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A 3,800-g infant is born to a primiparous woman following a vertex vaginal delivery at 37 weeks of estimated gestational age. The obstetric history is significant for trapping of the fetal head in the maternal pelvis. The delivery is assisted with mid-forceps and vacuum extraction. On the second day after birth, the infant has an enlarging, fluctuant mass with bruised skin on the posterior aspect of the head.

Of the following, the MOST likely cause of the mass in this infant is:

1. caput succedaneum

2. cephalhematoma

3. epidural hemorrhage

4. subarachnoid hemorrhage

5. subgaleal hemorrhage

You selected **2**, the correct answer is **5**.

The clinical circumstances surrounding the birth of the large infant to the primiparous woman described in the vignette are conducive to birth trauma. Cranial hemorrhage due to birth trauma varies in location, progression, and clinical manifestations. The hemorrhage is classified as extracranial or intracranial based on the affected tissue plane between the skin and the brain. The extracranial hemorrhage includes caput succedaneum, cephalhematoma, and subgaleal hemorrhage . The intracranial hemorrhage includes epidural hemorrhage subdural hematoma , and subarachnoid hemorrhage. The infant described in the vignette has clinical features that are consistent with the diagnosis of subgaleal hemorrhage.

Subgaleal hemorrhage refers to hemorrhage beneath the aponeurosis covering the scalp and connecting the frontal and occipital components of the occipito-frontalis muscle. Blood may spread beneath the entire scalp and into the subcutaneous tissue of the posterior neck. A subgaleal hematoma typically presents as a firm, fluctuant mass that initially increases in size after birth and resolves over 2 to 3 weeks. The hemorrhage is associated with vacuum extraction and is attributed to linear skull fracture, suture diastasis, or parietal bone fragmentation that often accompanies the hemorrhage. Management includes observation of the infant for blood loss, consumption coagulopathy, and hyperbilirubinemia.

Caput succedaneum refers to hemorrhagic edema of the skin and the subcutaneous tissue covering the presenting part of the head during vaginal delivery. The swelling is soft and pitting, crosses suture lines, and resolves without an initial increase in size over the first few days after birth. Blood loss and consumption coagulopathy are rare. Management involves expectant observation and monitoring of the infant for hyperbilirubinemia.

Cephalhematoma refers to hemorrhage in the plane between the bone and the periosteum on the outer surface of the skull. A cephalhematoma typically presents as a well-circumscribed, firm mass overlying the skull and confined by cranial sutures. The mass usually increases in size after birth before resolving over a few weeks. Calcification within the hematoma may result in a hard skull protuberance that may require months of skull growth and remodeling for resolution. Most cephalhematomas are unilateral and located over the parietal bone. The

hemorrhage is associated with forceps extraction and is attributed to shearing forces that separate the periosteum from the bone. An underlying linear skull fracture is detected in 10% to 25% of cases of cephalhematoma. No specific treatment is indicated other than observation and monitoring of the infant for blood loss, consumption coagulopathy, and hyperbilirubinemia. Rarely, a cephalhematoma may become infected, resulting in meningitis or osteomyelitis, which warrants treatment.

Epidural hemorrhage refers to hemorrhage in the plane between the bone and the periosteum on the inner surface of the skull. It represents the intracranial analog of a cephalhematoma, which is a frequent accompaniment. An epidural hematoma is not clinically evident as a mass because of its intracranial location. However, symptoms and signs of increased intracranial pressure, such as a bulging anterior fontanelle, may develop within the first few hours after birth. Seizures are common. Signs of uncal herniation, such as a fixed and dilated pupil on the ipsilateral side, may occur. The diagnosis is confirmed by demonstration of a convex, lentiform lesion on computed tomography. When accompanied by a linear skull fracture with overriding of the fracture segments, the epidural hemorrhage is attributed to tearing of branches of the middle meningeal artery or a large venous sinus. Although the hemorrhage most often resolves spontaneously, surgical evacuation may become necessary with the development of increased intracranial pressure or compression of the underlying brain. Medical management includes observation and monitoring of the infant for blood loss, consumption coagulopathy, and hyperbilirubinemia.

Subarachnoid hemorrhage refers to hemorrhage within the subarachnoid space between the arachnoid mater and the pia mater. It is termed primary subarachnoid hemorrhage when the hemorrhage is not due to extension from a subdural, intraparenchymal, or intraventricular hemorrhage. Moreover, the primary designation excludes subarachnoid blood resulting from a structural vascular lesion, such as an aneurysm or an arteriovenous malformation, tumor, coagulopathy, or hemorrhagic infarction. The clinical manifestations of primary subarachnoid hemorrhage are determined by the extent of the hemorrhage. In most cases that involve minor degrees of hemorrhage, infants exhibit minimal or no symptoms and signs. With moderate degrees of hemorrhage, infants have seizures that typically manifest on the second day after birth. These infants appear well and healthy in the interictal period. In rare cases of massive hemorrhage, the infants experience a catastrophic deterioration in clinical status and a rapidly fatal course. The suspicion of subarachnoid hemorrhage is raised by the findings of an elevated erythrocyte count and an elevated protein concentration in the cerebrospinal fluid. The diagnosis is confirmed by demonstration of increased attenuation located most prominently over the cerebral convexities and in the posterior fossa. The source of bleeding in primary subarachnoid hemorrhage is believed to be vascular channels derived from the involuting anastomoses between leptomeningeal arteries or bridging veins within the subarachnoid space. No specific treatment is indicated in most cases, especially those that have minor degrees of hemorrhage. In others, the treatment includes control of symptoms, such as seizures; monitoring for blood loss, consumption coagulopathy, and hyperbilirubinemia; and treatment of complications, such as posthemorrhagic hydrocephalus.

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Content Specifications:

Understand the pathogenesis, clinical and radiographic features, diagnosis, management, and outcome associated with subarachnoid hemorrhage

Understand the diagnosis, clinical and radiographic features of extracranial hemorrhage, including cephalhematoma and subgaleal hemorrhage

Understand the management and outcomes of extracranial hemorrhage, including cephalhematoma and subgaleal hemorrhage

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You are asked to see a 10-day-old male term large-for-gestational age infant of a diabetic mother. Delivery was complicated by shoulder dystocia and perinatal depression, with Apgar scores of 1 and 6 at 1 and 5 minutes, respectively. The infant's early clinical course was complicated by respiratory failure, hypotension, hypoglycemia, and anuria. These problems have been resolved. The infant presents now with continuing indirect hyperbilirubinemia despite phototherapy. He also has persistent hypertension at rest, with systolic blood pressures of 110 to 120 mm Hg. Direct Coombs test result is negative, and there is no evidence of hemolysis. White blood cell and platelet counts are normal. Hematocrit is 32% (0.32). Urinalysis findings are normal. Results of abdominal examination are normal. Abdominal ultrasonography, obtained to evaluate the hypertension, reveals a right suprarenal complex mass measuring 3x3 cm (Figure).

Of the following, the MOST likely diagnosis is

1. adrenal hemorrhage

2. horseshoe kidney

3. neuroblastoma

4. renal vein thrombosis

5. Wilms tumor

You selected **5**, the correct answer is **1**.

Adrenal hemorrhage has been found in 10% of infants at autopsy and is diagnosed in 2 per 1,000 live births. In most instances, it is found incidentally by noting adrenal calcifications on radiographic studies for other indications. The neonatal adrenal gland is predisposed to hemorrhage and trauma by virtue of its increased size and vascularity compared with adults. Risk factors for hemorrhage include birth trauma, macrosomia, breech delivery, infection, dystocia, hemorrhagic disorders, and asphyxia. In most cases, bleeding is unilateral and generally right sided (70%). In 5% to 8% of cases, it presents as severe bilateral bleeding. Ipsilateral renal vein thrombosis may occur with adrenal hemorrhage on the left because the left adrenal vein is a tributary of the left renal vein. Thrombus then may be propagated from one vessel to the other. Symptoms are related to the size and severity of bleeding, with most infants remaining asymptomatic. With larger hemorrhages, the infant may have unexplained persistent jaundice (11%), hypertension, and mild anemia. Classic symptoms with more extensive hemorrhage include fever, tachypnea, pallor, hypotensive shock, flank mass, poor feeding, hypoglycemia, coma, and seizures. If peritoneal extension occurs, a scrotal hematoma may be seen in males. Radiologic evaluation confirms the diagnosis. Mass displacement of the stomach and intestine may be seen on plain radiograph. Ultrasonography can document evolution of the hemorrhage from a solid hyperechoic clot to central liquefaction necrosis followed by cystlike anechoic fibrosis and calcification. Calcifications along the walls of the hemorrhage begin as early as 12 days after the insult, gradually increasing and contracting as the hemorrhage is absorbed. If the diagnosis is in question, serial ultrasonography over several weeks can document these changes and distinguish adrenal hemorrhage from other solid tumors. Magnetic resonance imaging (MRI) and radionuclide renal scans also may help differentiate atypical adrenal hemorrhages from renal lesions. Treatment is supportive, with volume replacement in severe hemorrhage. Surgery is indicated only rarely unless blood loss is severe and uncontrolled or peritoneal blood is present. Adrenocorticotropic hormone stimulation testing is recommended to evaluate adrenal function and cortisol response. The infant described in the vignette had multiple risk factors for adrenal hemorrhage at birth and demonstrates mild

symptoms with jaundice and hypertension. Additionally, the characteristics on ultrasonography are consistent with this diagnosis, showing central clot and surrounding liquefaction. No calcifications are seen yet.

Horseshoe kidney, ectopic kidney, and fused kidneys are abnormalities in the position of the kidney that typically are asymptomatic and have no long-term consequences unless they are associated with other anomalies. Horseshoe kidney occurs in 1 in 500 births, more frequently in Turner syndrome. It is the most typical type of renal fusion and one of the most common renal anomalies. Coexisting urinary tract anomalies must be ruled out. Ultrasonographic diagnosis shows the renal parenchyma in the abnormal location, lower than normal in the lumbar area, and often with abnormal associated vascular supply. Renal scan, intravenous pyelography, and MRI are adjunctive diagnostic studies that can be undertaken when the anatomy is in question. This patient's symptoms and ultrasonographic findings are not consistent with horseshoe kidney.

Neuroblastoma is the most common malignant tumor in neonates, with 20% presenting before 6 months of age. The tumor arises from neural crest cells, which migrate to form the adrenal medulla and sympathetic ganglia. Therefore, the tumor may be anywhere, but the primary locus in most cases is in the abdomen. Metastatic lesions may be a presenting feature, with spread to liver and skin most common. Other sites include bone marrow, bone, lung, and central nervous system. Neonatal neuroblastoma presents most commonly as liver enlargement alone (65%) followed by subcutaneous metastases (32%). Clinical symptoms include diarrhea, hypertension, tachycardia, myoclonus-opsoclonus, respiratory distress, jaundice, anemia, or symptoms related to the site of metastases. Urinary catecholamine levels are elevated. Approximately 95% of affected patients have increased urinary excretion of homovanillic acid and vanillylmandelic acid. Bone marrow biopsy and/or biopsy of the primary tumor confirm the diagnosis. The history for this infant and his normal liver size and lack of metastatic disease make neuroblastoma less likely.

Renal vein thrombosis is decreasing in incidence, probably due to better obstetric management. Approximately 60% to 75% of affected patients are infants younger than 1 month of age. Clots start in the small intrarenal veins after injury and are propagated distally toward the main renal vein and ultimately the inferior vena cava. Risk factors include dehydration, hyperviscocity, asphyxia, hypercoagulable states, diabetes, and indwelling catheters. The classic triad of symptoms is flank mass, hematuria, and thrombocytopenia, although they rarely are seen in the neonate. Hypotension may occur early in the course, with hypertension developing days or weeks later. The diagnosis is confirmed by ultrasonography and Doppler blood flow studies that show nephromegaly and thrombus. Radionuclide uptake on renal scan may be diminished or absent. Normal urinalysis results and platelet count in addition to the ultrasonographic findings make renal vein thrombosis unlikely in the infant described in the vignette.

Wilms tumor is the most common intra-abdominal tumor of childhood, but it rarely presents before 1 month of age; 80% of patients are diagnosed between 1 and 5 years of age. Generally, the initial presentation is an abdominal mass or enlargement. Extrarenal Wilms tumors are very rare and are believed to be associated with displaced metanephric tissue. Fifteen percent of Wilms tumors are associated with other anomalies or syndromes, and genes on the 11th and 16th chromosomes have been implicated. Approximately 5% to 10% of cases may be bilateral. Microscopic hematuria may be seen. Hypertension, sometimes seen in older infants and children, has not been found in neonates. On ultrasonography, the tumor appears as a smooth, well-delineated mass of uniform texture. Hemorrhage within the tumor is uncommon. This patient's age and history, hypertensive symptoms, and nature and location of the mass above the kidney make Wilms tumor unlikely.

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Content Specifications

Know the etiology, clinical and laboratory features, and treatment of abdominal masses in the neonate.

Know the laboratory and radiographic features, the differential diagnosis, and the management of abdominal masses in the neonate

Recognize the clinical and laboratory features of neuroblastoma in the newborn

Recognize the clinical and laboratory features of Wilms tumor in the newborn

Know the etiology, clinical manifestations, laboratory features and management of renal vein thrombosis
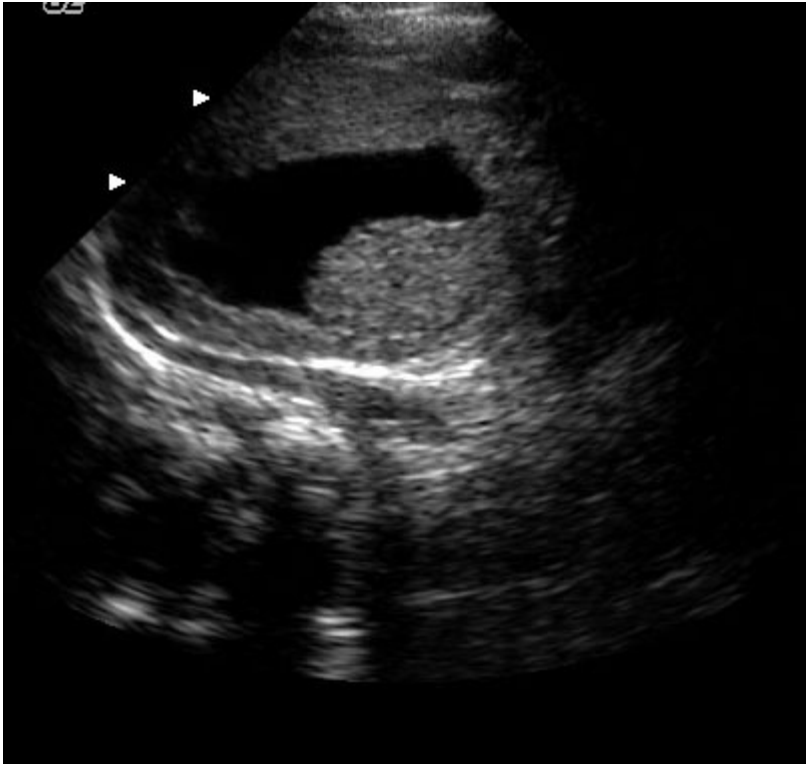
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You have been asked to attend the term delivery following an uncomplicated prenatal course because the fetal heart rate (FHR) monitor tracing began to show late decelerations of 10-12 beats per minute in association with the contractions. The fetal heart rate between contractions is 146 beats per minute and the beat-to-beat variability is 5 to 10 beats per minute. The obstetrician has raised the possibility of cesarean delivery to avert fetal neurologic damage and has introduced you to the mother. The mother asks you if there is a chance that her child will not have cerebral palsy.

