake, osmotic diuresis, diabetes insipidus, and diuretic therapy

The initial goal of treatment for dehydration is to restore the effective circulating volume. Once the intravascular volume has been restored, electrolyte imbalances can be slowly corrected. In children with mild or moderate hypovolemia, repletion of fluids and electrolytes can often be achieved with oral rehydration therapy. Based upon these criteria, this patient meets the definition of severe dehydration.

Patients with severe dehydration are at high risk of experiencing shock, hypoperfusion, and end organ damage. These patients require emergency treatment and rapid fluid repletion. A peripheral venous, central venous, or intraosseous catheter should be secured immediately in such patients for fluid repletion therapy. Isotonic crystalloid fluid should be infused in 10-20 mL/kg boluses over 15-30 min until vascular volume is restored, and blood pressure, perfusion, and capillary refill time have normalized. Given the percentage of fluid depletion in patients with severe dehydration, 60-80 mL/kg may be required to achieve this goal. Patients who require greater than 80 mL/kg of fluid to restore normal blood pressure should be evaluated for ongoing losses such as hemorrhage or other causes of hypotension, such as sepsis or cardiac disease. Patients should be monitored for electrolyte derangements during fluid repletion, and severe disturbances such as significant hyponatremia and hypoglycemia should be corrected.

Once vital sign abnormalities have been corrected and intravascular volume has been restored, maintenance fluid therapy can be initiated. Maintenance fluids should be tailored to replace expected losses from normal physiologic processes, as well as expected ongoing losses from the disease process or cause of dehydration. Close monitoring of volume status and serum electrolyte levels is crucial during maintenance fluid therapy. Isotonic fluid boluses may need to be repeated, and electrolyte disturbances may require correction, particularly during the first 12 to 24 hours. The choice of maintenance fluids will depend on the type of dehydration, but it should include at least 5% dextrose, as patients with severe dehydration are generally ketotic. Isonatremic and hyponatremic dehydration can be treated with 0.9% saline or other isotonic fluid (with added dextrose). Goal correction rates for hyponatremia and hypernatremia should be no more than 0.5 mEq/L/h to avoid neurologic complications. Once the patient improves and has stabilized, oral therapy may be introduced in some situations.

The patient in the vignette suffers from severe dehydration due to gastrointestinal losses. Despite receiving 40 mL/kg of 0.9% saline intravenously in the emergency department, she remains hypotensive and tachycardic with poor perfusion. The next step in this infant's management is to deliver more isotonic fluid boluses, up to 60-80 mL/kg, until her effective circulating volume is restored. Oral rehydration therapy is not an appropriate option for a hypotensive patient with severe dehydration, but it may be useful once she improves. Maintenance fluid therapy is not appropriate during the repletion phase of severe dehydration. Norepinephrine is not a correct choice for the management of hypovolemia.

PREP Pearls

- Dehydration in children must be recognized and treated promptly to reduce the risk of progression to hypovolemic shock, decreased perfusion, and end organ damage.
- Patients with severe dehydration, regardless of cause, require rapid intravenous (or intraosseous) rehydration with isotonic fluid to restore the effective circulating volume.

ABP Content Specifications(s)/Content Area

- Plan management for a child with severe dehydration

Suggested Readings

Freedman SB, Parkin PC, Willan AR, Schuh S. Rapid versus standard intravenous rehydration in paediatric gastroenteritis: pragmatic blinded randomised clinical trial. *BMJ*. 2011;343:d6976. doi:10.1136/bmj.d6976

Rouhani S, Meloney L, Ahn R, Nelson BD, Burke TF. Alternative rehydration methods: a systematic review and lessons for resource-limited care. *Pediatrics*. 2011;127(3):e748-e757. doi:10.1542/peds.2010-0952

Santillanes G, Rose E. Evaluation and management of dehydration in children. *Emerg Med Clin North Am.* 2018;36(2):259-273. doi:10.1016/j.emc.2017.12.004

June

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 5

A 4-month-old male infant was brought to the emergency department because he was experiencing seizures. His parents report decreased feeding and difficulty in arousing him over the last few hours. He recently has been able to sleep through the night without waking for a feeding and has had a few episodes of morning lethargy that improved after his first morning feeding.

Bedside blood analysis reveals a significant metabolic acidosis, including an elevated lactate level, a capillary blood glucose level of 35 mg/dL (1.9 mmol/L), and 3+ ketones in the urine. His newborn screening results were normal. The infant is small for his age (5th percentile) and lethargic, a state that improves with a glucose-containing infusion.

His vital signs are as follows:

Temperature	37.2°C
Blood pressure	75/45 mm Hg
Heart rate	150 beats/min
Respiratory rate	25 breaths/min

Cardiac examination reveals a normal precordium, no murmur, and a normal S1 and S2. The liver edge is palpable 3 cm below the right costal margin. The remainder of the physical examination findings are unremarkable.

Additional laboratory data are shown:

Laboratory Test	Result
White blood cell count	5,000/μL (7.0×10^9/L)
Ammonia	35 μg/dL (150 μmol/L)
Glucose	35 mg/dL (2.2 mmol/L)
Creatinine	0.2 mg/dL (18 μmol/L)
Blood urea nitrogen	15 mg/dL (5.4 mmol/L)
Bicarbonate	10 mEq/L (12 mmol/L)
Anion gap	24 mEq/L (24 mmol/L)
Lactate	71 mg/dL (4.6 mmol/L)

Results of a urinalysis are positive for +3 ketones.

Of the following, the MOST likely diagnosis is

- **A.** fatty acid oxidation disorder
- **B.** glycogen storage disease
- **C.** mitochondrial disorder
- **D.** organic acid disorder

The infant in the vignette exhibits lethargy after prolonged fasting, resulting in hypoglycemia with lactic acidosis and ketosis, all of which raises suspicion of an inborn error of metabolism (IEM). Given the presentation and laboratory findings, he most likely

has a glycogen storage disease (GSD). Glycogen storage disease type 1a (von Gierke disease) is caused by a deficiency in glucose-6-phosphatase. Although variable in presentation, GSD type 1a often presents in infancy and results in hepatomegaly, growth failure, and recurrent episodes of hypoglycemia with ketosis. Although some neonates with GSD experience severe hypoglycemia, it is more common for infants aged 3 to 4 months to manifest hepatomegaly, growth failure, lactic acidosis, recurrent episodes of hypoglycemia with ketosis, and hypoglycemic seizures. Genetic analysis confirms the diagnosis by identifying pathologic variants in specific genes, including *G6PC, SLC37A4*, or both. These genes encode for glucose-6-phosphatase activity and glucose-6-phosphate exchanger *SLC37A4* activity, respectively.

Acute neonatal presentation of IEMs can be distinguished on the basis of laboratory data. First-line investigations for an infant with a suspected IEM should include blood gas for determination of acid-base status, anion gap, glucose, serum lactate, serum ammonia, and urine ketones. Additional tests to consider adding are a full blood count, urea and electrolytes; liver function tests; levels of urine-reducing substances; and cerebrospinal fluid lactate.

Inborn errors of metabolism can involve abnormalities of the processing of carbohydrate, lipid, or protein, resulting in accumulation of toxic precursors and physiologically active metabolites or in a deficiency of biologically important end-products, such as nutrients or hormones. Early recognition, intervention, and appropriate therapy are needed to ensure favorable outcomes. Because many children with IEMs are brought for care in extremis, pediatric intensivists must have an increased suspicion of IEMs and be able to recognize the physical findings, characteristic histories, and laboratory abnormalities of their different forms.

Inborn errors of protein metabolism involve amino acid, organic acid, and urea cycle metabolism. Amino acids are metabolized by deamination, which removes the amine group producing the end-products: ammonia and an organic acid. Disorders early in the pathway of amino acid metabolism result in accumulation of precursor amino acids. Further along the processing pathway, unmetabolized organic acids will accumulate. In urea cycle defects, ammonia will not be metabolized to urea, resulting in hyperammonemia. As a result, these disorders often manifest in the neonatal period with lethargy, vomiting, coma, strokes, and, unfortunately, death. Laboratory investigations may show elevations of specific amino acids, organic acids, or ammonia in the serum or urine. The infant in the vignette has normal serum ammonia, making IEMs of protein or organic acids an incorrect choice.

Metabolic errors in lipid metabolism, or fatty acid oxidation disorders, result from abnormal β-oxidation of fatty acids. Fatty acid oxidation disorders present with hypoglycemia without the development of ketones. Hypoglycemia generally manifests during a period of fasting

when glycogen and gluconeogenesis are normally used to maintain sufficient serum glucose levels. Fats must be oxidized to produce glucose from gluconeogenesis; therefore, infants with fatty acid oxidation defects will not metabolize fatty acids to produce ketone bodies and will not release energy from glycogen. Patients with these fatty acid oxidation disorders often experience nonketotic hypoglycemia, seizures, rhabdomyolysis, cardiomyopathy, liver dysfunction, and sudden infant death. The infant in the vignette has ketonuria, indicating that the β-oxidation of fatty acids is normal and thus making a fatty acid oxidation disorder an incorrect response choice.

Mitochondrial disorders represent a complex constellation of illnesses resulting from mutations in the mitochondrial genome, leading to a decreased production of adenosine triphosphate and intracellular acidosis. Metabolically active tissues in the brain, skeletal muscles, and cardiac muscles are most affected. Patients often develop lactic acidosis and concurrent organ-specific findings such as strokes, seizures, cardiac conduction abnormalities, hypotonia, or weakness. The 4-month-old in the vignette does not have the characteristic neurological features of a mitochondrial disorder, including hypotonia, and recovers to his baseline status when given glucose. Although lactic acidosis is present in mitochondrial disorders, the other laboratory findings and clinical history are more consistent with GSD.

PREP Pearls

- Presentation of inborn errors of metabolism can be distinguished on the basis of routine laboratory data.
- Inborn errors of metabolism involve abnormalities of carbohydrate, lipid, or protein processing that may lead to toxic accumulation of metabolic precursors or metabolites or to a deficiency of nutrients.
- Inborn errors of metabolism should be included in the differential diagnosis of seizures in infants.
- Newborn screening includes evaluation for glycogen storage disease type 2, but not for type 1.

ABP Content Specifications(s)/Content Area

- Diagnose inborn errors of metabolism

Suggested Readings

Kruszka P, Regier D. Inborn errors of metabolism: From preconception to adulthood. *Am Fam Physician.* 2019;99(1):25-32. PMID:30600976

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June

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 6

A 3-week-old term infant was diagnosed with tetralogy of Fallot with pulmonary atresia and a secundum atrial septal defect. Twelve days ago, he underwent repair of his complex congenital heart lesion that included closure of a ventricular and atrial septal defect, ligation of his patent ductus arteriosus, and creation of a right ventricle-to-pulmonary-artery conduit. His postoperative course was complicated with junctional ectopic tachycardia successfully treated with amiodarone. He continues to require invasive mechanical ventilation and has failed extubation attempts twice. His chest radiograph is shown in the **Figure**.

Of the following, the MOST likely reason for failed extubation is

- **A.** congestive heart failure
- **B.** diaphragmatic paralysis
- **C.** pneumonia
- **D.** vocal cord paralysis

The diaphragm is the primary muscle of respiration. The diaphragm is innervated by the phrenic nerve. The phrenic nerve arises from the third, fourth, and fifth cervical nerve roots. Dysfunction of the diaphragm can be unilateral or bilateral. Causes of diaphragm dysfunction include congenital abnormalities, trauma including damage to vascular and nervous structures, connective tissue disorders, central nervous system, neuromuscular junction diseases, metabolic alterations, and infection. Dysfunction of the diaphragm is also a known complication following cardiac surgery with resultant injury to the phrenic nerve. The incidence of diaphragm dysfunction after complex congenital heart surgery in children has been reported between 0.3% to 12.8%. Injury to the diaphragm increases with younger

age and surgical complexity. Some complex congenital cardiac surgical procedures associated with diaphragm injury include Fontan operation, systemic to pulmonary artery shunts, tetralogy of Fallot, arterial switch, ventricular septal defect, and the bidirectional Glenn procedure.

The younger the patient, the more likely breathing will be affected. Older children more easily compensate for diaphragm dysfunction than younger children, in whom the diaphragm provides more support for the work of breathing. Diaphragm dysfunction is suspected in children who have persistent atelectasis; who fail extubation and have difficulty weaning from ventilator support when other causes such as pneumonia or cardiac failure have been ruled out; and who have a paradoxical breathing pattern but do not require positive-pressure ventilation.

Common imaging studies to identify dysfunction of the diaphragm include chest radiograph, fluoroscopy, and ultrasonography. A plain radiograph of the chest may show elevation of the hemidiaphragm, as presented in the **Figure**. Fluoroscopy is commonly used to determine movement of the diaphragm throughout the respiratory cycle. Fluoroscopy is useful for unilateral paralysis of the diaphragm to determine whether paradoxical movement during the respiratory cycle is present. Ultrasonography is commonly used to study the diaphragm and has the advantage of being easily performed, noninvasive, and without radiation exposure. Patients should be studied off positive-pressure ventilation so paradoxical movement during the respiratory cycle can be observed via fluoroscopy or ultrasonography.

When children with complex congenital heart disease have dysfunction of the diaphragm after surgery, treatment includes prolonged ventilation, allowing for diaphragm recovery or plication. Spontaneous recovery from diaphragm dysfunction after complex congenital heart surgery is unpredictable and can occur, but it is rare. Prolonged mechanical ventilation can lead to an increased length of stay with greater cost, greater risk of ventilator-associated pneumonia, and increased mortality. Optimal timing of plication is controversial; however, it is suggested that plication occur within 10 days for younger children unable to wean from ventilator support. The need for plication is associated with younger age, surgical complexity, and employment of deep hypothermic circulatory arrest.

PREP Pearls

- Injury to the diaphragm is a known complication after cardiac surgery and increases with younger age and complexity of the surgical procedure.
- Diaphragm dysfunction is suspected in children who have persistent atelectasis; who fail extubation and have difficulty weaning from ventilator support when other causes

such as pneumonia or cardiac failure have been ruled out; and who have a paradoxical breathing pattern but do not require positive-pressure ventilation.

- Evaluation of diaphragm dysfunction should be studied off positive-pressure ventilation so paradoxical movement during the respiratory cycle can be observed.
- Treatment includes prolonged ventilation, allowing for diaphragm recovery or plication. Plication of the diaphragm is associated with younger age, surgical complexity, and deep hypothermic circulatory arrest.

ABP Content Specifications(s)/Content Area

- Recognize diaphragm paralysis as a cause of respiratory failure following cardiac surgery

Suggested Readings

Foster C, Cabrera A, Bagdure D, et al. Characteristics and outcomes of children with congenital heart disease needing diaphragm plication. *Cardiol Young.* 2020;30(1):62-65. doi:10.1017/S1047951119002671

Fraser CD 3rd, Ravekes W, Thibault D, et al. Diaphragm paralysis after pediatric cardiac surgery: An STS Congenital Heart Surgery Database Study. *Ann Thorac Surg.* 2020;S0003-4975(20)31287-X. doi:10.1016/j.athoracsur.2020.05.175

Ricoy J, Rodríguez-Núñez N, Álvarez-Dobaño JM, Toubes ME, Riveiro V, Valdés L. Diaphragmatic dysfunction. *Pulmonology.* 2019;25(4):223-235. doi:10.1016/j.pulmoe.2018.10.008

Talwar S, Agarwala S, Mittal CM, Choudhary SK, Airan B. Diaphragmatic palsy after cardiac surgical procedures in patients with congenital heart disease. *Ann Pediatr Card.* 2010;3(1):50-57. doi:10.4103/0974-2069.64370

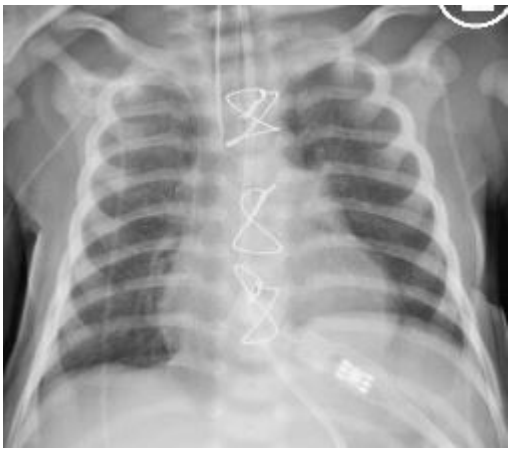


Figure: Chest radiograph for the patient described in the vignette.

Courtesy of T. Nakagawa

July

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 1

A 12-year-old boy is seen in the hospital with fever to 38.8°C and after a generalized tonic-clonic seizure. He has a 3-day history of not feeling well. Several episodes of nonbloody, nonbilious emesis were noted on the day of his seizure. On arriving at the emergency department, the child is lethargic but arousable. He reports headache, photophobia, and neck pain. Nuchal rigidity is noted on examination. Pupils are 4 mm, equal and reactive to light. Cough and gag reflexes are intact. He has intermittent tachypnea with good spontaneous respiratory effort, and oxygen saturation of 96% on 2 L/min oxygen via nasal cannula. His cardiovascular examination findings are unremarkable except for a blood pressure of 140/94 mm Hg. Abdominal examination findings are unremarkable. Laboratory data are pending. Over the next hour, the child becomes more obtunded and develops apnea. He is intubated, supported with mechanical ventilation, and admitted to the pediatric ICU. His medical history is unremarkable. He is up to date on his immunizations and takes no medications. Further history reveals that the child recently returned from a summer camp in Florida, where he swam every day in a nearby freshwater lake.

Of the following, the BEST treatment includes administration of

- **A.** ampicillin and gentamicin
- **B.** ceftazidime and fluconazole
- **C.** ceftriaxone and amphotericin B
- **D.** piperacillin/tazobactam

This child's presentation combined with his recent swimming in a freshwater lake during the summer has symptoms of meningitis that warrant concern for primary amoebic encephalitis (PAM).

Naegleria fowleri causes a rare and usually fatal PAM in humans and animals. There are few case reports of survivors of PAM. The first reported case of PAM resulting from *N fowleri* occurred in Florida in 1962. Since that time, data from the Centers for Disease Control and Prevention (CDC) through 2016 report 143 cases in the United States. *N fowleri* exists in fresh warm water environments such as ponds, lakes, rivers, and hot springs. The disease is commonly associated with diving in warm aquatic environments or any event that forces water into the nasal passages. Reports of this organism in the biofilm of drinking water systems also exist. *N fowleri* exists as a trophozoite (feeding and replicating forms) and as a dormant cyst. The meningoencephalitis caused by *N fowleri* occurs in the trophozoite phase and enters the body through the nose by attaching to the olfactory epithelium. The amoeba crosses the cribriform plate and enters the brain, resulting in a hemorrhagic meningoencephalitis that commonly results in death within 3 to 7 days. Infection with this amoeba does not occur through drinking water contaminated by this organism.

Different methods are available to identify *N fowleri,* including polymerase chain reaction (PCR), a technique that is more rapid and sensitive than are microscopic techniques and culturing of this organism. Current clinical diagnosis for *N fowleri* is often determined by cerebrospinal fluid (CSF) examination, including a wet mount preparation. Polymerase chain reaction testing can be performed on samples sent to the CDC. Microscopic evaluation using special staining techniques of the CSF may reveal presence of trophozoites (**Figure**). A wet mount preparation may reveal actively moving *N fowleri* (**Video**). Organisms may not be visible after heat fixation which can cause lysis of the trophozoites.

The typical clinical presentation for PAM is similar to that of any patient with meningitis. Patients may have headache, fever, nuchal rigidity, altered mental status, and seizures. Fever is common. Loss of taste or smell may also occur early in the disease. Cerebral spinal fluid results reveal a pleocytosis with elevated protein and a normal or low glucose level. Imaging studies of the brain may reveal cerebral edema and petechial or gross hemorrhage.

Amphotericin B is the treatment commonly used for PAM. Signs of meningitis require addition of a broad-spectrum antibiotic pending culture results, which makes ceftriaxone and amphotericin B the correct response. The blood–brain barrier may prevent adequate penetration of pharmacologic agents into the central nervous system. Amphotericin B can be administered both intravenously and intrathecally; however, therapy may be limited by renal toxicities of this drug. Liposomal amphotericin B is not a primary agent of choice because it has a minimum inhibitory concentration 10 times higher than that of amphotericin B. Amphotericin B has been combined with intravenous rifampin to potentiate treatment effects. The only known survivor of *N fowleri* in the United States was treated with intrathecal amphotericin B, miconazole, and intravenous rifampin. Other agents used in combination with amphotericin B to treat *N fowleri* include the imidazole

class of drugs (eg, miconazole, fluconazole, and ketoconazole); these drugs are potent antifungal agents. Miltefisine is an antileishmanial agent used for the treatment of breast cancer. This drug was administered in 2 patients who survived meningoencephalitis with *N fowleri*. Miltefisine is administered orally and can be nephrotoxic when used in higher doses. Corifungin is an antifungal agent that is similar to amphotericin B but with lower toxicity and has been approved for treatment of *N fowleri* in the United States. Other treatment for these critically ill patients includes use of dexamethasone and standard treatment for intracranial hypertension, including seizure prophylaxis.

The unusually high mortality rate associated with *N fowleri* is the result of the short incubation period and delayed recognition that results in delay of treatment with amphotericin B. A high index of suspicion based on the history and presentation of the patient is important; however, even with treatment, most cases are fatal. In fact, many cases are unfortunately diagnosed postmortem.

Adequately chlorinated water and public education about this disease are important preventive measures. This amoeba proliferates in the warmer months of the year and in water that has less chlorine. Additionally, use of nasal irrigation should be discouraged.

PREP Pearls

- *Naegleria fowleri* is commonly associated with diving in warm aquatic environments or any event that forces water into the nasal passages. Infection with this amoeba does not occur by drinking water contaminated by this organism.
- Amphotericin B administered both intravenously and intrathecally is the preferred treatment of primary amoebic meningoencephalitis.
- The high mortality rate associated with *Naegleria fowleri* is the result of the short incubation period and delayed recognition and treatment with amphotericin B. A high index of suspicion is required to diagnose this disease in a timely manner.
- Preventive measures include public education and adequately chlorinated water supplies.

ABP Content Specifications(s)/Content Area

- Central nervous system (CNS) infections
- Diagnosis and treatment of ameobic encephalitis

Suggested Readings

Bellini NK, Santo TM, da Silva MTA, Thiemann OH. The therapeutic strategies against *Naegleria fowleri. Exp Parasitol.* 2018;187:1-11. doi:10.1016/j.exppara.2018.02.010

Grace E, Asbill S, Virga K. *Naegleria fowleri*: Pathogenesis, diagnosis, and treatment options. *Antimicrob Agents Chemother.* 2015;59(11):6677-6681. doi:10.1128/AAC.01293-15

Harris GR, Batra R. *Naegleria fowleri. N Engl J Med*. 2020;383(11):1057. doi:10.1056/NEJMicm2002528

Jahangeer M, Mahmood Z, Muni N, et al. *Naegleria fowleri*: Sources of infection, pathophysiology, diagnosis, and management: A review. *Clin Exp Pharmacol Physiol.* 2020;47(2):199-212. doi:10.1111/1440-1681.13192

US Centers for Disease Control and Prevention. Parasites — *Naegleria fowleri* — Primary Amebic Meningoencephalitis (PAM) — Amebic Encephalitis — Treatment. Accessed April 18, 2022. https://www.cdc.gov/parasites/naegleria/treatment.html

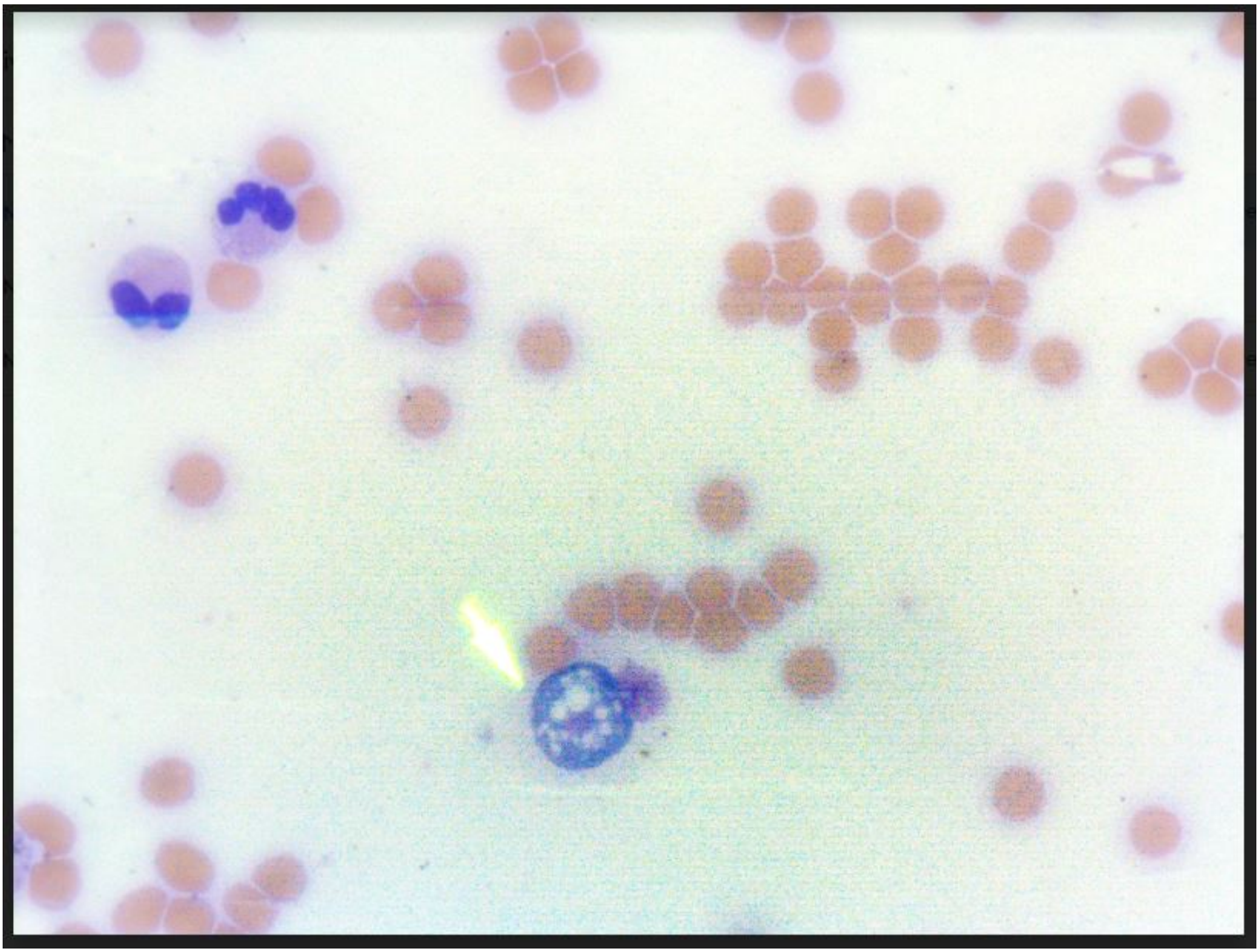


Figure: Wright stain of *Naeglaria fowleri* in cerebrospinal fluid.

Courtesy of F. Lam

July

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 2

A 2-month-old female infant is referred from a primary care physician's office owing to persistent wheezing and asymmetrical breath sounds noted on examination. Chest radiographs were obtained before her transfer (**Figure 1** and **Figure 2**). Initial evaluation in the pediatric ICU shows a thin infant with a weight of 4.2 kg (10th percentile). She is noted to have a resting respiratory rate in the 30s and room air oxygen saturations of 94% via pulse oximetry. Work of breathing appears normal. Rales and rhonchi are absent on her examination. An arterial blood gas analysis shows the following:

pH	7.38
$PaCO_2$	42 mm Hg
PaO_2	76 mm Hg on room air

A computed tomogram of the chest is obtained, and a representative axial image is shown (**Figure 3**).

Of the following, the BEST therapy indicated for this patient is

- **A.** chemical pleurodesis with talc
- **B.** intravenous steroid administration
- **C.** surgical resection before 6 months of age

D. thoracostomy tube placement

The images in this vignette support the diagnosis of congenital pulmonary airway malformation (CPAM). Close inspection of the lateral chest radiograph and chest computed tomographic scan shows a large intraparenchymal cyst (**Figure 4**). Congenital pulmonary airway malformation is the most common congenital lung malformation, with an incidence ranging from 1:10,000 to 1:35:000 among newborns. This pulmonary anomaly was originally described in 1949 as congenital cystic adenomatoid malformation. The name was later revised to congenital pulmonary airway malformation, as adenomatous tissue was inconsistently found on autopsy. Clinical presentation may vary. Up to 70% of antenatally diagnosed CPAMs are asymptomatic at birth, with 20% of affected neonates showing some degree of respiratory distress and 10% requiring intubation. Severe respiratory distress and mortality is increased if the CPAM is associated with hydrops, pulmonary hypoplasia, polyhydramnios, or cardiovascular compromise.

Classic histologic features of CPAMs include the following:

- Cyst formation lined by columnar, cuboid, or alveolar cells
- Polypoid projections of the mucosa
- Increased smooth muscle and elastic tissue in the wall of the cyst
- Presence of mucus secreting cells
- Absence of cartilage
- Lack of inflammation

In 2009, CPAMs were reclassified into 5 types.

- Type 0 is seen in ~1% to 3% of CPAMs. It is often discovered at birth and is associated with multiple small cysts in multiple pulmonary lobes.
- Type I accounts for almost 60% of CPAMs. It usually presents at birth with multiple large cysts (larger than 10 cm) or a single dominant cyst. Cysts are lined with ciliated columnar cells. Only one lobe is typically involved.
- Type II malformation causes 10% of cases. It typically presents in the first year of life with radiographs demonstrating multiple sponge-like cysts up to 2.5 cm in size in a single lobe. Concurrent cardiovascular, diaphragmatic or renal anomalies are most common with type II CPAMs (10% to 50%).
- Type III typically presents at birth with respiratory failure and accounts for ~10% of cases. Chest radiographs demonstrate a bulky adenomatoid mass with abundant small cysts (less than 1.5 cm) in a single lobe or lung.
- Type IV can be difficult to distinguish on radiographs from type I. It usually presents as a single cyst (5 to 10 cm) located peripherally in a single lobe. Histologically, the cyst is composed of flattened alveolar cells and lacks presence of mucus cells.

Ultrasonography is an important screening and prediction tool in prepartum care. Congenital pulmonary airway malformations can be diagnosed by prenatal ultrasonographic screening as early as 18 weeks of gestation. Interestingly, as many as 40% of CPAMs discovered by antenatal ultrasonography show complete resolution by the time of birth. The timing of the regression tends to occur in the mid-third trimester. Resolution of CPAMs is more common if the cysts have small volume. Antenatal ultrasonograms with a CPAM volume ratio (lesion height × length × width × 0.52 / head circumference) greater than 0.84, plus presence of polyhydramnios and ascites, significantly increase the risk of severe respiratory distress at birth. When ultrasonograms are unclear or difficult to interpret, maternal magnetic resonance imaging is a reasonable alternative. Postnatal diagnosis is often made clinically, with the infant experiencing persistent wheezing, dyspnea, poor feeding, or recurrent pneumonias. Chest radiographs may show a hyperlucent mass, which may be confused with other disease processes such as pneumothorax or intrapulmonary abscesses. Chest computed tomography is occasionally needed to confirm the diagnosis.

The pathogenesis of the abnormal airway branching and cyst formation in CPAM is unknown. Some researchers speculate that CPAMs arise from hamartomatous abnormalities of the bronchial tree; others believe it arises from an arrest in development of the fetal bronchi. Although multiple genetic abnormalities have been found in pulmonary tissue of CPAM patients (eg, increased expression of Hox and platelet-derived growth factor B genes; decreased expression of Yin Yang 1, fatty acid-binding protein 7 genes), their role in the morphogenesis of cystic development in the embryologic lung has yet to be elucidated. The important role of genetic abnormalities in CPAM is supported by the fact that 1% to 3% of undiagnosed lesions undergo malignant transformation into pleuropulmonary blastomas.

The treatment of CPAMs after antenatal diagnosis includes maternal administration of steroids, fetal thoracentesis, or fetal resection. Postpartum management centers on surgical resection. Lobectomy remains the standard resection method for CPAM management. There is debate as to the optimal time for resection of CPAM in symptomatic neonates, with most researchers recommending lobectomy by 6 months of age in symptomatic patients and between the ages of 6 months and 2 years in asymptomatic patients. In recent years, thoracoscopic resection is gaining favor. It shows similar outcomes to thoracotomy but involves shorter hospital stays and a decreased need for thoracotomy tubes. There is no role for postnatal treatment with steroids or chemical pleurodesis in management of CPAM. Thoracostomy tube placement may drain the cyst if the wall is ruptured by placement. However, surgical resection is still indicated, given the risk of recurrent pneumonias or malignant transformation.

PREP Pearls

- Congenital pulmonary airway malformations are the most common congenital lung malformation, with an incidence ranging from 1:10,000 to 1:35:000 among newborns.
- Congenital pulmonary airway malformations are most commonly found by antenatal ultrasonography, and up to 40% may regress by the time of birth.
- Although many congenital pulmonary airway malformations are asymptomatic, surgical removal is recommended by 6 to 24 months of age owing to the risk of recurrent pneumonias and malignant transformation.

ABP Content Specifications(s)/Content Area

- Recognize congenital pulmonary airway malformation (CPAM)
- Recognize radiographic characteristics of CPAM

Suggested Readings

David M, Lamas-Pinheiro R, Henriques-Coelho T. Prenatal and postnatal management of congenital pulmonary airway malformation. *Neonatology* 2016; 110: 101-15. doi:10.1159/000440894

Downard CD, Calkins CM, Williams RF et al. Treatment of congenital pulmonary airway malformations: a systemic review from the APSA outcomes and evidence based practice committee. *Pediatr Surg Int* 2017; 33(9): 939-53. doi:10.1007/s00383-017-4098-z

Leblanc C, Baron M, Desselas E et al. Congenital pulmonary airway malformations: state-of-the-art review for pediatrician's use. *Eur J Pediatr.* 2017; 176(12):1559-71. doi:10.1007/s00431-017-3032-7

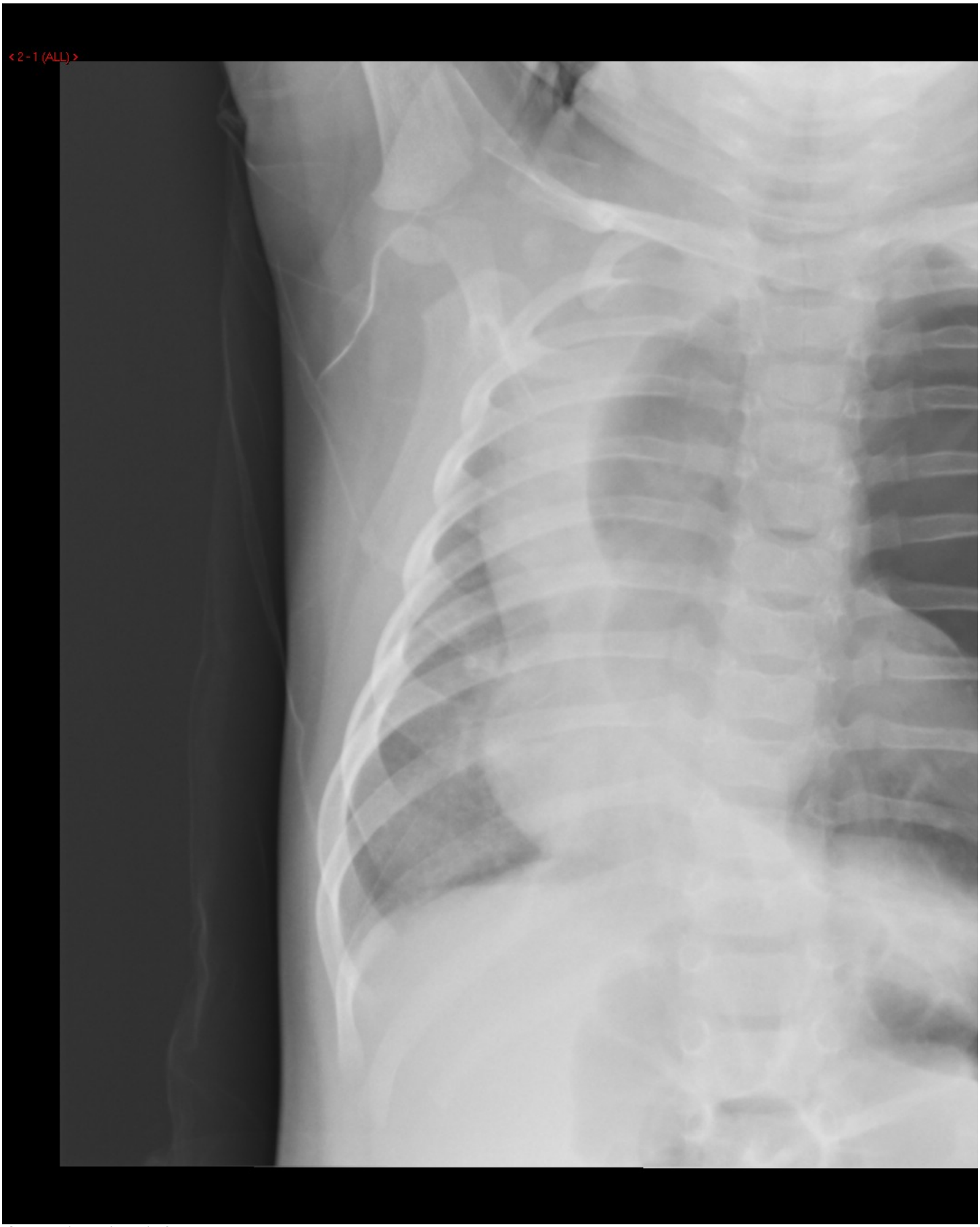


Figure 1: Chest radiograph of patient in vignette.

Courtesy of M. Rowin

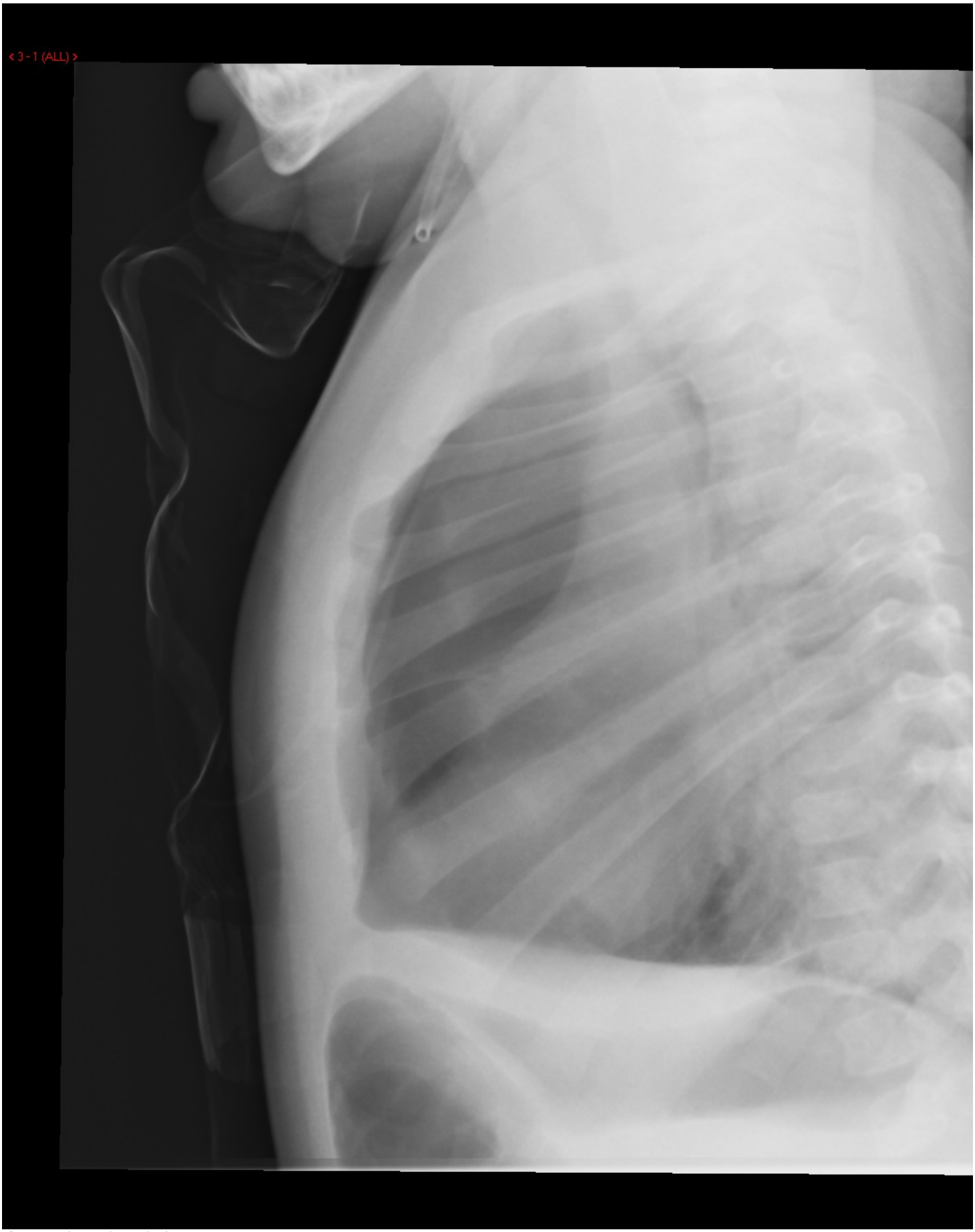


Figure 2: Chest radiograph of patient in vignette.

Courtesy of M. Rowin

July

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 3

A 3-month-old female infant is seen 5 hours after the repair of tetralogy of Fallot. Her blood pressure has declined from 84/56 mm Hg to 58/25 mm Hg over the last hour, and her heart rate has increased from 145 beats/min to 170 beats/min during the same period. During this time, her right atrial pressure has increased from 16 mm Hg to 24 mm Hg, and the atrial waveform is much more peaked than previously. She is receiving infusions of epinephrine (0.08 μg/kg per minute), calcium chloride (20 mg/kg per hour), and milrinone (0.5 μg/kg per hour). She is sedated with 0.05 mg/kg per hour of midazolam and is receiving 2 μg/kg per hour of fentanyl for analgesia. Her core temperature is 36°C. She has produced no urine in the last 2 hours. A surface electrocardiogram is shown in **Figure 1**.

Of the following, MOST appropriate next management step for this infant is to

- **A.** provide an intravenous bolus of amiodarone
- **B.** increase the epinephrine infusion
- **C.** provide an intravenous bolus of normal saline
- **D.** set atrial pacing at 175 beats/min

Junctional ectopic tachycardia (JET) is a narrow complex tachyarrhythmia that results from increased automaticity of the atrioventricular (AV) node. When the nodal rate exceeds the atrial rate, a bidirectional action potential travels both retrograde to the atria and anterograde to the ventricles. The result is a fast rhythm with dissociation between the atrial and ventricular depolarizations. Because the rhythm in JET arises from the AV node and uses the His-Purkinje system, the QRS complex is narrow except in cases of concomitant bundle branch block. Often, complete AV dissociation is observed. In infants

and newborns, a 1:1 AV retroconduction with inverted P waves can be seen. Although the rate in JET is often relatively consistent, it displays a “warm-up/cool-down” behavior in which the rate steadily increases over the sinus rate, rather than an abrupt increase in rate between one beat and the next as is seen in reentrant supraventricular tachycardia. Junctional ectopic tachycardia is primarily seen in the immediate postoperative period after congenital heart surgery involving the AV junction, including tetralogy of Fallot, complete AV canal defects, ventricular septal defects, and truncus arteriosus. A congenital form of JET affecting the fetus and newborn has been described, though it is rare. Both forms are difficult to control and both can be fatal. A precise estimate of the incidence of JET in the postoperative population has been difficult to ascertain, potentially because of variations in the definition of JET.

In addition to the type of surgery performed, a number of other factors are associated with the development of JET. Younger age at the time of surgery and higher preoperative heart rate are correlated with the development of JET. Patients treated with β-blockers before surgery seem to have a somewhat lower incidence. Hypomagnesemia before surgery appears to predispose patients to the development of JET. Some investigators have reported that longer periods of either cardiopulmonary bypass or aortic cross-clamping are associated with the development of JET postoperatively.

Diagnosis of this malignant dysrhythmia can be challenging. Because the rhythm arises from the AV node, administration of adenosine does not alleviate the tachycardia. It can, however, block retrograde conduction to the atrium and eliminate P waves with no effect on the ventricular rate or QRS morphology. Most patients undergoing cardiac surgery will have atrial pacing wires in place, which can be used to diagnose JET. An atrial electrogram is obtained by first obtaining a standard surface electrogram for comparison purposes, then repeating the study but with one of the atrial pacing wires connected directly to the electrocardiographic lead. Various authors suggest using a precordial lead or a limb lead. Regardless of the lead used, the temporary pacing wire provides for a very low impedance measurement of the P wave, which will therefore have a greater deflection than usual (**Figure 2**). This allows for easy comparison of the atrial and ventricular rates, even when the P wave as measured with surface electrography is buried in a much larger QRS complex or T wave. In situations where there is 1:1 retrograde ventriculoatrial conduction, the R-P interval generally is much shorter than the P-R interval. In addition, because of the lack of coordination of atrial and ventricular contractions, “cannon” A waves can be seen on the right atrial or central venous pressure tracings.

Treatment of JET can be challenging and is evolving. Adrenergic stimulation can be reduced by decreasing infusions of inotropic drugs. Native adrenergic tone can be reduced by providing adequate pain control. Temperature control appears to be helpful, and some authors advocate for mild cooling. Atrial overdrive pacing does not eliminate the

automaticity of the AV node, but pacing at a rate faster than the JET rate can sometimes restore A-V synchrony and aid a potentially marginal cardiac output by restoring the atrial kick. Historically, amiodarone has been the antiarrhythmic drug of choice for controlling JET. However, amiodarone is known to have a myocardial depressant effect, which may not be well tolerated in the setting of postoperative low cardiac output. Numerous case reports have described cardiovascular collapse with amiodarone, most often in newborns and infants with limited cardiac output in whom a bolus dose of amiodarone was administered over less than 20 minutes. More recently, the centrally acting α-blocker dexmedetomidine has been investigated for both the treatment and prevention of JET. Although large-scale trials do not exist, several smaller studies seem to suggest that the early (perhaps even pre-bypass) institution of a dexmedetomidine infusion may be associated with a reduction in the number of patients who will develop JET. Bolus dosing of dexmedetomidine at the time of development of a fast junctional rhythm may also help to limit its duration. Ivabradine selectively inhibits the hyperpolarization-activated cyclic nucleotide–gated channel, and thereby reduces heart rate. Several case reports have described its successful use in terminating refractory JET.

Postoperative JET generally appears to be a self-limited problem. However, if pharmacologic therapies and pacing are unsuccessful at resolving the dysrhythmia, support with extracorporeal membrane oxygenation may be required for a brief period while the rhythm recovers. Alternatively, congenital JET appears to be more persistent. In these situations, ablation may be necessary, though it can result in high-grade AV block.

Although amiodarone remains widely recommended as the antiarrhythmic of choice, the infant in the vignette has very limited cardiac output. In her age group, increases in cardiac output are largely dependent on increases in rate, and the relative bradycardia and myocardial depression that can result from an amiodarone bolus may result in further hypotension or arrest. Further adrenergic stimulation may only increase the automatic rate, thereby continuing to reduce cardiac output. The already significant elevation in right atrial pressure suggests that additional volume is unlikely to be helpful. Faster atrial pacing than the junctional rate will not improve the increased nodal automaticity, but it may help to restore the atrial kick and thereby improve cardiac output.

PREP Pearls

- Junctional ectopic tachycardia is a fast, narrow complex rhythm often characterized by atrioventricular dissociation, and a “warm-up/cool-down” pattern of change in heart rate that is most often seen after cardiac surgery.
- Junctional ectopic tachycardia is generally a self-limiting problem that resolves over time, but the problem of ensuring adequate cardiac output during the dysrhythmia can be challenging.

ABP Content Specifications(s)/Content Area

- Understand the pathogenesis of junctional ectopic tachycardia
- Plan the management of a patient with junctional ectopic tachycardia

Suggested Readings

Drago F, Battipaglia I, Di Mambro C. Neonatal and pediatric arrhythmias: clinical and electrocardiographic aspects. *Cardiol Electrophysiol Clin.* 2018;10(2):397-412. doi: 10.1016/j.ccep.2018.02.008

Ismail M, Arafat A, Hamouda T, et al. Junctional ectopic tachycardia following tetralogy of Fallot repair in children under 2 years. *J Cardiothorac Surg.* 2018;13(60). doi: 10.1186/s13019-018-0749-y

Maghrabi K, Uzun O, Kirsh J, Balaji S, Von Bergen N, Sanatani S. Cardiovascular collapse with intravenous amiodarone in children: a multi-center retrospective cohort study. *Pediatr Cardiol*. 2019;40:925-943. doi: 10.1007/s00246-019-02090-7

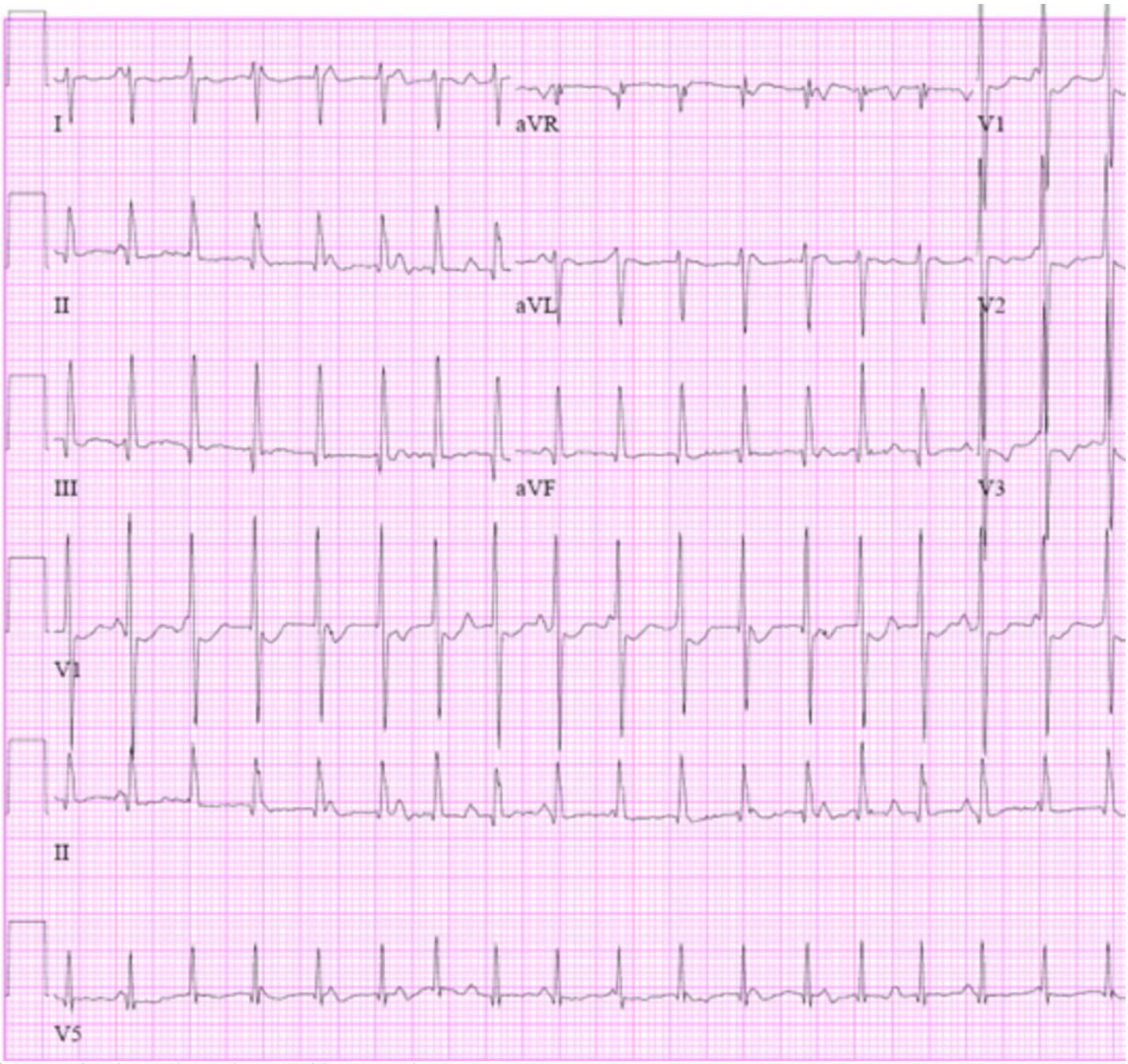


Figure 1: Surface electrocardiogram descriptive of the patient in the vignette.

Courtesy of A. Freedman

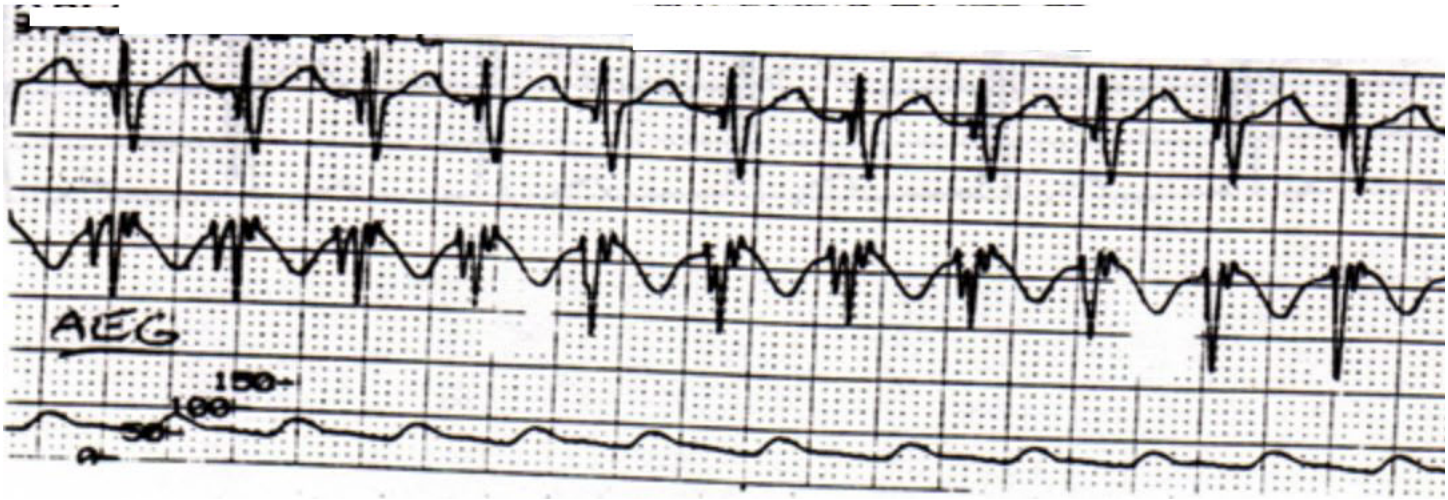


Figure 2: Atrial electrogram.

Courtesy of A. Freedman

July

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 4

A 13-month-old infant with a history of biliary atresia after a Kasai procedure (hepatoportoenterostomy) in the neonatal period is admitted to the pediatric intensive care unit after undergoing living related liver transplantation. She woke up after surgery and tolerated extubation on the first postoperative day; she is now well supported with high-flow nasal cannula at 6 L/min of 50% oxygen. She continues to receive low-dose vasoactives with an epinephrine infusion at 0.03 μg/kg per minute. She has been afebrile with a stable white blood cell count, at 19,300/μL (19.3×10^9/L). Because of an elevated international normalized ratio and postoperative bleeding, a heparin infusion has not yet been initiated, but surgical drain output has decreased and is now serosanguinous. On the morning of the second postoperative day, her morning laboratory findings demonstrate a significant increase in aspartate aminotransferase and alanine aminotransferase to 2,438 U/L and 2,190 U/L, respectively. In addition, her whole blood lactate has increased from 8.1 to 42.4 mg/dL (0.9-4.6 mmol/L) over the last 12 hours. Clinical assessment now demonstrates that she is less alert and interactive.

Of the following, the MOST appropriate next step in management is to

- **A.** consult transplant surgical staff about placement of a transhepatic drain
- **B.** obtain blood and urine specimens for cultures and start broad-spectrum antibiotics
- **C.** obtain a duplex ultrasonographic scan of the liver immediately
- **D.** start high-dose methylprednisolone

For the patient in the vignette, the most likely cause of elevated transaminases and lactate is either a portal vein or hepatic artery thrombosis, which is best diagnosed using Doppler ultrasonography of the liver. Surgical exploration and thrombectomy may be required.

Liver transplantation is a well-established strategy for treating children with end-stage liver disease or irreversible acute liver failure. Many advancements in preoperative, perioperative, and postoperative care have substantially improved survival in recent years, with long-term survival rates of more than 80% at most centers.

The indications for pediatric liver transplantation fall into 4 categories: acute liver failure, cholestatic liver disease, metabolic liver disease, and liver tumors. Biliary atresia accounts for about 40% to 50% of all pediatric liver transplantations. About one-third of patients are younger than 12 months at the time of transplantation. Contraindications for pediatric liver transplantation include unresectable or incurable extrahepatic malignancies, concomitant end-stage organ failure that cannot be corrected with liver transplantation, multisystem organ failure, and irreversible serious neurologic injury.

The preoperative evaluation for possible liver transplantation should be approached with a multidisciplinary, dedicated pediatric liver transplant team. Pretransplant evaluation must include assessments of renal, cardiac, and pulmonary function, given that comorbid hepatorenal syndrome or other causes of renal dysfunction, diastolic dysfunction, and pulmonary hypertension, as well as hepatopulmonary syndrome with intrapulmonary shunting may all affect intraoperative and postoperative management. Assessment for viral (especially adenovirus, cytomegalovirus, Epstein-Barr virus, human herpesvirus [HHV] 6 and HHV-8) and bacterial infections is also essential.

Once a patient is known to be a candidate for liver transplantation, graft allocation is based on complex and evolving policy. One of the factors that may be considered, but is not applicable to all patients with liver failure, is a patient's pediatric end-stage liver disease (PELD) score. The PELD score is based on total bilirubin, international normalized ratio, serum albumin, age, and growth failure. Other factors under consideration include the presence of hepatopulmonary and hepatorenal syndrome, metabolic and genetic diseases, and hepatic malignancies.

All pediatric patients receiving liver transplantation require postoperative management in the pediatric intensive care unit. General postoperative priorities include weaning of ventilator support and early extubation and balanced hemodynamics to promote adequate

graft perfusion, as well as cerebral perfusion in the presence of increased intracranial pressure, careful electrolyte and fluid management, and neurologic monitoring.

Postoperative considerations include close observations for medical or surgical complications. Primary nonfunction of the graft is a rare, severe complication that usually presents in the first 48 hours after transplantation, with depressed mental status, hepatic encephalopathy, vasoplegia, lactic acidosis, rising transaminases, and coagulopathy. This occurs likely because of donor factors including ischemia/reperfusion injury and is treatable only with emergent retransplantation.

Biliary complications, including bile leak, stenosis, and strictures, usually occur owing to technical problems with the anastomosis or from bile duct ischemia. They may present early with bile in the surgical drains or years after transplantation with recurrent cholangitis. They are usually treatable with decompression by a transhepatic drain, but severe leak causing biliary peritonitis may require surgical revision or even retransplantation.

Vascular complications are the most common postoperative complications that cause graft failure. Hepatic artery thrombosis occurs more commonly in children because of their smaller vessel size compared with adults. Postoperative management is aimed at preventing this complication and includes anticoagulation, antiplatelet therapy, and avoidance of red cell and platelet transfusions. Portal vein thrombosis may also occur in the first week postoperatively and is more common in patients with biliary atresia caused by portal vein hypoplasia. Frequently, patients are monitored with daily liver duplex ultrasonography.

Infections, especially gram-negative bacterial and fungal bloodstream infections, remain the major causes of morbidity and mortality in the postoperative period after liver transplantation. Clinicians must have a high index of suspicion regarding sepsis, because prompt initiation of therapy is critical.

Finally, although immunosuppressive regimens and protocols have improved greatly in recent years, about 25% to 50% of patients will develop an episode of acute rejection in the first several weeks after transplantation. Most are treatable with high-dose systemic corticosteroid therapy.

PREP Pearls

- Pediatric patients with acute liver failure must be referred to centers with expertise in liver disease and liver transplantation.

- Encephalopathy, coagulopathy, and growth failure are some of the primary severity criteria involved in prioritization for liver transplantation.
- Major complications seen in the first week after surgery include infection, bile leak, hepatic artery or portal vein thrombosis, and primary graft nonfunction.

ABP Content Specifications(s)/Content Area

- Understand the epidemiology of pediatric acute liver failure.
- Describe initial diagnostic work up for pediatric acute liver failure.
- Understand important prognostic indicators in pediatric acute liver failure.
- Describe the criteria for pediatric liver transplantation.

Suggested Readings

Duffy JP, Hong JC, Farmer DG, et al. Vascular complications of orthotopic liver transplantation: experience in more than 4,200 patients. *J Am Coll Surg*. 2009;208(5):896-903; discussion 903-5. doi:10.1016/j.jamcollsurg.2008.12.032

Rozenfeld RA, Harris ZL. Intensive care of the child after liver transplantation. In: Dunn S, Horslen S, eds. *Organ and Tissue Transplantation: Solid Organ Transplantation in Infants and Children.* New York, NY: Springer, Cham; 2018. doi:10.1007/978-3-319-07284-5_44

July

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 6

A 12-year-old boy with refractory acute lymphoblastic leukemia received chimeric antigen receptor (CAR) T-cell therapy with tisagenlecleucel 12 days ago. He has been monitored closely since his infusion on the hematology-oncology unit. Over the past day he has developed fatigue, myalgia, and nausea. He has had visually hallucinations and appears encephalopathic. Today, the patient developed hypotension and hypoxemia. He received 2 L of normal saline to support his blood pressure and 4 L oxygen via nasal cannula, which improved his oxygen saturations from 89% to 94%. Despite fluid resuscitation, he continues to experience tachycardia, with a heart rate of 130 beats/min, and hypotension, with blood pressure of 92/45 mm Hg. He is transferred to the pediatric ICU and a norepinephrine infusion is started. He is febrile to 39.2°C. Broad-spectrum antibiotics are administered after blood and urine cultures are obtained.

Of the following, the BEST recommended next treatment for this patient is

- **A.** dexamethasone and remdesivir
- **B.** levetiracetam and anakinra
- **C.** methylprednisolone and 3% sodium chloride
- **D.** methylprednisolone and tocilizumab

Treatment for refractory or relapsed B-cell acute lymphoblastic leukemia (ALL) has advanced significantly in the past 5 years with the evolution, and Food and Drug Administration (FDA) approval, of chimeric antigen receptor (CAR) T-cell therapy. CAR-T cell therapy is a genetically modified autologous T-cell immunotherapy directed at the B-lymphocyte antigen CD19. This therapy stimulates T-cell activation to recognize specific antigens on the surface of target cells such as ALL blasts. The patient undergoes apheresis

for collection of white blood cells that are cryopreserved, and T cells are processed for genetic manipulation by adding the specific CAR. Prior to CAR-T therapy, the patient undergoes lymphodepleting chemotherapy, allowing expansion of CAR-T cells once infused. A single infusion of tisagenlecleucel often results in lasting remission for children with relapsed B-cell ALL. In a multicenter study, a high response rate was demonstrated in 61% of children with relapsed B-cell ALL. The remission rate was 81% in 75 patients 3 months after a single infusion of tisagenlecleucel. The remission rate was sustained with a 6-month 80% relapse-free survival rate. Although this agent produces remission, there are associated risks with CAR-T therapy.

Toxicity from CAR-T therapy can be life threatening and includes the cytokine release syndrome (CRS) and neurotoxicity. The risk of toxicity increases in patients with a higher disease burden. Toxicities commonly occur within the first 8 weeks following the infusion. CRS usually occurs within the first 7 to 10 days after the infusion and occurs in a high percentage of patients after CAR-T therapy. CRS occurs as a result of CAR-T cell expansion and immune activation. CAR stimulates activation of T cells that specifically combine with malignant cell antigens. Proliferation of CAR-T cells results in release of cytokines, specifically interferon gamma (IFN γ,) IL-5, IL-6, IL-10, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Fever is one of the first presenting signs of CRS. This can be followed by myalgias, headache, fluid refractory hypotension, and multiorgan dysfunction resulting in capillary leak syndrome. The severity of CRS and toxicity correlates with elevation of cytokine levels of IL-6.

Common neurotoxic adverse effects—termed immune effector cell-associated neurologic syndrome (ICANS)—include delirium, visual hallucinations, tremors, altered mental status, disturbance in language (such as expressive aphasia), seizures, and encephalopathy. In severe but rare cases, cerebral edema can occur. The neurotoxicity associated with CAR-T therapy tends to be transient and occurs within the first 6 to 8 weeks after the infusion. Neurologic events seem to occur during or shortly following CRS. The severity of the neurotoxic events seems to correlate with the severity of CRS. Management of neurotoxicity includes supportive care and use of corticosteroids. Dexamethasone has been used in some cases. For severe cases, high-dose pulse steroid treatment with methylprednisolone is recommended. Other causes of neurologic alteration should be excluded. Cerebrospinal fluid studies typically reveal elevated levels of IL-6 and increased CAR-T cells. The higher number of cells seems to correlate with neurotoxicity.

Symptoms associated with CRS are similar to the systemic inflammatory response seen with sepsis and broad-spectrum antibiotic therapy is recommended until infection is ruled out. Treatment of CRS and neurotoxicity includes suppression of IL-6 using the monoclonal antibody receptor antagonist tocilizumab. Tocilizumab is FDA approved for severe CRS management. If there is no response to tocilizumab, corticosteroid therapy with

methylprednisolone is commonly employed to reduce the inflammatory response. Symptoms of CRS usually resolve fairly quickly after treatment with tocilizumab and corticosteroid therapy; however, severe CRS can further evolve into hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS). A high serum ferritin level, oliguria, elevated serum creatinine level, increased bilirubin and transaminase levels, and hemophagocytosis are common with the HLH/MAS.

Similar to a CRS crisis, treatment of neurotoxicity includes suppression of IL-6, supportive care, and corticosteroid therapy. The severity of CRS is predictive of neurotoxicity. Tocilizumab does not cross the blood–brain barrier. Siltuximab is a direct IL-6 antagonist that may be beneficial to prevent IL-6 from entering the CNS. High-dose corticosteroids have better CNS penetration and should be used in conjunction with tocilizumab. Seizure prophylaxis should be initiated with levetiracetam. The recommended treatment duration for antiepileptic therapy is at least 30 days after resolution of CRS. Acute seizures can be treated with benzodiazepine and antiepileptic medication.

For the patient in this vignette, treatment with tocilizumab for the CRS and methylprednisolone for neurotoxicity is the correct treatment of choice. Anakinra is an IL-1 receptor antagonist and remdesivir is an antiviral agent.

PREP Pearls

- Chimeric antigen receptor (CAR) T-cell immunotherapy stimulates T-cell activation to recognize specific antigens on the surface of target cells such as acute lymphoblastic leukemia blasts.
- A single infusion of chimeric antigen receptor (CAR) T-cell therapy has resulted in lasting remission for children with relapsed B-cell acute lymphoblastic leukemia.
- Cytokine release syndrome and neurotoxicity increase in patients with a higher disease burden.
- Treatment of cytokine release syndrome and neurotoxicity includes suppression of IL-6 using the monoclonal antibody receptor antagonist tocilizumab. Corticosteroids are also commonly administered to treat neurotoxicity or refractory cytokine release syndrome.

ABP Content Specifications(s)/Content Area

- Manage treatment strategies for a patient with refractory B-cell acute lymphoblastic leukemia

Suggested Readings

Badieyan ZS, Hoseini SS. Adverse effect associated with clinical applications of CAR engineered T cells. *Arch Immunol Ther Exp (Warsz)*. 2018;66(4):283-288. doi:10.1007/s00005-018-0507-9

Finch EA, Duke E, Hwang EI, Packer RJ. Immunotherapy approaches for pediatric CNS tumors and associated neurotoxicity. *Pediatr Neurol*. 2020;107:7-15. doi:10.1016/j.pediatrneurol.2020.01.004

Maude SL, Laetsch TW, Buechner S, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med.* 2018;378(5):439-448. doi:10.1056/NEJMoa1709866

Pehlivan KC, Duncan BB, Lee DW. CAR-T cell therapy for acute lymphoblastic leukemia: transforming the treatment of relapsed and refractory disease. *Curr Hematol Malig Rep*. 2018;13(5):396-406. doi:10.1007/s11899-018-0470-x

Yang X, Wand G, Zhou J. CAR-T Cell therapy for hematological malignancies. *Curr Med Sci.* 2019;39(6):874-882. doi:10.1007/s11596-019-2118-z

August

Question: 1

A 14-year-old adolescent girl with chronic hypertension and a body mass index of 45 kg/m² has been hospitalized with severe COVID-19 infection for 2 weeks. She was supported with venovenous extracorporeal membrane oxygenation (ECMO) for 1 week and then decannulated. She was sedated with dexmedetomidine and morphine for 10 days and received several days of vecuronium infusion during her pre-ECMO and ECMO support. She is currently extubated but requires bilevel positive airway pressure support during sleep and nasal cannula oxygen therapy while awake. She is receiving clonidine and methadone for alpha agonist and opiate withdrawal. On rounds, her Cornell Assessment of Pediatric Delirium (CAPD) score is 10, and nurses report she has been very agitated and intermittently disoriented, particularly at night, despite the use of nonpharmacologic interventions. She repeatedly attempts to remove her respiratory support, causing her to have desaturation and increased agitation. At other times, she is poorly responsive to commands and demonstrates psychomotor slowing. Her most recent electrocardiogram is shown (**Figure 1**).

Of the following, the medication that is the SAFEST and MOST effective agent to treat her delirium is

- **A.** intravenous haloperidol
- **B.** intravenous midazolam
- **C.** melatonin via nasogastric tube
- **D.** risperidone via nasogastric tube

The patient in the vignette is experiencing one of the unfortunate complications of prolonged hospitalization in the pediatric intensive care unit (ICU)—delirium. Although delirium has been long observed in both pediatric and adult ICUs, only more recently have we begun to formally identify risk factors for, quantify the degree of, and treat it. Delirium has been associated with increased mortality in adults as well as increased likelihood of cognitive decline and longer pediatric ICU and hospital stays in children. This patient appears to be primarily demonstrating symptoms of a mixed delirium, with features of

hypoactive and hyperactive delirium. Hyperactive delirium is best treated with an antipsychotic. Intravenous midazolam is inappropriate in this case because increased benzodiazepine exposure is associated with increased incidence and duration of delirium. Although improved sleep is extremely important in preventing and treating delirium, melatonin alone is unlikely to improve the hyperactive component of the patient's delirium. In this case, the patient is already on methadone, a drug with a known risk of QTc prolongation and torsades de pointes (TdP), so adding IV haloperidol would increase the risk of TdP. The patient has a borderline prolonged QTc at 470 ms. Therefore, risperidone, an antipsychotic with only conditional risk of TdP, is the safest and most efficacious choice for treating hyperactive delirium in this patient.

Haloperidol is a typical antipsychotic agent of the butyrophenone class. It was one of the first medications used to treat critically ill adults with delirium because of its efficacy and the availability of IV and intramuscular formulations. The mechanism of action for butyrophenones is nonselective blockade of brain postsynaptic dopaminergic D2-receptors. Although the most common adverse drug reactions associated with haloperidol are extrapyramidal effects, drowsiness, dystonia, and tremor, one of the more feared cardiovascular effects is prolongation of the QT interval. The QT interval is proportional in length to the heart rate; it becomes longer when the heart beats slower and is shorter when the heart beats faster. Therefore, the QT interval is "corrected" through the use of a mathematical formula (most commonly used is the Bazett formula, but the Fredericia formula may also be used) to correct the QT interval to what it would be if the heart rate was 60 beats per minute. For men, the normal QTc by the Bazett formula is less than 450 ms; for women, less than 460 ms. Several studies have found that a QTc > 500 ms regardless of age or sex increases the risk of serious dysrhythmias such as TdP.