Of the following, the false-positive rate of this FHR tracing in predicting cerebral palsy is CLOSEST to:

1	19%
2	39%
3	59%
☒ 4	79%
5	99%

You selected 4, the correct answer is 5.

Fetal heart rate (FHR) monitoring is nearly universal. Randomized, controlled studies have not shown consistent benefit of FHR monitoring in terms of reducing infant mortality or the long-term risk of cerebral palsy among women who have no identified antepartum risk factors. In addition, the increase in cesarean delivery has been attributed in part to routine FHR monitoring. For the infant described in the vignette whose FHR pattern is late decelerations with normal baseline variability (reflex late decelerations), the false-positive rate of FHR monitoring for predicting long-term cerebral palsy is closest to 99%.

The following FHR patterns are consistent with hypoxia and indicative of current or impending fetal asphyxia severe enough to place the fetus at risk for neurologic (or other organ) damage and/or death:

- Late decelerations with absent variability
- Variable decelerations with absent variability
- Sustained bradycardia with absent variability

FHR interpretation is plagued with problems that currently are being investigated. Among these are: 1) interobserver reliability in pattern identification, 2) validity of association(s) between specific FHR patterns and adverse neonatal outcomes, and 3) existence of a causal relationship between specific FHR patterns and neonatal outcome. The causal relationship must be linked to the ability to prevent damage by therapeutic intervention. For example, a meta-analysis of studies of FHR monitoring showed a reduction in neonatal seizures (relative risk, 0.5) among monitored neonates, but there was no association with long-term outcome.

Persistent late decelerations with normal FHR variability (called reflex late decelerations), such as seen in this vignette, may be tolerated by the infant. However, the mother should be evaluated (and treated if needed) for abnormal blood pressure (especially hypotension), strength of uterine contractions, hypovolemia, or supine hypotension. Deterioration to nonreflex late decelerations is manifested by deepening of the decelerations and reduction or loss of baseline

variability with continued late decelerations. Unless fetal well-being can be assessed by fetal scalp sampling, expedient (usually operative) delivery is recommended.

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Content Specification

Understand the significance, interpretation, and management of late fetal heart rate decelerations in labor

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A 6-week-old infant, whose birthweight was 680 g and estimated gestational age at birth was 25 weeks, requires ventilator support and supplemental oxygen at a concentration of 65%. The infant is being sustained with parenteral nutrition because of feeding intolerance and received a course of dexamethasone treatment in the preceding week. Other medications include furosemide for chronic diuresis and vancomycin and gentamicin for suspected sepsis. A complete blood count reveals: hemoglobin, 11.2 g/dL (112 g/L); hematocrit, 34% (0.34); erythrocyte count, $3.6x10^6$/mcL ($3.6x10^{12}$/L); platelet count, $252x10^3$/mcL ($252x10^9$/L); and total leukocyte count, $9.6x10^3$/mcL ($9.6x10^9$/L), with a differential count of 48% neutrophils, 1% band forms, 29% lymphocytes, 8% monocytes, and 14% eosinophils.

Of the following, the MOST likely cause of the elevated eosinophil count in this infant is

1 bronchopulmonary dysplasia

☒ 2 drug-induced eosinophilia

3 hypereosinophilic syndrome

4 necrotizing enterocolitis

5 parenteral nutrition

You selected 2, the correct answer is 1.

Eosinophilia is defined as an increase in the absolute number of circulating eosinophils in the blood. In neonates, eosinophilia can be classified as mild (absolute eosinophil count [AEC], 700 to 1,000/mcL [0.7 to $1.0x10^9$/L]), moderate (1,000 to 3,000/mcL [1 to $3x10^9$/L]), or severe (>3,000/mcL [$3x10^9$/L]). The infant described in the vignette has an AEC of 1,344/mcL ($1.344x10^9$/L), reflective of moderate eosinophilia.

The clinical course of the infant suggests bronchopulmonary dysplasia as the most likely cause of the eosinophilia. Although a causal mechanism has not been established, evidence supports an association between eosinophilia and bronchopulmonary dysplasia in neonates. This evidence includes elevations of eosinophil counts in the peripheral blood among neonates who have bronchopulmonary dysplasia, hypersegmented nuclei suggestive of eosinophil activation, elevated concentrations of eosinophilic cationic protein in the serum and tracheal aspirate, and demonstration by immunohistochemical techniques of eosinophilic infiltration in the lung. The postulated mechanism of eosinophil-induced lung injury in bronchopulmonary dysplasia involves the following steps. Eosinophils arise principally from the bone marrow under the influence of three key cytokines: interleukin-3, interleukin-5, and granulocyte-macrophage colony-stimulating factor. These cytokines are produced by CD4+ and CD8+ T lymphocytes from the peripheral blood as well as from the inflamed tissue. The eosinophils migrate to the lungs, a process that includes: a) tethering of the eosinophil to the luminal surface of the vascular endothelium during transport through the blood vessel, b) rolling of the eosinophil along the luminal surface of the activated endothelium, c) firm adhesion of the eosinophil to the endothelial cell, and d) transmigration of the eosinophil through the endothelium into the target tissue. Eosinophils within the lung tissue, activated by cytokines, chemokines, growth factors, and lipid mediators, undergo respiratory burst, with the release of reactive oxygen species, including superoxide. The latter is likely to be one of the mediators of lung injury in bronchopulmonary dysplasia.

Hypersensitivity to drugs is a potential cause of eosinophilia in the neonate. The drugs implicated in the development of eosinophilia include antimicrobials (penicillin, sulfonamide, trimethoprim-sulfamethoxazole, ceftriaxone), anticonvulsants (phenobarbital, phenytoin, carbamazepine), and H2 blockers (cimetidine, ranitidine). Persistent eosinophilia in the neonate has been reported with maternal ingestion of L-tryptophan during pregnancy. Some drugs, such as granulocyte colony-stimulating factor, can induce eosinophilia by specifically promoting the production of eosinophils. The drugs administered to the infant described in the vignette are not associated with eosinophilia.

Hypereosinophilic syndrome is a rare disorder characterized by persistent severe eosinophilia and diffuse organ infiltration by eosinophils. The spectrum of the syndrome varies from a benign condition to a fatal myeloproliferative disorder. Although hypereosinophilic syndrome affects mostly adults between the ages of 20 and 50 years, there are rare instances of affected neonates. The eosinophilia is attributed to an abnormal clonal population of T lymphocytes that secrete interleukin-5, which stimulates uncontrolled production of eosinophils. The most commonly involved organ system is the nervous system, and the resultant manifestations include diffuse encephalopathy, peripheral polyneuropathy, or focal strokelike deficits. Cardiac involvement is common, is attributed to endocardial thickening from the highly toxic eosinophilic major basic protein, and is a major source of morbidity and mortality. Other manifestations of the disorder include diffuse desquamating hyperkeratotic skin rash, hepatomegaly, and generalized lymphadenopathy. The eosinophilia in hypereosinophilic syndrome often is accompanied by other hematologic abnormalities, including anemia, leukocytosis, and thrombocytopenia. The absence of such features and the moderate severity of the eosinophilia make this diagnosis unlikely for the infant in the vignette.

Eosinophils have been associated with inflammation of the gastrointestinal tract, including eosinophilic esophagitis, eosinophilic gastroenteritis, and eosinophilic colitis. Allergy may play a role in this process, as suggested by the greater vulnerability of infants receiving cow's milk relative to those receiving human milk. A change in the infant's diet to casein hydrolysate or a change in the maternal diet to avoid dairy products often induces resolution of symptoms. Other gastrointestinal causes of eosinophilia include inflammatory bowel disease, such as ulcerative colitis, and gastrointestinal parasitic infections. Necrotizing enterocolitis, although common in high-risk, extremely low-birthweight neonates, such as the infant in the vignette, typically is not accompanied by eosinophilia.

Parenteral nutrition is less likely than bronchopulmonary dysplasia to cause eosinophilia in neonates. The mechanism for the development of eosinophilia in relation to specific constituents of the parenteral nutrition solution remains unknown. Transient eosinophilia has been described in association with the anabolic phase of growth in neonates, whether supported by parenteral or enteral nutrition.

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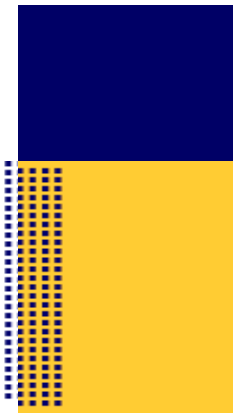
Content Specifications

Understand the distribution and function of eosinophils in the immune response

Recognize the laboratory features of bronchopulmonary dysplasia/chronic lung disease

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Soon after birth, a term infant develops severe respiratory distress requiring assisted mechanical ventilation. Prenatal ultrasonography at 20 weeks' gestation revealed markedly enlarged kidneys, oligohydramnios, and minimal bladder fluid. Postnatal ultrasonography reveals bilaterally enlarged kidneys with diffuse increased echogenicity, but no visible cysts. You suspect the child has autosomal recessive polycystic kidney disease (ARPKD).

Of the following, the MOST common associated anomaly of ARPKD in infants is

1. hepatic fibrosis
2. pancreatic cysts
3. urinary tract infections
4. cerebral aneurysms
5. urolithiasis ✗

You selected 5, the correct answer is 1.

With the advent of widespread prenatal ultrasonography, some cases of suspected autosomal recessive polycystic kidney disease (ARPKD) are detected in utero by the presence of enlarged kidneys and oligohydramnios. Most patients who have ARPKD present during the immediate postnatal period or early infancy. Because there is a wide spectrum of severity at birth, affected infants may exhibit various features, the most common of which is bilateral flank masses. Renal function may be normal or markedly reduced at birth. Other features observed in infants who have ARPKD include hepatic fibrosis, hypertension, and a urinary concentrating defect. Some patients may have adequate renal function for many years; others may require immediate renal replacement therapy. Other signs suggestive of but not exclusive to ARPKD are Potter facies (low-set ears, flattened face, micrognathia), respiratory distress due to pulmonary hypoplasia, and decreased glomerular filtration rate.

Because many other conditions (eg, posterior urethral valves with severe bilateral hydronephrosis) may mimic ARPKD clinically, radiologic evaluation frequently is required to confirm the diagnosis. In patients who have ARPKD, renal ultrasonography typically reveals bilateral renal enlargement, with increased echogenicity. Cysts usually are not visualized in the neonatal period. Intravenous pyelography also demonstrates bilateral renal enlargement as well as delayed excretion and medullary streaking. Computed tomography shows bilateral enlargement with opacification.

Cerebral aneurysms may be seen in patients who have autosomal dominant PKD (ADPKD), but rarely are they present in those who have ARPKD. Similarly, patients who have ADPKD exhibit cysts in other organs, including the pancreas and spleen, but these features are not seen in ARPKD. Although patients who have ARPKD occasionally experience pyuria, urinary tract infections (UTIs) are rare. The presence of a UTI in an infant should prompt evaluation for other congenital renal malformations (eg, posterior urethral valves, vesicoureteral reflux). Urolithiasis is rare in the neonatal period and most likely presents with hematuria but kidneys of normal size.

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Note: The above abstracts are available online, but the articles are available online for subscription or fee only.

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Content Specifications:

Recognize the clinical manifestations of anatomic abnormalities of the urinary tract in infants

Know the recommended supportive and corrective treatment of anatomic abnormalities of the urinary tract in infants

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A 4-week-old boy presents with a 2-week history of vomiting his formula. His mother describes the vomiting as forceful, occurring shortly after each feeding, and containing only formula. Bowel movements have been infrequent. Physical examination reveals a dehydrated infant who is eager to feed.

Of the following, the MOST likely diagnosis is

1. allergic reaction to formula

2. ☒ gastroenteritis

3. gastroesophageal reflux

4. pyloric stenosis

5. small bowel obstruction

You selected **2**, the correct answer is **4**.

After inguinal hernia, pyloric stenosis is the most common condition requiring surgery during the first few months after birth. The cause of the increase in the size of the circular muscle of the pylorus is unknown. The disease occurs in 1 in 500 births and is more common in term than preterm infants. Males are affected four to five times more frequently than females. Pyloric stenosis is congenital, often occurring in members of the same family. The clinical findings can vary, but the typical presentation is nonbilious vomiting beginning between the second and fourth postnatal weeks that increases in frequency and becomes projectile. Some infants do well for the first few postnatal weeks, then suddenly develop projectile vomiting that can lead to dehydration within a few days. Preterm infants present at a somewhat later chronologic age, but equivalent to 44 weeks' postconceptional age.

The diagnosis can be made with a high degree of accuracy in the patient who has a history of a progressive, nonbilious vomiting that becomes projectile. As with the infant in the vignette, there is a failure to gain weight or pronounced weight loss. The infant is ravenously hungry and nurses avidly. The upper abdomen can be distended, and gastric peristaltic waves may be seen. An olive-size mass just to the right and above the umbilicus may be felt in some patients. Dehydration, loss of skin turgor, fretfulness, and apathy may be present. The classic electrolyte picture is metabolic alkalosis accompanied by severe potassium depletion. Hemoconcentration may be reflected by elevated hemoglobin and hematocrit values. The serum chloride level is low, and the urine is concentrated; up to 30% of patients have indirect hyperbilirubinemia. In addition to the history and physical examination, diagnostic studies that may be helpful include abdominal ultrasonography (the imaging study of choice) and an upper gastrointestinal radiographic series. Criteria for ultrasonographic diagnosis of pyloric stenosis are a pyloric length greater than 14 mm or pyloric muscle thickness greater than 4 mm. Pyloromyotomy is the treatment of choice. It is not an emergency procedure and should be undertaken when the dehydration and electrolyte abnormalities are corrected.

Children who have small bowel obstruction typically present with bilious vomiting and abdominal distention. Gastroesophageal reflux is probably the most common cause of vomiting in infants. It is distinguished from pyloric stenosis by episodes that are typically effortless (without retching, not projectile). Infants who have gastroenteritis experience diarrhea with vomiting; infants who have pyloric stenosis often have constipation. Allergic reactions to milk frequently are associated with blood in the stool; the most likely allergens are milk and soy proteins.

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Content Specifications:

Recognize the clinical manifestations of the developmental defectsof the stomach, including absence, volvulus, and pyloric stenosis

PREVIOUS   NEXT

NeoReviewsPlus

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You are teaching medical students about the differences in the composition of human milk during the three stages of lactation: colostrum (within the first few days after childbirth), transitional milk (<3 wk after childbirth), and mature milk (>3 wk after childbirth). You explain the functional significance of these differences in composition.

Of the following, the MOST accurate statement regarding human milk constituents is that

1. arachidonic and docosahexaenoic acid contents increase with evolving lactation

2. colostrum prevents the development of zinc deficiency in preterm neonates

☒ 3. high ergo-cholecalciferol content of colostrum decreases the risk of rickets

4. lactose-derived oligosaccharides inhibit bacterial adhesion to mucosal surfaces

5. secretory immunoglobulin A activates complement and promotes phagocytosis

You selected 3, the correct answer is 4.