Prolongation of the QT interval is a result of blockade of potassium conductance on the rapid (Ikr) and slow (Iks) receptors within potassium ion channels. This causes prolongation of the ventricular action potential duration due to delayed ventricular repolarization. It can lead to multiple ventricular reentrant loops and TdP. This is a polymorphic ventricular tachycardia described as a "twisting of the points," or twisting of the QRS complexes around the isoelectric line. There is typically a "warm-up" phenomenon, with the first few beats of ventricular tachycardia characterized by longer cycle lengths and progressively becoming shorter. The typical rate of TdP is slower than ventricular fibrillation (VF) at 160 to 240 beats/min. Torsades de pointes frequently terminates spontaneously and also responds to treatment with IV magnesium sulfate. However, in some cases it degenerates into VF and can cause sudden cardiac death (**Figure 2**).

In 2007, a warning recommending electrocardiography monitoring was added to the product labeling for IV haloperidol due to case reports of QT interval prolongation, torsades de pointes, and sudden death with the use of IV haloperidol. Many medications used in the

ICU are associated with QT prolongation. The **Table** lists high-risk QT prolonging drugs commonly used in the pediatric ICU; a more complete list can be found at the CredibleMeds website. Many medications are reported to prolong QTc interval in susceptible patients, but most are considered lower risk. Risk factors for drug-induced torsades de pointes are

- QTc >500 ms
- Concurrent use of multiple QT-prolonging medications
- Underlying structural heart disease
- Known prolonged QTc at baseline
- Hypomagnesemia
- Hypokalemia
- Female sex

This patient is female and is already receiving one QT-prolonging medication (methadone). Risk increases with higher doses and increased numbers of QT-prolonging medications.

Current practice guidelines from the American Heart Association and the American College of Cardiology recommend discontinuing or reducing the dose of the offending medication if the QTc exceeds 500 ms or if the QTc is >60 ms from baseline after initial medication administration. The clinician should attempt to avoid combinations of medications that can prolong QTc and precipitate TdP. When adding high-risk medications, ECGs should be monitored at least daily while evaluating the effects of the medication.

In February 2022 a group of experts published practice guidelines on prevention and management of pain, agitation, neuromuscular blockade, and delirium in critically ill pediatric patients with consideration of the ICU environment and early mobility. These guidelines represent the most current recommendations for the evaluation and management of pediatric delirium and should be reviewed by pediatric critical care practitioners.

PREP Pearls

- Butyrophenones such as haloperidol and droperidol are known to increase the risk of experiencing QTc prolongation as well as torsades de pointes.
- Clinicians should avoid combining multiple QTc-prolonging medications when possible and carefully monitor patients who are receiving QTc-prolonging medications for electrocardiographic changes.

ABP Content Specifications(s)/Content Area

- Recognize the potential risk of cardiac dysrhythmias and their relation to prolonged QT interval associated with the use of butyrophenones

Suggested Readings

Capino AC, Thomas AN, Baylor S, Hughes KM, Miller JL, Johnson PN. Antipsychotic use in the prevention and treatment of intensive care unit delirium in pediatric patients. *J Pediatr Pharmacol Ther.* 2020;25(2):81-95. doi:10.5863/1551-6776-25.2.81

Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. Circulation. 2010;121:1047-1060. doi:10.1161/CIRCULATIONAHA.109.192704

Smith HAB, Besunder JB, Betters KA, et al. 2022 Society of Critical Care Medicine Clinical Practice Guidelines on prevention and management of pain, agitation, neuromuscular blockade, and delirium in critically ill pediatric patients with consideration of the ICU environment and early mobility. *Pediatr Crit Care Med.* 2022;23(2):e74-e110. doi:10.1097/PCC.0000000000002873

Wackel P, Cannon B. Heart rate and rhythm disorders. *Pediatr Rev*. 2017;38(6):243-253. doi:10.1542/pir.2016-0119

Vent. rate	76	BPM
PR interval	144	ms
QRS duration	76	ms
QT/QTc	418/470	ms
P-R-T axes	77 87	36

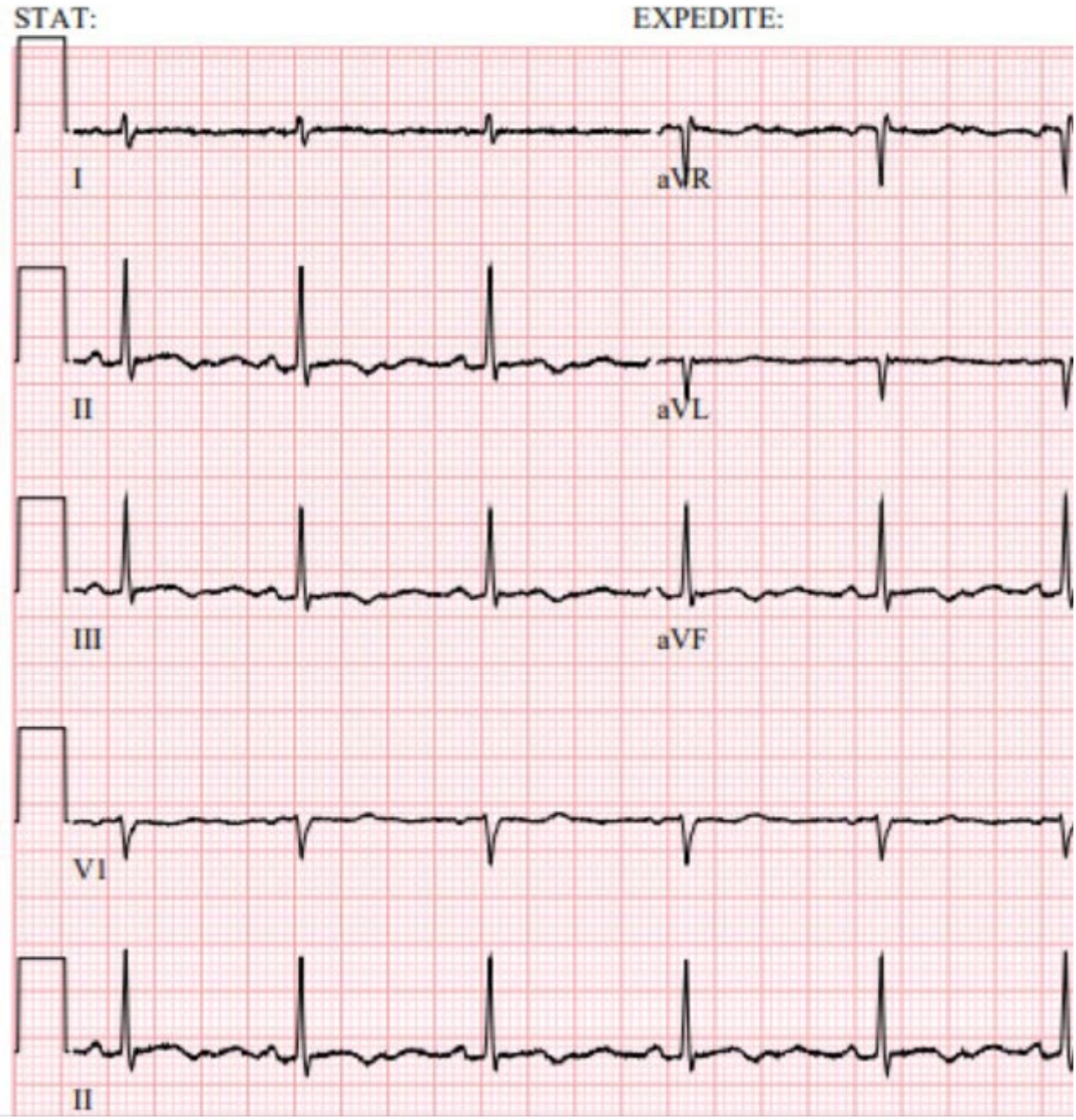


Figure 1:
Electrocardiogram descriptive of patient in vignette

Courtesy of E. Reade

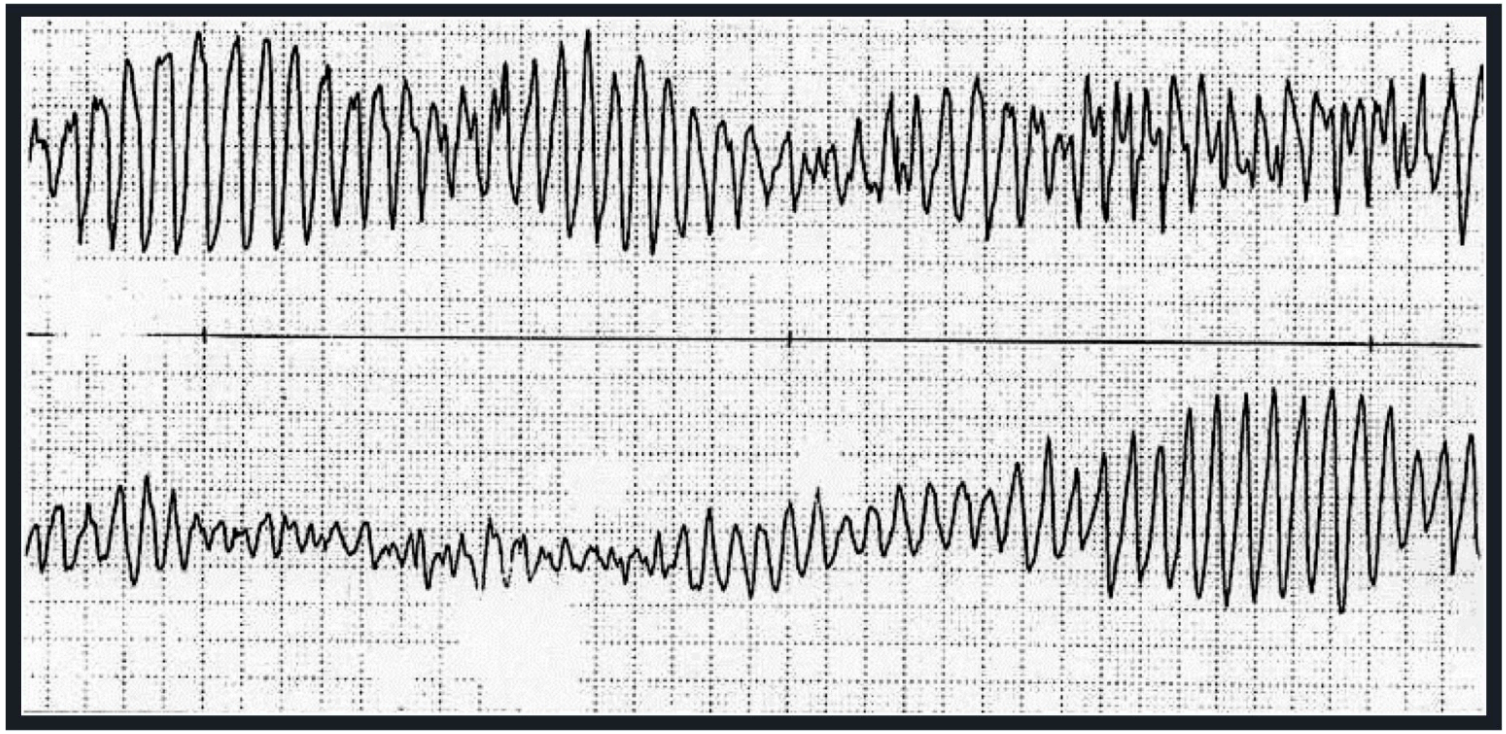


Figure 2:

Torsades de pointes.

Reprinted with permission from Wackel P, Cannon B. Heart rate and rhythm disorders. *Pediatr Rev*. 2017;38(6):249.

Table. Common PICU Medications with Known High Risk of Torsades de Pointes.

Medication Class	Medication
Anesthetics	Propofol Sevoflurane
Antiarrhythmics	Amiodarone Flecainide Procainamide Sotalol
Antibiotics	Azithromycin Ciprofloxacin Erythromycin Levofloxacin
Antifungals	Fluconazole Pentamidine
Antipsychotics	Droperidol Haloperidol
Gastrointestinal medications	Ondansetron
Narcotics	Methadone

Courtesy of E. Reade; Source: http://www.crediblemeds.org

August

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 2

A 3-year-old boy is brought to the emergency department in the southeastern United States after a snake bit his hand. The family has a photo of the snake responsible for the envenomation (**Figure**). The patient is admitted to the pediatric ICU for ongoing medical care.

Of the following, over the next 24 hours, the disease process that this patient is at HIGHEST risk of developing is

- **A.** anaphylaxis
- **B.** coagulopathy
- **C.** neurotoxicity
- **D.** renal failure

The **Figure** in this vignette demonstrates an eastern diamondback rattlesnake. Snakebite envenomation and resultant morbidity is a major public health concern in the developing world. Global estimates suggest greater than 3 million snakebites and more than 140,000 deaths per year, with India alone reporting more than 45,000 deaths per year. Snakebites are less common in industrialized countries located in temperate regions. Most venomous snakes in the United States are members of the *Viperidae* family and *Crotalinae* subfamily. These include rattlesnakes, cottonmouths (water moccasins), and copperheads. These snakes are commonly referred to as pit vipers (or crotalids) because of the presence of heat-sensing pits behind their nostrils. North America also contains venomous snakes from the subfamily *Elapidae*, often referred to as elapids. These include 3 species of coral snakes.

Almost 5,000 episodes of snake envenomation occur each year in the United States, and most of these are due to crotalids. Approximately 10% of snakebites from crotalids do not result in envenomation. Coral snake bites compose about 2% of envenomation events in the United States. Deaths resulting from snake envenomation in the United States are rare, usually about 5 per year.

Crotalid venom contains over 50 proteins and enzymes. These include hydrolase, collagenase, hyaluronidase, DNase, and acetylcholinesterase. Local tissue destruction and coagulopathy are hallmarks of crotalid envenomation. Myonecrosis may follow envenomation owing to the action of phospholipase A2, which can disrupt the integrity of muscle fiber plasma membranes. Crotalid venom causes destruction of the extracellular matrix and disruption of vascular endothelium. This causes local swelling, erythema, and discomfort within 60 minutes, progressing to bullae formation and necrosis over time, depending on the volume of venom injected. Generally, rattlesnakes tend to inject larger volumes of venom than do copperheads and water moccasins.

Coagulopathy is common after crotalid envenomation. Thrombocytopenia and hypofibrinogenemia are often noted and may last for days. Crotalid venom contains fibrinolysins and thrombin-like enzymes, which dissolve fibrin and result in unstable clot formation and further consumption of fibrinogen. The mechanism of thrombocytopenia after envenomation is unclear but thought to be related to either platelet membrane damage due to venom phospholipases or platelet aggregation at areas of endothelial damage.

Neurologic problems, outside of pain at the snakebite site, are rarely reported. However, one species of crotalid, the Mojave rattlesnake, has venom that contains a powerful neurotoxic agent called Mojave toxin. This venom prevents presynaptic release of acetylcholine and can produce cranial nerve dysfunction, weakness, and paralysis. Coral snake bites result in little or no local tissue injury, but their venom also contains powerful neurotoxic agents. Elapid envenomation results in postsynaptic acetylcholine blockade. Within 6 to 12 hours of a snakebite, the victim can exhibit cranial nerve palsies, dysarthria, weakness, and, in severe cases, paralysis.

In North America, envenomation management includes fluid resuscitation and pain management. Historic treatments such as use of venom extractors, excisions at the bite sites, and use of tourniquets are no longer advocated. Elevation of the affected limb can decrease edema. Bites to the face may require early intubation owing to concerns of upper airway obstruction from swelling. Intubation should also be considered after coral snake bites given the risk of paralysis of respiratory muscles. Perfusion status distal to the bite should be assessed frequently, because affected patients are at risk of developing compartment syndrome as a result of swelling and tissue destruction. Blood products may

be required to correct the coagulopathy and thrombocytopenia until administration of antivenom has occurred. Renal toxicity is not reported with North American snake envenomation.

Crotalidae polyvalent immune F(ab) and *Crotalidae* immune F(ab')2 are approved antivenom therapies for snakebites in the United States. They contain antigen-binding fragments derived from several species of rattlesnakes as well as the water moccasin. *Crotalidae* immune F(ab')2 also contains immunoglobulin fragments derived from the fer-de-lance snake. Treatment does not decrease swelling or necrosis but will improve coagulopathy and neurotoxicity. Antivenom is indicated in patients with presumed significant envenomation or with signs of systemic toxicity or neurologic deterioration. Reactions to antivenom are rare (5% to 8%) and generally mild. The Food and Drug Administration has also approved North American coral snake antivenom for coral snake envenomations. Anaphylactic reactions have been reported in up to 10% of recipients of North American coral snake antivenin. However, treatment of coral snake bites may become increasingly problematic. The manufacturer stopped making this product in 2006, and the last lot expired in January 2020.

PREP Pearls

- In the United States, most venomous snakebites are from members of the *Crotalinae* subfamily, including rattlesnakes, copperheads, and water moccasins.
- Crotalid venom contains multiple enzymes and proteins, which can cause hypofibrinogenemia and thrombocytopenia, resulting in persistent coagulopathy.
- Coral snake antivenom is no longer commercially available.

ABP Content Specifications(s)/Content Area

- Know the indications for use of antivenom therapies following a snake bite

Suggested Readings

Corbett B, Clark RF. North American snake envenomation. *Emerg Med Clin North Am.* 2017;35(2):339-354. doi:10.1016/j.emc.2016.12.003

Gutierrez JM, Calvete JJ, Habib AG, Harrison RA, Williams DJ, Warrell DA. Snakebite envenoming. *Nat Rev Dis Primers.* 2017;3:17063. doi:10.1038/nrdp.2017.63

Warrell DA. Venomous bites, stings, and poisoning: an update. *Infect Dis Clin North Am.* 2019;33(1):17-38. doi:10.1016/j.idc.2018.10.001

Figure: Photo of the snake responsible for the envenomation.

Courtesy of M. Rowin

August

Question: 3

An 8-year-old girl is admitted to the pediatric ICU for fever and neutropenia. She is now 6 months into her consolidation chemotherapy for acute lymphoblastic leukemia. After initial stabilization and initiation of broad-spectrum antibiotics, the patient begins to complain of lower extremity pain. She describes the pain as “burning” in her legs and receives no relief from repositioning. She cannot identify a specific site in her legs from which the pain originates. Examination shows the legs to be warm and well perfused and to have a 1-second capillary refill time. She has 2+ femoral and dorsalis pedis artery pulses bilaterally. There are no lesions or erythema on her legs. Treatment with 0.1 mg/kg morphine sulfate does not affect intensity of the painful sensation.

Of the following, the agent that MOST likely contributed to this patient’s condition is

- **A.** cisplatin
- **B.** cytarabine
- **C.** dexamethasone
- **D.** vincristine

Pain can accompany many disease processes. The International Association for the Study of Pain defines pain as “[a]n unpleasant sensory or emotional experience associated with actual or potential tissue damage.” Physical pain is often categorized into 3 groups, nociceptive pain (caused by tissue injury), functional pain, and neuropathic pain. Functional pain is defined as pain without an obvious source of origin (eg, fibromyalgia). Neuropathic pain is defined as pain arising from, or as a consequence of, lesions or diseases affecting the somatosensory system.

Mechanisms of generation of neuropathic pain are variable and poorly understood. The etiology of neuropathic pain is thought to be injury or alterations in nerve pathways resulting in persistent pain signaling. It can involve injury to either peripheral or central neural structures. Neuropathic pain typically is of long duration and is often poorly

responsive to traditional narcotic-based therapies. Neuropathic pain is typically spontaneous and often described as “burning,” “electric,” or “needle-like.” The pain is typically out of proportion to any stimulus that may have elicited its onset.

The prevalence of neuropathic pain in children is unknown. Causes of neuropathic pain in children are multiple. Trauma, such as spinal cord or brachial plexus injury, surgery, neurologic conditions (eg, Guillain-Barré, multiple sclerosis), metabolic disorders (eg, Fabry disease), infections (eg, HIV, herpes), and oncologic disorders are all associated with development of neuropathic pain. Certain pharmaceutical agents are frequently associated with development of neuropathic pain. Neuropathies commonly occur after treatment with vinca alkaloids, platinum compounds, and monoclonal antibody therapy directed against tumor-associated disialoganglioside GD2 (commonly found in neuroblastomas).

In the pediatric oncology patient, neuropathic pain can arise from multiple causes, including chemotherapy, tumor burden or location, surgery/amputation, and the complex circumstances surrounding end-of-life care. The prevalence of neuropathic pain in cancer patients varies from 19% to 39%. The chemotherapy agent most commonly associated with neuropathic pain in pediatrics is vincristine. In one pediatric study, the incidence of vincristine-related neuropathy in treatment of acute lymphoblastic leukemia was 35%, with 16% of patients experiencing repeated episodes of neuropathic pain. Vincristine’s ability to cause neuropathic pain is believed to occur through inhibition of microtubule polymerization and subsequent destruction of the peripheral neuronal axon. The neurotoxicity of vincristine is dose dependent and can affect both autonomic and sensorimotor nerves.

The diagnosis of neuropathic pain can be difficult. No specific laboratory tests are available to confirm the diagnosis. However, genetic analysis has detected point mutations in some patients on the *SCN9A* gene. This is associated with a sodium channel located on certain sympathetic nerve fibers. Although guidelines exist for adults, none has been published for pediatric patients. Diagnosis in adults often relies on screening tools such as the Leeds Assessment of Neuropathic Symptoms and Signs, Identify Pain score, and the Neuropathic Pain Questionnaire. A screening tool for neuropathic pain has recently been developed for children with cancer. The pediatric modified Total Neuropathy Scale (ped-mTNS) was developed in 2013 and is validated for children aged 5 to 18 years. A variation of this screening tool has also been developed specifically for children receiving vincristine, called the Total Neuropathy Score Pediatric Vincristine.

Severe, debilitating neuropathic pain is often refractory to typical opioid dosing regimens. Successful treatment is challenging and may require multiple forms of therapy (eg, pharmacologic, distraction, music, acupuncture, guided imagery). Drug therapies used most frequently in pediatric neuropathic pain include tricyclic antidepressants, serotonin-

norepinephrine reuptake inhibitors, and gabapentinoids (ie, gabapentin and pregabalin). Intravenous ketamine, methadone, intravenous or topical lidocaine, and topical capsaicin have all been used to treat some forms of chemotherapy-associated neuropathic pain. Clinicians can also consider spinal or peripheral nerve blocks in cases of regional pain. High-dose opioids may be considered late in pharmacologic escalation, and they are often used to treat neuropathic pain associated with end-of-life care.

There is emerging evidence that use of nonpainful electric superficial stimulation can block the painful sensations of neuropathic pain. “Scrambler” therapy consists of application of mild electric pulses on the skin of the affected area (eg, transcutaneous electrical nerve stimulation unit), thereby stimulating the non-injured nerves and “blocking” propagation from injured nerves. In one small study, use of scrambler therapy decreased the Total Neuropathy Score Pediatric Vincristine score from 9.2 to 0.1, and most of the patients weaned off medications by the end of the study.

PREP Pearls

- Neuropathic pain is complex and poorly defined in pediatrics. It is defined as pain that originates from a process affecting the central or peripheral nervous system and often presents as a burning or tingling sensation.
- Vincristine is the chemotherapy agent most commonly associated with development of neuropathic pain in pediatrics.
- Neuropathic pain does not traditionally respond to opioid analgesics.
- Tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, or gabapentinoids are more likely to provide relief of painful sensations.

ABP Content Specifications(s)/Content Area

- Understand the pathophysiology of pain

Suggested Readings

Anghelescu DL, Faughnan LG, Jeha S, et al. Neuropathic pain during treatment for childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer.* 2011; 57(7):1147-53. doi:10.1002/pbc.23039

Anghelescu DL, Tesney JM. Neuropathic pain in pediatric oncology: a clinical decision algorithm. *Paediatr Drugs.* 2019;21(2):59-70. doi:10.1007/s40272-018-00324-4

Howard RF, Wiener S, Walker SM. Neuropathic pain in children. *Arch Dis Child.* 2014;99(1):84-89. doi:10.1136/archdischild-2013-304208

August

Question: 4

A 2-year-old male with a medical history significant for prematurity, grade 1 intraventricular hemorrhage, hypothyroidism, and short bowel syndrome due to necrotizing enterocolitis totalis as an infant is admitted to the pediatric intensive care unit after undergoing a bowel-lengthening procedure. It is now postoperative day 6; on postoperative day 5, the patient was started on nasogastric feedings but developed evidence of severe malabsorption and bowel injury with diffuse bloody diarrhea, so a nothing-by-mouth instruction was established. The patient has developed worsening tachycardia and hypotension over the course of the day, requiring multiple fluid boluses for persistent hypotension. His current examination demonstrates a lethargic, pale, difficult-to-arouse child. His chest examination reveals coarse bilateral breath sounds. His cardiac examination findings include tachycardia, no murmur, warm extremities, a capillary refill time of 1 second, and bounding radial pulses. His abdomen is distended and tender to palpation.

The results of an arterial blood gas are as follows:

pH	7.10
$PaCO_2$	20 mmHg
PaO_2	75 mmHg
Serum lactate	13 mmol/L

Of the following, the bacteria MOST likely to be associated with the patient's symptoms are

- **A.** group A *Streptococcus*
- **B.** *Listeria monocytogenes*

C. *Neisseria meningitidis*

D. *Pseudomonas aeruginosa*

The patient in the vignette exhibits signs and symptoms of gram-negative bacteremia and septic shock. Despite many advances in treatment and diagnosis, bacterial sepsis continues to be a significant cause of pediatric morbidity and mortality, particularly among the most critically ill children. The symptoms of bacterial sepsis are secondary to microbial invasion of bacteria or endotoxin into the bloodstream triggering a systemic inflammatory response. Bacterial bloodstream infections can come from multiple routes, including entry via skin breakdown, indwelling central venous catheters, other indwelling devices, and bacterial translocation across the epithelial mucosa, most commonly of the gastrointestinal tract. Given that this patient has been exhibiting clinical signs of severe malabsorption with evidence of gastrointestinal injury and possible ischemic bowel, as demonstrated by his elevated lactate, the most likely source of his bacteremia is secondary to bacterial translocation across the injured gastrointestinal tract.

Bacterial translocation across the gastrointestinal tract is a common cause of pathogenic organism-mediated sepsis and organ dysfunction in critically ill children. The gastrointestinal tract is colonized with approximately 500 different species of microbes, with the most common pathogenic bacteria reported as *Escherichia coli, Klebsiella*, and *Pseudomonas aeruginosa*.

The gastrointestinal tract has many functions other than digestion and represents the single largest immunologic organ of the body. It is postulated that a form of bacterial translocation from the GI tract occurs regularly even in healthy patients as part of a physiologic process by which different luminal antigens are sampled, resulting in production of immunocompetent cells. This process requires an intact immune system.

Pathologic bacterial translocation, or bacteria's bioactive products, can also cross the intestinal barrier, causing an infection or stimulating the immune system and resulting in a massive inflammatory cascade. Critically ill children are particularly at increased risk of experiencing bacterial translocation because of significant bacterial overgrowth owing to prolonged nothing-by-mouth status, breakdown of the intestinal tight junctions from their critical illness, and compromised immune status. Luminal bacteria can cross the intestinal barrier via the transcellular or paracellular route. In healthy people, once the bacteria crosses the barrier, most of these bacteria are destroyed by macrophages; however, given the burden of bacteria due to overgrowth or gastrointestinal injury, this defense can be overwhelmed. Additionally, the first line of defense in preventing bacteremia is the mucosal

lining overlying the gastrointestinal epithelia. This lining is produced by the goblet cells, which are injured in patients with severe malabsorption and gastrointestinal injury. In the presence of significant bowel injury or infarction, these lines of defense are often inadequate.

The pathologic factors that increase the risk of bacterial translocation in critical illness are those that affect the homeostatic equilibrium of the luminal organisms and the gut barrier, promoting ingress of bacteria across the barrier. The risk of bacterial translocation has been shown to be particularly increased in patients with intestinal obstruction, jaundice, inflammatory bowel disease, GI malignancy, and severe gastric bacterial overgrowth.

Pseudomonas aeruginosa is a gram-negative aerobic bacilli commonly found in the gastrointestinal tract and implicated as a cause of bacteremia from gastrointestinal bacterial translocation. Group A *Streptococcus*, *Neisseria meningitidis*, and *Listeria monocytogenes* are all possible causes of bacteremia; however, they are not typically found in the gastrointestinal tract and are not associated with gastrointestinal bacterial translocation. It is imperative that the antibiotic regimen in the initial management of these patients be tailored toward coverage of these enteric gram-negative and anaerobic bacteria.

PREP Pearls

- Critical illness is a risk factor for bacterial translocation.
- Antibiotic management of suspected gastrointestinal bacterial translocation should be tailored to provide coverage of gram-negative and anaerobic bacteria.

ABP Content Specifications(s)/Content Area

- Recognize gastrointestinal bacterial translocation as a common cause of pathogenic organism-mediated sepsis and organ dysfunction in critically ill children

Suggested Readings

Haddad FC, Rao R, Kaur S, Redkey J, Karcz A, Ladd AP. The implication of intestinal bacterial translocation in central line associated bloodstream infections in the pediatric population. *J Pediatric Surg*. 2020;55(8):1651-1654. doi:10.1016/j.jpedsurg.2020.02.012

Longhitano Y, Zanza C, Thangathurai D, et al. Gut alterations in septic patients: A biochemical literature review. *Rev Recent Clin Trials.* 2020;15(4):289-297. doi:10.2174/1574887115666200811105251

August

Question: 5

A neurologically devastated 11-year-old boy who sustained abusive head trauma at 2 months of age has developed septic shock with acute respiratory distress syndrome. He has progressed to multisystem organ failure. He has developed barotrauma requiring placement of 3 chest tubes and is supported via high-frequency oscillation ventilation with oxygen saturations of 85%. Blood pressure support is being maintained with epinephrine and vasopressin infusions. He has developed acute kidney injury, with rising blood urea nitrogen and creatinine levels, as well as anuria. The parents have decided to allow natural death and withdraw life-sustaining medical therapies.

Of the following, the MOST accurate statement when death occurs is

- **A.** cardiac electrical activity ceases
- **B.** circulation ceases
- **C.** circulation and cardiac electrical activity cease
- **D.** respirations cease

The importance of defining death has emerged with advanced medical technologies allowing patients to be supported with mechanical ventilation, extracorporeal circulation, sedation, and anesthesia. All of this has complicated the unified traditional determination of death, which was defined as loss of circulation and respiration.

No national law to determine death exists. The Uniform Determination of Death Act (UDDA) was created to provide a consistent definition of death. The UDDA provides a legal definition of death and is a model for individual state laws governing the determination of death. This definition evolved from the 1981 report from the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. This report emerged from a new criterion for death set forth by the Harvard Ad Hoc Committee on Irreversible Coma. The UDDA defines death as the irreversible loss of circulatory and respiratory function or loss of function of the entire brain, including the brainstem. Thus, a person can be determined dead according to circulatory and respiratory criteria or neurologic criteria, also known as brain death.

This dual or bifurcated definition of death does not mention cardiac function. Although the heart is the organ that circulates oxygenated blood throughout the body, circulation can be supported by artificial means. Therapies that restore artificial support by providing anterograde circulation with oxygenated blood include extracorporeal support, cardiopulmonary bypass, closed chest compressions, and other mechanical devices. Despite having no cardiac function, patients supported by these artificial means are not considered dead because circulation is preserved. Electrical activity is a marker of cardiac activity; however, the presence of electrical activity does not guarantee circulation. Patients who have pulseless electrical activity lack circulation. Circulation is measured by contraction of the myocardium, generating anterograde flow. The absence of pulse pressure (mechanical asystole) serves as an indication for loss of circulation. It is cessation of circulation, not of electrical activity, that defines death.

The UDDA provided a legal definition of death. The legal definition of death does not mean that every cell in the body has died (biologic death). Dying is a process, and death is an event that occurs at a specific point in time during this process. The process of dying that ultimately results in death begins with individual cellular death, which leads to irreversible tissue and organ destruction once circulation has ceased. Depending on when death is declared, not every cell in the body has died. The process of cell death (biologic death) can continue despite a declaration of death.

The UDDA defines death but leaves to the medical community the determination of death according to currently accepted standards. Medical societies have established guidelines to determine death. Guidelines for the determination of neurologic death from the American Academy of Neurology and the Society of Critical Care Medicine, American Academy of Pediatrics, and Child Neurology Society provide clinicians with a standardized process to determine when a person has died. The determination of death is important to establish so that legal proceedings can move forward, medical treatments can cease because the physician-patient relationship ends, and, importantly, to allow for recovery of organs from patients declared dead according to neurologic or circulatory criteria.

Some scholars continue to debate specific issues related to neurologic and circulatory death. Specific issues have focused on legal versus biological death, and whether the patient meets the legal definition of death at the exact moment when death is declared specifically in regard to organ donation. An ethical discussion on these topics is beyond the scope of this review. The reader is referred to the literature for additional information.

PREP Pearls

- Death is defined as the irreversible loss of circulatory and respiratory function or loss of function of the entire brain, including the brainstem.
- Dying is a process and death is an event that occurs at a specific point in time during that process.
- When death is declared, not every cell in the body has died.
- Medical societies have provided guidelines to determine death by currently accepted medical standards.

ABP Content Specifications(s)/Content Area

- Definitions of death

Suggested Readings

Bernat JL. Controversies in defining and determining death in critical care. *Nat Rev Neurol.* 2013;9(3):164-173. doi:10.1038/nrneurol.2013.12

Capron AM. Beecher dépassé: Fifty years of determining death, legally. *Hastings Cent Rep.* 2018;48 Suppl 4:S14-S18. doi:10.1002/hast.945

Controversies in the determination of death: A white paper by the President's Council on Bioethics. December 2008. https://repository.library.georgetown.edu/bitstream/handle/10822/559343/Controversies%20in%20the%20Determination%20of%20Death%20for%sequence=1&isAllowed=y

Uniform Law Commission. Uniform determination of death act. Accessed April 3, 2022. https://www.uniformlaws.org/HigherLogic/System/DownloadDocumentFile.ashx?DocumentFileKey=4d19d096-be64-3c0f-ae71-a514b64c06a6&forceDialog=0

White FJ. Controversy in the determination of death: the definition and moment of death. *Linacre Q.* 2019;86(4):366-380. doi:10.1177/0024363919876393

August

Question: 6

A 12-year-old boy was admitted to the pediatric intensive care unit with tachypnea, increased work of breathing, abdominal pain, and severe acidosis. The results of arterial blood gas testing were as follows:

pH	6.97
PCO_2	19 mm Hg
PO_2	100 mm Hg

On further workup, he was found to have new-onset type I diabetes, as well as diabetic ketoacidosis. He was treated with intravenous fluids and an insulin infusion; as a result, his symptoms resolved and his anion gap and pH improved. He has been recovering well in the intensive care unit for 2 days and began receiving intermittent subcutaneous insulin therapy. Overnight, he was transitioned to self-administered insulin injections via an insulin pen and is now planned for transfer to the general pediatric floor today for further management and continued diabetes education. The physician is called to his room emergently because his 10-year-old brother, who has been visiting him unsupervised, developed generalized tonic-clonic seizure activity. His mother denies any significant medical history, prior seizure activity, recent ingestions, or trauma.

After ensuring that the airway is protected and applying a 100% fraction of inspired oxygen facemask, the MOST appropriate next step the clinician takes is likely to be

- **A.** administering 2 mL/kg of 3% hypertonic saline solution
- **B.** administering 0.25 mg/kg of intravenous labetalol
- **C.** obtaining a noncontrast computed tomographic scan of the head

D. obtaining a point-of-care glucose test

The treatment of new-onset seizure activity requires patient management and assessment of the etiology to be performed simultaneously. The management of seizure activity includes evaluation and possible support of the patient's circulatory functions, including airway, breathing, and circulation. Once this occurs, the clinician can take further steps to abort the seizure activity, assess for the underlying causes, and treat and prevent any complications of the seizure activity. If the seizure activity is not treated appropriately and aborted in a timely fashion, there is potential for the development of status epilepticus, prolonged seizure activity, and neurologic damage if the underlying cause is not recognized and reversed quickly.