Lactose-derived oligosaccharides inhibit bacterial adhesion to mucosal surfaces. Bacterial adhesion is a ligand-receptor interaction between structures on the bacterial surface (ligands) and complementary structures on the mucosal surface of the host (receptors). One of the microorganisms whose ligands are well characterized is *Escherichia coli*, a prevalent bacterium involved in early neonatal sepsis. Human milk has a high amount and large variety of free oligosaccharides and other glycoproteins, which prevent attachment of the microorganisms to the intestinal mucosa by acting as receptor analogues. Consequently, human milk feeding confers an immunologic advantage over infant formula feeding by preventing intestinal colonization of pathogenic organisms.

Arachidonic acid (AA) and docosahexaenoic acid (DHA) are long-chain polyunsaturated fatty acid (LCPUFA) derivatives of essential linoleic and alpha-linolenic fatty acids. The important source of LCPUFA in human milk is the milk phospholipid. The phospholipid content of human milk decreases during the first month after birth and is accompanied by a concomitant decrease in the AA and DHA content. The AA and DHA content of human milk from mothers of term infants does not differ from that of mothers of preterm infants. Additionally, the decline in AA and DHA content of human milk with evolving lactation is similar between mothers of term infants and those of preterm infants. The high LCPUFA content of human milk, especially in the early stages of lactation, may confer a beneficial effect by promoting neuronal growth and development. Some infant formulas, particularly those designed for preterm infants, currently are supplemented with AA and DHA in the hope of enhancing neurodevelopment.

The concentration of zinc in human colostrum is high, but it decreases rapidly with evolving lactation. The zinc content of mature milk averages 250 mcg/dL, which provides a daily zinc intake of approximately 375 mcg/kg per day for preterm infants fed milk volumes of 150 mL/kg per day. This intake is several-fold lower than the recommended zinc intake of 500 to 1,000 mcg/kg per day for preterm infants receiving enteral nutrition. Accordingly, preterm infants, particularly those fed exclusively human milk, are at risk for developing zinc deficiency. The clinical effects of zinc deficiency include growth failure, skin lesions, poor wound healing, hair loss, decreased protein synthesis, and depressed immune function.

The ergo-cholecalciferol content of human colostrum is low. Although it increases nearly threefold with evolving lactation, the intake of ergo-cholecalciferol in infants fed exclusively human milk remains below the minimal recommended intake for prevention of rickets.

Secretory immunoglobulin (Ig) A is a major glycoprotein in human milk. Much like the lactose-derived oligosaccharides, secretory IgA protects the host by agglutination of microorganisms and inhibition of their attachment to mucosal surfaces. Secretory IgA does not confer an immunologic advantage by activating complement or by promoting phagocytosis of the microorganisms.

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Content Specification:

Understand the immunologic constituents in human milk and their physiologic effects

◄ PREVIOUS   NEXT ►

Prenatal ultrasonography of a male fetus reveals bilateral hydronephrosis. Postnatal abdominal ultrasonography confirms bilateral hydronephrosis, with markedly reduced renal parenchyma. A voiding cystourethrogram reveals posterior urethral valves and bilateral grade IV vesicoureteral reflux (VUR). A urologist performs ablation of the valves and bilateral ureterostomies. The infant's serum creatinine at 2 weeks after birth is 2.1 mg/dL (185.6 mcmol/L). The remainder of the serum electrolyte concentrations are normal, and the urine output is 5.2 mL/kg per hour. The patient has no sign of volume depletion or overload.

Of the following, the MOST appropriate statement to provide the child's parents is that their son

1. is unlikely to progress to end-stage renal disease (ESRD)

2. is unlikely to reach ESRD until adulthood

3. likely will develop ESRD within 5 years

4. needs to start peritoneal dialysis immediately

5. should progress slowly to ESRD by adolescence

You selected 3, the correct answer is 3.

Posterior urethral valves (PUV) represent the most serious form of in utero urinary tract obstruction. It is disheartening that even after ablation of the valves and treatment of other related urinary tract lesions, if present, many children who have PUV progress to end-stage renal disease (ESRD) within the first decade of life, often by early childhood. The reasons for this remain unclear, but persistent urinary tract infections due to abnormal bladder function certainly result in renal scarring and deterioration of renal function. Generally, children who have severe urinary tract obstruction and more frequent urinary tract infections are more likely to progress earlier to ESRD. Other factors, such as activation of the renin-angiotensin system, stimulation of growth factors, and immune system activation, likely contribute to the progression toward ESRD.

Many attempts have been made to identify urinary indices that are consistent with the diagnosis of fetal urinary tract obstruction, but amniotic fluid electrolyte analysis has not proven to be reproducible or predictive of obstruction. In utero fetal surgery to channel urine out of the bladder (proximal to the level of obstruction) and into the amniotic fluid has proven difficult, and there are many potentially serious complications. Thus, the most important step for pediatricians is postnatal management of children who have PUV and urinary tract obstruction.

The diagnosis of PUV is established by performing a voiding cystourethrogram (VCUG). The classic radiologic finding on VCUG in infants who have PUV is a dilated proximal urethra and a narrowed distal urethra, creating the "spinning top deformity." A large bladder that has a thickened wall also is seen in infants who have PUV. A VCUG also can ascertain the presence of vesicoureteral reflux (VUR), which is seen commonly in patients who have PUV. Renal ultrasonography should be performed to visualize the kidneys and determine if there is hydronephrosis (commonly seen in conjunction with PUV) and to verify the presence of normal renal parenchyma. Finally, measurement of serum electrolytes and close monitoring of urine output are essential in any patient who has urinary tract obstruction.

Despite the reduced renal function of the patient in the vignette, there is no immediate need to commence dialysis. Except for the elevated serum creatinine, the serum electrolytes are normal and the patient exhibits no sign of fluid overload.

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Abstract available online, article available online for subscription or fee.

Content Specifications:

Recognize the clinical manifestations of anatomic abnormalities of the urinary tract in infants

Know the recommended supportive and corrective treatment of anatomic abnormalities of the urinary tract in infants

NeoReviewsPlus

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A pediatrician asks for your input on a 4-month-old baby who has dysmorphic features and presented to her clinic for a health supervision visit. The baby has normal growth parameters, but a depressed nasal bridge, a short nose with anteverted nares, a long philtrum, and hypoplastic fingernails. A heart murmur is suggestive of a small ventricular septal defect.

Of the following, the prenatal exposure that is MOST likely to be associated with these features is

1 amphetamines

2 angiotensin-converting enzyme inhibitors

3 barbiturates

4 retinoids

5 selective serotonin reuptake inhibitors

You selected 3 , the correct answer is 3 .

The pattern of dysmorphic features described for the infant in the vignette is consistent with "anticonvulsant embryopathy." The anticonvulsants encompassed in this descriptive term are phenytoin, trimethadione, valproic acid, carbamazepine, and barbiturates. Infants who have anticonvulsant embryopathy typically have a broad, depressed nasal bridge; short nose with anteverted nares; long philtrum; maxillary hypoplasia; and hypoplasia of the fingernails and toenails. Additionally, they may have major malformations, such as congenital heart defects (especially in association with barbiturates). There is an estimated 12% to 15% risk for anticonvulsant embryopathy associated with prenatal exposure to this group of drugs.

The data regarding prenatal exposure to amphetamines are scant. Case reports describe an association between amphetamine exposure and cardiac malformation, exencephaly, and limb reduction defects. Additionally, a potential increase in the incidence of congenital heart disease has been suggested. However, prospective studies have failed to confirm any of these associations, although they have suggested an increased risk for cleft palate. Angiotensin-converting enzyme inhibitors are potent antihypertensives that typically are not associated with malformations when used during the first trimester. However, several case reports and small studies support an association with oliguria, renal failure, hypertension, and skull hypoplasia following second and third trimester use. Selective serotonin reuptake inhibitors (SSRIs) are among the most common prescription drugs used during pregnancy. Fluoxetine has been especially well studied. There does not appear to be an increased risk for birth defects associated with the SSRIs. There has been some question about a neonatal withdrawal syndrome, but this has not been confirmed. Certain retinoids (eg, isotretinoin) can be potent teratogens when consumed orally, interfering with normal branchial arch development as well as development of the eyes, heart, hands, and feet.

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Content Specification

Understand the effects of maternal seizure disorders and their management on the fetus

PREVIOUS   NEXT

NeoReviewsPlus

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A pediatrician calls for your advice regarding a 2-month-old infant who presents with a 1-week history of intermittent vomiting appears jaundiced on physical examination. At 4 weeks of age, the exclusively breastfed baby was gaining weight well and was not icteric. The mother subsequently returned to work, and the infant has been receiving supplements of formula and apple juice while at day care. A urine test for reducing substances is positive.

Of the following, the MOST likely cause of jaundice in this infant is

1 alpha-1-antrypsin deficiency

❌ **2** biliary atresia

3 cystic fibrosis

4 fructose intolerance

5 homocystinuria

You selected **2**, the correct answer is **4**.

A careful history and physical examination coupled with fractionation of the bilirubin can begin to narrow the etiologic possibilities and guide the evaluation of the infant who appears jaundiced. The development of jaundice and vomiting with the introduction of fruit juice in the diet of the infant in the vignette suggests the diagnosis of fructose intolerance, which is supported by a positive urine test for reducing substances. A definitive diagnosis is made by the measurement of fructose 1,6-biphosphate aldolase activity in liver tissue. Fruit juices are not recommended for 2-month-old infants.

The presence of jaundice in a 2-month-old infant may be caused by an increase in serum levels of unconjugated (indirect), conjugated (direct), or both forms of bilirubin. Physiologic hyperbilirubinemia of the newborn should resolve by 2 weeks of age, and prolonged jaundice associated with breastfeeding rarely persists beyond the first 8 postnatal weeks. Unconjugated hyperbilirubinemia may be the result of an increased bilirubin load due to hemolytic disorders, enterohepatic recirculation (eg, cystic fibrosis and pyloric stenosis), hypothyroidism, sepsis, drugs, or other underlying conditions. Direct hyperbilirubinemia may be due to infectious, toxic, metabolic, or genetic causes; functional impairment of bile secretion; or mechanical obstruction of bile excretion.

Infectious causes include viral hepatitis (eg, cytomegalovirus; hepatitis A, B, or C) toxoplasmosis, and syphilis. Toxic causes include parenteral nutrition and drugs such as erythromycin. Among the metabolic diseases are disorders of carbohydrate metabolism (eg, galactosemia, fructosemia), disorders of amino acid metabolism (eg, tyrosinemia), and disorders of lipid metabolism (eg, Niemann-Pick, Gaucher disease). Down syndrome, Turner syndrome, and other conditions, such as alpha-I-antitrypsin deficiency, hypothyroidism, and cystic fibrosis, have been associated with elevated levels of conjugated bilirubin. Intrahepatic duct disease (eg, neonatal hepatitis, Alagille syndrome) and extrahepatic duct failure (eg, biliary atresia, sclerosing cholangitis, choledochal cyst) lead to obstruction of bile flow.

Some infants who have alpha-1-antitrypsin deficiency, progressive liver disease, or cystic fibrosis may be jaundiced and have elevated conjugated bilirubin levels. However, the history and presence of reducing substances makes these less likely causes of jaundice for the infant in the vignette. Homocystinuria, a disorder of amino acid metabolism, is not associated with jaundice in early infancy. Characteristic features of this progressive disorder include Marfanlike habitus, developmental delay, downward subluxation of the ocular lens, and osteoporosis, with

the development of thromboembolism in the second decade of life.

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Content Specifications:

Know the factors associated with an increase in neonatal serum bilirubin concentrations

Understand the differential diagnosis, evaluation, and approach to management of mixed forms of jaundice

A 6-week-old infant, whose birthweight was 984 g and estimated gestational age at birth was 28 weeks, has a systolic blood pressure of 98 mm Hg and a diastolic blood pressure of 60 mm Hg. These measurements were obtained by oscillometric method, with the right arm, using an appropriately sized cuff, and while the infant was asleep. The neonatal history is significant for initial respiratory distress managed with brief mechanical ventilation and umbilical arterial catheterization, sedation with fentanyl during the first 10 days after birth, and a course of caffeine for apnea during the second and third weeks after birth. The infant is receiving full enteral feedings, is maintaining normal oxygen saturations in room air, and has normal physical examination findings, including vital signs.

Of the following, the diagnostic test MOST likely to confirm the cause of hypertension in this infant is:

☒ 1   chest radiography

2   echocardiography

3   head computed tomography

4   renal ultrasonography

5   thyroid radionuclide scan

You selected **1**, the correct answer is **4**.

The infant described in the vignette has systemic hypertension, which is defined as systolic and/or diastolic blood pressure equal to or greater than the 95th percentile adjusted for postmenstrual age. The oscillometric method of blood pressure measurement is based on the oscillation of the arterial wall as pulsatile blood flows through the artery during automatic deflation of the cuff after its initial inflation. The systolic blood pressure is identified at a point at which the amplitude of oscillations increases rapidly; the diastolic blood pressure is identified at a point at which the amplitude of oscillations decreases rapidly. The point of greatest average oscillation identifies the mean blood pressure, which can be estimated by the following equation: mean BP = diastolic BP + 1/3 (systolic BP - diastolic BP). For accuracy, the blood pressure measurements in neonates should be obtained on at least three separate occasions, using a cuff that has a cuff-width/arm-circumference ratio between 0.45 and 0.55, and while the infant is asleep. Consistent use of the extremity is important to avoid differences in measurements between the arm and the leg.

The causes of neonatal hypertension can be summarized using a mnemonic shown in the table. The most common cause of neonatal hypertension is related to renovascular and renal parenchymal disease. The renovascular cause commonly involves thromboembolism affecting either the aorta or the renal arteries associated with umbilical arterial catheterization. The incidence of thrombosis related to an umbilical arterial catheter may be influenced by several factors, including the size and type of catheter, the duration of catheter placement, the use of heparin through the catheter, the location of the catheter tip in the aorta, and the practice of infusing medications, blood products, hyperosmolar solutions, and calcium through the catheter. The mechanism of hypertension is believed to be disruption of vascular endothelium by the catheter, embolization of the renal artery, renal hypoperfusion, and release of renin. Other renovascular causes of neonatal hypertension include renal artery stenosis from fibromuscular dysplasia, renal vein thrombosis from polycythemia and hyperviscosity, and renal vascular abnormalities from metabolic and infectious causes.

Congenital renal parenchymal diseases that can result in neonatal hypertension include

polycystic kidney disease, multicystic/dysplastic/hypoplastic kidney, and obstructive uropathy. Acquired diseases that can be related to neonatal hypertension include acute tubular necrosis, renal cortical necrosis, and interstitial nephritis. The mechanism of hypertension in such instances is unclear, although the renin-angiotensin system has been implicated. The best modality for diagnosing renal parenchymal disease is renal ultrasonography. Assessment of renal blood flow and function by Doppler sonography, plasma renin activity, and renal radionuclide scan are useful in establishing the diagnosis of renovascular hypertension.

Neonatal hypertension is about two- to nine-fold more common among preterm infants who have bronchopulmonary dysplasia (BPD) compared with those who do not have lung disease. The incidence of neonatal hypertension varies with the severity of lung disease. The mechanism of hypertension in BPD remains unconfirmed. It may be related to the effects of chronic hypoxemia on peripheral vascular resistance; medications such as dexamethasone, xanthines, and bronchodilators; nephrocalcinosis from chronic furosemide therapy; or cor pulmonale with associated sodium retention. Although the infant described in the vignette was at risk for the development of BPD because of prematurity and initial lung disease, the lack of need for supplemental oxygen at the postmenstrual age of 34 weeks precludes that diagnosis. A chest radiograph, therefore, is unlikely to elucidate the cause of hypertension in this infant.

Congenital heart disease, specifically coarctation of the aorta with intact ventricular septum, is a cause of neonatal hypertension. The blood pressure is elevated moderately in the arms, and the brachial and radial pulses are readily palpable. Conversely, the blood pressure is reduced in the legs, and the femoral and dorsalis pedis pulses may be weak or absent. The infant usually becomes symptomatic within the first week or two after birth, a time coinciding with the spontaneous closure of the ductus arteriosus. Restlessness, irritability, and poor feeding are common, as are tachycardia and tachypnea. The infant may become severely compromised, with manifestations of lethargy, rales, cardiomegaly, hepatomegaly, poor perfusion, and metabolic acidosis. The absence of such symptoms and signs, coupled with a relatively advanced age at the time of diagnosis of hypertension, makes congenital heart disease unlikely in the infant in the vignette. Echocardiography, therefore, may not reveal the cause of hypertension.

Neurologic causes of neonatal hypertension include seizures, intracranial hemorrhage, intracranial hypertension, pain, and withdrawal from prolonged sedation or analgesia. The hypertension tends to be episodic and to manifest early in life when the infant is unstable during transition from intrauterine to extrauterine life. Although the infant described in the vignette is at risk for the development of germinal matrix hemorrhage because of prematurity and initial sickness, systemic hypertension is a rare primary manifestation of such hemorrhage. The brief use of sedation early in life also makes withdrawal from sedation or analgesia unlikely as a cause of hypertension in this infant. Head computed tomography, therefore, may not yield information pertinent to the cause of hypertension.

Neonatal hypertension due to endocrine disorders is unusual. The disorders include congenital adrenal hyperplasia, hyperaldosteronism, Cushing syndrome, and hyperthyroidism. Pheochromocytoma is an extremely rare cause of hypertension in neonates. Unless suspected on the basis of newborn metabolic screening, fluid-electrolyte abnormalities, or other clinical manifestations, evaluation for an endocrine disorder is not the first diagnostic measure to establish the cause of hypertension in a neonate. Thyroid radionuclide scan, therefore, is not warranted.

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Content Specification(s):

Know how to diagnose and evaluate an infant with hypertension
Know the most common predisposing factors to hypertension in early infancy

Table. Shenai Mnemonic for Causes of Neonatal Hypertension

H: Heart disease (coarctation, patent ductus arteriosus)

Y: Yet undetermined (idiopathic)

P: Pulmonary disease (bronchopulmonary dysplasia)

E: Endocrine disorder (congenital adrenal hyperplasia, adrenal hemorrhage, hyperaldosteronism, hyperthyroidism, Cushing disease)

R: Renal disease (renovascular thromboembolism, polycystic/multicystic/dysplastic/hypoplastic kidney, obstructive uropathy, acute tubular necrosis)

T: Total parenteral nutrition (high calcium, high salt)

E: Extracorporeal membrane oxygenation

N: Neoplasm (Wilms tumor, mesoblastic nephroma, neuroblastoma, pheochromocytoma)

S: Surgery (abdominal wall defect repair)

I: Intoxication (dexamethasone, xanthines, adrenergic drugs, phenylephrine eye drops, cocaine)

O: Opioid withdrawal (withdrawal from any sedation)

N: Neurologic cause (seizures, pain, intracranial hemorrhage, intracranial hypertension)

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A newborn has a <u>violaceous patch</u> involving the face, including the upper and lower eyelids.

Of the following, the MOST likely associated finding is

1	arrhythmias
2	consumptive coagulopathy
3	glaucoma
☒ 4	polycystic kidney disease
5	renovascular hypertension

You selected 4 , the correct answer is 3 .

The infant described in the vignette has a facial port-wine stain (PWS), a permanent vascular malformation that is present at birth in 0.3% of infants. Although a PWS may be located anywhere on the body and usually is an isolated finding, its presence on the face raises concern about Sturge-Weber syndrome (SWS). The risk of SWS is greatest if the PWS involves both the upper and lower eyelids (the distribution of the first and second branches, respectively, of the trigeminal nerve), is bilateral, or involves the distribution of all three branches of the trigeminal nerve, as seen in the figure.

In children who have SWS, the vascular malformation involves not only the skin, but the ipsilateral leptomeningeal vessels, particularly those in the parieto-occipital region. Altered blood flow in these vessels produces ischemia that, in turn, may cause seizures or contralateral hemiparesis. The vascular malformation also may involve the ipsilateral eye. Abnormalities of the episcleral vessels may lead to glaucoma; involvement of choroidal vessels may cause retinal detachment.

A number of disorders characterized by cutaneous abnormalities have associated systemic complications, but these do not occur in SWS. Children who have tuberous sclerosis may have cardiac rhabdomyomas (that may cause mechanical obstruction, heart failure, or arrhythmias) or hamartomas or multiple cysts of the kidneys (that may cause pain, hemorrhage, or renal failure). Kasabach-Merritt syndrome is characterized by a large, atypical hemangioma (actually a hemangioepithelioma) that may trap platelets and cause consumptive coagulopathy. Finally, renovascular hypertension may occur in individuals who have neurofibromatosis type 1.

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<u>**Content specifications:**</u>

Know how to diagnose Port wine stain
Know how to diagnose Sturge-Weber syndrome

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You attended the term birth of a male infant delivered by cesarean section and discharged the infant into the care of his family physician after three days in the normal nursery. Two months later, the mother calls you because her 2-month-old exclusively breastfed infant has not had a stool in 4 days. During the first 2 weeks after birth, the infant passed stools twice a day, usually after nursing. Gradually, the stools have become less frequent, occurring once every 4 to 5 days. The infant continues to gain weight well, voids six to seven times per day and when he finishes nursing, the mother has noticed that both breasts seem empty. The infant had normal physical examination by the family physician at six weeks of age. The mother asks for your advice.

1	addition of apple juice to the diet
2	administration of a glycerin suppository
☒ **2**	addition of cereal to the diet
4	daily rectal stimulation
5	observation with reassurance

You selected 2 , the correct answer is 5 .

During the first few postnatal weeks, breastfed infants have loose, yellow stools that may occur after every feeding. Gradually, the bowel movements become less frequent. By 2 months of age one stool per day is common, but it is not uncommon for breastfed babies to have one large, soft bowel movement every 7 days. The infant described in the vignette has gained weight well and has normal physical examination findings. Accordingly, the parents should be reassured and followed-up with phone calls in a few days. Bottle-fed infants usually have one or more stools daily, although soft stools every 2 days are normal.

For a 2-month-old infant, there is no nutritional benefit to the addition of apple juice or cereal, which should not be introduced until 4 to 6 months of age. The administration of a glycerin suppository or daily rectal stimulation is not necessary. Such manipulations undermine the reassurance that the infant has a normal bowel movement pattern.

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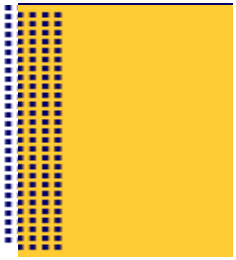
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Content specifications:

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View course using IE 8

Realize the problems associated with breast feeding

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Education Module Learner

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A pregnant woman is involved in a motor vehicle accident that causes blunt trauma to her abdomen. As you await evaluation by the emergency physicians and obstetricians, you discuss the potential risk to the fetus with colleagues and medical students.

Of the following, the MOST accurate statement regarding fetal risk in motor vehicle accidents is that:

1. absence of vaginal bleeding is reassuring regarding placental abruption
2. fetal death often occurs with maternal survival
3. fetal risk is proportional to gestational age
4. maternal trauma score predicts pregnancy risk
5. monitoring of the fetus for 24 hours is mandated

You selected 4, the correct answer is 3.

Fetal risk increases with gestational age because of the protective effect during the first trimester of the intrapelvic location of the uterus early in pregnancy, the fluid in the amnionic sac, and the pelvic soft tissues. However, severe pelvic fractures may result in fetal loss in early gestation. Except for situations of maternal death from motor vehicle accidents, first trimester fetal loss rarely is explained by trauma. After 12 weeks' gestation, as the uterus ascends above the pelvis, the uterus and fetus become more vulnerable to blunt trauma or penetrating injuries. The risk to the mother and fetus are proportional to the degree of damage to the vehicle. Injury to the fetus may be direct, such as skull fracture or hemorrhage, or indirect as a result of disruption of uteroplacental exchange, such as placental abruption or uterine rupture.

Placental abruption may follow abdominal trauma and should be considered in all cases. Fetal monitoring for uterine contractions and fetal heart rate (FHR) abnormalities, marking and monitoring of the uterine fundal position, and evaluation for uterine tenderness are recommended. Although vaginal bleeding may accompany placental abruption, its absence is not reassuring. In a series of 16 cases of placental abruption resulting in fetal death, only 6 were associated with vaginal bleeding.

Fetal death from motor vehicle accidents after 12 weeks' gestation most often is the result of maternal death. Placental abruption and uterine rupture are the most common causes of fetal demise in cases of maternal survival. In one report of pregnant women in severe accidents, abruption occurred only in 3.4%.

As in nonpregnant patients, trauma severity scoring such as the Glasgow Coma Scale is useful in triaging the mother, but the scores are not predictive of pregnancy outcome.

Fetal monitoring is useful after abdominal trauma. Obstetric ultrasonography can help to determine gestational age, placental location, and fetal position. FHR is a proxy for fetal well-being, adequacy of maternal blood volume, and compensatory alpha-adrenergic response. Fetal bradycardia (<120 beats/min) or late decelerations may reflect maternal hypovolemia, maternal hypoxia, abruption, or uterine rupture. If the mother has been resuscitated and is stable after a major trauma, cesarean delivery should be considered if fetal distress is present. Monitoring for 4 to 8 hours is recommended for pregnant women involved in motor vehicle accidents even if there is no history of abdominal impact. With fewer than six contractions per hour and no FHR abnormalities, monitoring can be discontinued. If contractions occur more frequently than every

10 minutes, the risk of abruption is 20%. If there are frequent uterine contractions or fetal heart abnormalities, monitoring should be extended to at least 24 hours unless fetal compromise or maternal deterioration dictates urgent delivery. Relatively minor abdominal trauma may result in fetal-maternal hemorrhage. A Kleihauer-Betke test and measurement of maternal serum alpha-fetoprotein may be used to estimate the presence and volume of fetal-maternal hemorrhage. Only a tiny amount of Rh(+) blood is needed to sensitize the Rh(-) mother. Rh(-) women should receive Rh immunoglobulin G (RhIgG). Larger doses of RhIgG and ongoing fetal surveillance may be indicated if more than 30 mL of fetal blood is detected in the mother.

<u>References:</u>

Gonik B, Foley MR. Intensive care monitoring of the critically ill pregnant patient. In: Creasy RK, Resink R, Iams JD, eds. *Maternal-Fetal Medicine.* 5th ed. Philadelphia, Pa: Saunders; 2004:925-952

[Mackenzie S. Obstetrics: trauma and pregnancy](.).

[Newton ER. EMedicine-Trauma and pregnancy.](.)

<u>Content specifications:</u>

Know the maternal and fetal risks and the management of a pregnant patient involved in a traumatic injury

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A pediatrician has admitted a 2-week-old infant with a 12-hour history of fever. He continues to breastfeed well. The mother documented a rectal temperature of 102° F (38.9° C) at home. At the time of physical examination the infant is afebrile and has good tone, with the remainder of the examination being normal.

In addition to a complete blood count and blood culture, the BEST additional management for this infant includes

	Cerebrospinal Fluid Anaylsis	Urine Culture	Chest Radiography	Parenteral Antibiotic Therapy *
	* Pending Culture Results			
1	Yes	Yes	Yes	Yes
2	Yes	Yes	No	Yes
☒ 3	Yes	No	No	Yes
4	No	Yes	No	No
5	No	No	Yes	No

You selected 3, the correct answer is 2.

 The presence of fever in any 2-week-old infant requires careful evaluation and management. Signs and symptoms of sepsis and meningitis are often subtle or absent. In addition to a complete blood count and blood culture, cerebrospinal fluid analysis and cultures of the cerebrospinal fluid should be obtained. Urinalysis and urine culture also are mandatory in febrile neonates beyond the immediate neonatal period. Parenteral antibiotic therapy expected to be effective against common bacterial pathogens seen in the neonate is instituted pending culture results. Flora that colonized the intestinal or genital tract of the mother or infant represent the most frequent source of infection. Group B Streptococcus, Escherichia coli, and Listeria monocytogenes are among the most frequent pathogens in this age group.

A chest radiograph should be obtained if there are signs or symptoms suggestive of respiratory problems, but this examination is not indicated for the infant described in the vignette who, except for fever, has normal findings on history and physical examination.

References:
Baker MD. Evaluation and management of infants with fever. Pediatr Clin North Am. 1999;46:1061-1072

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Jaffe DM. Assessment of the child with fever (neonatal fever). In: Rudolph CD, Rudolph AM, eds. Rudolph's Pediatrics. 21st ed. New York, NY: McGraw-Hill; 2003:304-305

McCarthy PL. Fever. Pediatr Rev. 1998;19:401-408

Content specifications:
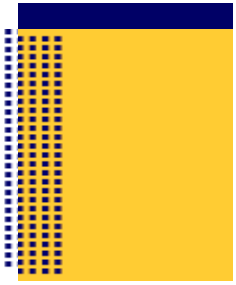
Understand the clinical manifestations and differential diagnosis of sepsis

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You are asked to evaluate a newborn who has had only one wet diaper (estimated 10 mL of urine) over the first 24 hours after birth. On physical examination, his general appearance reveals very <u>soft abdominal musculature with overlying excessive and wrinkled skin</u>, a distended urinary bladder, and bilateral undescended testes. Upon palpation of the bladder he produces urine, but the stream is weak.

Of the following, the MOST likely cause of this infant's weak urinary stream is

1. end-stage renal disease

2. ☒ hydronephrosis

3. posterior urethral valves

4. prostatic hypoplasia

5. vesicoureteral reflux

You selected **2**, the correct answer is **4**.

The infant described in the vignette has reduced urine output and a weak stream even with bladder pressure. It is noteworthy that about 99% of newborns have urine output by 24 hours after birth and usually void several times during that period. The presence of soft abdominal musculature, overlying wrinkled skin, and bilateral undescended testes in this infant suggests prune belly syndrome. Thought to be due to either a mesodermal injury at 4 to 10 weeks' gestation or to urinary tract obstruction, infants with prune belly syndrome almost always have anomalies of the urinary tract and are prone to develop chronic renal failure. The bladder is enlarged and poorly contractile. Prostatic hypoplasia results in proximal urethral dilatation producing findings on prenatal studies similar to posterior urethral valves. Prognosis is affected by the degree of associated renal dysplasia. Surgery to effect optimal drainage of urine, medical and dietary management of renal insufficiency, orchidopexy, reconstruction of the abdominal wall, and renal transplantation may become part of the eventual long-term course of infants and children with prune belly syndrome.