As stated, the initial management of a patient experiencing a seizure includes the assessment of the ABCs (airway/breathing/circulation), with a specific evaluation for a patent airway. A 100% fraction of inspired oxygen non-rebreather facemask should be applied to maximize oxygen delivery, and oxygen saturation should be assessed to ensure the patient is receiving appropriate levels of oxygen. The patient should be assessed for signs of dehydration, intravascular volume depletion, and decreased cardiac output. Vascular access via intravenous (IV) or intraosseous routes should be established as quickly as possible according to the Pediatric Advanced Life Support (PALS) guidelines. The clinician should evaluate the underlying cause of the seizure on the basis of the patient's history. Regardless of the history, the clinician should check the patient's whole blood glucose level immediately given the expeditious results of this point-of-care test and need for immediate reversal of hypoglycemia.

In general, serum electrolyte, liver function, and urine toxicology testing should be done in all patients with new-onset seizure activity. Altered mental status and focal findings on a neurological examination can suggest an intracranial lesion or process, and in such patients the clinician should consider imaging studies and a lumbar puncture for further evaluation. Given the description of the events and the history, the patient in our vignette is likely experiencing a hypoglycemic seizure resulting from accidental administration of insulin, possibly from playing with the insulin pen.

Physiologic glucose homeostasis is achieved by the actions of endogenous insulin and the counter regulatory hormones. Hypoglycemia is defined as a serum glucose of less than 40 mg/dL (2.2 mmol/L), with mild symptoms typically starting at a serum glucose level of approximately 70 mg/dL (3.9 mmol/L) and lower. Hypoglycemia is commonly found in neonates owing to their poor glycogen stores, with the incidence significantly decreasing

with age. The most common occurrence of hypoglycemia in older patients is due to the treatment of insulin-dependent type 1 diabetes, when the patient or caregiver has not balanced the administered insulin correctly with the patient's food intake or exercise.

The patient with hypoglycemia can experience weakness, sweating, tachycardia, tremors, and, in severe or rapid onset, hypoglycemic seizure activity. The central nervous system and cerebral cortex rely on glucose for continued homeostasis and appropriate function and, therefore, are very sensitive to fluctuations in serum glucose levels and particularly hypoglycemia. During an episode of prolonged hypoglycemia, it is postulated, the excitatory neurotransmitters glutamate and aspartate increase out of proportion to the inhibitory neurotransmitter gamma aminobutyric acid, leading to seizure activity.

If a patient is experiencing neurological changes secondary to hypoglycemia, he or she should receive glucose as quickly as possible. The hypoglycemia should be reversed by administering 0.5 g/kg of glucose; however, the clinician should be aware that when giving more, the higher dose can cause rebound hypoglycemia due to a spike in the patient’s endogenous insulin. A common rule of thumb in treating hypoglycemia and administering approximately 0.5 g/kg of IV glucose is to administer 1 mL/kg of D50, 2 mL/kg of D25, or 5 mL/kg of D10. If a glucose concentration greater than D10 is being administered, central access is preferred; however, administration can be done via a peripheral IV line in an emergency. In situations in which only D25 or D50 is available, it is preferable to dilute the solution further to prevent injury to the peripheral veins. After the initial hypoglycemia is reversed with the administration of glucose, rebound hypoglycemia should be prevented by using a continuous infusion of a dextrose containing solution run at a glucose infusion rate of approximately 5 to 8 mg/kg/min in neonates and 3 to 5 mg/kg/min in older children. Children with persistent hyperinsulinemia may require infusions at a much higher rate. In cases of an insulin overdose in patients without IV access, glucagon can be given intramuscularly to help reverse the hypoglycemia and the effects of the administered insulin.

PREP Pearls

- Patients with new-onset seizure activity should be immediately evaluated with point-of-care testing for hypoglycemia.
- The clinician should reverse hypoglycemia with 0.5 g/kg of intravenous glucose, which is equivalent to 1 mL/kg of D50, 2 mL/kg of D25, or 5 mL/kg of D10.

ABP Content Specifications(s)/Content Area

- Evaluate patient with new-onset seizure activity for hypoglycemia

Suggested Readings

Abraham MB, Jones TW, Naranho D, et al. ISPAD Clinical practice consensus guidelines 2018: assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes*. 2018;9(suppl 27):178-192. doi:10.1111/pedi.12698

Tas E, Garibaldi L, Muzumdar R. Glucose homeostasis in newborns: an endocrinology perspective. *Neoreviews.* 2020;21(1):e14-e29. doi:10.1542/neo.21-1-e14

September

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 1

A 4-week-old male infant is admitted to the pediatric ICU with lethargy, hypothermia, and significant failure to thrive with weight 10% below his birth weight, now at 3 kg. He was born at 40 weeks' gestation via a normal vaginal delivery. He has had 3 weeks of intermittent diarrhea, which has worsened over the last 3 days. His formula was recently changed to a hydrolyzed formula by his pediatrician because of concern about a possible milk protein allergy. The patient was evaluated in the emergency department, where he underwent a full evaluation to rule out sepsis, including blood, urine, and cerebrospinal fluid cultures. He has been started on antibiotics because of concern regarding possible sepsis. On his arrival in the pediatric ICU, the patient manifested a generalized tonic-clonic seizure.

Laboratory data from the emergency department are shown:

Laboratory Test	**Result**
White blood cell count	18,000/μL (18×10^9/L)
Hemoglobin	15.6 g/dL (156 g/L)
Hematocrit	45.5%
Platelet count	256×10^3/μL (256×10^9/L)
Sodium	115 mEq/L (115 mmol/L)
Potassium	3.3 mEq/L (3.3 mmol/L)

Chloride	95 mEq/L (95 mmol/L)
Carbon dioxide, total (mEq/L)	9 mEq/L (9 mmol/L)
Blood urea nitrogen	25 mg/dL (8.9 mmol/L)
Creatinine (mg/dL)	0.5 (44.2 µmol/L)
Glucose	100 mg/dL (5.6 mmol/L)

The patient's airway is protected and supplemental oxygen is provided.

Of the following, the MOST appropriate next step in treatment is to

- **A.** administer intravenous dextrose
- **B.** administer intravenous lorazepam
- **C.** administer intravenous 3% hypertonic saline
- **D.** order a noncontrast head computed tomographic scan

Hyponatremia is classified on the basis of a patient's extracellular fluid volume status as hypervolemic, euvolemic, or hypovolemic hyponatremia, and generally is defined as a serum sodium of less than 135 mEq/L. The serum sodium level fluctuates and is relative to the volume of total-body free water. A low serum sodium may be caused by any of the following:

- Increased water intake (eg, resulting from excessively dilute infant formula)
- Increased water retention (eg, owing to the syndrome of inappropriate antidiuretic syndrome or renal insufficiency);
- Increased sodium losses (eg, due to diarrhea, gastroenteritis, or overuse of diuretics)

The patient in this vignette likely has severe hypovolemic hyponatremia, in which he developed a loss of sodium in excess of water loss owing to his severe diarrhea and likely chronic malabsorption.

Hyponatremia can lead to significant neurologic symptoms. It also can result in the syndrome of hyponatremic encephalopathy, consisting of poor feeding, irritability, nausea and vomiting, lethargy, and, in severe cases, seizure activity and subsequent neurologic injury if left untreated.

Treatment of new-onset seizure activity requires patient management and evaluation of the etiology to be performed simultaneously. The initial management of a convulsing patient begins with assessment of airway, breathing, and circulation, with a specific evaluation for a patent airway. Oxygen should be administered via a 100% non-rebreather facemask to ensure appropriate O_2 delivery, and SpO_2 should be assessed to ensure the patient is oxygenating appropriately. Once this occurs, further steps can be taken to abort the seizure activity, assess the underlying causes, and prevent any complications of the seizure activity. If the seizure activity is not treated appropriately in a timely manner, there is potential for the development of status epilepticus and prolonged seizure activity particularly if the underlying cause is not recognized and reversed quickly.

An evaluation for an underlying cause of the seizure should be performed on the basis of the patient's history. Given the description of events and the described history, the patient in the vignette is likely experiencing a hyponatremic seizure, with a sodium value of 115 mEq/L.

A serum sodium concentration of less than 120 mEq/L is considered a significant risk for neurologic sequela and should be immediately corrected. If the patient is exhibiting neurologic changes or seizures as a sequela of any level of hyponatremia even when serum sodium levels are higher than 120 mEq/L, treatment should be started immediately with the administration of hypertonic saline to rapidly reverse the symptoms. The serum sodium level should be increased to a level higher than 120 mEq/L or until the seizure activity is terminated. Hypertonic saline should be administered over a period of 10 to 15 minutes to correct the electrolyte abnormality and reverse the seizure activity. Three percent hypertonic saline is recommended for rapid correction and should be given via central venous access when possible; however, it can be administered via a peripheral intravenous line or intraosseous in an emergency. Because normal saline is relatively hypertonic to the patient with hyponatremia, a bolus of 20 mL/kg can be used to raise the serum sodium when hypertonic saline is not available.

The formula below can be used to determine the mEq of sodium (Na) needed to correct the serum sodium to the determined/appropriate level:

0.6 × (weight of the patient in kg) × (Target Na- Serum Na) = mEq of Na required to raise the serum Na to the determined level

Using the example patient from our vignette, the equation would be as follows:

0.6 × 3(kg) × (120 mEq/L - 115 mEq/L) = 9 mEq of Na required to raise the serum Na to 120 mEq/L

1 mL of 3 % saline contains 0.5 mEq. This patient would therefore require 18 mL of 3% saline for correction.

Once the serum sodium is corrected to the determined level, and if the patient is not experiencing continued neurologic changes, treatment should proceed more slowly with a goal correction of 0.5 to 1 mEq/L every hour to prevent a rapid rise and possible subsequent development of osmotic demyelination syndrome.

PREP Pearls

- Hyponatremia with neurologic sequelae should be corrected rapidly to prevent further neurologic damage.
- The formula for sodium correction is 0.6 × (weight of the patient in kg) × (Target Na-Measured Na) = Total mEq of Na required to raise the serum sodium to the determined level.
- Once sodium is corrected to the target amount of ~120 mEq/L, the correction should be slowed to an increase of 0.5-1.0 mEq/L per hour to prevent a rapid rise and possible central pontine myelinolysis.

ABP Content Specifications(s)/Content Area

- Treat a neonate experiencing a hyponatremic seizure.
- Recognize findings associated with severe hypovolemic hyponatremia.

Suggested Readings

Sterns RH, Silver S. Complications and management of hyponatremia. *Curr Opin Nephrol Hypertens.* 2016;25(2):114-119. doi:10.1097/MNH.0000000000000200

Wang J, Xu E, Xiao Y. Isotonic versus hypotonic maintenance IV fluids in hospitalized children: a meta-analysis. *Pediatrics.* 2014;133(1):105-113. doi:10.1542/peds.2013-2041

September

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 2

A 7-year-old girl is admitted to the pediatric ICU for fever, headache, and respiratory distress. She states that she has had ear pain and a sore throat for the past several days. Initial examination shows an erythematous pharynx, an enlarged exudative right palatine tonsil, erythema behind the right ear, and pain to palpation of the area over the right mastoid air cells. Broad-spectrum antibiotics are initiated. Head and neck computed tomographic scans are obtained and images are shown in **Figure 1** and **Figure 2**. Additionally, a gram-negative organism is noted growing from the anaerobic specimen bottle within 24 hours.

Of the following, the associated process that should prompt initiation of anticoagulation therapy is

- **A.** facial vein thrombosis
- **B.** intracranial sinus thrombosis
- **C.** mastoiditis
- **D.** splenic infarction

The patient in this vignette demonstrates the presence of an internal jugular thrombus with accompanying bacteremia and sepsis, consistent with the diagnosis of Lemierre syndrome (LS). Historically, LS was originally described in 1936 as a complication of pharyngitis with resultant bacteremia, thrombophlebitis of the internal jugular vein, and subsequent septic emboli. It is most often caused by *Fusobacterium necrophorum,* but cases are also reported with other *Fusobacterium* species, *Staphylococcus*, group A *Streptococcus*, and *Enterococcus*. *F necrophorum* is an anaerobic gram-negative bacillus, often found as part of the normal flora of the mouth and pharynx.

The incidence rate of LS is unknown but estimated to be 0.6 to 2.3 per million people. The incidence of LS has increased over the past 2 decades. The reasons for this are unclear, but speculation includes decreased use of antibiotics for ear, nose, and throat infections as well as decreasing numbers of tonsillectomies. The mortality rate is approximately 2%, but can be as high as 10% when antibiotic therapy is delayed.

Lemierre syndrome is often difficult to diagnose owing to its nonspecific symptoms and low incidence. Patients are typically young adults who present with a history of oropharyngeal infection, fever, neck pain, tachycardia, tachypnea, and respiratory distress. Diagnosis is often suspected after ultrasonography, computed tomography scan, or magnetic resonance images show thrombus formation in neck veins, most commonly the internal jugular (**Figure 3** and **Figure 4**). Facial veins and the transverse sinus may also be involved. Thrombosis of the sigmoid or transverse sinus is more common when the primary infection involves the ear or mastoid sinus, rather than the oropharynx. The diagnosis of LS is confirmed by discovery of *F necrophorum* (or other bacteria) in blood or pharyngeal abscess fluid. Further investigation often shows septic pulmonary emboli, but emboli may involve other locations including liver, spleen, heart, joints, and the central nervous system.

The management of LS focuses on systemic antibiotic therapy. Drainage of any abscess collections at secondary sites of infection and anticoagulation are frequently also considered. *F necrophorum* is susceptible to metronidazole, clindamycin, β-lactam/β-lactamase inhibitor combinations, and carbapenems, variably susceptible to penicillin, and commonly resistant to macrolides, fluoroquinolones, and aminoglycosides. Metronidazole is increasingly cited as the treatment of choice because it is active against all isolates of *Fusobacterium* species while also providing high tissue penetration, cerebrospinal fluid penetration, and high oral bioavailability. Duration of antibiotic therapy ranges from 10 days to 6 weeks, depending on the number of organs involved.

Anticoagulation remains an area of controversy overall owing to the paucity of data and lack of randomized controlled trials. The literature suggests a trend toward increasing use of anticoagulation to treat LS patients. Investigators in a 2007 review of LS cases found 23% of cases received anticoagulation. A follow-up review in 2016 showed this had increased to 46% of cases. However, the authors of the 2016 review noted no differences in mortality among those treated with anticoagulation and those who were not. Current consensus supports use of anticoagulation in cases of LS in which there is little clinical improvement with antibiotics alone, there is evidence of propagation of the primary thrombus, or the patient is predisposed to thrombophilia. Further, several recent papers advocate the use of anticoagulation therapy if there is evidence of cavernous sinus thrombosis or other intracranial thrombus formation. Uncomplicated mastoiditis or facial vein thrombosis does not require anticoagulation. Splenic infarction is not commonly associated with LS.

PREP Pearls

- Anticoagulation remains an area of controversy in Lemierre syndrome, with initial management focusing on antibiotic therapy.
- Anticoagulation should be considered in Lemierre syndrome when there is little clinical improvement with antibiotics alone, propagation of the primary thrombus, evidence of thrombophilia, or presence of cavernous sinus thrombosis or other intracranial thrombus formation.

ABP Content Specifications(s)/Content Area

- Recognize the clinical features of Lemierre syndrome and plan the appropriate treatment.

Suggested Readings

Campo F, Fusconi M, Ciotti M et al. Antibiotic and anticoagulation therapy in Lemierre's syndrome: case report and review. *J Chemother.* 2019:31(1):42-48. doi:10.1080/1120009X.2018.1554992

Johannesen KM, Bodtger U. Lemierre's syndrome: current perspectives on diagnosis and management. *Infect Drug Resist.* 2016;9:221-227. doi:10.2147/IDR.S95050

Osowicki J, Kapur S, Phuong LK, Dobson S. The long shadow of Lemierre's syndrome. *J of Infection*. 2017;74(suppl 1):S47-S53. doi:10.1016/S0163-4453(17)30191-3

Rebelo J, Nayan, S, Choong K, Fulford M, Chan A, Sommer DD. To anticoagulate? Controversy in the management of thrombotic complications of head and neck infections. *Int J Pediatr Otorhinolaryngol* 2016;88:129-35. doi:10.1016/j.ijporl.2016.06.013

Riordan T. Human infection with *Fusobacterium necrophorum* (necrobacillosis), with a focus on Lemierre's syndrome. *Clin Microbiol Rev.* 2007;20(4):622-59. doi:10.1128/CMR.00011-07

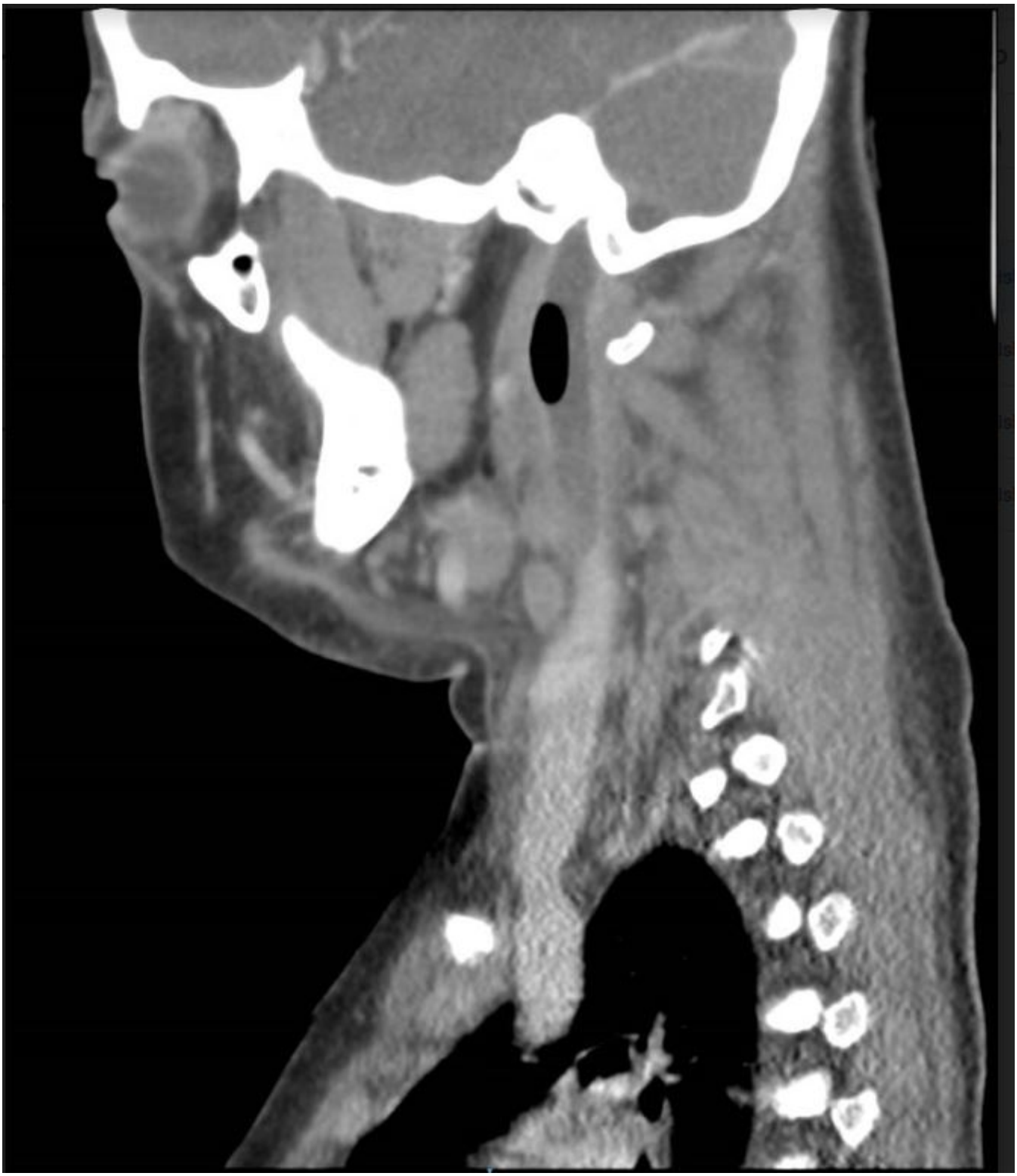


Figure 1: Head and neck computed tomography descriptive of patient in vignette.

Courtesy of M. Rowin

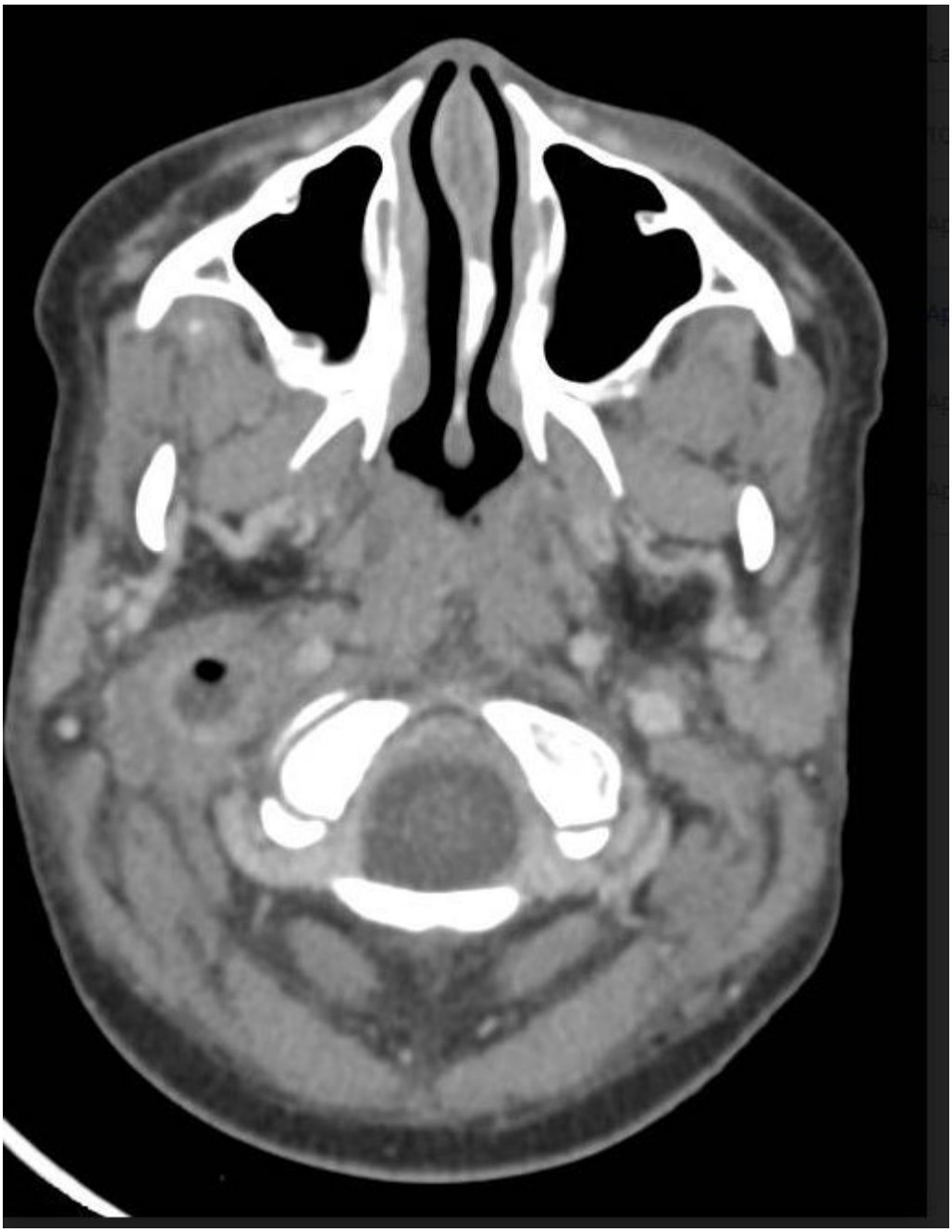


Figure 2: Head and neck computed tomography descriptive of patient in vignette.

Courtesy of M. Rowin

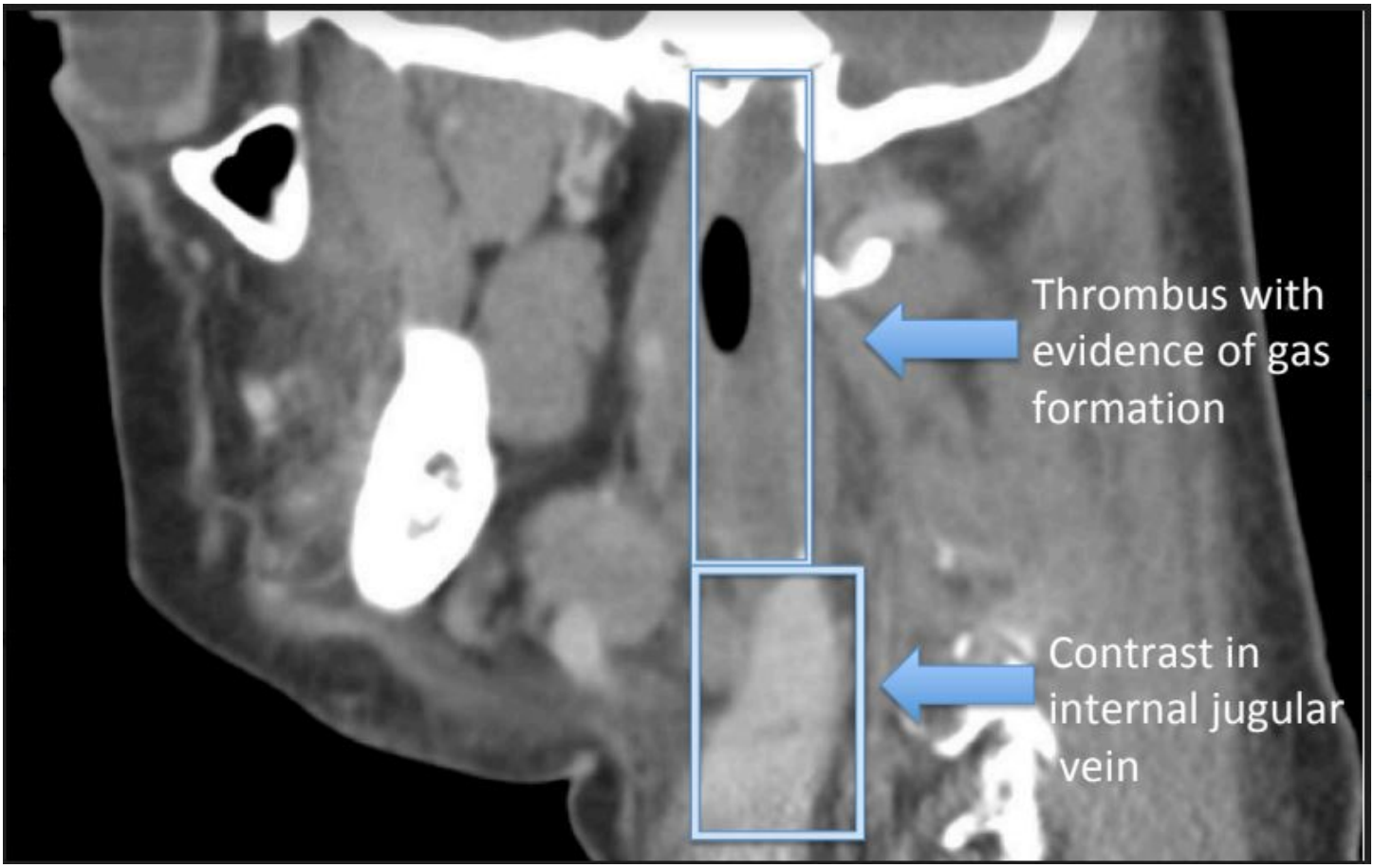


Figure 3: Head and neck computed tomography descriptive of patient in vignette.

Courtesy of M. Rowin

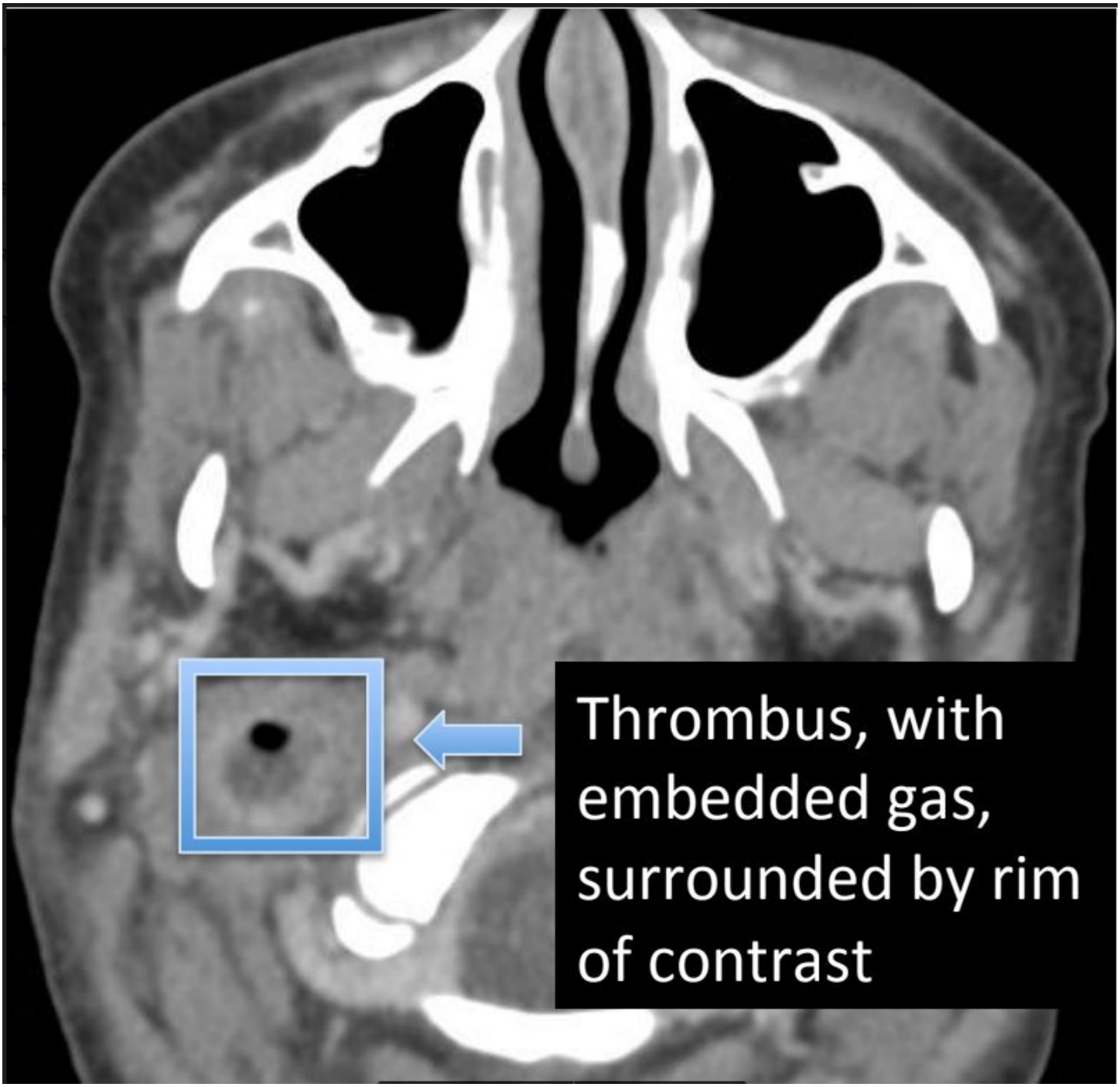


Figure 4: Head and neck computed tomography descriptive of patient in vignette.

Courtesy of M. Rowin

September

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 3

A 2-year-old, 12-kg boy was admitted to the pediatric ICU with respiratory failure secondary to necrotizing staphylococcal pneumonia. During his course, he developed severe acute respiratory distress syndrome and multisystem organ dysfunction requiring vasopressor support with norepinephrine, now running at 0.2 μg/kg/min. Current ventilator settings are as follows:

Pressure regulated volume control rate	20 breaths/min
Positive end-expiratory pressure	10 cm H_2O
Inspiratory time	1 second
Tidal volume	72 mL
FiO_2	0.60
Peak inspiratory pressure	25-30 cm H_2O

The patient is sedated and receiving neuromuscular blockade. He is evaluated for acute desaturation and hypotension. His vital signs are as follows:

Blood pressure	62/39 mm Hg

Heart rate	180 beats/min
Oxygen saturation	65%
FiO_2	1.0

His central venous pressure is 18 mm Hg, and the peak inspiratory pressure is 42 cm H_20. Physical examination findings are significant for severely diminished breath sounds on the left, jugular venous distention, tracheal deviation to the right, and poor peripheral pulses.

Of the following, the MOST definitive next step in management is to

- **A.** administer 10 mL/kg intravenous bolus push of normal saline
- **B.** order a chest radiograph to evaluate the position of the endotracheal tube
- **C.** perform a left-sided needle thoracostomy
- **D.** start an epinephrine infusion

The patient in this vignette is showing clinical signs of the development of a left-sided tension pneumothorax. Given the patient's known acute respiratory distress syndrome, poor lung compliance, and need for elevated ventilatory pressures, the risk of barotrauma and subsequent development of a pneumothorax from positive pressure ventilation in this patient is significant. Owing to the poor compliance of the lung, the elevated pressures can cause damage to the alveoli, developing a communication between the alveoli and chest cavity and allowing air to expand into the space between the visceral and parietal pleura. This damage to the alveoli and communication of air into the space can occur in a ball valve mechanism—allowing air to collect in the space without an egress passageway, thus creating a collection of air with subsequent compression of the lung and, ultimately, a tension pneumothorax. The compression of the lung itself alters the functions of the lung on the affected side, fundamentally precipitating a change in both oxygenation and ventilation. This compression of the lung will shift the mediastinum away from the affected side, causing diminished venous return, decreased cardiac filling, and ultimately lowering cardiac output. This leads to the hemodynamic changes and physical examination findings

seen in the patient described in the vignette—tachycardia, hypotension, decreased breath sounds on the affected side, jugular venous distention, and tracheal deviation away from the affected side.

Once a tension pneumothorax has been identified, treatment should be performed immediately without waiting for diagnostic imaging, given the significant potential further harm to the patient and hemodynamic compromise. A fluid bolus and an increase in vasopressor support may potentially be helpful and temporarily improve the patient's blood pressure; however, this will not reverse the underlying cause. An emergent needle thoracostomy should be performed with a large-bore angiocatheter, allowing for immediate decompression of the tension pneumothorax and resolution of the hemodynamic compromise. Once the patient is hemodynamically stable, a tube thoracostomy can be performed for more conclusive therapy.

Although mechanical ventilation is initiated to support the patient, it is not without consequence. The physiologic modifications that arise once the patient is transitioned to positive pressure ventilation can lead to injury. Among these are

- Barotrauma and the development of an air leak/pneumothorax
- Ventilator-associated lung injury (VALI)
- Ventilator-associated pneumonia (VAP)
- Decreased cardiac output and hypotension
- Auto-positive end-expiratory pressure (PEEP)

These complications should be anticipated and rapidly treated if they develop. A full discussion of each listed complication is beyond the scope of this critique; however, the hypotension and VALI are among the problems this patient developed and are among the immediate life-threatening complications that can occur. The hypotension can be a sequela of the sedation, decreased venous return, and decreased intravascular volume/preload. This frequently develops immediately after endotracheal intubation during the transition to positive pressure ventilation, and the practitioner should be aware of the need for possible fluid resuscitation. The VALI/barotrauma results from the increased pulmonary pressures once the patient is receiving positive pressure ventilation. This complication is further exacerbated in the patient described in the vignette by the development of acute respiratory distress syndrome and poor lung compliance. The risk of barotrauma can potentially be reduced by keeping the plateau airway pressure (the pressure to which the small airways and alveoli are exposed) at a minimum. Plateau pressure, which can be determined by performing an inspiratory pause on the ventilator allowing evaluation of the static compliance of the lung. Reducing the airway pressures and minimization of tidal volumes as much as possible can help to minimize this risk of VALI.