Posterior urethral valves (PUV) is a medical emergency. This in utero lesion often results in abnormal renal development (dysplasia and frequently concomitant hypoplasia). Obstruction along the urinary tract usually is evidenced by bilateral hydronephrosis. Because normal urine flow is obstructed, the bladder generally is distended. One characteristic of PUV may be a weakened urinary stream, but the urinary stream may be normal if the valves do not occlude normal urine flow completely.Once the PUV is detected, immediate consultation with a urologist is mandatory. Ablation of the valves is recommended to relieve the urinary tract obstruction. Voiding cystourethrography also is compulsory to ascertain the presence of vesicoureteral reflux (VUR). VUR often is seen in conjunction with PUV and cannot be treated surgically until the valves are ablated. Finally, close monitoring of urine output and serum electrolytes is necessary because renal function frequently remains reduced, even after surgical repair of PUV and possibly VUR.It is unusual for children who have prune belly syndrome to be born with end-stage renal disease. Although hydronephrosis and VUR frequently are present in the infant who has PUV, these are not the causes of a weak urinary stream

<u>References:</u>

Kaplan GW, McAleer IM. Structural abnormalities of the genitourinary system. In: Avery GB, Fletcher MA, MacDonald MG. Neonatology: Pathophysiology and Management of the Newborn. Philadelphia, PA: Lippincott Williams & Wilkins; 1999:975-1004.

Vogt BA, Avner ED. The kidney and urinary tract. In: Fanaroff AA, Martin RJ. Neonatal-Perinatal Medicine 7th ed. St. Louis, MO; Mosby;2002:1517-36.

Content specifications:

Recognize the clinical manifestations of anatomic abnormalities of the urinary tract in infants
Know how to diagnose specific anatomic abnormalities of the urinary tract in infants
Know the recommended supportive and corrective treatment of anatomic abnormalities of the urinary tract in infants

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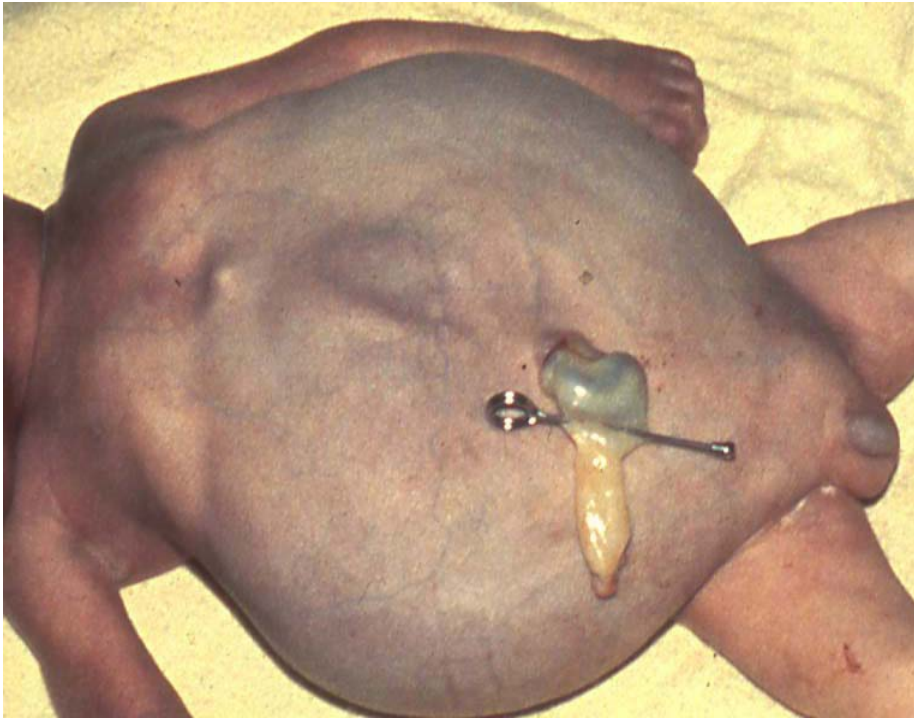
A term newborn is delivered vaginally with forceps assistance to a 30-year-old primiparous Caucasian woman. Maternal history is significant for pelvic vein thrombosis related to factor V Leiden mutation and a positive drug screen for cocaine. The Apgar scores are 3 and 5 at 1 and 5 minutes, respectively. The infant presents with left-sided focal, clonic seizures at approximately 10 hours of age, which are controlled with phenobarbital. Computed tomography shows a right-sided focal lesion in the occipital cerebral hemisphere.

Of the following, the MOST likely cause of the cerebral lesion in this infant is

☒ **1**   fetal cocaine exposure

2   maternal factor V Leiden mutation

3   neonatal birth trauma

4   neonatal meningoencephalitis

5   perinatal asphyxia

You selected 1, the correct answer is 2.

The infant described in the vignette has clinical features and laboratory findings consistent with right-sided occipital cerebral infarction. The prevalence rate of cerebral infarction (perinatal stroke) in near-term and term neonates is estimated at 1 per 4,000 live births. Approximately 73% of the strokes are ischemic in origin (arterial infarction); the remainder is hemorrhagic (venous infarction). A more accurate estimate of the prevalence of perinatal stroke requires a comprehensive survey of maternal, placental, fetal, and neonatal diseases that cause or contribute to brain infarction.

Maternal factor V Leiden mutation is the most likely cause of cerebral infarction in the infant in the vignette. Factor V Leiden mutation, a form of activated protein C (APC) resistance, currently is the most common inherited thrombotic disorder among Caucasian people of European descent. Protein C is a vitamin K-dependent protein synthesized by the liver. It exerts its anticoagulant function after activation to the serine protease, APC, which inactivates factor V and prevents coagulation. Factor V Leiden mutation in most cases is a single point mutation in which a guanine is substituted by adenine at nucleoside position 1691, resulting in the replacement of arginine-506 by glutamine in the factor V molecule. This mutated factor V molecule is resistant to inactivation by APC, resulting in hypercoagulability and consequent spontaneous thrombosis. The thrombosis may affect the mother, the placenta, or the fetus. Pulmonary thromboembolism and thrombosis involving a deep vein of the leg are examples of maternal manifestations of thrombosis. Thrombosis on the maternal side of the placenta may contribute to hypertensive disorder, intrauterine growth restriction, or fetal death; thrombosis on the fetal side of the placenta may predispose the fetus to emboli that bypass the pulmonary and hepatic circulations to lodge in the cerebral vasculature. A typical neonatal manifestation of thrombosis is focal or diffuse cerebral infarction. The distribution of the lesion documented on the computed tomographic scan for the infant in the vignette suggests focal involvement of the right posterior cerebral artery.

Cocaine is one of the common illicit drugs used by women of childbearing age. The rate of cocaine use during pregnancy varies geographically and among different age groups, races, and social classes. Maternal cocaine use is associated with a high incidence of obstetric complications, including spontaneous abortions, stillbirths, preterm labor, and placental abruption. Although cocaine crosses the placenta freely, vasoconstriction of the maternal uterine arteries induced by cocaine may limit fetal exposure. Nonetheless, fetal cocaine

exposure, particularly among heavy users of the drug, may contribute to severe central nervous system abnormalities in the fetus, such as porencephaly and hydranencephaly. Isolated focal cerebral infarction, as seen in the infant in the vignette, is an unusual complication of fetal cocaine exposure.

Neonatal birth trauma may result from mechanical pressure on the skull during a forceps-assisted vaginal delivery. Stretching or laceration of cerebral blood vessels during a difficult delivery may result in intracranial hemorrhage, such as epidural, subdural, or subarachnoid hemorrhage. Compression of a cerebral blood vessel may accompany an intracranial hemorrhage and contribute to cerebral infarction. Thus, although cerebral infarction is a possible consequence of neonatal birth trauma, it is a rare occurrence, particularly in its isolated form unaccompanied by other forms of intracranial hemorrhage, as for the infant in the vignette.

Although meningitis, especially from bacterial pathogens, and encephalitis, predominantly of viral origin, can contribute to cerebral infarction, the decline in the incidence of neonatal meningoencephalitis with modern intensive care makes it an unlikely cause of cerebral infarction in the neonate. Typically, the pattern of cerebral infarction in meningoencephalitis is a multifocal distribution in both cerebral hemispheres, and involvement of the brainstem as well as the cerebellum is common. The infarction is attributed to vascular occlusion from inflammatory vasculitis, cytokine-mediated injury, and abnormalities in coagulation induced by infection. The pattern of cerebral infarction makes neonatal meningoencephalitis an unlikely cause for the infant in the vignette.

The topography of neuronal injury in perinatal asphyxia and resultant hypoxic-ischemic encephalopathy varies, depending on the severity of the insult and the gestational age of the infant. In term neonates, severe perinatal asphyxia can cause diffuse neuronal injury involving much of the brain, including the cerebellum, the brainstem, and the spinal cord. In moderate-to-severe perinatal asphyxia, neuronal injury involves the frontal, parietal, and occipital cerebral cortex as well as the subcortical structures, including basal ganglia (especially putamen) and the thalamus. In mild perinatal asphyxia, the neuronal injury may be milder and more restricted in distribution. Although cerebral infarction is a possible consequence of perinatal asphyxia, it is a rare occurrence, particularly in its isolated focal form.

References:

Bauer KA. Inherited disorders of thrombosis and fibrinolysis. In: Nathan DG, Ginsburg D, Orkin SH, Look AT, eds. *Hematology of Infancy and Childhood*, 6th ed. Philadelphia, Pa: WB Saunders; 2003:1583-1596

Govaert P, Vanhaesebrouck P, de Praeter C. Traumatic neonatal intracranial bleeding and stroke. *Arch Dis Child*. 1992;67:840-845

King TA, Perlman JM, Laptook AR, et al. Neurologic manifestations of in utero cocaine exposure in near-term and term infants. *Pediatrics*. 1995;96:259-264

Lynch JK, Hirtz DG, DeVeber G, et al. Report of the National Institute of Neurological Disorders and Stroke Workshop on perinatal and childhood stroke. *Pediatrics*. 2002;109:116-123

Mariet S, Lardennois C, Mercier A, et al. Fetal and neonatal cerebral infarcts. *Biol Neonate*. 2001;79:236-240

Scher MS, Wiznitzer M, Bangert BA. Cerebral infarctions in the fetus and neonate: maternal-placental-fetal considerations. *Clin Perinatol*. 2002;29:693-724

Volpe JJ. Hypoxic-ischemic encephalopathy: neuropathology and pathogenesis. In: *Neurology of the Newborn*. 4th ed. Philadelphia, Pa: WB Saunders; 2001:296-330

Content Specification(s):

Understand the pathogenesis, clinical and radiographic features,diagnosis, management, and outcome associated with perinatal cerebral and cerebellar infarction
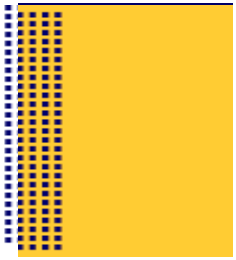
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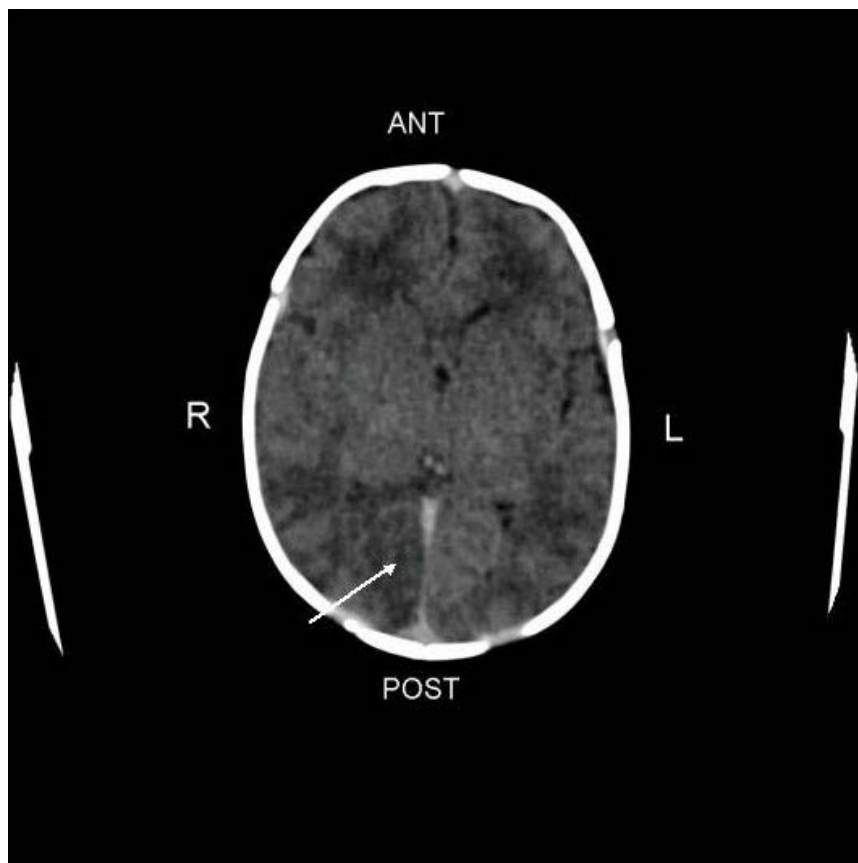
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A term female newborn develops bilious vomiting at 48 hours of age. She has not passed meconium, and her abdomen is distended. Physical examination shows a normal-appearing perineum. No other anomalies are apparent.

Of the following, the MOST likely diagnosis is

1. annular pancreas

2. anorectal malformation

3. duodenal atresia

4. Hirschsprung disease

5. jejunal atresia

You selected 5, the correct answer is 4.

The infant described in the vignette has clinical features consistent with distal intestinal obstruction. Hirschsprung disease, occurring in approximately 1 in 5,000 births, is a common cause of neonatal bowel obstruction. The typical presentation of Hirschsprung disease in the newborn includes delay or failure to pass meconium, bilious emesis, and abdominal distension. The disease is characterized by a congenital absence of intramural ganglia in the affected segment of the bowel. The defect exists in the distal colon and extends for a variable distance proximally. This aganglionic segment is functionally abnormal and does not propagate the normal peristaltic wave from the proximal ganglionic bowel. A functional bowel obstruction at the level of aganglionosis is the result. Radiographic findings are presented in the Yoshida reference.

Although an anorectal malformation has clinical features similar to those of Hirschsprung disease, the physical examination reveals an absent external anal opening. Low anal agenesis occurs with a perineal fistula in slightly more than 50% of males or with posterior fourchette fistula in nearly all females. High anal agenesis occurs with no anal opening and no perineal fistula.

Duodenal obstruction can result from an intrinsic abnormality, as in duodenal atresia, or extrinsic compression caused by malrotation of the gut or an annular pancreas. The typical presentation of such a proximal intestinal obstruction includes bilious or nonbilious vomiting and minimal abdominal distension. Meconium is passed normally in most cases. The earliest clue to the possible existence of duodenal obstruction is polyhydramnios. Prenatal diagnosis is possible with ultrasonography. A characteristic double-bubble appearance on abdominal radiography allows postnatal confirmation of the diagnosis. Approximately 30% of affected infants have Down syndrome.

The clinical presentation of isolated jejunal atresia is indistinguishable from that of duodenal atresia. Jejunoileal atresia, however, may present with bilious vomiting, abdominal distension, and failure to pass meconium. Polyhydramnios is seen in one third of patients who have jejunal atresia, but rarely in those affected by ileal atresia. Hyperbilirubinemia occurs more frequently in infants who have proximal intestinal lesions than in those who have distal lesions. The diagnosis of jejunal atresia can be confirmed by abdominal radiography, which reveals multiple air-fluid levels.