As stated, acute respiratory or hemodynamic decompensation and instability in an intubated patient has many potential causes. A commonly used mnemonic for the evaluation of a decompensating patient on a ventilator is “DOPE”:

- Dislodgement of the endotracheal tube
- Obstruction of the endotracheal tube
- Pneumothorax
- Equipment failure

When this develops acutely, the clinician should remove the patient from the ventilator and initiate bag-mask ventilation with an FiO_2 of 1.0. Performing hand ventilation in this way can allow the clinician to further assess the patient and remove any problems caused by the ventilator or circuit itself. This will also allow the clinician to assess the lung compliance.

The clinician should assess the patient’s chest rise and bilateral breath sounds to confirm proper positioning and patency of the endotracheal tube. The clinician should also evaluate the patient’s adequacy of sedation and analgesia and assess him or her for an underlying cause of patient-ventilator dyssynchrony. The respiratory distress can be further treated by evaluating the patient’s breathing pattern and adjusting the ventilator settings to improve the patient’s comfort and avoid significant patient-ventilator dyssynchrony.

PREP Pearls

- A tension pneumothorax requires immediate needle decompression. The clinician should not wait for a chest radiograph to further assess whether the patient is hemodynamically unstable.
- A mechanically ventilated patient should be assessed via manual bag ventilation during an acute respiratory decompensation.

ABP Content Specifications(s)/Content Area

- Treat tension pneumothorax.
- Recognize the complications resulting from mechanical ventilation.

Suggested Readings

DaSilva PS, de Aguiar VE, Fonseca MCM. Iatrogenic pneumothorax in mechanically ventilated children: incidence, risk factors and other outcomes. *Heart Lung*. 2015;44(3):238-42. doi:10.1016/j.hrtlng.2015.01.005

Principi T, Fraser D, Morrison GC, et al. Complications of mechanical ventilation in the pediatric population. *Pediatr Pulmonol.* 2011;46(5):452-457. doi:10.1002/ppul.21389

September

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 4

A 6-week-old boy living with Down syndrome recently was diagnosed with acute myeloid leukemia (AML). He has been experiencing lethargy, vomiting, and diarrhea with moderate to severe dehydration since he received daunorubicin and cytarabine 3 days ago. The nursing staff is concerned about an acute increase in his heart rate (from 120 to 200 beats/min) after a 40-mL/kg bolus of normal saline was pushed through a right internal jugular central venous line. Via ultrasonographic examination, the PICU fellow who placed the line confirmed that the tip of the central venous line is in the upper portion of the right atrium.

The child's vital signs after the bolus are as follows:

Temperature	37° C
Blood pressure	95/65 mm Hg
Heart rate	188 beats/min
Respiratory rate	30 breaths/min

The cardiac monitor shows normal sinus rhythm without atrial or ventricular premature contractions or ST changes. The infant's heart rate is slowly returning to his earlier baseline.

Of the following, the BEST explanation of this patient's transient tachycardia is

- **A.** a cardiac paraneoplastic syndrome affecting the cardiac conduction system

B. heart failure as a consequence of cardiotoxic chemotherapy

C. increased atrial volume and stimulation of stretch receptors

D. paroxysmal supraventricular tachycardia due to an alternate conduction pathway

The large fluid bolus of normal saline directly into the right atrium resulted in an increase in cardiac preload and, hence, an increase in atrial pressure and stimulation of stretch receptors. This reflex is called the Bainbridge or atrial reflex. The more common manifestation of this reflex is respiratory sinus arrhythmia, in which intrathoracic pressure decreases during inspiration, thereby increasing venous return and stimulating stretch receptors, which in turn increases heart rate.

A normal finding on electrocardiography (EKG) rules out the other options, each of which would produce distinct EKG findings. Daunorubicin produces QRS complex widening and increased R and S wave voltages. Cardiac paraneoplastic syndromes can present as third-degree heart block and other conduction delays. In infants with supraventricular tachycardia, the EKG shows a narrow complex QRS tachycardia at a rate greater than 200 beats/min; P waves are often hidden within the QRS complex and therefore appear to be absent.

Knowledge of basic cardiac physiology and history affecting the cardiovascular system, as well as an understanding of the causes of tachycardia and the effects of treatment (including medications or alterations in physiology), can lead to an appropriate diagnosis and avert unnecessary workups and stress for the patient.

PREP Pearls

- Increase in atrial pressure and stimulation of stretch receptors can result in a transient tachycardia after a fluid bolus.

ABP Content Specifications(s)/Content Area

- Understanding of the causes of tachycardia including responses to treatment.

Suggested Readings

Crystal GJ, Salem MR. The Bainbridge and the "reverse" Bainbridge reflexes: History, physiology, and clinical relevance. *Anesth Analg*. 2012;114(3):520-532. doi:10.1213/ANE.0b013e3182312e21

Pakkam ML, Brown KN. Physiology of the Bainbridge reflex. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. 2021 May 9.

September

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 5

A 4-year-old boy was admitted to the general pediatric floor yesterday with nausea, vomiting, lethargy, and signs of dehydration thought to be secondary to a viral gastroenteritis that had not resolved despite several days of over-the-counter medications. He has been treated with intravenous fluid hydration for approximately 24 hours with significant resolution of his symptoms; however, now he is complaining of mild pain in the right upper quadrant.

Laboratory tests were again performed this morning before his planned discharge. The results are notable for the following values:

Laboratory Test	**Result**
Alanine aminotransferase	1,126 U/L (normal, < 40 U/L)
Aspartate aminotransferase	980 U/L (normal, < 40 U/L)
International normalized ratio	2.7 (normal range, 1-2)
Blood urea nitrogen	35 mg/dL (12.49 mmol/L) (normal, < 20 mg/dL [7.14 mmol/L])

Of the following, the MOST appropriate next step in management is

- **A.** administration of activated charcoal
- **B.** administration of *N*-acetylcysteine

C. repeat laboratory tests of liver functions in 24 hours

D. treatment based on the Rumack-Matthew nomogram

The patient in the vignette is exhibiting signs and symptoms of an acute acetaminophen toxicity. Acetaminophen is a commonly used medication, available without a prescription and widely used as an ingredient in commercially available cold remedies. Acetaminophen overdose is a commonly known cause of hepatoxicity and hepatic necrosis. Although most cases of acetaminophen toxicity are due to an intentional ingestion, multiple doses given by a well-intentioned caregiver can be associated with significant hepatotoxicity, especially when given to patients with decreased appetite and volume depletion.

Owing to the ubiquitous nature of acetaminophen and incidence of unintended overuse, it is the most common cause of deaths due to poisoning in developed countries, and levels should be checked in all incidences of ingestion.

The natural history of an acute single ingestion causing toxicity can be divided into four stages:

- **Stage I (up to 24 hours after the overdose/ingestion):** Malaise, nausea, vomiting, pallor, lethargy, diaphoresis; laboratory findings are typically normal, and some patients may be asymptomatic
- **Stage II (24 to 72 hours after the overdose/ingestion):** Right upper quadrant pain; stage I symptoms resolve; hepatotoxicity and possible nephrotoxicity develop; laboratory findings are significant for elevated aminotransferase levels, prothrombin time, elevated INR, and possibly elevated levels of blood urea nitrogen/creatinine; elevated levels of serum amylase with or without clinical pancreatitis may occur
- **Stage III (72 to 96 hours after the overdose/ingestion)**: Transaminases and function abnormalities peak (can be >10,000 U/L); recurrence of stage I symptoms, jaundice, hepatic encephalopathy, hyperammonemia, bleeding diathesis, hypoglycemia, and lactic acidosis; in severe cases, renal failure and multiorgan failure are seen; death resulting from multiorgan failure most commonly occurs in this stage unless liver transplant is provided
- **Stage IV (4 to 14 days after the overdose/ingestion):** Recovery phase; symptoms and laboratory values may not normalize for several weeks; histological recovery lags behind clinical recovery and may take months

Acetaminophen is metabolized in the liver via glucuronidation, sulfonation, and CYP-450 oxidation. When a toxic ingestion occurs, the CYP-450 system creates the metabolite *N*-acetyl-p-benzoquinoneimine (NAPQI). This toxic metabolite cannot be easily cleared and is usually further reduced by glutathione to a metabolite that can be subsequently cleared. When this system is overwhelmed by a toxic ingestion, the glutathione stores are

diminished; this leads to an accumulation of NAPQI and significant hepatotoxicity. Children are relatively protected from the toxicity when compared with adults, given that the younger the patient is, the greater are the glutathione reserves.

The minimal toxic dose for an acute ingestion is 150 mg/kg for a child or 7.5 to 10 g for an adult. However, in children who are chronically malnourished or have chronic liver disease, much lower doses can cause toxicity because of the lower stores of glutathione in these patients. Referral to an emergency department for evaluation is generally recommended for any acute ingestion at or above the aforementioned doses. Acetaminophen concentrations should not be obtained until 4 hours after the ingestion, as the peak serum concentrations may not be reached before this time. If the patient seeks care sometime after the 4-hour mark, concentrations should be obtained as soon as possible to help assess the risk of toxicity. The Rumack-Matthew nomogram can be used to assess the need for treatment and risk of toxicity when a single acute ingestion has occurred. The timing of the concentration is significant, as those obtained earlier than 4 hours after the ingestion will likely underestimate the toxicity. When an ingestion of an extended-release formulary is suspected, further concentrations should be obtained to assess for a continued rise in the serum level. It is also important to remember that the nomogram can be used only for an acute single exposure and not for toxicity due to chronic overuse; for ingestions that have occurred more than 24 hours before acetaminophen level determination; or for intravenous acetaminophen use.

N-acetylcysteine should be administered in all suspected cases of acetaminophen toxicity to help prevent or ameliorate the development of hepatotoxicity. *N*-acetylcysteine is a precursor of glutathione and therefore replaces the glutathione stores, subsequently helping to reduce the NAPQI into a metabolite that can be easily cleared. Treatment with *N*-acetylcysteine has been shown to be effective when given within 8 hours of the acetaminophen ingestion; however, it likely has a benefit at any time after the ingestion and should be given whenever acetaminophen toxicity is considered. Patients who seek treatment in an emergency department immediately after a suspected acetaminophen ingestion should be given activated charcoal; however, if the ingestion took place more than 4 hours before presentation, there is no role for this, given that the medication has already likely been absorbed into the systemic circulation.

PREP Pearls

- Acetaminophen toxicity should be considered in all cases of acute hepatic toxicity.
- *N*-acetylcysteine is most effective if given within 8 hours after acetaminophen ingestion; however, it should be administered whenever acetaminophen toxicity is considered.

- The Rumack-Matthew nomogram does not apply within 4 hours of exposure or more than 24 hours after acetaminophen ingestion.

ABP Content Specifications(s)/Content Area

- Manage a patient with acute acetaminophen toxicity.

Suggested Readings

Chiew AL, Gluud C, Brok J, Buckley NA. Interventions for paracetamol (acetaminophen) overdose. *Cochrane Database Syst Rev.* 2018;2(2):CD003328. doi:10.1002/14651858.CD003328.pub3

Ishitsuka Y, Kondo Y, Kadowaki D. Toxicological property of acetaminophen: the dark side of a safe antipyretic/analgesic drug? *Biol Pharm Bull.* 2020;43(2):195-206. doi:10.1248/bpb.b19-00722

Sztajnkrycer MJ, Bond GR. Chronic acetaminophen overdosing in children: Risk assessment and management. *Curr Opin Pediatr.* 2001;13(2):177-182. doi:10.1097/00008480-200104000-00016

September

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 6

A 12-year-old boy is taken to the emergency department after a high-speed motor vehicle crash. The emergency medical services staff report his vital signs at the scene were stable and his initial oxygen saturations were 98%. On arrival at the emergency department, his vital signs were as follows:

Blood pressure	160/90 mm Hg
Heart rate	50 beats/min
Respiratory rate	12 breaths/min
Oxygen saturation	96% on supplemental oxygen via nasal cannula

A computed tomographic scan of the head revealed a large epidural hematoma, and he was immediately taken to the operating room. Surgery was uncomplicated, and his vital signs were stable during the procedure. He returned to the pediatric intensive care unit intubated and undergoing mechanical ventilation. On postoperative day 3, he remains comatose, with a Glasgow Coma Scale score of 5. His vital signs are stable, and his oxygen saturations have remained above 98% on a FiO_2 of .3. He has not needed sedation while receiving mechanical ventilation.

Of the following, the MOST likely cause of this patient's continued neurological condition is

- **A.** diffuse axonal injury

B. epidural bleed

C. postictal state

D. subdural hemorrhage

Motor vehicle crashes (MVCs) are a major cause of morbidity and mortality in the pediatric population. They are the leading cause of death in children younger than 15 years. Motor vehicle deaths in 2020 were the highest in 13 years.

Traumatic brain injury (TBI) is frequently seen in MVCs. These injuries are responsible for most trauma-related deaths, with the peak incidence occurring in the adolescent-to-young-adult period.

Diffuse axonal injury (DAI) is thought to be the predominant mechanism in 40% to 50% of TBI. It is also believed that a component of DAI is probably present in all patients who lose consciousness as a result of MVCs. The mechanism of DAI is thought to result from rotational or acceleration/deceleration forces. This force then results in shear injury to the white matter axons. The damage is often microscopic and not picked up by computed tomography. Diffuse axonal injury is not associated with skull fractures.

Some feel that the diagnosis of DAI is often one of exclusion. Computed tomography will not detect DAI. Magnetic resonance imaging (MRI) is more sensitive for detection of DAI. In a recent study, 88% of patients with TBI had evidence of DAI on MRI scans obtained within the first 5 days of hospitalization. Almost 45% of MRIs showed abnormal signals in the cortex, corpus callosum, and brainstem. MRI fluid-attenuated inversion recovery (FLAIR) and diffusion MRI are increasingly used modalities for identifying and quantifying white matter disruption and diffuse or traumatic axonal injury.

Clinically, diffuse axonal injury is characterized by rapid progression to coma, and furthermore the coma is unexplained by hypoxia. It is often seen in patients who fail to improve after evacuation of epidural/subdural hemorrhages. After TBI, DAI is also the most common cause of persistent vegetative state and severe disability.

PREP Pearls

- Diffuse axonal injury is often seen in traumatic brain injuries.
- Diffuse axonal injury should be considered in coma not otherwise explained by imaging or hypoxia.

- Diffuse axonal injury should be considered in patients who fail to improve after evacuation of epidural/subdural hemorrhages.

ABP Content Specifications(s)/Content Area

- Recognize a diffuse axonal injury

Suggested Readings

Janas AM, Qin F, Hamilton S. Diffuse axonal injury grade on early MRI is associated with worse outcome in children with moderate-severe traumatic brain injury. *Neurocrit Care*. 2022;36(2):492-503. doi:10.1007/s12028-021-01336-8

Lerner JT, Giza CC. Traumatic brain injury in children. In: Swaiman KF, Ashwal S, Ferrero DM, et al, eds. *Swaiman's Pediatric Neurology.* 6th ed. Elsevier; 2017:781-785.

Li XY, Feng DF. Diffuse axonal injury: Novel insights into detection and treatment. *J Clin Neurosci.* 2009;16(5):614-619. doi:10.1016/j.jocn.2008.08.005

Meythaler JM, Peduzzi JD, Eleftheriou E, Novack TA. Current concepts: Diffuse axonal injury-associated traumatic brain injury. *Arch Phys Med Rehabil.* 2001;82(10):1461-1471. doi:10.1053/apmr.2001.25137

Smith DH, Meaney DF, Shull WH. Diffuse axonal injury in head trauma. *J Head Trauma Rehabil.* 2003;18(4):307-316. doi:10.1097/00001199-200307000-00003

October

Question: 1

A 5-month-old, ex-28-week premature girl with bronchopulmonary dysplasia has had nasal congestion and occasional cough for the past 12 days. She was seen by her pediatrician 10 days ago and tested positive for respiratory syncytial virus (RSV). She had adequate oral intake and her usual level of activity until last night when she became febrile and had more difficulty breathing. She is seen in the emergency department in respiratory distress with the following vital signs:

Heart rate	168 beats/min
Respiratory rate	62 breaths/min
Oxygen saturation	81% in room air
Blood pressure	82/43 mm Hg
Temperature	39°C

She weighs 7 kg. She is placed on 15 L/min of 60% oxygen via high-flow nasal cannula with improvement in her oxygen saturation to 92% and with a reduction in her respiratory rate to 44 breaths/min.

Of the following, the MOST likely reason for her worsening respiratory status is

- **A.** coinfection with a bacterial pathogen
- **B.** coinfection with influenza
- **C.** coinfection with COVID-19
- **D.** natural progression of respiratory syncytial virus infection

Respiratory syncytial virus (RSV) is the most frequent cause of bronchiolitis in children under 1 year of age. The usual time course of this disease in previously healthy infants is a 7- to 10-day illness that self-resolves. The deterioration of this patient after the typical time period when symptoms resolve should raise suspicion for an additional process. In addition, her history of prematurity and bronchopulmonary dysplasia put her at higher risk for severe disease and death. Her extended duration of symptoms with rapid worsening raise the likelihood of bacterial coinfection with possible necrosis of the lung parenchyma. Along with the respiratory support that she is receiving, initiation of antibiotic therapy would be indicated. Bacterial coinfection occurs in approximately one-third of severe respiratory syncytial virus infections. A single center retrospective study found that most common bacterial coinfections were *Haemophilus influenzae* and *Staphylococcus aureus.* The appropriate antibiotic therapy would be ceftriaxone and vancomycin until infection with methicillin-resistant *Staphylococcus* can be excluded. If the patient is not a carrier for methicillin-resistant *Staphylococcus*, then a single agent such as piperacillin/tazobactam would be appropriate.

Bronchiolitis can be caused by other viruses such as rhinovirus but the symptoms are usually milder. The most common virus associated with bronchiolitis is RSV followed by rhinovirus, adenovirus and human metapneumovirus. Influenza A or B, is rare as either a single or coinfection agent and would be unlikely to cause the worsening symptoms seen in this patient.

Although COVID-19 has dominated much of the medical and general public news recently, the incidence of RSV bronchiolitis during the 2020-2021 winter was much lower than in prior years. The decreased incidence of respiratory illness is thought to be a combination of school closure, mask usage and social distancing. As schools reopen and social distancing becomes less stringent, the incidence of respiratory diseases is likely to increase. A review of the Multicenter Airway Collaborative Study by Mansbach found that coronaviruses did not significantly differ from RSV in the use of intensive care resources. However, their review did not include children who had congenital heart or chronic lung disease. Hence, although consideration of COVID-19 would be appropriate in this patient and proper precautions should be taken until testing had been completed, our current knowledge of COVID-19 and bronchiolitis would suggest that the diagnosis most consistent with her presentation is bacterial coinfection.

Procalcitonin assays have been suggested as a way to distinguish viral infections from bacterial infections, but there is a lack of consensus on what the appropriate cut-off value would be in children under 1 year of age. A more widely accepted use of the procalcitonin assay is to intermittently follow the level to determine when antibiotics can be

discontinued. Hence, the procalcitonin level could be checked every few days and antibiotics would be discontinued when the level is below 0.2 ng/mL. The use of protocols using this strategy has been shown to improve antibiotic stewardship.

PREP Pearls

- Bacterial coinfection occurs in approximately one-third of severe respiratory syncytial virus infections.
- Prematurity, congenital heart disease and chronic lung disease patients are at higher risk for severe disease and death.

ABP Content Specifications(s)/Content Area

- Describe the progression of respiratory syncytial virus infection in patients at high-risk for severe disease

Suggested Readings

Branche A, Neeser O, Mueller B, Schuetz P. Procalcitonin to guide antibiotic decision making. *Curr Opin Infect Dis*. 2019;32(2):130-135. doi:10.1097/QCO.0000000000000522

Ghazaly M, Nadel S. Characteristics of children admitted to intensive care with acute bronchiolitis. *Eur J Pediatr*. 2018;177(6):913-920. doi:10.1007/s00431-018-3138-6

Mansbach JM, Hasegawa K, Piedra PA, Sullivan AF, Camargo CA Jr. Severe coronavirus bronchiolitis in the pre-COVID-19 era. *Pediatrics*. 2020;146(3):e20201267. doi:10.1542/peds.2020-1267

Teshome G, Gattu R, Brown R. Acute bronchiolitis. *Pediatr Clin North Am*. 2013;60(5):1019-1034. doi:10.1016/j.pcl.2013.06.005

Thorburn K, Harigopal S, Reddy V, Taylor N, van Saene HK. High incidence of pulmonary bacterial co-infection in children with severe respiratory syncytial virus (RSV) bronchiolitis. *Thorax*. 2006;61(7):611-615. doi:10.1136/thx.2005.048397

October

Question: 2

A 5-year-old child sustained 40% partial- and full-thickness burns to his torso and extremities. Laboratory results are shown.

Laboratory Test	Patient Result
Complete blood cell count	
White blood cells	3,200/μL (3.2 × 109/L)
Hemoglobin	8.2 g/dL (82 g/L)
Hematocrit	28%
Electrolytes	
Sodium	154 mEq/L (154 mmol/L)
Potassium	5.8 mEq/L (5.8 mmol/L)
Chloride	108 mEq/L (108 mmol/L)
Carbon dioxide	15 mEq/L (15 mmol/L)
Blood urea nitrogen	28 mg/dL (10 mmol/L)
Creatinine	1.3 mg/dL (115 μmol/L)
Glucose	132 mg/dL (7.3 mmol/L)

Lactate	3.1 mmol/L (0.34 mmol/L)
Arterial blood gas	
pH	7.21
$PaCO_2$	58 mm Hg
PaO_2	146 mm Hg
Bicarbonate	16 mEq/L (16 mmol/L)
Base excess	−5
Urinalysis	
Urine	Slightly blood tinged
Red blood cells	Positive
Specific gravity	1.030

Débridement occurs under general anesthesia. The child undergoes extubation after the administration of sugammadex. In the pediatric ICU, he develops respiratory distress and requires escalation of respiratory support using noninvasive ventilation. Despite bilevel positive airway pressure and a FiO_2 of 1.0, his oxygen saturations are 86%. The child continues to experience tachycardia and becomes lethargic. Intubation is planned.

Of the following, the BEST next step in treatment is intravenous administration of

- **A.** atracurium
- **B.** rocuronium
- **C.** succinylcholine
- **D.** vecuronium

Intubation of this child must take into account his burn trauma, which can result in intravascular volume depletion and renal insufficiency, hyperkalemia associated with tissue injury, and previous reversal of neuromuscular blockade (NMB) with sugammadex.

Successful reversal of NMB relies on a low concentration of the paralytic agent at the neuromuscular junction. The response to the train of 4 stimulations allows neuromuscular function to be determined as the NMB clears. Competitive reversal of NMB is common with acetylcholinesterase inhibition using an agent such as neostigmine. Recurarization can occur because of inadequate clearance of the NMB agent. Residual NMB can be found if the paralytic agent has not cleared significantly after a larger administered dose or use of an agent with a longer half-life. Residual NMB can affect respiratory effort once extubation has occurred.

Sugammadex is the first noncompetitive antagonist to reverse the aminosteroid non-depolarizing neuromuscular blocking agents. Sugammadex is a cyclodextrin that is a new selective binding agent used to reverse NMB of vecuronium and rocuronium. Sugammadex essentially encapsulates the aminosteroid through chelation. This makes the neuromuscular blocking agent unavailable to bind to the acetylcholine receptor at the neuromuscular junction. Sugammadex has a higher affinity for rocuronium compared with vecuronium. Pancuronium can be reversed with sugammadex but requires much larger doses. The half-life of sugammadex is 2 hours. It is not dependent on hepatic metabolism and is excreted unchanged in the urine.

Unlike neostigmine, sugammadex does not inhibit acetylcholinesterase-reducing cholinergic side effects such as bradycardia. Recurarization and side effects such as bradycardia associated with the anticholinesterase agents are uncommon with sugammadex. Sugammadex will not reverse succinylcholine or the benzylisoquinolinium neuromuscular blocking agents such as atracurium or cisatracurium. Unlike aminosteroids, which are dependent on hepatic metabolism and renal excretion, succinylcholine and the benzylisoquinolinium agents are degraded in the plasma. Succinylcholine is metabolized by plasma pseudocholinesterase and the benzylisoquinolinium agents are degraded in the plasma by ester hydrolysis and nonenzymatic, organ-independent Hofmann elimination. If NMB is required after the administration of sugammadex, it is recommended that agents such as rocuronium and vecuronium not be administered within 24 hours. If NMB is required, use of an agent other than an aminosteroid, such as atracurium or cisatracurium, is recommended. Succinylcholine could be used; however, life-threatening hyperkalemia can occur in patients with burn trauma and altered renal function. Succinylcholine would

not be the ideal agent for intubation of the patient in this vignette because of altered renal function, elevated potassium, and burn trauma. It is important to remember that NMB agents possess no analgesic or sedative properties.

PREP Pearls

- Sugammadex is a noncompetitive antagonist used to reverse the aminosteroid nondepolarizing neuromuscular blocking agents such as rocuronium and vecuronium. If neuromuscular blockade with an aminosteroid agent is required after the administration of sugammadex, it is recommended that agents such as rocuronium and vecuronium not be administered within 24 hours.
- If neuromuscular blockade is required after the administration of sugammadex, succinylcholine or a benzylisoquinolinium such as atracurium or cisatracurium can be used.
- Neuromuscular blocking agents possess no analgesic or sedative properties.

ABP Content Specifications(s)/Content Area

- Review metabolism of neuromuscular blocking agents
- Discuss use of sugammadex to reverse neuromuscular blockade

Suggested Readings

Grigg E. Sugammadex and neuromuscular reversal: special focus on neonatal and infant populations. *Curr Opin Anesthesiol*. 2020;33(3):374-380. doi:10.1097/ACO.0000000000000847

Keating GM. Sugammadex: a review of neuromuscular blockade reversal. *Drugs*. 2016:76;1041-1052. doi:10.1007/s40265-016-0604-1

Renew JR, Ratzlaff R, Hernandez-Torres V, Brull SJ, Peilipp RC. Neuromuscular blockade management in the critically ill patient. *J Intens Care*. 2020:8(7):37. doi:10.1186/s40560-020-00455-2

October

Question: 3

A 6-year-old girl who suffered near-drowning at the age of 2 years is admitted to the pediatric intensive care unit with respiratory distress and pneumonia. This child has remained neurologically devastated since the near-drowning incident and has required chronic mechanical ventilation after placement of a tracheostomy. She is fed through a gastrostomy tube and has had multiple medical admissions for aspiration and pneumonia. During this hospitalization, her clinical course has deteriorated, and she has significant lung injury that requires high-frequency oscillation ventilation. She remains persistently desaturated in the mid-80s despite aggressive mechanical ventilation and inhaled nitric oxide therapy. She is not a candidate for extracorporeal membrane oxygenation support. Her deteriorating status is discussed with the parents, and they agree that they do not want their child resuscitated. A do-not-resuscitate (DNR) order is initiated. Over the next 24 hours, this child develops further hemodynamic instability with worsening hypoxia.

Of the following, the MOST correct decision regarding ongoing treatment of this child with a DNR order in place is

- **A.** escalate medical care as needed
- **B.** not to escalate medical treatment
- **C.** provide comfort measures only
- **D.** withdraw life-sustaining medical treatment

Advancement in medical therapies and technology to treat cardiorespiratory disease—such as artificial circulation (including cardiopulmonary resuscitation [CPR] and extracorporeal support), mechanical ventilation, anesthesia, and vasoactive agents to support blood pressure—have resulted in increased survival rates for critically ill patients. The use of technology at end of life requires appropriate conversations to determine what therapies will be used and when life-saving therapies will cease because survival may not be possible. Issues related to aggressive interventions for respiratory and circulatory support can save

lives but also inflict ongoing suffering for terminally ill patients in whom medical therapies are only prolonging death. Goals of care should be established at end of life as they would for any other patient receiving life-saving treatments in a medical facility.

When resuscitation of a patient may not be warranted or the family desires no resuscitation, a do-not-resuscitate (DNR) order is initiated. The DNR is also known as do not attempt resuscitation (DNAR) or allow natural death (AND). A DNR order

- Implies discussions with the patient, family, or guardian about resuscitation decisions and interventions
- Establishes treatment criteria when cardiopulmonary arrest occurs
- Applies to living individuals and can be included as part of medical orders for life-sustaining treatment (MOLST) or physician orders for life-sustaining treatment (POLST)

Inconsistencies in implementation, misunderstanding, and communication errors regarding DNR/AND orders can result in poor care delivered to patients at end of life. DNR does not mean do not treat. The American Academy of Pediatrics emphasizes that a DNR should never signal the abandonment of a patient. Medical therapies should continue for any patient until decisions about resuscitation and ongoing medical care have been determined between the family and the medical team. Forgoing medical treatment for a patient without discussing issues related to ongoing care with the family ignores our responsibility as health care professionals. The importance of understanding that DNR only applies when cardiopulmonary arrest occurs is highlighted in a study about clinical perspectives and the DNR order. This study revealed that one-third of the survey participants considered DNR a threshold for limiting treatment not specific to cardiopulmonary arrest and that healthcare professionals use DNR as a surrogate for broader treatment directives. Importantly, a DNR does not mean that the patient will die after the conversation. In fact, the patient's condition may improve in some cases, in which case the DNR is rescinded. Many medical centers will temporarily suspend the DNR order if a patient is undergoing procedures in the operating room. The temporary suspension can include the postoperative period as well.

A DNR order may be perceived as giving up on the patient. AND is being used more frequently during end-of-life care discussions. In one study regarding conflict of decisions, the terms DNR and AND were compared in 2 separate groups. Participants in the AND group were more likely to view their decision as good, be sure of their decision, and sign the document than were participants in the DNR group. There was a more favorable response to AND than DNR, indicating that patients and families may view AND to be a more acceptable term than DNR.

When a DNR or an AND order is initiated, it should be clear what DNR and AND mean. Issues related to resuscitation should be clearly documented to avoid confusion for other members of the health care team who might have to intervene if cardiopulmonary arrest

occurs. Documentation should include direction about intubation, manual ventilation, closed chest compressions, and the use of vasoactive agents and defibrillation to restart cardiac activity. Physicians should be cautious about selectively defining treatment orders. Parents and families should understand that the process of resuscitation attempts to restore blood flow and oxygenation after the heart and breathing has stopped. Resuscitation should be viewed and presented as a process that involves closed chest compressions, administration of drugs to restart the heart, manual ventilation that can include intubation to provide oxygenation and ventilation, and defibrillation with use of electricity to shock the heart in an attempt to restart circulation. Choosing individual components such as vasoactive agents or manual ventilation without closed chest compressions defeats the purpose of trying to resuscitate a person and restore circulation. Selectively defining treatment orders can have unintended consequences, such as confusion for the medical team about what things can and cannot be performed for a patient when cardiac arrest occurs. Importantly, families should be made aware that resuscitation is not a guarantee of survival or survival with the same quality of life before cardiac arrest occurred.

Levels of life-sustaining treatment such as POLST or MOLST more clearly define the goals of care at end of life. POLST or MOLST offer options such as full treatment, limited interventions (including no further escalation of care or withdrawal of life-sustaining medical treatments), and comfort measures only. A DNR or AND order can accompany any of these treatment goals. Issues related to treatment before cardiac arrest, such as intubation and mechanical ventilation, should be clarified. A do-not-intubate (DNI) order specifies instructions for airway support when a patient is deteriorating and does not want to be mechanically ventilated. This order specifies what should specifically occur before intubation and can be included with levels of life-sustaining treatment orders. The health care professional should ensure that there is clarification about invasive and noninvasive ventilation when initiating a DNI order. A DNR/AND and DNI can be ordered in conjunction with limitations of care. In this vignette, no further discussions regarding ongoing care have been mentioned. The correct answer is to continue medical therapies and escalate care until discussions regarding goals for end-of-life treatment can be discussed with the parents.

The readers are encouraged to become familiar with end-of-life policy and DNR or AND orders in their respective institution.

PREP Pearls

- Do not resuscitate (DNR), or allow natural death (AND), establishes treatment criteria only when cardiopulmonary arrest occurs. It should not be used as a surrogate for other medical treatments or limitations of medical treatments before cardiac arrest.

Do-not-intubate (DNI) orders establish treatment goals for a patient who does not want to be intubated and mechanically ventilated before cardiopulmonary arrest.

- If a patient is undergoing procedures in the operating room, many medical centers will temporarily suspend the do-not-resuscitate (DNR) order. This temporary suspension can include the postoperative period as well.
- Allow natural death (AND) is becoming a preferred term instead of do not resuscitate (DNR).
- Physician orders for life-sustaining treatment (POLST) or medical orders for life-sustaining treatment (MOLST) provide levels of treatment to help clarify goals of care at end of life.

ABP Content Specifications(s)/Content Area

- Understand issues related to resuscitation at end-of-life
- Recognize what treatment should be provided when a do-not-resuscitate order is initiated

Suggested Readings

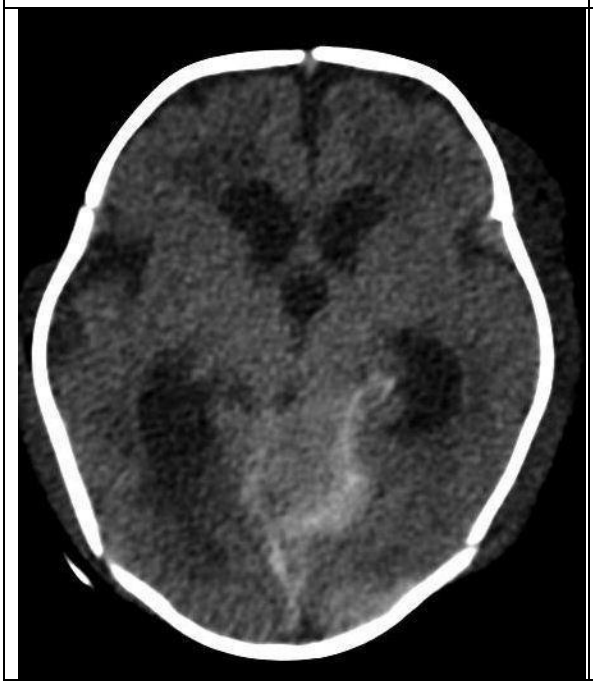
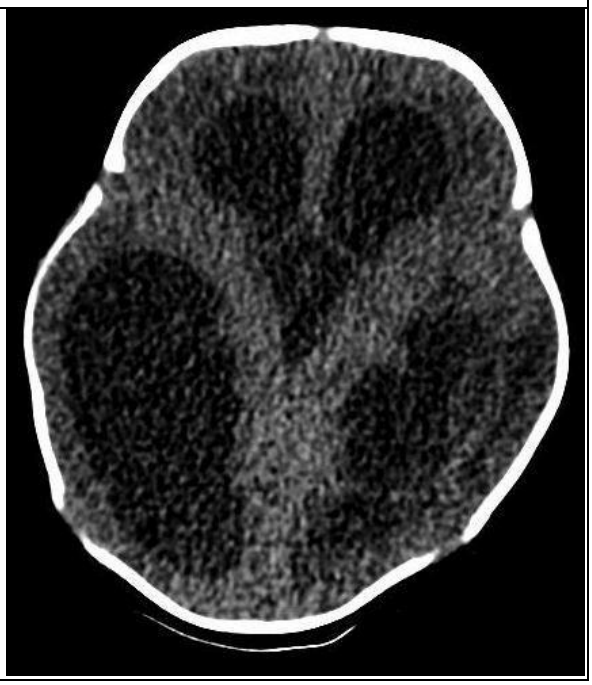
Bester J, Kodish E. Cardiopulmonary resuscitation, informed consent, and rescue: what provides moral justification for the provision of CPR? *J Clin Ethics.* 2019;30:67-73. PMID: 30896446.

Fallat ME, Hardy C. Section on Surgery, Section on Anesthesia and Pain Management and Committee on Bioethics. Interpretation of do not attempt resuscitation orders for children requiring anesthesia and surgery. *Pediatrics*. 2018;141(5):e20180598. doi:10.1542/peds.2018-0598

Osinki A, Vreugdenhil, de Koning J, van der Hoven, J. Do-not-resuscitate orders in cancer patients: A review of literature. *Support Care Cancer*. 2017;25(2):677-685. doi:10.1007/s00520-016-3459-9

Weise KL, Okun AL, Carter GS, Christen CW, Committee on Bioethics; Section on Hospice and palliative medicine; Committee on Child Abuse and Neglect. Guidance on forgoing life-sustaining medical treatment. *Pediatrics*. 2017;140(3):e20171905. doi:10.1542/peds.2017-1905

Figure. Serial coronal brain computed tomographic images.

Four months earlier	Present
	

Courtesy of M. Rowin

October

Question: 4

A 6-month-old girl is admitted to the pediatric intensive care unit (PICU) after gastrostomy tube placement. This is her second admission to the PICU; she was admitted 4 months earlier with acute respiratory failure and new-onset seizure activity requiring intubation. Evaluation at that time showed a subdural intracranial bleed, bilateral retinal hemorrhages, and multiple rib fractures. She was diagnosed with injuries due to nonaccidental trauma and placed in protective custody. The patient was eventually discharged into the care of a foster medical family. They report that she has been compliant with her seizure medications and has had no seizure activity over the past 2 months. The foster family does note that the patient's suck and swallow reflexes have deteriorated, with frequent coughing spells after attempts to give thickened feedings. Current examination reveals worsening spasticity. Repeat computed tomographic images of her brain are obtained for comparison with images from her initial admission (**Figure**).

Of the following, the electrolyte MOST likely involved with the changes noted in this patient's clinical course and brain images is

- **A.** copper
- **B.** magnesium
- **C.** sodium
- **D.** zinc

The neuron is a remarkably specialized cell, susceptible to both traumatic and hypoxic injury. The biochemical mechanisms that cause neuronal injury have been the focus of significant research and investigators have gained significant insight into the cellular pathways involved. The vignette describes a typical presentation and sequelae of hypoxic-ischemic brain injury in a neonate.

Hypoxic neuronal injury begins with oxygen and glucose deprivation, causing a primary cellular energy failure and initiating a cascade of biochemical events that ultimately lead to cellular dysfunction and death. Oxygen deprivation can be secondary to lack of oxygen

(hypoxia), lack of blood flow (ischemia) or both. Presentation in nonaccidental trauma patients often involves some degree of hypoxic-ischemic injury (HIE), because these infants often experience apnea and poor perfusion. Regions of the infant's brain most sensitive to long-term effects of HIE include the motor cortex, thalamus, hippocampus, and brainstem.

Clinical and animal models suggest there are 3 phases of neuronal injury in HIE. The immediate phase consists of exhaustion of the cell's high-energy stores. A secondary phase occurs within hours of the primary event and is thought to be due to the effects of excitatory neurotransmitters, inflammation, reactive oxygen species generation, and necrosis. This secondary phase is often associated with encephalopathy and seizure activity. A third latent phase of neuronal cell death can occur and is believed to be associated with persistent neuronal apoptosis long after the initial injury. This delayed neuronal cell death accounts for a significant proportion of final cell loss after the initial insult.

In response to hypoxia, stored pools of the excitatory amino acids glutamate and aspartate are released by presynaptic neurons. Glutamate is considered the primary mediator of excitatory synaptic transmission in the brain and binds to the postsynaptic N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors. Persistent stimulation results in damage to neurons possessing glutamate receptors, often referred to as "excitotoxicity." Multiple neuronal pathways use glutamate as a principal neurotransmitter, including those involved with movement, hearing, vision, learning, and memory. Researchers speculate that this may explain why there is often significant developmental delay in patients who recover from severe hypoxic-ischemic events.

Glutamate receptors play an important role in neuronal plasticity and, if unregulated activation occurs, early neuronal cell death. AMPA receptors are the most commonly found receptors in the nervous system. AMPA receptors are responsible for a majority of fast excitatory synaptic transmission; they also play a role as a gatekeeper for NMDA receptors. Upon activation, AMPA receptors assist with removal of Mg^{2+} from the NMDA receptor channel, allowing influx of Ca^{2+} into the stimulated neuron. AMPA receptors are tetrameric assemblies of subunits GluR 1-4. Most AMPA receptors are resistant to the passage of calcium and zinc. However, units lacking the GluR2 unit are highly permeable to calcium and zinc. Persistent glutamate activation of AMPARs lacking GluR2 has been shown to result in injury to neurons in the motor cortex.

Within minutes of hypoxia, energy stores are depleted and neurons become unable to meet their metabolic demands. Owing to loss of mitochondrial energy stores, Na^{+}/K^{+} ATPase pump dysregulation develops, with subsequent influx of sodium and water into cells. Calcium influx from NMDA and AMPA activation further contributes to mitochondrial

dysfunction and release of $Ca2^{+}$ from intracellular stores. Increased neuronal cytosolic calcium causes numerous deleterious effects, including activation of nitric oxide synthase, degradation of cellular lipids causing loss of integrity of the plasma membrane, activation of proteases, and induction of cellular necrosis. Cellular necrosis involves cytoplasmic swelling, unregulated nuclear dissolution, and production of an inflammatory state.

Reperfusion injury contributes to delayed neuronal cell death after HIE. Reperfusion of ischemic tissue results in generation of reactive oxygen radicals. These can further damage neuronal DNA and plasma membranes. Release of tissue factors from necrotic cells results in cytokine production, inflammation, and an influx of leukocytes. These reactive neutrophils may further contribute to production of oxygen free radicals as well as proteases, causing further tissue injury.

Leukocyte proteases likely release free Zn^{2+} from metallothioneins, extracellular matrix proteins and cellular stores. Recent studies suggest that Zn^{2+} contributes to chronic neuronal injury after HIE. Zn^{2+} is normally maintained in high concentrations in presynaptic excitatory synapses, especially in the hippocampus. HIE is associated with depletion of presynaptic Zn^{2+} and concurrent Zn^{2+} accumulation in postsynaptic neurons. Zinc is able to gain entry into neurons through voltage sensitive Ca^{2+} channels as well as NMDA and AMPA receptors. Elevated intracellular Zn^{2+} can be neurotoxic by causing depletion of intracellular energy stores, oxidative stress, and activation of apoptosis cascades.

The process of delayed neuronal cell death is an area of intense study. Animal models of ischemia demonstrate an increased expression of Ca^{2+} and Zn^{2+}–permeable AMPA receptors on surviving neurons. This process is regulated through neuronal repressor element-1 silencing transcription factor (REST). HIE increases expression of REST, which suppresses GluR2 gene expression in AMPA receptors. These GluR2 deficient AMPA receptors allow Zn^{2+} passage with neuronal stimulation and subsequent accumulation. REST activation can persist for weeks to months after the initial HIE event. Elevated intracellular Zn^{2+} can cause initiation of delayed neuronal apoptosis via the p75(NTR), poly ADP-ribose polymerase, and AMP-activated protein kinase pathways. These result in increased cytosolic levels of Bim, a pro-apoptotic Bcl-2 family member, which in turn activates caspase 3. The exact mechanisms of Zn^{2+} homeostasis and activation of apoptosis are incompletely understood. Interestingly, while Zn^{2+} excess activates apoptosis, the converse (zinc depletion) also activates neuronal apoptosis. Copper is not considered an activator of neuronal apoptotic pathways.

PREP Pearls

- There are 3 phases of neuronal injury after a hypoxic-ischemic event. The first phase is due to loss of energy stores. The second phase involves necrosis from excitatory neurotransmitters. The third phase involves long-term activation of pro-apoptotic pathways and likely results in the majority of neuronal loss after a hypoxic-ischemic injury event.
- Glutamate's activation of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors allows calcium and zinc to enter neuronal cells. Prolonged stimulation may initiate apoptosis.
- Zinc homeostasis plays a key role in neuron survival.

ABP Content Specifications(s)/Content Area

- Review the cellular pathways involved in neuronal injury following oxygen deprivation
- Understand the pathophysiology of acute and chronic neuronal injury following oxygen deprivation

Suggested Readings

Aizenman E, Loring RF, Reynolds IJ, Rosenberg PA. The redox biology of excitotoxic processes: the NMDA receptor, TOPA quinone, and the oxidative liberation of intracellular zinc. *Front Neurosci*. 2020;14:778. doi:10.3389/fnins.2020.00778

Eom JW, Lee JM, Koh JY, Kim YH. AMP-activated protein kinase contributes to zinc-induced neuronal death via activation of LKB1 and induction of Bim in mouse cortical cultures. *Mol Brain*. 2016;9:14. doi:10.1186/s13041-016-0194-6

Ferreira-Rocha E, Hristova M. Plasticity in the neonatal brain following hypoxic-ischaemic injury. *Neural Plast*. 2016;2016:4901014. doi:10.1155/2016/4901014

Hansen KB, Feng Y, Perszyk RE, Menniti FS, Traynelis SF. NMDA receptors in the central nervous system. *Methods Mol Biol.* 2017;1677:1-80. doi:10.1007/978-1-4939-7321-7_1

Novak CM, Ozen M, Burd I. Perinatal brain injury: Mechanisms, prevention, and outcomes. *Clin Perinatol*. 2018; 45(2): 357-375. doi:10.1016/j.clp.2018.01.015

Tang XJ, Xing F. Calcium-permeable AMPA receptors in neonatal hypoxic ischemic encephalopathy. *Biomed Rep*. 2013;1(6):828-832. doi:10.3892/br.2013.154

October

Question: 5

A previously healthy 14-month-old male is admitted to the pediatric intensive care unit with lethargy, poor feeding, vomiting, and diarrhea. His symptoms began 48 hours ago, and he has produced 2 small wet diapers in the past 24 hours. On physical examination he has tachycardia with diminished capillary refill time, dry mucous membranes, and a weak cry. Laboratory data are shown:

Laboratory Test	Result
Sodium	159 mEq/L (159 mmol/L)
Chloride	121 mEq/L (121 mmol/L)
Potassium	4.6 mEq/L (4.6 mmol/L)
Bicarbonate	11 mEq/L (11 mmol/L)
Creatinine	0.4 mg/dL (35 µmol/L)
Blood urea nitrogen	26 mg/dL (9.3 mmol/L)
Glucose	99 mg/dL (5.5 mmol/L)

Of the following, the MOST likely finding in this patient would be

- **A.** decreased urine specific gravity
- **B.** fractional excretion of sodium less than 1%
- **C.** fractional excretion of urea greater than 50%

D. increased glomerular filtration rate

The child in the vignette has signs, symptoms, and laboratory findings consistent with dehydration and likely has acute kidney injury (AKI) resulting from prerenal azotemia. His fractional excretion of sodium (FENa) in this setting would be less than 1%.

The FENa is a measure of the percentage of filtered sodium excreted in the urine, and it requires analysis of urine electrolytes for calculation:

$$FENa\ (\%) = 100 \times [(U_{Na} \times P_{Cr})/(P_{Na} \times U_{Cr})],$$

where U_{Na} is urinary sodium (mmol/L), P_{Cr} is plasma creatinine (mg/dL), P_{Na} is plasma sodium (mmol/L), and U_{Cr} is urine creatinine (mg/dL).

This calculation can be used in patients with AKI to differentiate between prerenal azotemia and intrinsic kidney disease caused by acute tubular necrosis (ATN). In the setting of prerenal azotemia, the kidney responds to decreased perfusion by reabsorbing sodium in an effort to restore normal effective circulating volume. The urine sodium level is low, generally less than 20 mEq/L, and FENa is less than 1%. In patients with intrinsic kidney disease, renal tubular damage leads to sodium wasting and the inability to reabsorb sodium, regardless of volume status. Urine sodium is high, usually greater than 40 mEq/L, and FENa is greater than 2%.

Under normal conditions, in the absence of AKI, the FENa is highly variable. Sodium excretion parallels dietary sodium intake, and the FENa is affected by diet, as well as by glomerular filtration rate and tubular function. Thus, the FENa must be interpreted carefully, and primarily in the clinical context of AKI. The FENa must also be interpreted cautiously in infants, owing to their immature tubules and diminished ability to reabsorb sodium. In term neonates, a FENa less than 3% is consistent with hypovolemia.

Although the FENa is the most common calculation used to distinguish prerenal azotemia and intrinsic disease, its use is limited in patients exposed to certain drugs causing natriuresis, such as loop diuretics. In such cases, the fractional excretion of urea (FEUrea) may be used, and is calculated as follows:

$$FEUrea\ (\%) = 100 \times [(U_{Urea} \times P_{Cr})/(P_{Urea} \times U_{Cr})],$$

where U_{Urea} is urinary urea (mmol/L), P_{Cr} is plasma creatinine (mg/dL), P_{Urea} is plasma urea (mmol/L), and U_{Cr} is urine creatinine (mg/dL).

The excretion of urea is not affected by the use of natriuretic drugs, and thus the FEUrea may be used as an alternative or adjunct to the FENa in determining the cause of AKI. In the setting of prerenal azotemia, the kidney reabsorbs urea in order to maximally reabsorb sodium; the urine urea is therefore low, and the FEUrea is less than 35%. In patients with ATN, urea absorption is impaired, and the FEUrea is typically greater than 50%.

The patient described in the vignette is volume depleted and would be expected to have a low urine sodium level, a FENa less than 1%, and a FEUrea less than 35%. Urine specific gravity is increased and the glomerular filtration rate is decreased in the setting of dehydration.

PREP Pearls

- Urine electrolytes can be a valuable diagnostic tool in a variety of clinical situations, particularly when differentiating between prerenal and intrinsic kidney disease in patients with acute kidney injury.
- A fractional excretion of sodium (FENa) less than 1% suggests prerenal azotemia, while a FENa greater than 2% indicates acute tubular necrosis.
- A fractional excretion of urea (FEUrea) less than 35% suggests prerenal azotemia, while a FEurea greater than 50% indicates acute tubular necrosis.

ABP Content Specifications(s)/Content Area

- Calculate and interpret fractional excretion of sodium
- Calculate and interpret fractional excretion of urea

Suggested Readings

Carmody BJ. Focus on diagnosis: Urine electrolytes. *Pediatr Rev*. 2011;32(2):65-68. doi:10.1542/pir.32-2-65

Jain A, Mattoo TK. Oliguria and anuria. In: McInerny TK, Adam HM, Campbell DE, DeWitt TG, Foy JM, Kamat DM, eds. *American Academy of Pediatrics Textbook of Pediatric Care*. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2017:301.

Schreuder MF, Bokenkamp A, van Vijkb JA. Interpretation of the fractional excretion of sodium in the absence of acute kidney injury: A cross sectional study. *Nephron Clin Pract*. 2017;136(3):221-225. doi:10.1159/000468547

October

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 6

A 16-year-old adolescent girl is seen in the emergency department with fever, chills, and shortness of breath. She has a history of aortic coarctation, which was repaired during infancy. Her medical history is otherwise negative. She has not had any recent sick contacts, although she visited a relative in prison 2 months ago who subsequently was diagnosed with tuberculosis. She reports no frequent drug use but says that she drinks alcohol and occasionally smokes marijuana. Her immunizations are up to date, although she has not received an annual influenza vaccination.

On examination, her temperature is 38.8°C. She has tachypnea, tachycardia, and has a harsh diastolic murmur on auscultation. Abdominal examination reveals hepatomegaly, and petechiae are noted on her buccal mucosa and extremities.

Of the following, given this patient's likely diagnosis, the factor MOST likely to increase her risk of developing this condition is

- **A.** failure to receive an annual influenza vaccination
- **B.** history of congenital heart disease
- **C.** recent exposure to a relative with tuberculosis
- **D.** use of alcohol and marijuana

The patient described has signs and symptoms consistent with infective endocarditis (IE). History of congenital heart disease (CHD) is the number 1 risk factor for developing IE in children, and between 50% to 90% of pediatric patients with IE have a history of CHD or

have had cardiac surgery. The incidence of IE has increased in recent years owing to improved survival rates among patients with CHD. Although treatment modalities have improved, IE still carries a mortality rate of 5% to 10% in children.

Infective endocarditis occurs when damage to cardiac endothelium leads to exposure of the extracellular matrix, production of tissue factor, and fibrin and platelet deposition. This thrombotic process provides a nidus for bacterial adherence and facilitates infection and vegetation formation, most commonly involving the aortic or mitral valves. Risk factors for endothelial damage include turbulent blood flow through damaged or abnormal valves, catheters and foreign bodies, and inflammation.

Common pathogens include *Staphylococcus aureus*, *Viridans* group streptococci, and *Enterococcus* species. Less common causes include gram-negative bacteria such as the HACEK group (*Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella,* and *Kingella* species), *Candida,* and *Aspergillus* species. Coagulase-negative *Staphylococcus* strains are common in certain patient populations, particularly in those with indwelling central catheters. *Bartonella* species, *Tropheryma whipplei*, *Coxiella burnetii*, *Brucella* species, *Legionella pneumophila*, and *Mycoplasma* species are rare but should be considered in patients with culture-negative IE.

Clinical manifestations result from bacteremia, valvulitis, immunologic responses, and emboli formation. Valvulitis may lead to new cardiac murmurs or the development of congestive heart failure. Extracardiac findings are less common in children than adults but include vascular or immunologic phenomena such as Roth spots, Janeway lesions, Osler nodes, petechiae, and hemorrhages. Glomerulonephritis may result from immune-related processes or embolic events. Emboli to other organs are common, producing associated symptoms of organ damage.

The presentation can be acute or subacute. Acute IE occurs over days to weeks, is often associated with cardiovascular compromise, and requires rapid diagnosis and treatment. However, children with IE usually present subacutely, with nonspecific symptoms such as low-grade fever, fatigue, myalgias, arthralgias, and weight loss. Fever is the most common presenting sign, and IE should be suspected in patients with fever associated with any of the following: new heart murmur, congestive heart failure, sepsis of unknown origin, embolic events, history of CHD, presence of intracardiac prosthetic material, positive blood culture with organisms typical of IE, evidence of vascular or immunologic phenomena, or other predisposing factors.

Evaluation should include blood cultures and echocardiography. Cultures should be obtained by venipuncture on 3 separate occasions within the first day. If there is no growth on day 2, obtaining 2 to 3 more cultures is recommended. In children who are stable, it may

be reasonable to withhold antibiotic therapy for 48 hours while additional cultures are obtained. In patients who are unstable, 3 separate cultures should be obtained over 1 to 2 hours, and empirical antibiotic treatment should be initiated. Additional laboratory analysis may reveal hemolytic anemia, thrombocytopenia, leukocytosis, elevated acute-phase reactants, and evidence of end organ damage.

Transthoracic echocardiography (TTE) is the accepted method for identifying intracardiac manifestations in children (97% sensitivity). Transesophageal echocardiography (TEE) should be considered in patients >60 kg and those with chest wall abnormalities or other conditions that may limit the effectiveness of TTE. Transesophageal echocardiography is superior to TTE in diagnosing left ventricular outflow tract complications, paravalvular leakage or dehiscence, involvement of the sinuses of Valsalva, and prosthetic valve endocarditis, and should be considered when these conditions are suspected.

The diagnosis of IE relies on the Duke criteria, which have clinical, microbiologic, and echocardiographic components separated into major and minor criteria (**Table**). Definitive IE requires the presence of 2 major criteria, 1 major and 3 minor, or 5 minor. Possible IE requires the presence of 1 major and 1 minor or 3 minor criteria. The diagnosis should be rejected if clinical findings can be attributed to another etiology, or if symptoms resolve after less than 4 days of antibiotic therapy.

Treatment involves a combination of supportive measures and prolonged intravenous antimicrobial therapy (usually 4 to 8 weeks). Antibiotics are tailored to the patient and culture results but should be bactericidal. Daily blood cultures are necessary to monitor treatment responses. Home intravenous treatment may be considered in patients once they are stable, afebrile, have negative blood cultures, and are not at high risk of experiencing complications. Cardiovascular surgery may be necessary in some children with IE. Common indications include congestive heart failure, valve dysfunction, and emboli formation. Early surgery should also be considered in patients with fungal IE, persistent bacteremia, ruptured sinus of Valsalva, and mycotic aneurysms.

The child in the vignette has a history of CHD, which places her at an increased risk of developing IE. Exposure to tuberculosis and failure to receive an influenza vaccination do not significantly increase her risk. Intravenous drug abuse is a major risk factor, but the use of alcohol and marijuana is not.

PREP Pearls

- Congenital heart disease is the number 1 risk factor for developing pediatric infective endocarditis, and the incidence of infective endocarditis has increased in recent years owing to improved survival rates of children with congenital heart disease.

- Diagnosis of infective endocarditis in children is based on the Duke criteria, which involve clinical, microbiologic, and echocardiographic findings.
- Treatment of pediatric infective endocarditis involves supportive measures and antimicrobial therapy, and the condition may require surgical management.

ABP Content Specifications(s)/Content Area

- Diagnose and treat pediatric infective endocarditis

Suggested Readings

Baltimore RS, Gewitz M, Baddour L, et al. Infective endocarditis in childhood: 2015 update. A scientific statement from the American Heart Association. *Circulation*. 2015;132(15):1487-1515. doi:10.1161/CIR.0000000000000298

Bragg L, Alvarez A. Endocarditis. *Pediatr Rev*. 2014;35(4):162-167. doi:10.1542/pir.35-4-162

Garg P, Ko DT, Bray Jenkyn KM, Li L, Shariff SZ. Infective endocarditis hospitalizations and antibiotic prophylaxis rates before and after the 2007 American Heart Association Guidelines revision. *Circulation*. 2019;140(3):170-180. doi:10.1161/CIRCULATIONAHA.118.037657

Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135(25):1159-1195. doi:10.1161/CIR.0000000000000503

Table. Modified Duke Criteria.

Major criteria	Blood culture positive for IE ▯typical microorganisms consistent with IE from 2 separate cultures, including viridans group streptococci, *Streptococcus bovis* group, *HACEK group, Staphylococcus aureus,* or community-acquired enterococci with absence of a primary focus or ▯typical microorganisms consistent with IE from a persistently positive culture, defined as ≥2 positive cultures drawn >12 hours apart, or all of 3 or a majority of ≥4 separate cultures drawn at least 1 hour apart or ▯single positive culture for *Coxiella burnetii* or antiphase-I IgG antibody titer >1:800
	Evidence of endocardial involvement
	Echocardiogram positive for IE, defined as evidence of ● vegetation ● abscess ● pseudoaneurysm ● intracardiac fistula ● valvular perforation ● new partial dehiscence of prosthetic valve
	New valvular regurgitation
Minor criteria	Predisposing heart condition or intravenous drug use Fever >38°C Vascular phenomena, including arterial emboli, splenic infarction, mycotic aneurysms, intracranial hemorrhage, and Janeway lesions Immunological phenomena including glomerulonephritis, Osler's nodes, Roth spots, and rheumatoid factor Microbiological evidence, including positive blood cultures not meeting major criteria above or serological evidence of infection with organism consistent with IE

Definite infective endocarditis = 2 major, or 1 major and 3 minor, or 5 minor;
Possible infective endocarditis = 1 major and 1 minor, or 3 minor.
Abbreviations: HACEK, *Haemophilus* spp, *Aggregatibacter* spp, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* spp; IE, infective endocarditis; IgG: immunoglobulin G

Courtesy of C. Preissig

November

Question: 1

A 3-year-old previously healthy girl presents to the pediatric emergency department with altered mental status and vomiting after being found with an open bottle of pills about 3 hours earlier. The family is not sure what she ingested but reported having acetaminophen, diphenhydramine, aspirin, and some leftover antibiotics in the home. Her vital signs are as follows:

Blood pressure	90/48 mm Hg
Heart rate	155 beats/min
Respiratory rate	52 breaths/min
Oxygen saturation	100% in room air

Intravenous access is established, and 20 mL/kg of 0.9% saline is administered. The team orders laboratory tests, including venous blood gas; a metabolic panel; acetaminophen, salicylate, and ethanol levels; and a urine toxicology panel.

On examination, the child has a Glasgow Coma Scale score of 13 (opens eyes to voice; is confused, but follows commands). Her lungs are clear to auscultation, her heart examination findings are normal, her abdomen is mildly tender diffusely, and the skin is normal. Her pupils are mid-position and briskly reactive; her deep tendon reflexes are normal.

Venous blood gas evaluation subsequently reveals the following values:

pH	7.37
PCO2	24 mm Hg

PO2	86 mm Hg
Bicarbonate	14 mEq/L

The anion gap is calculated at 28. The blood salicylate concentration is 64 mg/dL, the blood acetaminophen concentration is less than 4 µg/mL, and other laboratory values are reassuring.

Of the following, the MOST appropriate next step in management is to

- **A.** add sodium bicarbonate to intravenous fluids
- **B.** administer activated charcoal
- **C.** begin gastric lavage
- **D.** initiate hemodialysis

This patient has a moderate to severe salicylate intoxication and likely ingested at least 150 mg/kg of aspirin. The salicylate toxidrome includes vomiting, tinnitus, tachypnea, and confusion/agitation. Patients may develop hyperreflexia, hypotension, noncardiogenic pulmonary edema, and acute respiratory distress syndrome with severe salicylate intoxication. There is typically a mixed respiratory alkalosis and anion gap metabolic acidosis, such as that seen in this patient.

Many toxins are rapidly absorbed from the gastrointestinal tract, skin, and respiratory system. Severe toxicity can be mitigated if further absorption can be prevented or excretion can be promoted.

One method of enhanced excretion is urine alkalinization with the addition of bicarbonate to promote renal clearance of weakly acidic drugs by increasing the proportion of ionized drug, which is nonresorbable, in the renal tubule. This is known as ion trapping. Urinary alkalinization can be achieved with the addition of 50 to 75 mEq/L of bicarbonate to maintenance intravenous fluids, and by targeting a urine pH higher than 7.5. Indications for urinary alkalinization include salicylate, isoniazid, and phenobarbital ingestions. Urine acidification to increase excretion of weak bases is potentially harmful and not recommended.

Other mechanisms of enhanced excretion include extracorporeal techniques such as hemodialysis. To be removed via hemodialysis, the toxin must have low molecular weight, low protein binding, low volume of distribution, and high water solubility. Some toxins readily removed by hemodialysis include lithium, phenobarbital, alcohols, salicylates, and procainamide. Continuous venovenous hemodialysis can be used for toxin removal in the setting of hemodynamic instability. Particularly for salicylate intoxication, continuous veno-venous hemodialysis can also be considered for salicylate levels higher than 90 mg/dL. The 30-60-90 rule for salicylate ingestions may be helpful: levels greater than 30 mg/dL require urinary alkalinization; levels greater than 60 mg/dL for chronic use and 90 mg/dL for acute ingestions may be life threatening and require hemodialysis.

Activated charcoal administration can be considered if a patient has ingested a potentially toxic amount of a poison and is brought for medical care within about 1 hour of the ingestion. There is no evidence that the administration of activated charcoal improves clinical outcomes. It is contraindicated if the patient does not have an intact or protected airway. Gastric lavage and whole bowel irrigation are rarely performed and should be done only in consultation with a toxicology expert.

PREP Pearls

- Ion trapping is the enhanced excretion of weakly acidic drugs in their alkalized form by increasing the pH of the urine.
- Hemodialysis can remove toxins with low molecular weight, low protein binding, low volume of distribution, and high water solubility.

ABP Content Specifications(s)/Content Area

- Describe the toxidrome associated with salicylate intoxication.
- Understand the mechanism of action of ion trapping.
- Describe the general protocol for urinary alkalinization.

Suggested Readings

Toce MS, Burns MM. The poisoned pediatric patient. *Pediatr Rev.* 2017;38(5):207-220. doi:10.1542/pir.2016-0130

November

Question: 2

A 5-year-old boy was involved in a motor vehicle collision. He was improperly restrained with only a seat belt and sustained a grade 4 liver laceration and pancreatic transection. For the past month, he has been dependent on total parenteral nutrition because of persistent vomiting and continued abdominal fluid collections with concerns of peritonitis and continued leakage of pancreatic fluid. Over the past 24 hours, his lactate level has increased from 12.6 mg/dL (1.4 mmol/L) to 207.2 mg/dL (23 mmol/L) despite fluid resuscitation, administration of sodium bicarbonate, and broad-spectrum antibiotic and antifungal therapy for suspected sepsis. He develops cardiac arrest, requiring 2 rounds of epinephrine with return of spontaneous circulation. Hemodynamic support continues with an epinephrine infusion, and his lactic acidosis persists. The clinician was recently notified that because of a national shortage, total parenteral nutrition has not been routinely supplemented with multivitamins.

Of the following, the BEST next treatment is administration of

- **A.** ascorbic acid (vitamin C)
- **B.** hydroxocobalamin (vitamin B_{12})
- **C.** thiamine (vitamin B_1)
- **D.** tocopherol acetate (vitamin E)

Thiamine or vitamin B_1 is one of 8 water-soluble B vitamins. Dietary intake provides the primary source of thiamine. Thiamine deficiency should be considered in patients who are malnourished, have severe sepsis, burns, unexplained heart failure with lactic acidosis, chronic long-term total parenteral nutrition (TPN) administration, malabsorption and short gut syndrome, bariatric surgery, starvation, and alcoholism. Enteral absorption of thiamine is affected by nutritional status and alcohol use.

Thiamine concentrations are highest in the heart, kidneys, liver, and brain. Thiamine is not stored in tissues, and the half-life of thiamine has been estimated to be 9.5 to 18.5 days. Thiamine is important for mitochondrial activity and energy production. Thiamine deficiency affects the entrance of pyruvate into the mitochondria resulting in lactate formation. Decreased levels of thiamine can result in impaired oxidative phosphorylation and carbohydrate metabolism resulting in lactic acidosis and cell death. Cardiac failure with increased lactate production can occur from profound thiamine deficiency, making this the correct response choice for this vignette. A study in children showed increased mortality with low thiamine levels in severe sepsis or septic shock. Current international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children do not recommend use of thiamine to treat children with sepsis-associated organ dysfunction because of the low quality of evidence.

Nutritional supplementation with total parenteral nutrition requires addition of multivitamins. A recent shortage of multivitamins for total parenteral nutrition prompted the American Society of Parenteral and Enteral Nutrition (ASPEN) to recommend administration of individual multivitamins appropriate for patient weight when a shortage exists. Importantly, ASPEN notes, “Thiamine is critical as several deaths have resulted from cardiac failure due to thiamine deficiency when patients on long-term parenteral nutrition did not receive vitamins for three to four weeks. Patients receiving a carbohydrate load are particularly susceptible to thiamine deficiency.” Adult intravenous multivitamins can be used as a substitute; however, caution is advised for use in neonates. Adult multivitamins should be used with caution because they contain propylene glycol and aluminum, which can be toxic to neonates. Lactic acidosis resolves quickly, usually within 24 hours, once thiamine supplementation is provided.

Other complications commonly seen with thiamine deficiency are related to poor nutrition and alcohol abuse. Both malnutrition and alcohol decrease absorption of thiamine from the gastrointestinal tract. Wernicke-Korsakoff syndrome and beriberi are frequently seen in patients with alcohol abuse or poor nutrition. Wernicke-Korsakoff syndrome affects the central nervous system, and thiamine deficiency also causes beriberi. Wet beriberi includes progressive symptoms of cardiac failure with cardiomegaly and pulmonary edema, and dry beriberi results in primarily neurologic and peripheral nervous system involvement.

Hydroxocobalamin is vitamin B_{12}. The injectable form is used to treat B_{12} deficiencies and macrocytic anemias. Hydroxocobalamin is also the treatment for cyanide toxicity. Scurvy occurs as a result of vitamin C deficiency and can result in bleeding and poor wound healing. Vitamin E is a fat-soluble vitamin that is important for its antioxidant and antiplatelet effects, as well as for immunomodulation. Vitamin E deficiency is extremely rare and can result in muscle weakness, visual disturbances, and peripheral neuropathy.

PREP Pearls

- Thiamine deficiency can cause significant lactic acidosis and cardiovascular failure.
- Thiamine deficiency can occur in a matter of days and should be considered in patients who are malnourished or have severe sepsis, burns, unexplained heart failure with lactic acidosis, chronic long-term total parenteral nutrition administration, malabsorption and short gut syndrome, bariatric surgery, starvation, and alcoholism.
- Nutritional supplementation with total parenteral nutrition requires addition of multivitamins. Administration of individual multivitamins based on patient weight should be administered if a shortage of multivitamins exists.
- Adult multivitamins should be used with caution because they contain propylene glycol and aluminum, which can result in toxicity to neonates.

ABP Content Specifications(s)/Content Area

- Understand the relationship between thiamine and metabolism
- Recognize that metabolic acidosis can result from thiamine deficiency

Suggested Readings

American Society for Parenteral and Enteral Nutrition. 2021 Parenteral nutrition multivitamin product shortage considerations. Accessed April 3, 2022. https://www.nutritioncare.org/Guidelines_and_Clinical_Resources/Product_Shortages/2021_Parenteral_Nutrition_Multivitamin_Product_Shortage_C

Centers for Disease Control and Prevention. Deaths associated with thiamine-deficient total parenteral nutrition. *MMWR Wkly Rep.* 1989;38(3):43-46. https://www.cdc.gov/mmwr/preview/mmwrhtml/00001339.htm

Centers for Disease Control and Prevention. Lactic acidosis traced to thiamine deficiency related to nationwide shortage of multivitamins for total parenteral nutrition—United States, 1997. *MMWR Wkly Rep.* 1997;46(23):523-528. https://www.cdc.gov/mmwr/preview/mmwrhtml/00047949.htm

Frank LL. Thiamin in clinical practice. *J Parenter Enteral Nutr.* 2015;39(5):503-520. doi:10.1177/0148607114565245

Nakasaki H, Ohta M, Soeda J, et al. Clinical and biochemical aspects of thiamine treatment for metabolic acidosis during total parenteral nutrition. *Nutrition.*1997;13(2):110-117. doi:10.1016/s0899-9007(96)00384-x

November

Question: 3

A physician is rounding with the hospital infection control team to determine if appropriate isolation precautions are being applied. The following patients are on this service:

Patient 1: A 7-year-old boy with no significant medical history was admitted to the hospital for moderate dehydration. He had profuse, foul-smelling, bloody, watery diarrhea for 4 days prior to admission and complains of diffuse abdominal pain. He was taking oral clindamycin, prescribed by his primary care physician for a left anterior forearm cellulitis secondary to a “spider bite.” His physical examination findings are notable for resolving forearm cellulitis, a heart rate of 125 beats/min, a respiratory rate of 20 breaths/min, and absence of fever. His eyes are dry and deep set with reduced tearing, his skin has mild tenting, and his capillary refill time is 2 to 3 seconds. Findings of an enzyme immunoassay of his stool are positive for *Clostrioides difficile* (formerly known as *Clostridium difficile*) A toxin.

Patient 2: An 8-year-old, unvaccinated girl was admitted from the emergency department for respiratory distress, productive cough, and fever (39°C). A rapid antigen test from a nasal aspirate is positive for influenza A virus.

Patient 3: A 6-month-old girl admitted for airway management is brought to the emergency department with a history of constipation, weak cry, and “choking” when she eats formula or solid foods. Physical examination findings are notable for bilateral ptosis, decreased facial movement, head lag, and diminished deep tendon reflexes. She is treated with intravenous human antitoxin. Her stool test is positive for botulinum toxin.

Patient 4: An unimmunized, 5-year-old girl is seen in the emergency department with a 4-day history of a fever and rash that appeared today. She also has rhinorrhea, cough, and bilateral conjunctivitis. Because of her irritability and temperature of 40°C, she was admitted to the intermediate care unit. Examination shows a maculopapular rash covering her head, trunk, and extremities. A throat swab sample reverse transcription–polymerase chain reaction is reported as positive for measles.

Of the following, the MOST appropriate isolation precaution for each patient is

A.

Isolation Precaution, by Patient			
Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Contact	Droplet	Standard	Airborne

B.

Isolation Precaution, by Patient			
Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Standard	Airborne	Contact	Contact

C.

Isolation Precaution, by Patient			
Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Contact	Airborne	Airborne	Droplet

D.

Isolation Precaution, by Patient			
Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Airborne	Contact	Droplet	Droplet

Preventing health care–associated infections (HAI) can reduce morbidity and mortality in all hospitalized children, particularly immunocompromised children and children in the intensive care unit. The standard precautions of good hand hygiene before and after each patient contact is the most important control measure. Appropriate isolation precautions can reduce nosocomial infections and spread of infectious diseases to health care staff.

Patient 1 has *Clostrioides difficile* gastroenteritis, which requires contact isolation. Additionally, alcohol-based hand sanitizers do not inactivate *C difficile*; therefore, washing hands with soap and water is preferred. Other organisms that require contact isolation include vancomycin-resistant *Enterococcus* (VRE); multidrug-resistant *Staphylococcus aureus* (MRSA); respiratory syncytial virus (RSV); and norovirus and other gastrointestinal pathogens.