References:

Adamson W, Hebra A. Bowel obstruction in the newborn.

Yoshida C, Faintuch S. Hirschsprungs disease.

Content specifications:

Understand the significance of vomiting and abdominal distention in the neonate
Know the clinical manifestations of Hirschsprung disease

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 A boy is born at term with intrauterine growth retardation. He has sensorineural hearing loss and periventricular calcifications on computed tomography of the head. He remains in the hospital with feeding difficulty.

Of the following, the examination you are MOST likely to request prior to hospital discharge is

☒ **1** abdominal ultrasonography

2 chest radiography

3 echocardiography

4 ophthalmologic examination

5 renal ultrasonography

You selected 1, the correct answer is 4.

The infant described in the vignette has intrauterine growth retardation, hearing loss, and cerebral calcifications consistent with congenital intrauterine infection. Among the many causes of intrauterine infection, the more common ones are cytomegalovirus (CMV), Toxoplasma gondii, rubella, and herpes simplex virus (HSV). Other causes of congenital infection include human immunodeficiency virus, parvovirus, and syphilis. Infants who have any of these infections may experience developmental sequelae, whether asymptomatic or obviously ill. It is important to recognize these sequelae so that infants are evaluated properly both in the hospital and after discharge.

Infants who have symptomatic congenital CMV infection may have microcephaly, intracranial calcifications, and chorioretinitis. Approximately 50% of children who have symptomatic CMV infection have associated sensorineural hearing loss. The hearing loss is progressive, and children known to have been infected with CMV should receive repeated audiologic examinations.

Infants who have toxoplasmosis present with many of the same signs as infants infected with CMV. Although most infants have subclinical infection, many have evidence of ophthalmologic or central nervous system changes on more in-depth evaluation. Infants who have symptomatic toxoplasmosis may present with microcephaly, intracranial calcifications, seizures, chorioretinitis, optic atrophy, microphthalmia, and sensorineural hearing loss.Infants who have congenital rubella infection may experience encephalitis, cataracts, microphthalmia, and sensorineural hearing loss.

Although HSV more typically is transmitted perinatally, infants who have congenital HSV infection may experience hydrocephalus, encephalitis, microcephaly, chorioretinitis, and microphthalmia.

Because ophthalmologic complications are common in infants who have congenital infections, the infant in the vignette should receive an ophthalmologic examination. Infants who have pneumonitis may require chest radiography. Similarly, echocardiography and abdominal and renal ultrasonography may be indicated clinically for specific patients, but they are not routinely indicated.

References:

Chescheir NC, Hansen WF. What's new in perinatology. Pediatr Rev. 1999;20:57-63

Lynfield R, Guerina NG. Toxoplasmosis. Pediatr Rev. 1997;18:75-83

Kleigman RM, Das UG. Intrauterine growth retardation. In: Fanaroff AA, Martin RJ. Neonatal-Perinatal Medicine 7th ed. St. Louis, MO; Mosby;2002:228-62

Pass RF. Cytomegalovirus infection. Pediatr Rev. 2002;23:163-170

Stoul BJ. Infections of the neonatal infant. In: Behrman RE, Kliegman RM, Jenson HB, eds. Nelson Textbook of Pediatrics. 17th ed. Philadelphia, Pa: WB Saunders Co; 2004:623-639

<u>**Content specifications:**</u>

Know the incidence of severe visual impairments in high risk groups, such as premature infants, infants with congenital infection, and infants with hypoxic-ischemic encephalopathy

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You receive an urgent message to call the mother of one of your patients. Upon reaching her, she anxiously reports that she has just learned that she is 8 weeks pregnant, and she has been exposed to multiple substances.

Of the following reported exposures, which is a known teratogen?

1	codeine
2	fluoxetine
☒ 3	heparin
4	lead
5	marijuana

You selected 3, the correct answer is 4.

Lead exposure during pregnancy has been a longstanding concern. Lead freely crosses the placenta as early as 12 weeks' gestation and accumulates in bone throughout the lifetime of an individual. Mobilization of lead stores is more likely during pregnancy and lactation due to bone demineralization at these times. A number of minor malformations have been associated with elevated maternal blood lead levels during pregnancy, including skin tags, hydroceles, hemangiomas, lymphangiomas, and undescended testes. Of major concern is the effect of elevated lead levels on central nervous system function. Several well-designed studies have shown a statistically significant reduction in the mental development index in association with elevated lead levels in cord blood at the time of delivery. Therefore, it is recommended that women who are at increased risk for elevated lead levels during pregnancy have their blood levels monitored. Every effort should be made to reduce their exposure. Because the woman described in the vignette is 8 weeks pregnant, there is still time to measure her blood lead levels and to try to reduce them, if necessary.

Use of codeine, which has been well documented during pregnancy, is not associated with any known increase in anomalies. The newborns of women who use high doses of codeine may experience a withdrawal syndrome characterized by tremor, jitteriness, diarrhea, and poor feeding.

Fluoxetine is one of the most frequently prescribed antidepressants used during pregnancy, and there have been no demonstrable birth defects associated with it.

Heparin is the anticoagulant of choice in pregnant women who have hypercoagulability. Prenatal exposure to heparin is not associated with birth defects.

Although case reports suggest an association between marijuana use and certain defects, prospective studies fail to confirm its teratogenicity.

References:

Jones KL. Known teratogens. In: Haun J, Ormond K, eds. Clinical Teratology Educational Modules. National Society of Genetic Counselors Special Projects Grant, Great Lakes Regional Genetics Group; 139-162

Reproductive Toxicology Center. Reprotox-An Information System on Environmental Hazards to

Human Reproduction and Development. Bethesda, Md, Philadelphia, Pa: Reproductive Toxicology Center, Information Venture, Inc; 1994-2003

Content specifications:

Understand the probable gestational age of teratogen exposure for common fetal anomalies
Know the effect on the fetus of environmental ionizing radiation and other environmental hazards

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A male newborn was delivered by emergent cesarean section for fetal distress following spontaneous placental abruption. At birth, the infant weighed 580 g, and the estimated gestational age was 23 weeks. The Apgar score was 1 at 1 minute and improved to 6 at 5 minutes following resuscitation that included oxygen administration, positive pressure ventilation, and volume expansion. The infant's initial clinical course was characterized by respiratory distress, which was managed with surfactant administration and mechanical ventilation, and persistent hypotension, which required infusion of vasopressors. Cranial ultrasonography at 4 weeks of age shows bilateral cystic lesions in the periventricular cerebral white matter (Figure 1 and Figure 2).

Of the following, the MOST likely mediator of injury resulting in the cerebral lesion in this infant is

1. carbon dioxide

2. insulin-like growth factor-1

3. nitric oxide

4. oxygen free radicals

5. tumor necrosis factor-alpha

You selected 4, the correct answer is 4.

The infant described in the vignette has cranial ultrasonographic evidence of cystic periventricular leukomalacia (PVL). Volpe has described two principal components of PVL: focal and diffuse (Figure 3). The focal component, located deep in the cerebral periventricular white matter, is characterized by localized necrosis of all cellular elements, with subsequent cyst formation. The diffuse component, located more superficially and extensively in the cerebral white matter, is characterized by diffuse apoptosis of oligodendroglial precursor cells. Focal PVL can be diagnosed with cranial ultrasonography; diffusion-weighted magnetic resonance imaging is required to diagnose diffuse PVL. The primary clinical sequela of focal PVL is spastic diplegia; diffuse PVL often results in cognitive and behavioral deficits. The principal neuropathologic sequela of either focal or diffuse PVL is loss of cerebral white matter from deficiency of myelin and consequent ventriculomegaly.

The pathogenesis of PVL generally involves ischemic-hypoxemic injury to cerebral white matter. The two major contributors to the ischemia-hypoxemia are immaturity of the brain and impairment of cerebral blood flow. The vascular supply of an immature brain is characterized by an incomplete development of penetrating cerebral arteries, which renders the cerebral tissue susceptible to ischemic-hypoxemic injury. Moreover, the immature precursors of oligodendroglial cells, in contrast to mature oligodendrocytes, are intrinsically vulnerable to ischemic-hypoxemic injury as well as to injury during subsequent reperfusion and reoxygenation. Whereas the cerebral blood flow in healthy term neonates is maintained within a narrow range, despite fluctuations in systemic blood pressure, autoregulation of cerebral blood flow is impaired in preterm neonates, especially sick and extremely immature infants such as the baby in the vignette. A pressure-passive cerebral circulation in preterm neonates makes them vulnerable to ischemia when systemic blood pressure falls and to hemorrhage when systemic blood pressure rises.

Oxygen free radicals are the principal mediators of tissue injury during reperfusion and reoxygenation of previously ischemic-hypoxemic tissue. These highly reactive compounds have an uneven number of electrons in the outermost orbital that can react with various cellular components and cause irreversible injury in the form of lipid peroxidation, membrane lysis, and

cell necrosis. The primary oxygen free radicals involved in the pathogenesis of PVL are superoxide anion, hydrogen peroxide, and hydroxyl radical. The latter, the most toxic form of oxygen free radical, is produced in the presence of iron, which may be deposited at the site of local injury following hemorrhage that may accompany PVL. The deficiency of antioxidant enzymes, such as superoxide dismutase, glutathione peroxidase, and catalase, in immature precursors of oligodendroglial cells and other neuronal cells of cerebral white matter makes them vulnerable to oxidant injury.

The Pco_2 in arteriolar blood influences cerebral blood flow. A high Pco_2 (hypercarbia) induces vasodilation by increasing perivascular hydrogen ion concentration and increases the cerebral blood flow. An increase in the availability of oxygen as well as the substrate resulting from such cerebral vasodilation protects against ischemic-hypoxemic injury to the neuronal cells. In contrast, a low Pco_2 (hypocarbia) induces vasoconstriction and decreases the cerebral blood flow. It is plausible, therefore, that sustained hypocarbia can result in poor perfusion of the brain and consequent ischemic-hypoxemic injury to neuronal cells. However, unless the Pco_2 is regulated poorly during mechanical ventilation, resulting in sustained hypocarbia, carbon dioxide is an unlikely mediator of injury in PVL.

The role of growth factors, such as insulin-like growth factor (IGF)-1, in the mediation of neuronal injury in PVL is unclear. In neuronal cultures, IGF-1 and other growth factors, such as nerve growth factor and brain-derived neurotrophic factor, can prevent apoptosis and prolong neuronal survival. Such an effect may protect against the injury induced by apoptosis of oligodendroglial precursor cells characteristic of diffuse PVL. However, under certain conditions, including exposure to oxygen free radicals, IGF-1 and brain-derived neurotrophic factor can promote neuronal cell necrosis. Such an effect may accentuate the injury induced by oxygen free radicals in focal PVL. Thus, the net effect of IGF-1 in the mediation of neuronal injury in PVL is uncertain.

NO is produced in selected neurons of the brain, and the pathway for its synthesis involves the conversion of L-arginine to citrulline by the catalytic cytosolic enzyme nitric oxide synthase (NOS). At least three forms of NOS are recognized: a constitutive neuronal form (nNOS), a constitutive endothelial form (eNOS), and an inducible form (iNOS) found in astrocytes and microglia. Activation of eNOS results in NO-induced vasodilation and preservation of cerebral perfusion, which may be neuroprotective. Conversely, activation of iNOS results in generation of peroxynitrite, which may be neurotoxic. Activation of nNOS varies between the generation of neuroprotective nitrosonium ion and neurotoxic peroxynitrite. Thus, the net effect of NO in the mediation of neuronal injury in PVL is uncertain.

Several clinical, epidemiologic, neuropathologic, and experimental studies have suggested an association between maternal/placental/fetal infection and PVL. The development of PVL in infection is believed to be mediated by inflammatory cytokines acting either directly on oligodendroglial and other neuronal cells or indirectly through oxygen free radicals. The major cytokines involved in the pathogenesis of PVL appear to be interleukin (IL)-1-beta, IL-6, and interferon-gamma, all of which are neurotoxic. The role of tumor necrosis factor (TNF)-alpha, on the other hand, is unclear. In neuronal cultures, TNF-alpha shows little or no toxicity to oligodendroglial cells and, therefore, may not be the cytokine involved in the pathogenesis of PVL. However, under certain conditions, such as exposure to interferon-gamma, TNF-alpha may potentiate cytokine-mediated neurotoxicity to oligodendroglial and other neuronal cells. Thus, the net effect of TNF-alpha in the mediation of neuronal injury in PVL varies, depending on the milieu of other inflammatory cytokines.

References:

Shalak L, Perlman JM. Hemorrhagic-ischemic cerebral injury in the preterm infant: current concepts. *Clin Perinatol*. 2002;29:745-763

Volpe JJ. Neurobiology of periventricular leukomalacia in the premature infant. *Pediatr Res*. 2001;50:553-562

Volpe JJ. Hypoxic-ischemic encephalopathy: biochemical and physiological aspects. In:

Neurology of the Newborn. 4th ed. Philadelphia, Pa: WB Saunders; 2001:217-276

Volpe JJ. Hypoxic-ischemic encephalopathy: neuropathology and pathogenesis. In: *Neurology of the Newborn*. **4th ed. Philadelphia, Pa: WB Saunders: 2001:296-330**

Weindling M. Clinical aspects of brain injury in the preterm infant. In: Lagercrantz H, Hanson M, Evrard P, Rodeck C, eds. *The Newborn Brain: Neuroscience and Clinical Applications*. **Cambridge, England: Cambridge University Press; 2002:443-478**

Content Specification(s):

Understand the risk factors of intraparenchymal cysts/periventricular leukomalacia, and intraparenchymal echodensities
Understand the evolution of intraparenchymal cysts/periventricular leukomalacia, and intraparenchymal echodensities
Understand the outcome of intraparenchymal cysts/periventricular leukomalacia, and intraparenchymal echodensities

---

Figure 1. Coronal view on cranial ultrasonography.