Patient 2 is infected with influenza virus A and therefore requires droplet isolation precautions. Infectious agents that require droplet isolation precautions include *Bordetella pertussis*, adenovirus, *Neisseria meningitidis,* and group A *Streptococcus*.

Patient 3 has botulism, an illness caused by *Clostridium botulinum* that is not transmissible from person to person. Standard precautions are sufficient measures. Standard precautions are the minimal infection prevention practices that apply to all patient care

settings; transmission-based precautions (ie, droplet, contact, airborne) supplement standard precautions when necessary.

Patient 4 is infected with measles virus, an enveloped, single-stranded, negative sense RNA virus in the *Paramyxoviridae* family. Airborne isolation precautions are required to prevent transmission, and no susceptible person should enter the room. Other pathogens requiring airborne precautions include chickenpox (varicella) and pulmonary tuberculosis.

In addition, to standard precautions, which apply to all patients, additional levels of isolation precaution for any given infectious disease can be found in the American Academy of Pediatrics' *Red Book: 2021–2024 Report of the Committee on Infectious Diseases* at : https://publications.aap.org/redbook/book/347/chapter/5749619/Infection-Prevention-and-Control-Precautions# The Centers for Disease Control and Prevention also provides up-to-date guidelines online at http//www.cdc.gov/infectioncontrol/guidelines/isolation/index.html.

Table 1 and **Table 2** present a summary of these guidelines.

PREP Pearls

- Standard precautions apply to all hospitalized patients.
- Isolation precautions should be based on the disease process.

ABP Content Specifications(s)/Content Area

- Implement isolation procedures

Suggested Readings

American Academy of Pediatrics. Infection prevention and control precautions. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. Red Book: 2021–2024 *Report of the Committee on Infectious Diseases.* 32nd ed. American Academy of Pediatrics; 2021. Accessed May 26, 2022. Red Book Online

Seigel JD, Rhinehart E, Jackson M, Chiarello L; Health Care Infection Control Practices Advisory Committee. 2007 Guidelines for isolation precautions: Preventing transmission of infectious agents in healthcare settings. *Am J Infection Control*. 2007;35(10 suppl 2):565-164. doi:10.1016/j.ajic.2007.10.007

Table 1. Isolation Precautions.

Transmission-Based Precautions

- Special guidelines based on disease or organism-specific recommendations

Contact Precautions ● Prevents transmission of infectious agents that are spread by direct or secondary contact with the care environment ● Recommended when there is wound drainage, fecal contamination or other body discharges that contaminate the environment and increase the risk of infection	● Private room ● Wear clean, nonsterile gloves ● Wear clean, nonsterile gown ● Limit hospital transports and no sharing of common areas ● Avoid sharing noncritical patient care equipment (eg, stethoscopes)
Droplet Precautions ● Prevents transmission of infectious agents spread by droplets (>5 microns) through close respiratory or mucous membrane contact with respiratory secretions via coughing, sneezing, talking, or droplet-producing procedures	● Private room or cohort ● Special airflow is NOT needed and door may remain open ● Wear mask, preferably N95 ● Droplet mask on patient when they leave the room ● Limit hospital transports and no sharing of common areas ● Follow respiratory hygiene/cough etiquette ● Gown and gloves as per Standard Precautions
Airborne Precautions ● Prevents transmission of infectious agents that are spread via airborne droplets (<5 μm) that can remain infectious and suspended in the air for more than 1 hour and can be widely dispersed by air currents	● Private room with negative-pressure ventilation and 6-12 air exchanges/hour ● Vent air through HEPA filter before recirculation ● Closed doors and windows at all times ● Wear N95 mask ● Droplet mask on patient when they leave the room ● Limit hospital transports and no sharing of common areas ● Follow respiratory hygiene/cough etiquette ● Gown and gloves as per Standard Precautions

Courtesy of B. Johansson

Source: US Centers for Disease Control and Prevention

Table 2. Isolation Precautions.

Standard Precautions

- The minimum standard of protection for ALL patients, at all times, to protect health care workers, visitors, and other patients.
- Applies to all patients regardless of confirmed or suspected infection in all health care settings
- Standard precautions are derived from the presumption that all blood, body fluids, secretions, excretions potentially contain infectious organisms

Hand Hygiene	● After touching blood, body fluids, secretions, and contaminated items ● Immediately after removing gloves and between patients
Personal Protective Equipment (PPE)	● Gloves: for contact with blood, body fluids, secretions, contaminated items, mucous membranes, and non-intact skin ● Gown: for procedures and patient care activities, with potential contact of skin/clothes to contaminated body fluids, secretions, and excretions ● Mask/eye protection: for procedures and patient care activities with possible sprays of blood, body fluids, secretions, or excretions
Safe Injections	● Single-use needles and syringes ● Limit use of multi-use vials and if possible dedicated to a single patient
Safe Handling	● Clean/disinfect contaminated equipment and surfaces in the patient care environment ● Environmental cleaning/disinfection as per policy
Respiratory Hygiene	● Instruct patient to cover their mouth and nose when sneezing/coughing ● Perform hand hygiene after touching the patient and items in the care environment ● Wear a mask or maintain spatial distance of >3 feet when possible

Courtesy of B. Johansson

Source: US Centers for Disease Control and Prevention

November

Question: 4

A 17-year-old adolescent girl is brought to the emergency department after a high-speed motor vehicle collision. She was unrestrained in the rear passenger seat, and her injuries include a right frontal skull fracture with underlying small subdural hematoma, a left femur fracture, pulmonary contusions, and blunt abdominal trauma. She received 2 liters of intravenous 0.9% saline in the field and was placed on supplemental oxygen.

On admission, she is awake but anxious. Her vital signs are as follows:

Temperature	35°C
Blood pressure	90/50 mm Hg
Heart rate	120 beats/min
Respiratory rate	30 breaths/min
Oxygen saturation	93% on 2 L/min via nasal cannula
Weight	50 kg

Her laboratory values are as follows:

Laboratory Test	**Result**
Hematocrit	21%
Platelet count	$200 \times 10^3/\mu L$ ($200 \times 10^9/L$)

Prothrombin time	18 seconds (INR, 1.5)
Activated partial thromboplastin time	50 seconds
Fibrinogen	90 mg/dL (0.9 g/L)
D-dimer	>20 µg/mL (>109.5 nmol/L) fibrinogen equivalent units

An arterial blood gas test shows the following results:

pH	7.25
$PaCO_2$	28 mm Hg
Bicarbonate	13 mEq/L
PaO_2	70 mm Hg on 4 L/min nasal cannula

Results of a rotational thromboelastogram are shown in **Figure 1**. Emergency release red blood cells, plasma, and platelets are ordered as her type and screen is processed.

Of the following, the additional treatment from which this patient would MOST benefit is

- **A.** factor VIII inhibitor bypass activity
- **B.** prothrombin complex concentrate
- **C.** recombinant factor VII^a
- **D.** tranexamic acid

As understanding of the complex interplay between platelets, endothelial cells, and inflammatory cells increases, there is a greater appreciation of the nuances that lead to various types of coagulopathies seen in critically ill patients. Disseminated intravascular coagulation (DIC) is the most well known of the dysregulated coagulation states. However, DIC is increasingly being recognized as a final common pathway of different coagulopathies, including sepsis-induced coagulopathy (SIC) and trauma-induced coagulopathy (TIC).

Sepsis-induced coagulopathy begins with the signaling of leukocytes (primarily monocytes and neutrophils) by pathogen-associated molecular patterns. Monocytes release tissue factor, which activates the coagulation cascade by binding to factor VIIa and leading to downstream activation of factor X and XI. Stimulated neutrophils, in turn, release their granular and nuclear components in the form of neutrophil extracellular traps to activate platelets, endothelial cells, and other leukocytes. Finally, stimulated endothelial cells shed their protective (and anticoagulant) glycocalyx and express von Willebrand factor, which leads to platelet adhesion and thrombosis. All of this is occurring simultaneously and leads to microvascular thrombosis, tissue ischemia, and, ultimately, organ failure. This can be seen clinically in patients with thrombocytopenia-associated multiple organ failure. As SIC progresses, patients may develop overt DIC (as defined by the International Society for Thrombosis and Hemostasis) due to the plummeting of coagulation factor levels as a result of continued consumption. According to work by Iba and others, SIC can be diagnosed earlier (using only platelet count, international normalized ratio for prothrombin time, and total sequential organ failure assessment score) than DIC and might discriminate between septic patients who may benefit from anticoagulation therapy.

Severe trauma, with hypovolemic/hemorrhagic shock and tissue damage, can lead to TIC. This is a complex disorder resulting from a combination of endothelial dysfunction caused by tissue hypoxia and injury and release of inflammatory mediators, leading in turn to dysregulation of coagulation, with both procoagulation and anticoagulation processes occurring simultaneously. The combination of tissue hypoperfusion and hypoxia with direct injury and release of damage-associated molecular patterns stimulate endothelial release of multiple factors that can serve to promote (eg, tissue factor and collagen exposure and von Willebrand factor release) and inhibit/break down (eg, activated protein C, tissue plasminogen activator, and heparan sulfate) clot formation. Hyperfibrinolysis is the process in which excess tissue plasminogen activator is unchecked to convert plasminogen to plasmin. This, in turn, leads to excess cleavage of crosslinked fibrin by plasmin, dissolution of clots, and bleeding. In addition to the clotting cascade, platelets may also become dysfunctional in severe trauma. Thus, in the untreated patient, a cascade of events may ensue that leads to death.

This trauma patient is at a high risk of mortality, given her acidosis, hypothermia, and coagulopathy. She has clinical evidence of bleeding according to her low hematocrit and abnormal vital signs. Bleeding is likely exacerbated by her coagulopathy, which is due to a combination of dilutional coagulopathy, consumptive coagulopathy, and hyperfibrinolysis. Hyperfibrinolysis is evident in her markedly elevated D-dimer (>20 fibrinogen equivalent units; signifying fibrin cleavage) and abnormal rotational thromboelastometry findings (specifically, the tapering of the tracing and markedly elevated maximal lysis in both extrinsically-activated test with tissue factor and the fibrin-based extrinsically activated test with tissue factor and the platelet inhibitor cytochalasin D; **Figure 1**). To diagnose hyperfibrinolysis via rotational thromboelastometry, one can use a maximal lysis of greater than 15% on the extrinsically activated test with tissue factor and/or fibrin-based extrinsically activated test with tissue factor and the platelet inhibitor cytochalasin D (Wang; Raza). Although marked hyperfibrinolysis can occur within the typical 60-min window, there may be cases in which prolongation of rotational thromboelastometry may elucidate it (**Figure 2**). Consultation with an expert in the performing and interpretation of rotational thromboelastometry (eg, one who works in transfusion medicine or hematology) may be useful for rare cases.

Given the patient's anemia and coagulopathy, transfusion with red blood cells, plasma, and platelets is warranted. Her hyperfibrinolysis indicates that she would also benefit from tranexamic acid (TXA), a lysine analog that prevents the conversion of plasminogen to active plasmin—thereby preventing fibrinolysis. According to the investigators in the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2 (CRASH-2) study, TXA has been shown in a randomized controlled trial to reduce mortality in bleeding trauma patients. Prothrombin complex concentrate (PCC) is a combination of inactivated factors 2, 9, and 10 with or without inactivated factor 7 (4PCC or 3PCC, respectively). Typically, PCCs are used to correct coagulopathies with prolonged INR while reducing the volume infused or for rapid reversal of vitamin K antagonists. Factor VIII inhibitor bypass activity (FEIBA) is an activated form of 4PCC with activated factor VII and inactivated factors II, IX, and X. Traditionally, FEIBA has been used to treat hemophilia patients who also have inhibitory antibodies to factors VIII or IX. Finally, the use of recombinant factor VIIa is similar to FEIBA and PCC for the treatment of bleeding in people who have hemophilia with inhibitory antibodies. In this case, the patient's INR is only slightly elevated, she is already receiving plasma, and she has significant hyperfibrinolysis to be treated.

PREP Pearls

- Trauma-induced coagulopathy is a distinct disorder in hemostasis, with both hypercoagulable and hypocoagulable (including hyperfibrinolytic) states.
- Hyperfibrinolysis can be detected via thromboelastography or rotational thromboelastometry.

- Tranexamic acid stops fibrinolysis and reduces the risk of death in bleeding trauma patients.

ABP Content Specifications(s)/Content Area

- Use of tranexamic acid (TXA) in mass transfusion protocols

Suggested Readings

CRASH-2 trial collaborators, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): A randomised, placebo-controlled trial. *Lancet.* 2010;376(9734):23-32. doi:10.1016/S0140-6736(10)60835-5

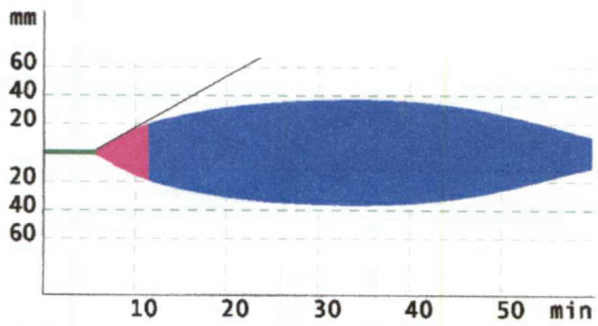
Iba T, Levi M, Levy JH. Sepsis-induced coagulopathy and disseminated intravascular coagulation. *Semin Thromb Hemost.* 2020;46(1):89-95. doi:10.1055/s-0039-1694995

Moore HB, Gando S, Iba T, et al; Subcommittees on Fibrinolysis, Disseminated Intravascular Coagulation, and Perioperative and Critical Care Thrombosis and Hemostasis. Defining trauma-induced coagulopathy with respect to future implications for patient management: Communication from the SSC of the ISTH. *J Thromb Haemost.* 2020;18(3):740-747. doi:10.1111/jth.14690.

Raza I, Davenport R, Rourke C, et al. The incidence and magnitude of fibrinolytic activation in trauma patients. *J Thromb Haemost*. 2013;11(2):307-314. doi:10.1111/jth.12078

Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: Fourth edition. *Crit Care.* 2016;20:100. doi:10.1186/s13054-016-1265-x

Wang IJ, Park SW, Bae BK, et al. FIBTEM improves the sensitivity of hyperfibrinolysis detection in severe trauma patients: A retrospective study using thromboelastometry. *Sci Rep.* 2020;10(1):6980. doi:10.1038/s41598-020-63724-y



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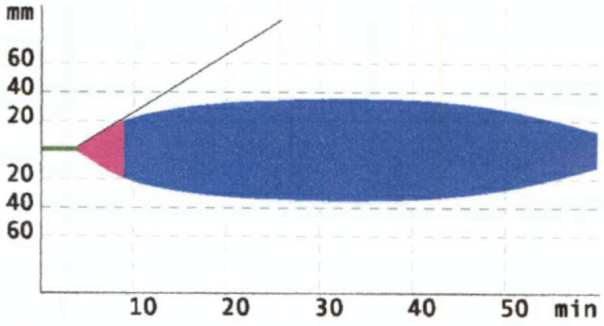

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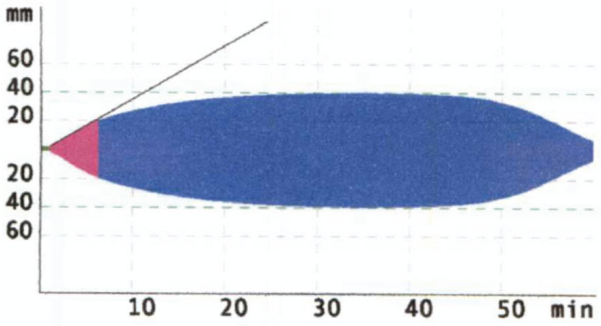

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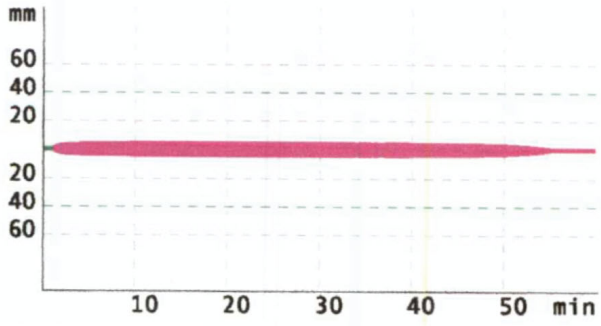

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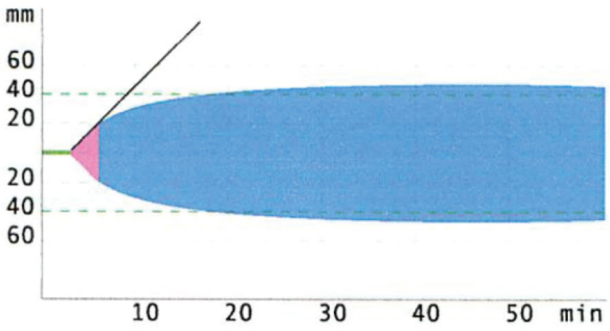

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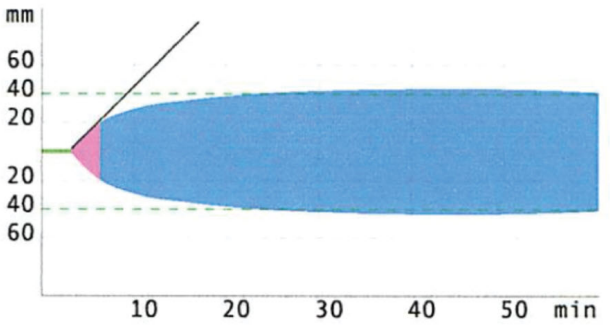

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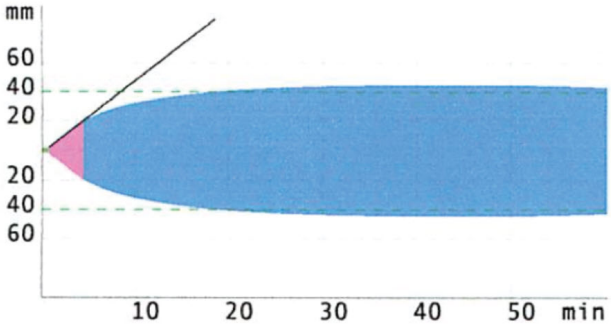

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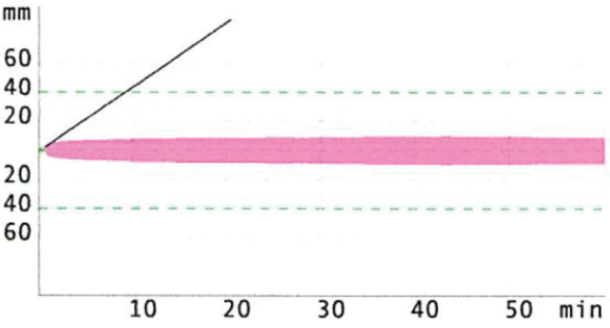

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November

Question: 5

A 12-year-old boy is admitted to the pediatric intensive care unit late in the evening for evaluation of fever and weight loss over the past several weeks. His medical history and current medications reveal no pertinent information regarding his condition. His oxygen saturation is 100% in room air. He is hemodynamically stable.

Laboratory data are shown:

Laboratory Test	**Result**
White blood cell count	250,000/μL (250×10^9/L)
Hemoglobin	10 g/dL (110 g/L)
Hematocrit	40%
Sodium	140 mEq/L (140 mmol/L)
Potassium	4.1 mEq/L (4.1 mmol/L)
Chloride	95 mEq/L (95 mmol/L)
Bicarbonate	20 mEq/L (20 mmol/L)
Blood urea nitrogen	19 mg/dL (6.8 mmol/L)
Creatinine	1.2 mg/dL (1.6 μmol/L)
Uric acid	12.3 mg/dL (0.7 mmol/L)

The hematology-oncology service is consulted. They recommend a 1.5 maintenance fluid rate and rasburicase for the elevated uric acid. They also request he be made nil per os status for a bone marrow aspirate and biopsy in the morning.

The physician is called to the bedside 6 hours after admission secondary to respiratory distress. The boy's vital signs are shown:

Blood pressure	130/85 mm Hg
Heart rate	150 beats/min
Respiratory rate	30 breaths/min
Oxygen saturation	88% via pulse oximetry

His lung sounds are clear. A chest radiograph is without significant pathology. An arterial blood gas test via co-oximetry reveals the following:

pH	7.3
$PaCO_2$	30 mm Hg
PaO_2	95 mm Hg
Oxygen saturation	95%
Lactate	72 mg/dL (8 mmol/L)

Of the following, the MOST important immediate treatment for this patient is

- **A.** bicarbonate bolus

- **B.** furosemide
- **C.** methylene blue
- **D.** supplemental oxygen

Methemoglobinemia occurs when hemoglobin is structurally changed from its reduced form (ferrous $Fe2^{+}$) to its oxidized form (ferric $Fe3^{+}$). The oxidized form of hemoglobin is not able to bind oxygen well. The decreased binding of oxygen leads to poor oxygen delivery.

Poor oxygen delivery in methemoglobinemia can be manifested in many ways. Tachycardia, tachypnea, nasal flaring, and accessory muscle use are all commonly seen in methemoglobinemia. Often the oxygen delivery is insufficient to meet the metabolic demands and an ensuing lactic acidosis develops. Pulse oximetry often does not reflect the true arterial oxygen saturations physiologically because of the wavelength characteristics of the monitor.

Drugs are reportedly the most frequent causes of methemoglobinemia. Anesthetic agents (eg, lidocaine, benzocaine, prilocaine), certain antibiotics (eg, dapsone, nitrates, sulfa), and antimalarials are frequently implicated. An infrequent and underrecognized cause in the PICU is undiagnosed glucose-6-phosphate dehydrogenase (G6PD) deficiency. This disease is caused by a deficiency in nicotinamide adenine dinucleotide phosphate oxidase (NADPH). This enzyme converts oxidized hemoglobin to reduced hemoglobin. Deficiency in NADPH is more common in ethnic groups from Africa, Southeast Asia, and the Mediterranean.

The patient in the case had no history of drug exposure until he was given rasburicase in the pediatric ICU. Rasburicase is a known precipitin of methemoglobinemia in patients with G6PD deficiency. The immediate treatment for these patients is supplemental oxygen. In severe cases, blood transfusions or exchange transfusions are needed. Methylene blue is the treatment in the majority of other causes of methemoglobinemia. However, it does not work well in G6PD deficiency secondary to the lack of NADPH in these patients. In fact, methylene blue may trigger hemolysis in individuals with methemoglobinemia. There is no clinical or radiographic evidence of pulmonary edema, so furosemide would not be useful. Although the patient is acidotic, bicarbonate is not indicated for treatment of methemoglobinemia. The patient might need intubation if his condition worsened, but there is no indication for this at the time of presentation.

Although it is impractical to screen all patients for G6PD deficiency before initiating rasburicase, it is important to recognize the symptoms of methemoglobinemia in susceptible patient populations who receive it.

PREP Pearls

- Methemoglobinemia can be a medical emergency.
- Drug exposure is the most common cause of methemoglobinemia.
- Methylene blue is the most frequent treatment of drug-induced methemoglobinemia.
- Underlying (or undiagnosed) G6PD deficiency makes patients more vulnerable to certain types of drug-induced methemoglobinemia.

ABP Content Specifications(s)/Content Area

- Diagnose and treat a patient with methemoglobinemia.
- Identify patients vulnerable to certain types of drug-induced methemoglobinemia

Suggested Readings

Borinstein SC, Xu M, Hawkins DS. Methemoglobinemia and hemolytic anemia caused by rasburicase administration in a newly diagnosed child with Burkitt lymphoma/leukemia. *Pediatr Blood Cancer.* 2008;50(1):189. doi:10.1002/pbc.21193

Cheah CY, Lew TE, Seymour JF, Burbury K. Rasburicase causing severe oxidative hemolysis and methemoglobinemia in a patient with previously unrecognized Glucose-6-Phosphate dehydrogenase deficiency. *Acta Haematol.* 2013;130(4):254-259. doi:10.1159/000351048

Ibrahim U, Saqib A, Mohammad F, Atallah JP, Odaimi M. Rasburicase-induced methemoglobinemia: the eyes do not see what the mind does not know. *J Oncol Pharm Practice*. 2018;24(4):309-313. doi:10.1177/1078155217701295

Rehman HU. Methemoglobinemia. *West J Med*. 2001;175(3):193-196. doi:10.1136/ewjm.175.3.193

November

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 6

A 3-year-old, 15-kg boy is recovering from a prolonged course of mechanical ventilation for acute hypoxemic respiratory failure due to *Streptococcus pneumoniae* pneumonia with septic shock. He is orally intubated with a 4.5-mm cuffed endotracheal tube. His current ventilatory settings and mechanics, as well as his vital signs, are as follows:

Ventilation Settings	
Mode	Synchronized intermittent mandatory ventilation/volume control
Flow waveform	Decelerating
Rate	16 breaths/min
Inspiratory time	0.8 s
Tidal volume	105 mL
Pressure support	7 cm H_2O
Positive end expiratory pressure	6 cm H_2O
FiO_2	0.30

Ventilation Mechanics	
Peak inspiratory pressure	20 cm H_2O
Mean airway pressure	10.5 cm H_2O
End tidal carbon dioxide	20 mm Hg

Arterial Blood Gas	
pH	7.37
PCO_2	55 mm Hg
PO_2	95 mm Hg
Bicarbonate HCO_3 (calc)	30 mEq/L

Vital Signs	
Blood pressure	90/60 mm Hg
Heart rate	103 beats/min
Respiratory rate	24 breaths/min

Oxygen saturation	99% in room air

He undergoes a spontaneous breathing trial of continuous positive airway pressure at 6 cm H_2O and breathes 24 times per minute. His tidal volume is 80 mL, and he appears comfortable. At the end of an hour, his previous settings are restored and his cuff is deflated. No air leak is audible around his endotracheal tube; therefore, he is started on intravenous dexamethasone. The nursing and respiratory care staff ask if the intensivist would like to proceed with extubation.

Of the following, the factor that MOST suggests the patient may be extubated successfully is the

- **A.** administration of dexamethasone
- **B.** rapid shallow breathing index
- **C.** result of his spontaneous breathing trial
- **D.** use of protocol-directed sedation management

The duration of mechanical ventilation and the ability to successfully liberate a patient from it are complex, but common, processes in intensive care units. Many pulmonary and extrapulmonary factors play a role, including, but not limited to, the following:

- Etiology of acute respiratory failure
- Patient nutritional status and physical conditioning
- Duration of mechanical ventilation (both ventilator-associated lung injury and atrophy of respiratory muscles)
- Presence of comorbidities (especially those affecting respiratory drive, mechanics, or both)
- Level and duration of sedative use

If the patient's primary indication for mechanical ventilation is resolved, then the intensivist should attempt to liberate the patient from mechanical ventilation. There are established protocols and processes for predicting success in intubated adults, but data regarding children are less robust.

Many practitioners rely on the endotracheal tube (ETT) leak test to predict whether a patient will develop postextubation upper-airway obstruction and subsequent acute respiratory failure. Although low or absent air leak in patients with cuffed ETT (but not in those with properly sized uncuffed ETT) is associated with upper airway obstruction after

extubation (Khemani, 2016), the absence of an air leak does not reliably predict extubation failure in children (Wratney). Despite this, the use of corticosteroids to prevent upper-airway obstruction in children is commonly performed but debated. In a meta-analysis, Khemani found that the routine use of corticosteroids did not significantly prevent reintubation due to upper airway obstruction (Khemani, 2009). In a more recent systematic review, Kimura found a lower risk of reintubation in children who received corticosteroids. However, this meta-analysis included a study which evaluated low-dose dexamethasone use in chronically ventilated, very-low-birth-weight and/or extremely premature neonates, a population that is typically limited to neonatal intensive care units. Therefore, according to data for pediatric patients outside the neonatal period, the routine use of corticosteroids to prevent postextubation respiratory failure is not supported. Patients at high risk of experiencing upper-airway edema, however, may benefit from corticosteroid use.

The use of protocols is beneficial in many aspects of medicine through reducing practice variability. However, Aitken reported in a recent Cochrane meta-analysis that there was no difference in duration of mechanical ventilation or mortality when comparing protocol-driven sedation versus usual care in pediatric ICU patients. This meta-analysis included a large clustered randomized, multicenter trial that included 2,449 children receiving mechanical ventilation (Curley).

The ability to confidently predict which patients will remain off of the ventilator after extubation is a goal of any intensivist to help in counseling families and to minimize unnecessary time on the ventilator. Two early indices to predict extubation success in adults were developed by Yang and Tobin (NEJM 1991): the rapid shallow breathing index in adults (RSBI) and the compliance, rate, oxygenation, and pressure index (CROP). RSBI is simply calculated as the ratio of respiratory frequency and tidal volume (f/V_T), whereas CROP is a more complex, integrative index that combines dynamic compliance (C_{dyn}), maximal inflation pressure ($P_I max$), ratio of arterial:alveolar pressure of oxygen (P_aO_2/P_AO_2), and the respiratory rate (f) (see below).

$$CROP = \frac{C_{dyn} \times P_I max \times \frac{P_aO_2}{P_AO_2}}{f}$$

In their report, Yang and Tobin found that the area under the curve for RSBI (0.89) was higher than for CROP (0.78) for predicting extubation success in adults. Despite their use in adults, these indices do not have the same utility in children (Farias).

Many practitioners assess patients' readiness for extubation by using spontaneous breathing trials (SBTs). This typically involves reducing sedation so the patient's respiratory drive is not suppressed. The patients are then given positive end-expiratory pressure (PEEP, also known as continuous positive airway pressure [CPAP]). The patient's vital signs, use of accessory muscles, and exhaled tidal volume are monitored. Patients who are breathing comfortably with reassuring vital signs are predicted to successfully extubate (Chavez). In a large prospective study by Khemani (2016), the use of pressure support above PEEP was not necessary to overcome airway resistance by the ETT. In fact, the use of pressure support during SBT underestimates the postextubation effort of breathing, potentially leading to a false sense of reassurance that the patient will be extubated successfully. They recommended performing SBT by using PEEP alone to assess work of breathing.

PREP Pearls

- Despite validated scoring systems in adults, the utility of respiratory scoring systems in children is less well defined.
- Sedation protocols are not associated with shorter duration of mechanical ventilation.
- Properly sized endotracheal tubes should not increase airway resistance in children with normal tracheal anatomy.
- Spontaneous breathing trials should optimally be performed with positive end-expiratory pressure alone in predicting the likelihood of successful liberation from mechanical ventilation.

ABP Content Specifications(s)/Content Area

- Understand the principles of weaning patients from mechanical ventilation
- Understand factors that support or discourage patient liberation from the ventilator and extubation

Suggested Readings

Aitken LM, Bucknall T, Kent B, Mitchell M, Burmeister E, Keogh SJ. Protocol-directed sedation versus non-protocol-directed sedation to reduce duration of mechanical ventilation in mechanically ventilated intensive care patients. *Cochrane Database Syst Rev.* 2015;1:CD009771. doi: 10.1002/14651858.CD009771.pub3

Chavez A, dela Cruz R, Zaritsky A. Spontaneous breathing trial predicts successful extubation in infants and children. *Pediatr Crit Care Med.* 2006;7(4):324-328. doi: 10.1097/01.pcc.0000225001.92994.29

Curley MA, Wypij D, Watson RS, et al; RESTORE Study Investigators and the Pediatric Acute Lung Injury and Sepsis Investigators Network. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: A randomized clinical trial. *JAMA.* 2015;313(4):379-389. doi:10.1001/jama.2014.18399

Farias JA, Alia I, Retta A, et al. An evaluation of extubation failure predictors in mechanically ventilated infants and children. *Intensive Care Med*. 2002;28(6):752-757. doi:10.1007/s00134-002-1306-6

Khemani RG, Hotz J, Morzov R, Flink R, Kamerkar A. Evaluating risk factors for pediatric post-extubation upper airway obstruction using a physiology-based tool. *Am J Respir Crit Care Med*. 2016;193(2):198-209. doi:10.1164/rccm.201506-1064OC

Khemani RG, Randolph A, Markovitz B. Corticosteroids for the prevention and treatment of post-extubation stridor in neonates, children and adults. *Cochrane Database Syst Rev.* 2009;(3):CD001000. doi:10.1002/14651858.CD001000.pub3

Newth CJI, Hotz JC, Khemani RG. Ventilator liberation in the pediatric ICU. *Respir Care.* 2020;65(10):1601-1610. doi:10.4187/respcare.07810

Wratney AT, Benjamin DK Jr, Slonim AD, He J, Hamel DS, Cheifetz IM. The endotracheal tube air leak test does not predict extubation outcome in critically ill pediatric patients. *Pediatr Crit Care Med.* 2008;9(5):490-496. doi:10.1097/pcc.0b013e3181849901

Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. *New Engl J Med.* 1991;324(21):1445-1450. doi:10.1056/NEJM199105233242101

December

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 1

A 15-year-old adolescent boy is a bone marrow transplant recipient with cardiomyopathy. He developed ventricular dysrhythmias that have been controlled with amiodarone. He remains intubated after 2 weeks and has been sedated with higher-dose infusions of midazolam for sedation and fentanyl for pain control. Enteral nutrition has been tolerated, and the physician is considering transitioning his medications to an enteral route. He will complete a course of levofloxacin for tracheitis in 3 days. Diuresis with furosemide continues, and potassium is being sparingly supplemented given his impaired renal function. His most recent potassium level was 3.1 mEq/L (3.1 mmol/L). Vascular access includes a peripherally inserted central catheter and arterial line with heparin and papaverine.

Of the following, the agent that should be used with caution as his medications are transitioned to the enteral route is

- **A.** clonidine
- **B.** lorazepam
- **C.** methadone
- **D.** oxycodone

This vignette demonstrates a patient who is at high risk of experiencing cardiac electrical abnormalities. He has structural heart disease and electrolyte abnormalities and is receiving medications that can alter cardiac electrical transduction. This patient is already receiving a combination of medications that increase the risk of experiencing prolonged QT syndrome. Addition of new medications that might worsen this condition should be approached with caution.

Causes of a prolonged QT interval can be acquired or congenital and include structural heart disease, medications, and electrolyte disturbances. A prolonged QT interval associated with structural heart disease can be affected by medications and electrolyte disturbances. Medications that prolong the QT interval can be affected by end-organ function, resulting in drug accumulation. The normal corrected QT interval (QTc) is less than 440 ms for men and less than 460 ms for women.

Methadone is the drug that should be used with caution for this patient. He is already receiving amiodarone and levofloxacin, both of which can prolong the QT interval. The patient has hypokalemia and impaired renal function that can exacerbate the combination of drugs and prolong the QT interval further. Additionally, papaverine in the arterial line adds another agent that could exacerbate prolongation of the QT interval.

Methadone is a synthetic analgesic that affects the μ receptor. Methadone also produces pain relief as a *N*-methyl-D-aspartate (NMDA) receptor antagonist and blocks serotonin and norepinephrine reuptake in the central nervous system. Methadone is used for treatment of acute and chronic pain. Intraoperative methadone has lowered pain scores and decreased opiate requirements in the postoperative period. It is also indicated for maintenance therapy among individuals with opiate addiction. In the critical care setting, methadone is used to assist with weaning patients from opiate infusions who are at risk of developing opioid dependency. Risk of withdrawal is dependent on duration, dose, and exposure to other opiates and sedatives. Methadone is typically tapered to prevent medication withdrawal. This drug is commonly administered intravenously or orally. It has also been administered rectally, sublingually, intramuscularly, and subcutaneously. It has a large volume of distribution, with a longer terminal half-life, and is highly lipid soluble. Dosing can be challenging because of variability in pharmacokinetics. Methadone is hepatically metabolized and excreted through the kidneys. Many drugs coadministered with methadone can influence pharmacokinetics and pharmacodynamics.

Interactions between numerous medications can increase the risk of a prolonged QT interval and require consideration when prescribing these pharmacologic agents. Maintenance methadone therapy is estimated to increase the QTc by an average of 10 ms. Drug effect and metabolism can cause electrolyte disturbances that must also be considered when prescribing drugs that can prolong the QT interval. Hypokalemia is a primary risk factor for prolonged QT syndrome, as are hypomagnesemia and hypocalcemia. A baseline electrocardiogram is recommended when methadone therapy is initiated and whenever medications that can prolong the QT interval are added, or if dysrhythmias occur. A prolonged QT can deteriorate into a polymorphic ventricular tachycardia known as torsades de pointes. Torsades de pointes is treated with electrical cardioversion and administration of intravenous magnesium sulfate. Common drugs that can prolong the QT interval for patients in the pediatric ICU are shown in the **Table**. Intracardiac administration

of papaverine is known to prolong the QT interval and can induce ventricular dysrhythmias. The mechanism of action is thought to be similar to that of class III antiarrhythmic agents by inhibiting potassium current.