periventricular cysts

periventricular cysts

right ventricle

left ventricle
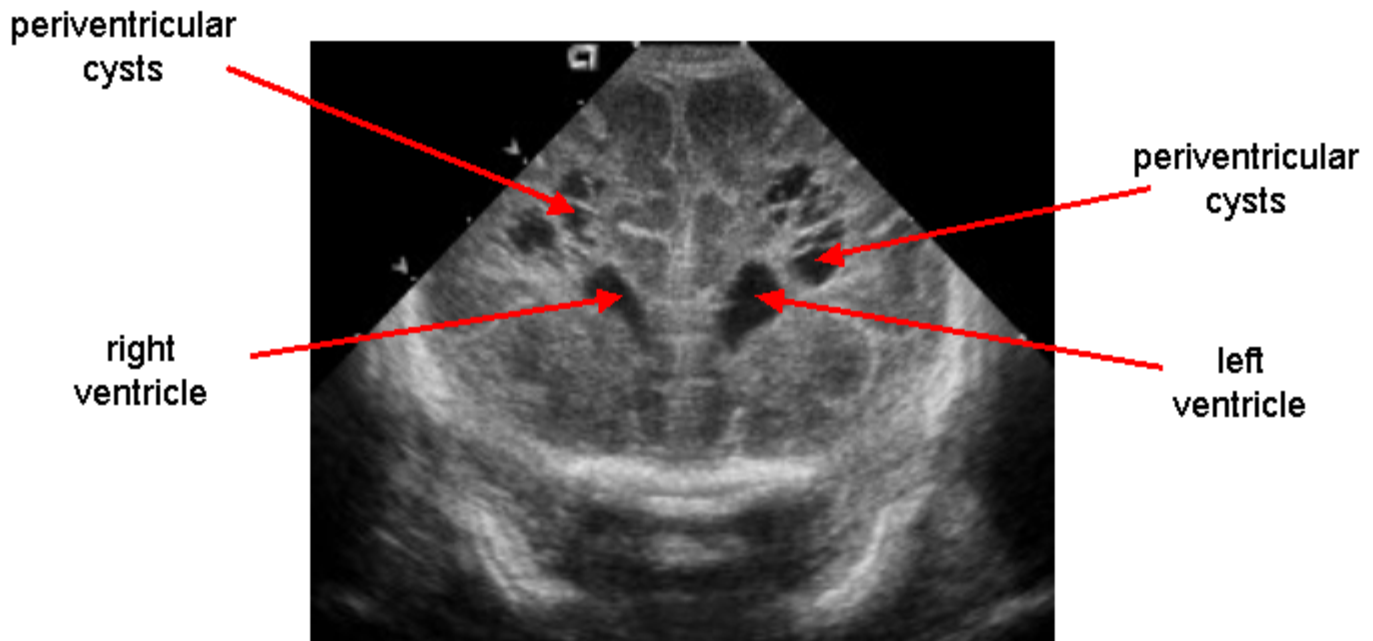
Bilateral cystic lesions in periventricular cerebral white matter

Figure 2. Sagittal view on cranial ultrasonography.

periventricular cysts
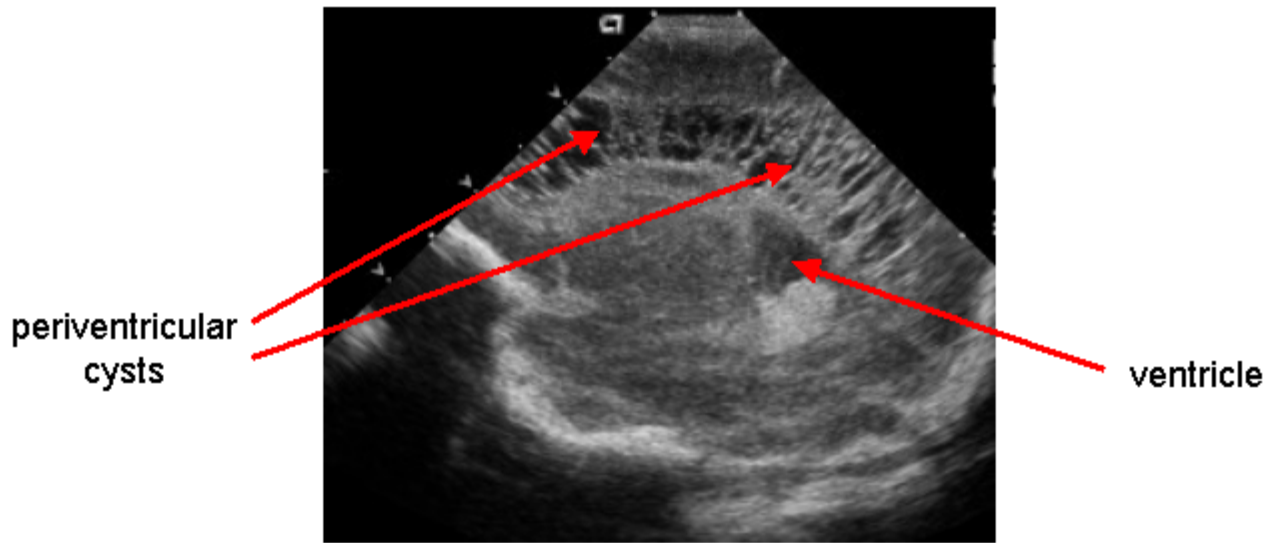
ventricle

Bilateral cystic lesions in periventricular cerebral white matter
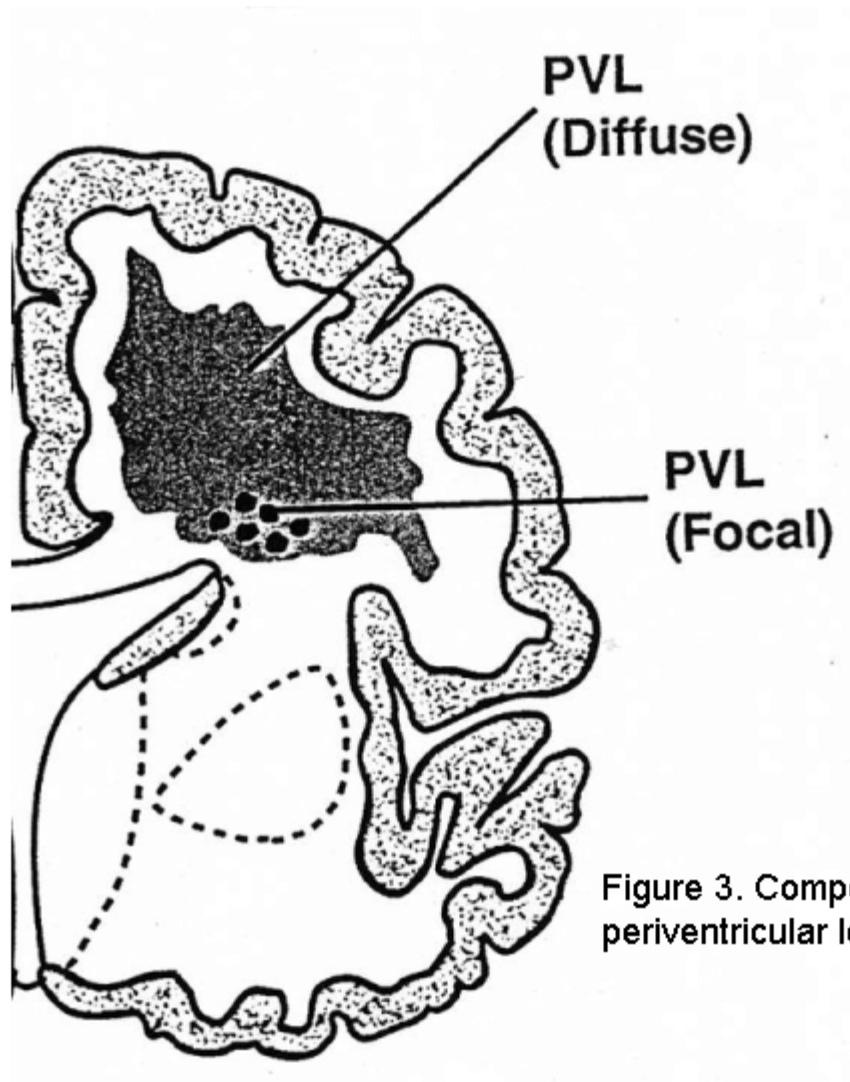
Figure 3. Components of periventricular leukomalacia.

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A 32 year old mother delivers a female infant at term. Family history includes Alzheimers, breast cancer, colon cancer, Hirschsprungs disease, and Duchenne Muscular Dystrophy.

Of the following, the familial disorder MOST appropriate for testing this infant during infancy or early childhood is

1. adenomatous polyposis

2. Alzheimer's disease

3. breast cancer

☒ 4. Duchenne muscular dystrophy

5. Huntington's disease

You selected 4, the correct answer is 1.

Studies of the human genome continue to identify genetic causes of many disorders, some of which manifest early in life and result in severe morbidity or death if treatment is delayed or not initiated. Genetic testing for familial disorders during infancy or early childhood is indicated when the patient can benefit from early diagnosis before the appearance of clinical manifestations and when effective treatments are available to correct or ameliorate the disorder. Newborn screening to identify such disorders is implemented throughout the United States. Other hereditary disorders, however, may not present problems or have their impact in childhood or may have no effective treatments available. However, some screening is performed for disorders for which treatments are currently unavailable to allow early entry into investigational protocols.

Familial adenomatous polyposis is characterized by intestinal polyps that progress to cancer if not removed. DNA-based predictive testing is available and is recommended routinely for adolescents. A positive result affords the adolescent the benefits associated with polypectomy via colonoscopy. Although testing can be performed safely in the early adolescent years, some families have requested and obtained testing on infants or young children to avoid the anxiety of uncertainty and to plan for colon evaluation at the appropriate time. Because polyps first occur at an average of 16 years of age and cancers have been reported in the late adolescent years, testing for familial adenomatous polyposis in infancy or later in childhood is the most appropriate of the conditions listed.

In some families that have a history of Alzheimer's disease, there is an association between the e4 allele of the apolipoprotein E gene on chromosome 19 and the risk for Alzheimers disease. Individuals who are heterozygous for the e4 allele possess a two- to three-fold increase in the risk for Alzheimer's disease and homozygous individuals have a 15-fold increase. No treatment is available for asymptomatic carriers, and experience with patients who have Huntington's disease and other autosomal dominant diseases of adult onset has shown that not all individuals at risk desire to be tested. In this situation, the infant can receive no benefit, carrier status could lead to discrimination in the future, and patient autonomy regarding testing requires waiting until the child is an adult.

Genetic testing for BRCA1 and BRCA2 genes associated with breast cancer in some families yields no opportunities for prevention or treatment for the infant or the child. In this condition, the genetic information is best presented to the patient, who can decide on resultant actions after providing informed consent. Thus, it is better that such information be presented to the

patient as an adult. Discovery of this gene provides no benefit in childhood and, despite of attempts at preserving confidentiality, knowledge of its presence could result in difficulties obtaining insurance coverage as an adult.

Duchenne muscular dystrophy is inherited as an X-linked recessive condition. Testing male infants of known or likely carriers would be reasonable. Testing in infancy presents no benefit to the female infant. Testing should be offered to potential female carriers later in life along with the genetic counseling needed to understand the implications of the testing. Although counseling and testing during adolescence may be prudent, the urgency for such testing is not as great as associated with adenomatous polyposis.

Huntington's disease (HD) is associated with deterioration and death, with disease onset generally occurring late in or after the childbearing years. Although genetic testing for HD has been available for some time, only 20% of at-risk individuals undergo the test. This disease has taught clinicians about the importance of an individual's right not to know. For that reason, testing for HD should not be offered or performed on infants or children; the choice should be left to individuals who have reached the adulthood.

Ethical arguments against testing children for adult-onset conditions include violation of the young person's future autonomy, breach of his or her confidentiality, and potential psychological harm to the young person. Arguments in favor of testing children for HD, breast cancer, Alzheimer's disease, and other diseases of adult onset also address the issues of autonomy, confidentiality, and psychological harm. Some young people may be sufficiently mature to make important decisions regarding their life.   Denying them this opportunity may be detrimental to their autonomy by not allowing them to adapt to their genetic knowledge during formative years. Not allowing such testing supersedes parental rights to make decisions based on their calculation of what is best for their child and family. Testing young children and disclosing results to their parents clearly breaches confidentiality, although parents are privy to most, if not all, sensitive information about their children. For adolescents, certain health information, such as sexual health, is held confidential. Psychological harms that may result from childhood testing include altered parent-child bonding, the vulnerable child syndrome, loss of self-esteem, feelings of guilt (including survivor guilt among those who have negative test results), stigmatization, discrimination, and associated anxiety or depression. Those in favor of testing minors cite the potential anxiety associated with waiting or not knowing and the inability to incorporate the test results into life planning earlier.

Guidelines for testing minors for genetic information with parental consent or parental disclosure of results are needed for such testing to be accepted practice. In general, the "wait until adulthood" guideline is the preferred default position, but some flexibility in dealing with specific situations is helpful.

References:

Dickenson DL. Can children and young people consent to be tested for adult-onset genetic disorders? *BMJ*. 1999;318:1063-1065.

Duncan RE. Predictive genetic testing in young people: when is it appropriate? *J Paediatr Child Health*. 2004;40:593-595

Hamilton BA, Wynshaw-Boris A. Basic genetics and patterns of inheritance. In: Creasy RK, Resnik R, eds. *Maternal-Fetal Medicine: Principles and Practice*. 5th ed. Philadelphia, Pa: Saunders; 2004:3-36

Mathew C. Postgenomic technologies: hunting the genes for common disorders. *BMJ*. 2001;322:1031-1034

Parker M, Lucassen A. Genetic information: a joint account? *BMJ*. 2004;329:165-167

Content Specification(s):

Know the components of a complete family history for genetic disorders
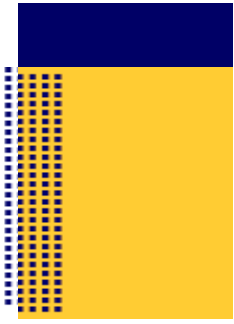
Understand how age at presentation (in utero, neonate, infancy, or later) affects the differential diagnosis of genetic disorders

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A 2-week-old male infant has a family history of severe recurrent infections. A male sibling had multiple episodes of suppurative lymphadenitis and died at 4 years of age from *Aspergillus fumigatus* pneumonia. A maternal uncle has recurrent carbuncles and perianal abscesses caused by *Staphylococcus aureus*.

Of the following, the laboratory method MOST likely to confirm a diagnosis in this infant is

1. immunoglobulin G measurement

2. immunoglobulin M measurement

3. nitroblue tetrazolium test

4. total hemolytic complement test

5. total lymphocyte count

You selected 4 , the correct answer is 3 .

Primary immunodeficiency disorders are genetically determined conditions that result in increased susceptibility to infections. More than 100 primary immunodeficiency disorders have been described. Primary immunodeficiency disorders may affect phagocytes, T lymphocytes, natural killer cells, B lymphocytes, or complement. Specific laboratory methods are used to identify which component of the host defense system is abnormal. The type and severity of infections guide the clinician toward which arm of the immune system to evaluate and which laboratory test to order.

Chronic granulomatous disease (CGD) is an inherited disorder in which phagocytic cells (neutrophils and macrophages) can ingest but cannot kill certain microorganisms. The incidence of CGD is 1 in 200,000 individuals. As described in the family history of the infant in the vignette, most affected patients present in early childhood with recurrent skin infections, suppurative lymphadenitis, or pneumonia. They also may develop granulomas of the skin or gastrointestinal tract; osteomyelitis; and perianal, hepatic, or splenic abscesses. Affected patients are particularly susceptible to infections by catalase-producing microorganisms. Catalase permits microorganisms to break down hydrogen peroxide. If the NADPH oxidase complex is deficient, the phagocyte cannot generate sufficient oxygen radicals to kill the microorganism. *S aureus*, *Serratia marcescens*, *Pseudomonas cepacia*, *A fumigatus*, and *Torulopsis (Candida) glabrata* are the most common microorganisms infecting patients who have CGD.

The ability of phagocytes to assemble the enzyme NADPH oxidase is impaired in patients who have CGD. The NADPH oxidase complex is necessary to trigger the respiratory burst (increase in oxygen consumption) and generate microbicidal oxygen radicals and hydrogen peroxide.