PREP Pearls

- Methadone is a synthetic analgesic that produces pain relief by affecting the μ receptor, and acting as a *N*-methyl-D-aspartate (NMDA) receptor antagonist that blocks serotonin and norepinephrine reuptake.
- Methadone is used for treatment of acute and chronic pain and prevention of opioid withdrawal.
- Methadone should be used with caution when combined with other drugs that prolong the QT interval. A baseline electrocardiogram should be obtained and periodically followed up.
- A prolonged QT interval can occur from congenital or acquired causes such as pharmacologic agents, electrolyte disturbances, and structural heart disease.

ABP Content Specifications(s)/Content Area

- Know the uses and precautions needed when prescribing methadone.

Suggested Readings

Beitland S, Platou ES, Sunde K. Drug-induced long QT syndrome and fatal arrhythmias in the intensive care unit. *Acta Anaesthesiol Scand.* 2014;58(3):266-72. doi:10.1111/aas.12257

Dervan LA, Yaghmai B, Watson RS, Wolf FM. The use of methadone to facilitate opioid weaning in pediatric critical care patients: A systematic review of the literature and meta-analysis. *Paediatr Anaesth.* 2017;27(3):228-239. doi:10.1111/pan.13056

Kreutzwiser D, Tawfic QA. Methadone for pain management: A pharmacotherapeutic review. *CNS Drugs.* 2020;34(8):827-839. doi:10.1007/s40263-020-00743-3

Nakayama M, Tanaka N, Sakoda K, et al. Papaverine-induced polymorphic ventricular tachycardia during coronary flow reserve study of patients with moderate coronary artery disease. *Circ J.* 2015;79(3):530-536. doi:10.1253/circj.CJ-14-1118

Table. Common Drugs That Can Cause a Prolonged QT Interval in PICU Patients.*^

Antiarrhythmic Agents	Amiodarone Flecainide Procainamide Sotalol
Antiemetic and Promotility Agents	Droperidol Metoclopramide Ondasetron Azithromycin Erythromycin
Antibiotics	Macrolides Fluoroquinolones Other: ● Amantadine ● Clindamycin
Miscellaneous Drugs	Immunosuppressive agents Antipsychotic and tricyclic antidepressants Other: ● Methadone ● Fosphenytoin ● Phenytoin ● Octreotide ● Papaverine ● Risperidone ● Terlipressin

Courtesy of T Nakagawa

Abbreviations: PICU, pediatric intensive care unit.

*There are other drugs prescribed or seen in clinical practice that are not listed and can prolong the QT interval.

^Risk of a prolonged QT interval can occur when drugs are combined for patient treatment.

December

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 2

A 10-month-old boy is admitted to the pediatric ICU with 2 days of fever, decreased oral intake, lethargy, increased work of breathing, and inspiratory stridor. The patient was given a 20 mL/kg bolus of normal saline in the emergency department for possible dehydration and received multiple doses of nebulized albuterol for presumed bronchiolitis with no improvement in his symptoms. His mother stated that he was born at 27 weeks' gestation and required prolonged intubation and nasogastric feedings in the neonatal intensive care unit. She stated that he always has "noisy" breathing, which is significantly louder now. Upon arrival to the intensive care unit he was found to be in respiratory failure, requiring endotracheal intubation. The practitioner performing the intubation stated that there was a Cormack-Lehane grade I view of the larynx however they were only able to successfully intubate the patient with a 3.5 endotracheal tube due to the inability to pass a 4.0 endotracheal tube below the vocal cords.

Of the following, the MOST likely etiology of this patient's noisy breathing at baseline is

- **A.** bilateral congenital choanal atresia
- **B.** parainfluenza infection
- **C.** subglottic stenosis
- **D.** tonsillar-adenoidal hypertrophy

Pediatric subglottic stenosis (SGS) is defined as narrowing of the airway immediately caudal to the glottis, between the vocal folds and lower border of the cricoid cartilage. The subglottic lumen is typically 4.5 mm to 5.5 mm in a full-term neonate at birth, and 3.5 mm in a premature infant at birth. A subglottic diameter of 4 mm or less in a full-term neonate would be considered significantly narrowed and defined as SGS. Since airway resistance is

inversely proportional to the fourth power of the radius, even a small decrease in airway diameter increases airway resistance and work of breathing significantly. The Cotton-Myer staging system is used to describe the severity of SGS and is typically used in the literature discussing this topic. The severity of the stenosis is defined as grade 1 through 4 based on the degree of tracheal obstruction. The etiology of SGS is either congenital, acquired, or idiopathic. Idiopathic SGS is rare and described as the development of circumferential stenosis in the subglottic region later in life without a precipitating cause. Congenital subglottic stenosis is also rare, presenting early in life and in patients without a history of endotracheal intubation. It can be associated with rare genetic disorders such as Pallister-Killian syndrome, which involves multiple morphologic defects of the respiratory system and progressive subglottic stenosis.

The most common cause of SGS is the acquired form resulting from tracheal intubation. Advances in neonatal resuscitation and knowledge of neonatal physiology led to the development of advanced modalities of ventilation to premature infants and likely contributed to the increase in cases of acquired SGS due to prolonged intubation. Premature infants generally tolerate intubation due to their more pliable cartilage and high neonatal larynx; however, prolonged intubation can lead to SGS in these patients owing to mucosal pressure and disruption. This can result in an inflammatory cascade in the subglottic mucosa that further leads to perichondritis, scar formation, and ulceration. This ulceration and mucosal edema disrupt the normal ciliary flow, causing an aberration in the mucociliary system that can potentially lead to infection. The mobile and loose subglottic mucosa along with the incomplete vascularization of the cartilage in these young patients prevents primary healing of the injury and worsens the stenosis owing to proliferation of granulation and scar tissue.

In discussing the development of acquired SGS in pediatric patients, it is pertinent to discuss the anatomical differences between the adult and pediatric airway. The narrowest portion of the adult airway is at the vocal cords or laryngeal inlet; however, the pediatric and infant airway becomes narrower below the vocal cords. Until the child is approximately 8 years of age, the narrowest portion of the airway is in the subglottic space, reaching the smallest diameter at the level of the cricoid cartilage. This narrowing is more exaggerated during the neonatal period. Typically, the pediatric larynx can be described as funnel shaped, whereas the adult larynx is barrel shaped. Although endotracheal intubation always potentially places patients at risk of experiencing laryngeal and vocal cord injury, this funnel shape and narrowing below the cords significantly increases the risk of subglottic injury in these patients. This anatomical difference has clinical significance not only in the potential development of SGS but increases infants' and pediatric patients' risk of susceptibility to airflow compromise in the presence of any airway and subglottic tissue edema. As the airway diameter gets larger with growth, the potential for an increase in airway resistance secondary to airway edema decreases.

Given that not all intubated neonates develop SGS, it is likely multiple confounding factors contribute to the development of SGS in these patients, including the movement and size of the endotracheal tube (ETT), inappropriately large ETT, prolonged duration of intubation, history of a traumatic intubation, gastroesophageal reflux disease, inappropriately high cuff pressures in an ETT, and the presence of a nasogastric feeding tube. The incidence of SGS has significantly improved as the management of mechanical ventilation in neonates has evolved, decreasing in this population since the 1980s, which was as high as 9.8% of intubated neonates, to <1% in the most recent studies.

An acute viral respiratory infection, such as seen in the patient in the vignette, can cause SGS to advance from a chronically compensated problem to an uncompensated episode of respiratory failure quickly. Dexamethasone, heliox, and racemic epinephrine can be used to help mitigate progressive respiratory failure; however, patients with severe SGS require evaluation with a pediatric otolaryngologist, airway endoscopy for diagnosis, and possible laryngotracheal reconstruction in severe cases.

While a parainfluenza infection would certainly worsen airway edema and potentially cause respiratory compromise in patients with SGS, it would not explain the more chronic findings of the baseline noisy breathing of the patient in the vignette. Tonsillar-adenoidal hypertrophy is generally not seen in patients under the age of 2, as the tonsils and adenoids are underdeveloped in infancy. Congenital choanal atresia would likely have presented early in infancy and would have been ruled out by the presence of a nasogastric tube in the neonatal ICU.

PREP Pearls

- Subglottic stenosis can be a complication of endotracheal intubation in neonates and pediatric patients.
- The risk of subglottic stenosis is increased due to inappropriately large endotracheal tubes, prolonged intubation, gastroesophageal reflux, and concurrent use of nasogastric tubes.

ABP Content Specifications(s)/Content Area

- Recognize the risk factors for subglottic stenosis after intubation.

Suggested Readings

McCormick M. Trends in subglottic stenosis management: Resource utilization and pediatric otolaryngology training. *Laryngoscope.* 2022;132(suppl 5):S1-S9. doi:10.1002/lary.28927

Walner DL, Loewen MS, Kimura RE. Neonatal subglottic stenosis—incidence and trends. *Laryngoscope.* 2001;111(1)48-51. doi:10.1097/00005537-200101000-00009

December

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 3

A 16-year-old adolescent boy is seen in the emergency department after being struck by an automobile. He was intubated at the scene with a Glascow coma score of 6 and received 1 L of 0.9% sodium chloride for hypotension. Computed tomography scan of the head shows a right frontal skull fracture, a right subdural hematoma with 5-mm, right-to-left midline shift, and multiple punctate intraparenchymal bleeds. He also has bilateral pulmonary contusions, a grade II liver laceration, and a left, nondisplaced femur fracture. He is immediately taken to the operating room for evacuation of the subdural hematoma and placement of a right-sided external ventricular drain (EVD) as well as fixation of his femur fracture.

After surgery, he is brought to the pediatric intensive care unit (PICU), still intubated and with both central and arterial lines in place. He weighs 60 kg. His vital signs are shown:

Temperature	37.5°C
Heart rate	95 beats/min
Respiratory rate	15 breaths/min
Blood pressure	115/70 mm Hg
Oxygen saturation	100% on FiO_2 0.5

His central venous pressure is 11 mm Hg, and his intracranial pressure ranges between 10 and 16 mm Hg while on midazolam and fentanyl infusions. He is receiving intravenous fluids with 0.9% sodium chloride at 1,600 mL/m^2/day. One hour after PICU admission, he has 5 mL of clear fluid from his external ventricular drain and 15 mL of urine output.

Laboratory data are shown:

Arterial Blood Gas	
pH	7.35
pCO_2	38 mm Hg
pO_2	100 mm Hg
HCO_3(c)	20 mm Hg
Lactate	2 mmol

Serum Chemistry	
Sodium	128 mEq/L
Potassium	4.3 mEq/L
Chloride	110 mEq/L
CO_2	21 mEq/L
Blood urea nitrogen	10 mg/dL (3.6 mmol/L)
Creatinine	0.8 mg/dL (70.7 µmol/L)

Glucose	140 mg/dL (7.8 mmol/L)
Osmolality	270 mOsm/kg (270 mmol/kg)

Hemogram with Platelets	
Hemoglobin	10 g/dL (100 g/L)
Hematocrit	31%
Platelet count (x10^3/µL)	324 × 10^3/µL (324 × 10^9/L)

Coagulation Markers	
Protime	13 s
Partial thromboplastin time	25 s
Fibrinogen	200 mg/dL (2 g/L)

Liver Panel	
Aspartate aminotransferase	100 U/L
Alanine aminotransferase	80 U/L
Total bilirubin	0.3 mg/dL (5.1 µmol/L)

Urinalysis	
Specific gravity	1.028
Nitrites	Negative
Leukocyte esterase	Negative
Reducing substances	Negative
Red blood cells	Trace
Osmolality	340 mOsm/kg (340 mmol/kg)
Sodium	100 mEq/L
Creatinine	40 mg/dL (3,536 µmol/L)

Of the following, after administering a 5 mL/kg 3% sodium chloride bolus, the MOST appropriate next step is to

- **A.** initiate fludrocortisone daily
- **B.** initiate a 3% sodium chloride infusion
- **C.** replace the external ventricular drain output with 0.9% sodium chloride
- **D.** restrict fluid intake to 800 mL/m^2/day

Hyponatremia in the pediatric trauma patient is common and can be caused by multiple factors. The patient in this vignette is seen with traumatic brain injury (TBI) and is hyponatremic owing to syndrome of inappropriate antidiuretic hormone secretion (SIADH). Patients with TBI and hyponatremia (serum sodium <135 mM) are at risk of experiencing increased morbidity and mortality through development of complications such as seizures and increased intracranial pressure. These patients often require frequent monitoring of

serum sodium to minimize complications. Although recognizing abnormally low serum sodium levels is important, other information is necessary to identify the cause and optimize therapy. This is especially true in patients with acute brain injury because of the potential of developing hyponatremia owing to different and disparate mechanisms such as SIADH and cerebral salt wasting (CSW).

Antidiuretic hormone (ADH) (ie, arginine vasopressin) is made in the hypothalamus and secreted from the posterior pituitary gland. Its secretion is normally triggered primarily by increased blood hyperosmolality (sensed by osmoreceptors) as well as hypovolemia (sensed by baroreceptors) to increase water retention by the kidneys. ADH binds to vasopressin receptors in the collecting ducts to increase aquaporin channel expression on the lumenal side of the collecting duct cells. ADH has additional arterial vasoconstricting effects by binding to vascular smooth muscle vasopressin receptors. SIADH can occur for a variety of reasons, including infection (particularly pneumonia), cancer, brain injury, drugs (eg, drugs of abuse, chemotherapy, and antiepileptic medications), and genetic causes. SIADH leads to inappropriate water retention, which leads to euvolemic (or hypervolemic) hyponatremia. Therefore, the mainstay of SIADH treatment is identifying and stopping the cause and fluid restriction. If hyponatremia persists despite fluid restriction (or if restriction is contraindicated), then additional treatment includes sodium supplementation (eg, sodium chloride tablets or high-concentration sodium fluid), furosemide, demeclocycline, and vasopressin receptor antagonists (eg, conivaptan, tolvaptan).

Cerebral salt wasting is a phenomenon that has been described in patients with neurologic injury, most commonly with subarachnoid hemorrhage. However, there is debate on whether CSW is truly a unique entity or the effects of previous treatments (such as unaccounted resuscitation fluids). Two theories regarding the pathophysiology of CSW are increased circulating brain natriuretic peptide and/or a dysfunctional sympathetic nervous system resulting in excessive sodium excretion by the kidneys. Although the presence of CSW is debated, findings of hypovolemic hyponatremia with increased urine sodium and urine output in the presence of brain injury may warrant both sodium and water supplementation.

There are causes of hyponatremia aside from CSW and SIADH; therefore, additional findings and tests are warranted to optimize treatment. Some of the more common causes of hyponatremia in children can be differentiated according to a combination of findings (**Table**).

This patient has SIADH, as suggested by (1) hyponatremia, (2) low serum osmolality, (3) inappropriately elevated urine osmolality, (4) euvolemia (based on his CVP), and (5) low urine output despite adequate blood pressure and a normal serum creatinine level. Therefore, after correcting his hyponatremia acutely with 3% sodium chloride (to minimize

the risk of seizures and elevated ICP), the next step would be to restrict the patient's fluids to minimize the inappropriate resorption of water in the collecting ducts. Although the patient may develop a need for a 3% sodium chloride infusion, starting this infusion without decreasing his "maintenance" fluids may deliver too much water to the patient. Fludrocorisone is a mineralocorticosteroid that is typically used in patients with adrenal insufficiency to supplement deficient aldosterone production. Similar to aldosterone, fludrocortisone stimulates increased sodium reabsorption in the kidneys. Although excessive salt loss (such as from an indwelling drain with high output) could result in sodium loss, there is no evidence of that in this patient.

PREP Pearls

- Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a common cause of hyponatremia in critically ill children and is initially managed by fluid restriction.
- Evaluation for hyponatremia includes measuring serum and urine sodium, creatinine, and osmolality.

ABP Content Specifications(s)/Content Area

- Know how to establish the diagnosis of SIADH and how to differentiate it from cerebral salt wasting, diuretic therapy, and water intoxication
- Recognize the instability of the antidiuretic hormone function after head injury
- Differentiate between SIADH and other causes of increased total body water

Suggested Readings

Driano JE, Lteif AN, Creo AL. Vasopressin-dependent disorders: what is new in children? *Pediatrics.* 2021;147(5):e2020022848. doi:10.1542/peds.2020-022848

von Bismarck P, Ankermann T, Eggert P, Claviez A, Fritsch MJ, Krause MF. Diagnosis and management of cerebral salt wasting (CSW) in children: the role of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). *Childs Nerv Syst.* 2006;22(10):1275-1281. doi:10.1007/s00381-006-0091-x

Table. Common Causes of Hyponatremia in Children.

Etiology	Volume status	Serum osmolality	Urine sodium	Urine osmolality	Urine specific gravity	Urine output	Other findings
SIADH	= / ↑	↓	↑	↑	↑	↓	Presence of inciting events (cancer, infection, brain injury, drugs, etc.)
CSW	↓	↓	↑	↑	↑	↑	Brain injury
Congestive heart failure	↑	↓	↓	↑	= / ↑	↓	Gallop; poor perfusion
Cirrhosis	↑	= / ↓	↓	↑	= / ↑	↓	Evidence of liver injury/failure; ascites; jaundice
Adrenal insufficiency	↓	↓	↑	↑	↑	Variable	Risk factors for adrenal insufficiency; hypotension (if uncontrolled)
Primary polydipsia	= / ↑	↓	↓	↓	↓	↑	History of inappropriately excess water; incorrect mixing of formula
GI losses or poor intake	= / ↓	↓	↓	↓	↑	= / ↓	History of poor feeding, diarrhea, or vomiting
Renal failure	↑	↑	↑	↑	= / ↑	↓	Elevated blood urea nitrogen and serum creatinine levels

Abbreviations: CSW, cerebral salt wasting; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Courtesy of F. Lam

December

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 4

A 14-year-old adolescent girl with neuromuscular scoliosis undergoes a posterior spinal fusion from T7 to the sacrum. The procedure is uneventful overall. The patient loses an estimated 500 mL of blood, which is appropriately replaced with packed red blood cells that she had previously donated for the procedure. The patient tolerates anesthesia well and is hemodynamically stable. For pain control after the procedure, the anesthesiologist places an epidural catheter with bupivacaine in addition to prescribing a patient-controlled analgesia pump with hydromorphone. Shortly after arriving at the pediatric ICU, the patient requires a new peripheral intravenous line; owing to the girl's fear of needles, the patient's mother requests 4% lidocaine cream, which is applied. Approximately 1 hour later, the patient develops somnolence, bradycardia, and hypotension and then has a generalized tonic-clonic seizure.

Of the following, the BEST medication with which to begin treatment immediately is

- **A.** amiodarone
- **B.** ceftriaxone
- **C.** lipid emulsion
- **D.** naloxone

The patient is experiencing local anesthetic systemic toxicity (LAST). The patient is at risk of experiencing LAST owing to the bupivacaine in her epidural catheter in combination with the topical lidocaine applied for peripheral intravenous placement. Clinicians need to be aware of the possible adverse effects of the medications in a patient's epidural, because these medications may have systemic effects (local anesthetics and clonidine, for example).

LAST is a rare but serious complication of local anesthetic administration, and its recognition is especially important given the increase in use of local anesthetics as part of multimodal pain control, including the use of lidocaine infusions. LAST has both central nervous system and cardiovascular manifestations. Central nervous system toxicity can include numbness, visual changes, somnolence, and eventually seizures. Cardiovascular toxicity can include arrhythmias and myocardial depression. Patients displaying these symptoms should be treated with a 20% lipid emulsion at a dose of 1.5 to 2 mL/kg in addition to supportive care such as seizure abortives, airway management, arrhythmia management, and blood pressure support. The exact mechanism of lipid emulsion is unclear, and the proposed mechanism has changed over time; however, it may help to shunt the local anesthetic away from the central nervous system and cardiovascular systems.

Although the patient is at risk of developing infection given her recent procedures, ceftriaxone would not reverse these acute postoperative effects. Amiodarone may be used to treat a ventricular arrhythmia, which could happen in these patients but has not occurred in this case. Finally, although the patient is also at risk of experiencing opioid toxicity—which may cause somnolence, bradycardia, and hypotension—it would be unlikely to cause a seizure; thus, administration of naloxone is not indicated.

PREP Pearls

- Clinicians should be aware of local anesthetic systemic toxicity signs and symptoms, including cardiovascular and central nervous system effects.
- Patients who display signs of central nervous system or cardiovascular toxicity should receive 20% lipid emulsion.

ABP Content Specifications(s)/Content Area

- Recognize the side effects of local anesthetics
- Describe the toxidrome of local anesthetic toxicity
- Describe the treatment for local anesthetic toxicity

Suggested Readings

Hoegberg LCG, Bania TC, Lavergne V, et al; Lipid Emulsion Workgroup. Systematic review of the effect of intravenous lipid emulsion therapy for local anesthetic toxicity. *Clin Toxicol (Phila)*. 2016;54(3):167-193. doi:10.3109/15563650.2015.1121270

Neal JM, Barrington MJ, Fettiplace MR, et al. The Third American Society of Regional Anesthesia and Pain Medicine practice advisory on local anesthetic systemic toxicity: Executive summary 2017. *Reg Anesth Pain Med.* 2018;43(2):113-123. doi:10.1097/AAP.0000000000000720

Neal JM, Neal EJ, Weinberg GL. American Society of Regional Anesthesia and Pain Medicine local anesthetic systemic toxicity checklist: 2020 version. *Reg Anesth Pain Med.* 2021;46(1):81-82. doi:10.1136/rapm-2020-101986

December

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 5

A 16-year-old adolescent boy with Duchenne muscular dystrophy is admitted to the pediatric ICU for treatment of pneumonia. His bilevel positive airway pressure requirements at baseline were an inspired positive airway pressure of 16 cm water and an expiratory positive airway pressure of 5 cm water / FiO_2 0.21. Now these requirements have increased to an inspired positive airway pressure of 20 cm water and an expiratory positive airway pressure of 10 cm water / FiO_2 0.7. The patient states that he is becoming increasingly tired and is requesting intubation. After intubation, the trainee asks why a nondepolarizing agent was used as the neuromuscular blocking agent.

Of the following, the MOST likely reason for use of a nondepolarizing agent was to minimize the risk of

- **A.** cardiac arrhythmias
- **B.** prolonged apnea
- **C.** seizures
- **D.** sialorrhea

Neuromuscular blockade (NMB) is an important aspect of endotracheal intubation, because it allows the laryngoscopist to open the mouth and position the head and neck for optimal visualization of the glottis. Furthermore, use of neuromuscular blocking agents relaxes the vocal cords into their open position and prevents laryngospasm due to irritation of the airway during intubation. The two main classes of NMB agents are depolarizing and nondepolarizing. The only depolarizing NMB agent in clinical use is succinylcholine.

Nondepolarizing NMB agents include (cis)atracurium, pancuronium, rocuronium, and vecuronium. Both classes of NMB agents induce skeletal muscle paralysis through the nicotinic acetylcholine (ACh) receptor on the motor end plate of skeletal muscles. However, depolarizing NMB agents are ACh receptor agonists, whereas nondepolarizing NMB agents are ACh antagonists.

Depolarizing NMB agents (succinylcholine) competitively bind to and activate ACh receptors to cause initial depolarization by opening voltage-gated sodium channels. As opposed to normal muscle activation with ACh, succinylcholine is not hydrolyzed by acetylcholinesterase. Therefore, succinylcholine remains bound to the ACh receptor and prevents a new action potential from being initiated. This leads to flaccid paralysis after the depolarization (fasciculation) phase of succinylcholine. Eventually, succinylcholine dissociates from the ACh receptor into plasma and is hydrolyzed by plasma cholinesterase.

Succinylcholine is an NMB agent with some useful attributes but many adverse effects and contraindications. The main benefit of succinylcholine is its rapid onset (usually within 30-60 seconds) and short duration (usually less than 5 minutes in patients without renal or muscular disease). Because of this, it may be a useful NMB agent (in patients without contraindications) for rapid sequence intubation, difficult airways, or for management of severe laryngospasm. However, it has a number of adverse effects and contraindications that make use of this medication less favorable. Because succinylcholine activates ACh receptors, fasciculations and muscle pain or spasm may occur. This can be mitigated by premedication with a small dose (typically ~1/10th of the usual dose) of a nondepolarizing NMB agent (sometimes termed a defasciculating dose). Succinylcholine may also induce bradycardia owing to direct activation of the muscarinic ACh receptor in the sinoatrial node (in addition to its primary effect on nicotinic receptors). Bradycardia can be prevented or blunted with anticholinergic medications, such as atropine or glycopyrrolate. More serious adverse effects include rhabdomyolysis, hyperkalemia, and malignant hyperthermia. The risk of these serious adverse effects is increased in patients with muscle injury (crush/burn injury and muscular disorders). Although transient hyperkalemia may occur in healthy patients receiving succinylcholine, life-threatening hyperkalemia leading to cardiac arrhythmias are more likely to occur in patients with significant muscle injury or abnormalities. Therefore, succinylcholine is contraindicated in patients with known or suspected muscular dystrophy. There is no reversal agent or antidote for succinylcholine. The FDA has assigned a black box warning regarding use of succinylcholine in infants and children.

Nondepolarizing NMB agents competitively block ACh receptors to prevent activation by ACh in the postsynaptic junction. Because nondepolarizing NMB agents are competing with ACh to bind to and block the ACh receptor, onset of NMB tends to be slower and duration of NMB longer than with succinylcholine.

Nondepolarizing NMB agents have a wider therapeutic index and are more widely used than succinylcholine. Most of the nondepolarizing NMB agents are excreted via the urine and bile except for atracurium and cisatracurium, which are eliminated via Hoffman degradation and ester hydrolysis in plasma. Of the available agents, pancuronium has the highest likelihood of causing tachycardia because of its vagolytic effects. As opposed to succinylcholine, nondepolarizing NMB agents can be reversed by using acetylcholinesterase inhibitors, such as neostigmine, which increase the amount of ACh at the motor end plate to competitively bind to and activate the ACh receptor. Of note, neostigmine can cause bradycardia owing to the increased ACh activating muscarinic ACh receptors in the heart and increasing vagal tone. Premedication or treatment with atropine or glycopyrrolate can minimize bradycardia. Sugammadex is a recently developed specific reversal agent for rocuronium and vecuronium. Although studies show that it is more effective than neostigmine in restoring muscle activity, its use is limited to reversing rocuronium and vecuronium, and its cost is significantly higher than that of neostigmine.

In this patient with Duchenne muscular dystrophy, the use of a depolarizing NMB agent—ie, succinylcholine—may increase the risk of significant hyperkalemia owing to fasciculation of damaged muscles. This hyperkalemia, in turn, may lead to cardiac arrhythmias. The risk of prolonged apnea, seizures, or sialorrhea would not be increased with use of succinylcholine as compared with use of nondepolarizing NMB agents.

PREP Pearls

- Succinylcholine is contraindicated for use in patients with suspected or known muscular dystrophies.
- There are no reversal agents for succinylcholine.
- Nondepolarizing neuromuscular agents can be reversed with neostigmine.

ABP Content Specifications(s)/Content Area

- Discriminate between depolarizing and nondepolarizing neuromuscular blocking agents
- Identify the adverse effects of succinylcholine
- Recall the mechanism of action of neuromuscular blocking agents

Suggested Readings

Appiah-Ankam J, Hunter JM. Pharmacology of neuromuscular blocking drugs. *Contin Educ Anesthesia Crit Care Pain.* 2004;4(1):2-7. doi:10.1093/bjaceaccp/mkh002

Birnkrant DJ, Panitch HB, Benditt JO, et al. American College of Chest Physicians consensus statement on the respiratory and related management of patients with Duchenne muscular

dystrophy undergoing anesthesia or sedation. *Chest.* 2007;132(6):1977-1986. doi:10.1378/chest.07-0458

December

✓ **CONGRATULATIONS**

THIS ASSESSMENT IS NOW COMPLETE.

Question: 6

A 5-year-old girl (weight 20 kg, height 100 cm) is admitted to the pediatric intensive care unit (PICU) after being found facedown in a backyard swimming pool. She required 15 minutes of cardiopulmonary resuscitation before return of spontaneous circulation. She is on mechanical ventilation and has a central venous line, an arterial line, and a Foley catheter in place. Despite maintenance of her blood pressure above 90/40 mm Hg since PICU admission 28 hours ago, her urine output has declined and has averaged 0.2 mL/kg/h over the past 24 hours. She continues to receive an epinephrine infusion at 0.1 μg/kg/min. Her initial creatinine concentration in the emergency department was 0.5 mg/dL and is now 2.1 mg/dL.

Of the following, the BEST classification of this patient's acute kidney injury according to the Pediatric Risk, Injury, Failure, Loss, End-stage renal disease (pRIFLE) criteria is

- **A.** failure
- **B.** injury
- **C.** loss
- **D.** risk

This patient's creatinine level has more than quadrupled since admission, indicating that the estimated creatinine clearance (eCCl) has declined by more than 75% (to less than 25% of baseline). There has been a concomitant reduction in urine output to less than 0.3 mL/kg/h for 24 hours. A decline in estimated creatinine clearance by 75% (or below 35 mL per 1.73 m2) and urine output less than 0.3 mL/kg/h for 24 hours meet the definition of renal failure under the Pediatric Risk, Injury, Failure, Loss, End-stage renal disease (pRIFLE) criteria.

The consensus definition of acute kidney injury (AKI) in adults was established in 2004 as a rise in creatinine level of 50% or more from its baseline value and/or a fall in the eCCl or estimated glomerular filtration rate (eGFR) by 25% or more, and/or a decrease in urine output below 0.5 mL/kg/h for 6 hours or more. The pediatric classification (pRIFLE) is also based on similar criteria and stages AKI according to the decrease in eGFR, increase in creatinine level, or decrease in urine output. If an actual baseline eGFR is not available, a previously normal GFR of 100 mL/min per 1.73 m^2 can be assumed to be the starting point for calculation, given that children have an extremely low probability of having undiagnosed chronic kidney disease. The revised Schwartz equation can be used to calculate the eGFR as follows:

$$\text{eGFR (mL/min per 1.73 mL/m}^2\text{)} = \frac{0.413 \times \text{length or height (in cm)}}{\text{Serum creatinine (mg/dL)}}$$

With this information, pediatric AKI can then be defined as risk, injury, failure, or loss. These are defined as follows:

- Risk: Decline in eGFR by 25% or urine output less than 0.5 mL/kg/h for 8 hours
- Injury: Decline in eGFR by 50% or urine output less than 0.5 mL/kg/h for 16 hours
- Failure: Decline in eGFR by 75% or urine output less than 0.3 mL/kg/h for 24 hours or anuria for 12 hours
- Loss: Persistent failure more than 4 weeks
- End-stage renal disease: Persistent failure more than 3 months

For the patient in the vignette, using the revised Schwartz equation would yield the initial estimated creatinine clearance of 82.6 mL/min per 1.73 ml/m^2 and the 24-hour follow-up reading of 19.6 mL/min per 1.73 mL/m^2. However, the eGFR can also be roughly estimated without any formal calculation because an increase in creatinine by 2 times implies a reduction in eGFR by 50%, and an increase to more than 4 times further reduction by >25%. Thus, the patient fits the definition of renal failure.

In the Assessment of Worldwide Acute Kidney Injury, Renal Angina, and Epidemiology (AWARE) study, Kaddourah and colleagues found that the development of severe AKI (plasma creatinine level 2 times or more the baseline level or urine output less than 0.5 mL per kilogram of body weight per hour for 12 hours or more) within the first 7 days of hospitalization is associated with increased use of mechanical ventilation and renal-replacement therapy, as well as risk of death. Kidney injury occurred in 26.9% of 4,283 patients in this study and was categorized as severe in 11.6% of patients.

Some centers may use other classifications for AKI such as the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. Comparative studies have shown some differences in AKI incidence and staging (A crosswalk between pRIFLE and KDIGO is shown in the **Table**); however, regardless of the definition used, occurrence of AKI is associated with greater mortality and LOS in the ICU and greater LOS outside the ICU. Thus, prevention and early detection remain crucial for optimal management of AKI. Initial supportive care includes optimization of volume status, maintaining an adequate blood pressure, avoidance of nephrotoxic agents (eg, aminoglycoside, vancomycin, nonsteroidal antiinflammatory drugs), and nutritional support. Exogenous potassium administration should be avoided and serum chemistry and acid-base status closely monitored. Once normal intravascular volume is restored, fluid intake should be limited to insensible losses (400 mL/m^2/d) plus urine output and any extrarenal losses. Diuretics should be considered for hypervolemic patients once hemodynamics are stable. Because there is an association between the degree of fluid overload and patient outcomes, interventions such as continuous renal replacement therapy should be considered when the degree of fluid overload reaches 10% to 20% of body weight.

PREP Pearls

- Both estimated glomerular filtration rate and urine output can be used to stage acute kidney injury under the pRIFLE (Pediatric Risk, Injury, Failure, Loss, End-stage renal disease) criteria.
- In a patient with acute kidney injury, continuous renal replacement therapy should be considered when the degree of fluid overload reaches 10% to 20% of body weight.

ABP Content Specifications(s)/Content Area

- Know the life-threatening complications of acute kidney injury
- Understand that creatinine and urine output are used in categorizing renal function according to RIFLE criteria
- Plan fluid management for a patient with renal failure

Suggested Readings

Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL. Epidemiology of acute kidney injury in critically ill children and young adults. *N Engl J Med.* 2017;376(1):11-20. doi:10.1056/NEJMoa1611391

Selewski DT, Goldstein SL. The role of fluid overload in the prediction of outcome in acute kidney injury. *Pediatr Nephrol.* 2018;33(1):13-24. doi:10.1007/s00467-016-3539-6

Soler YA, Nieves-Plaza M, Prieto M, García-De Jesús R, Suárez-Rivera M. Pediatric risk, injury, failure, loss, end-stage renal disease score identifies acute kidney injury and predicts

mortality in critically ill children: a prospective study. *Pediatr Crit Care Med.* 2013;14(4):e189-e195. doi:10.1097/PCC.0b013e3182745675

Sutherland SM, Byrnes JJ, Kothari M, et al. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. *Clin J Am Soc Nephrol.* 2015;10(4):554-561. doi:10.2215/CJN.01900214

Table. Crosswalk Between Pediatric Modified RIFLE (pRIFLE) Criteria and Kidney Disease: Improving Global Outcomes (KDIGO) Criteria for Diagnosis and Classification of Acute Kidney Injury in Children.

Classification		Creatinine Clearance (eCCr) or Serum Creatinine (Scr)		Urine Output	
pRIFLE	**KDIGO**	**pRIFLE criteria**	**KDIGO criteria**	**pRIFLE criteria**	**KDIGO criteria**
Risk	Stage 1	eCCr Decrease by 25%	Increase in SCr by 1.5-1.9 times baseline; OR Increase in SCr by >0.3 mg/dL (>26.5 mol/L);	<0.5 mL/kg/h for >8 h	<0.5 mL/kg/h for 6-12 h
Injury	Stage 2	eCCr Decrease by 50%	Increase in SCr by 2.0-2.9 times baseline	<0.5 mL/kg/h for >16 h	<0.5 mL/kg/h for >12 h
Failure	Stage 3	eCCr Decrease by 75% OR eCCr <35 mL/min/1.73 m^2	Increase in SCr by 3.0 times baseline OR eGFR <35 mL/min/1.73 m^2	<0.3 mL/kg/h for >12 h; OR anuria for >12 h	<0.3 mL/kg/h for >24 h; OR Anuria for >12 h
Loss: Persistent failure for >4 wk	Equivalent stage not defined	Meets "Failure" criteria for >4 wk	No equivalent staging criteria	Meets "Failure" criteria for >4 wk	No equivalent staging criteria
End Stage: Persistent failure for >3 mo	Equivalent stage not defined	Meets "Failure" criteria for >3 mo	No equivalent staging criteria	Meets "Failure" criteria for >3 mo	No equivalent staging criteria

Courtesy of M. Mathur