The NADPH oxidase complex consists of five component proteins. Two component proteins, gp91 ^{phox} and p22 ^{phox}, are bound to the phagosomal membrane and make up the subunits of cytochrome b$_{558}$. The other three component proteins-p47^{phox}, p67 ^{phox} , and GTPase rac-are cytoplasmic proteins that are recruited to the phagosomal membrane after stimulation by phagocytosis (^{phox} is an abbreviation for phagocytic oxidase). These three proteins combine with cytochrome b$_{558}$ to act as the enzyme NADPH oxidase. This enzyme complex catalyzes the oxidation of NADPH to produce superoxide anions:

NADPH + 2O$_2$à NADP$^+$ + 2O$_2^-$ + H$^+$

Superoxide then is converted to the toxic metabolite, hydrogen peroxide, by the action of superoxide dismutase:

$$2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$$
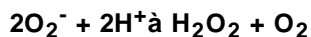
Within the azurophilic granules of the neutrophil, hydrogen peroxide combines with chloride by the action of myeloperoxidase:

$$H_2O_2 + 2Cl \rightarrow 2HOCl$$

HOCl is a powerful oxidant that causes bacterial cell wall dissolution.

The most common defect in CGD is an X-linked mutation that results in decreased production of gp91 ^{phox}. This mutation accounts for approximately 60% of CGD cases. Approximately 30% of affected patients have a genetic defect in the production of p47^{phox}. This mutation has an autosomal recessive inheritance pattern.

The nitroblue tetrazolium (NBT) test is a dye reduction test used to diagnose CGD. Neutrophils are mixed with colorless NBT dye in the presence of an inflammatory stimulant such as *Candida*. Normal phagocytes ingest the NBT dye, and the resulting respiratory oxidative burst reduces NBT to purple-blue formazan. Because CGD phagocytes do not have an oxidative burst, the NBT remains colorless.

Immunoglobulin (Ig) levels are measured to evaluate humoral immunodeficiencies that result in recurrent pyogenic respiratory tract infections with encapsulated bacteria such as *Haemophilus influenzae* and *S pneumoniae*. Hereditary agammaglobulinemia (Bruton agammaglobulinemia) is an X-linked disorder characterized by low or absent levels of IgG and IgM. The hyper-IgM syndrome is characterized by low serum concentrations of IgA, IgG, and IgE and markedly elevated IgM levels. Patients who have hyper-IgM syndrome may present in infancy with *Pneumocystis carinii* pneumonia. The types of microorganisms reported in the vignette make immunoglobulin abnormalities less likely than CGD.

Total hemolytic complement test is used to detect deficiencies in complement, another component of the immune system. Complement deficiencies typically are associated with infections caused by neisserial organisms, hereditary angioedema, membranoproliferative glomerulonephritis, and systemic lupus erythematosus.

Total lymphocyte counts are used to evaluate B- or T-cell immunodeficiency disorders such as severe combined immunodeficiency disorders, ataxia telangiectasia, DiGeorge anomaly, and Wiskott-Aldrich syndrome. These counts are not helpful in diagnosing phagocytic disorders. Patients who have B-cell deficiencies develop recurrent pyogenic infections. Patients who have T-cell deficiencies are susceptible to opportunistic viral, protozoal, and fungal infections.

References:

Backerman S, Backerman P, Strausbauch P. *Backerman's ABC's of Interpretive Laboratory Data*. 4th ed. Scottsdale, Ariz: Interpretive Laboratory Data Inc; 2002:171, 325-326, 372-374, 394

Buckley RH. Primary immunodeficiency diseases. In: Paul WE, ed. *Fundamental Immunology*. 5th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2003:1593-1620

Kamani NR. eMedicine: chronic granulomatous disease. Available at: http://www.emedicine.com/ped/topic1590.htm. Accessed November 2004

Rosen FS. Primary immunodeficiency. In: Roitt I, Brostoff J, Male D, eds. *Immunology*. 6th ed. Edinburgh, Scotland: Mosby; 2001:303-311

Content Specifications:

Know the laboratory methods (nitroblue tetrazolium, quantitation of immunoglobulins IgM, quantitation
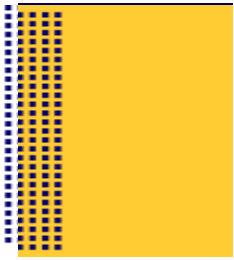
of immunoglobulins IgG) for diagnosing immune deficiencies

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You work in a perinatal center that has active services in genetics and maternal-fetal medicine. Infants delivered by these services usually are referred to you for delivery room care and neonatal care. Prenatal diagnosis of the fetal condition is usual.

Of the following, the fetal condition MOST likely to predispose to fetal heart rate (FHR) abnormalities during labor is

1. Down syndrome

2. meningomyelocele

3. Potter syndrome

4. prematurity

5. trisomy 18

You selected 4, the correct answer is 3.

Potter syndrome occurs in about 1 in 4,000 births and is associated with renal agenesis and resultant oligohydramnios. In contrast, Potter sequence refers to conditions characterized by diminished amniotic fluid in the presence of kidneys. The oligohydramnios associated with these conditions may result from amniotic fluid loss or decreased fetal urinary output from renal or urinary tract abnormalities. Fetal compression due to the lack of amniotic fluid results in chest compression, limb contractures, distinctive "compressed" facial features, pulmonary hypoplasia, and respiratory failure after birth. The oligohydramnios predisposes the infant during labor to cord compression and resultant FHR abnormalities, which are more likely due to the direct effect on the cord than to fetal effects of hypoxia. Because variable decelerations reflect abnormal umbilical cord blood flow, frequent variable decelerations may occur early in labor when the cord is not protected in Potter syndrome or sequence. Prolonged labor may compromise umbilical cord blood flow to the fetus that progresses to fetal acidosis with delayed recovery of the FHR.

Down syndrome may be associated with fetal anomalies, most of which do not affect the infant's tolerance for labor and vaginal delivery. FHR monitoring in labor can be interpreted using the same criteria as for infants who do not have Down syndrome.

Meningomyelocele often is diagnosed prenatally. The criteria for interpreting FHR patterns during labor in fetuses that have meningomyelocele are unchanged from those used in monitoring of normal fetuses.

Prematurity affects the median baseline FHR. At 28 weeks' gestation, the baseline heart rate is 150±20 beats/min. There is variability in FHR, albeit at lower amplitude (eg, 5 beats/min) than seen near term. A flat baseline reading should not be attributed solely to prematurity. Vibroacoustic stimulation results in a reactive (normal) response to nonstress testing in 90% of preterm fetuses that are at least at 26 weeks' gestation. FHR monitoring during labor of the preterm fetus can be useful as long as the gestational age-specific norms are considered.

Fetuses that have trisomy 18 have basal FHR rates and responses to hypoxia similar to those seen in normal fetuses, unless specific renal anomalies result in oligohydramnios.

References:

Intrapartum assessment. In: Cunningham FG, Gant NF, Leveno KJ, Gilstrap LC, Hauth JC,

Wenstrom KD, eds. *Williams Obstetrics*. 21st ed. New York, NY: McGraw-Hill; 2004:331-360

Parer JT, Nageotte MP. Intrapartum fetal surveillance. In: Creasy RK, Resnik R, eds. *Maternal-Fetal Medicine: Principles and Practice*. 5th ed. Philadelphia, Pa: WB Saunders; 2004:403-427

Parilla BV. Evaluation of the intrapartum fetus. In: Fanaroff AA, Martin RJ, eds. *Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. 7th ed. St. Louis, Mo: Mosby; 2002:131-138.

Content Specification(s):

Know how to assess fetal well-being during labor
Understand the significance, interpretation, and management of variable fetal heart rate decelerations in labor

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You are examining a 28-hour-old female infant who was born at 41 weeks' gestation and had meconium aspiration syndrome. On physical examination, she has normal blood pressure, pink color, normal perfusion, and mild hypotonia. She responds to touch and has no dysmorphic features. She is asleep and breathing with the oscillation of the ventilator. She is being treated with a fraction of inspired oxygen (Fio_2) of 1.0, high-frequency oscillation (mean airway pressure, 21 cm H_2O; frequency, 8 Hz; power, 48 cm H_2O), fentanyl, surfactant, dopamine, epinephrine, and dexamethasone. Chest radiography shows patchy infiltrates scattered throughout the lung fields and lungs expanded to the ninth rib in the right hemithorax. Umbilical arterial blood gas measurements are: pH, 7.31; $Paco_2$, 46 torr; Pao_2, 48 torr; and base excess, 0 mEq/L. Oxygen saturation in the right hand and right foot is 93% and 86%, respectively.

Of the following, the intervention that is MOST likely to improve oxygenation with the least risk for this infant is

1	extracorporeal membrane oxygenation
2	high-frequency jet ventilation
3	inhaled nitric oxide
☒ **4**	liquid ventilation
5	surfactant lavage

You selected **4**, the correct answer is **3**.

A complex array of pathophysiologic disturbances occurs after meconium is aspirated into the lungs of newborns. Mechanical obstruction of airways, chemical pneumonitis, surfactant dysfunction, and pulmonary hypertension contribute to segmental hyperexpansion and atelectasis, ventilation-perfusion mismatching, inflammation, and right-to-left shunting through the foramen ovale or ductus arteriosus. Hypoxemia, hypercarbia, and respiratory acidosis may occur.

Supplemental oxygen and mechanical ventilation are used to maintain acceptable oxygenation and ventilation goals. The infant described in the vignette is poorly oxygenated, despite acceptable ventilation and acid-base balance with an Fio_2 of 1.0; high settings on high-frequency oscillation; administration of surfactant; and cardiac output supported by dopamine, epinephrine, and dexamethasone. The oxygenation index (OI), which quantifies the oxygenation response for the level of mechanical ventilation provided, is calculated by the following formula:

$$OI = Pao_2 \text{ (torr)} \times Fio_2 \times 100 / \text{mean airway pressure}$$

For the patient in the vignette, the OI is 43.8. An OI greater than 40 is an indication for use of extracorporeal membrane oxygenation (ECMO) when all medical interventions have been maximized. Although the infant in the vignette is being supported aggressively, some might consider additional interventions. Such interventions include inhaled nitric oxide (NO), hyperventilation to induce respiratory alkalosis, pharmacologic paralysis, administration of magnesium sulfate, surfactant lavage, change of ventilator to high-frequency jet ventilation (HFJV), volume ventilation or time-cycled pressure-limited ventilation, liquid ventilation, and administration of sildenafil.

Of the additional interventions suggested for treatment of hypoxemic respiratory failure due to meconium aspiration complicated by pulmonary hypertension, inhaled NO has been proven to be effective and safe for improving oxygenation and reducing the need for ECMO. Inhaled NO

can be administered easily through the ventilator circuit to reverse pulmonary hypertension selectively. NO normally is produced by pulmonary vascular endothelial cells. NO synthetase catalyzes the conversion of arginine and oxygen to citrulline and NO. NO then diffuses into the perivascular smooth muscle cell and activates guanylate cyclase to convert guanosine triphosphate into cyclic guanosine monophosphate (cGMP). cGMP produces pulmonary vascular smooth muscle relaxation, thereby improving pulmonary blood flow and reducing ventilation-perfusion mismatching. Inhalation of NO into alveoli is an alternative route for delivery to pulmonary vascular smooth muscle cells to maintain normal pulmonary vascular resistance when the endothelial NO supply is insufficient (Figure 1). Once in the smooth muscle cell, NO activates guanylate cyclase, then diffuses into the pulmonary blood vessels, where it binds with hemoglobin to form methemoglobin. Methemoglobin is reduced rapidly, yielding nontoxic nitrates that are excreted in the urine. In rare patients who have abnormal methemoglobin reductase or at high doses of inhaled NO (>20 ppm), the conversion is slow or enzyme activity is overwhelmed, and methemoglobinemia may occur. Serial methemoglobin levels should be measured to monitor this risk. The other major concern with inhaled NO is production of nitrogen dioxide and peroxynitrites because NO is a very reactive oxygen species. Continuous monitoring of nitrogen dioxide levels in exhaled gas to keep levels lower than 5 ppm and limiting the duration of inhaled NO exposure are recommended to reduce such risks.

ECMO is a proven treatment for hypoxemic respiratory failure unresponsive to maximal medical therapy. However, cardiopulmonary bypass is invasive, and the risks are greater than for a trial of inhaled NO. Hemorrhage, air emboli, thromboemboli, ischemic brain injury, hypertension, renal insufficiency, exposure to large amounts of blood, and mechanical complications may complicate the course of critically ill infants receiving cardiopulmonary bypass. Despite a higher risk for complications, outcomes for critically ill infants who are treated with or without cardiopulmonary bypass do not differ. This suggests that the underlying cause for morbidity is the illness itself and that safeguards to minimize complications of ECMO generally are successful. Although proven successful for severe meconium aspiration, ECMO is not preferred over inhaled NO administration because of the invasiveness and potential risks. Nevertheless, arrangements for ECMO should be considered in critically ill infants because the need for ECMO has been shown to be 64% to 71% in control patients compared with 40% to 46% in those receiving inhaled NO.

HFJV has not been proven effective in large, multicenter, randomized trials for treatment of severe meconium aspiration syndrome. The infant described in the vignette is critically ill and at high risk for dying from hypoxemic respiratory failure and pulmonary hypertension. During conversion from high-frequency oscillation to HFJV, pulmonary hypertension may worsen. If inhaled NO and ECMO are not available and the patient continues to deteriorate, alternative ventilation modes such as HFJV, volume ventilation, and other interventions could be considered.

Liquid ventilation devices using perfluorocarbons to carry oxygen and carbon dioxide have been successful in animal studies, but no clinical trials in human infants have demonstrated efficacy and safety in meconium aspiration syndrome. Liquid ventilation use should be limited to the context of clinical research.

Surfactant administered as a bolus has been found effective and safe in small numbers of neonates who had meconium aspiration studied in randomized trials. Surfactant lavage, however, has not been proven effective and safe in preliminary clinical trials. As with liquid ventilation, surfactant lavage for severe meconium aspiration syndrome should be used within the context of clinical research.

References:

Ballard RA, Hansen TN, Corbet A. Respiratory failure in the term infants. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Disease of the Newborn*. Philadelphia, Pa: Elsevier Saunders; 2005:705-722

Kinsella J, Abman SH. Special ventilatory techniques and modalities. III. Inhaled nitric oxide therapy. In: Goldsmith JP, Karotkin EH, eds. *Assisted Ventilation of the Neonate.* 4th ed. Philadelphia, Pa: Saunders; 2003:235-248

Lewis FC, Reynolds M, Arensman RM. Extracorporeal membrane oxygenation. Goldsmith JP, Karotkin EH, eds. *Assisted Ventilation of the Neonate.* 4th ed. Philadelphia, Pa: Saunders; 2003:261-277

Mercier JC, Lacaze T, Storme L, et al. Disease-related response to inhaled nitric oxide in newborns with severe hypoxaemic respiratory failure. *Eur J Pediatr*. 1998;157:747-752

The Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. *N Engl J Med*. 1997;336:597-604

Spitzer AR, Greenspan JA, Fox WW, Shaffer T. Special ventilatory techniques and modalities. II. Lung protective strategies and liquid ventilation. In: Goldsmith JP, Karotkin EH, eds. *Assisted Ventilation of the Neonate.* 4th ed. Philadelphia, Pa: Saunders; 2003:219-234

<u>**Content Specifications**</u>:

Understand the prevention and management of meconium aspiration syndrome
Understand the indications for and techniques for administration of inhaled nitric oxide
Understand the risks of administration of inhaled nitric oxide
Understand the indications for and techniques of high frequency ventilation
Understand the indications for and techniques of extracorporeal membrane oxygenation

PREVIOUS   NEXT

Figure. Nitric oxide and the lung.
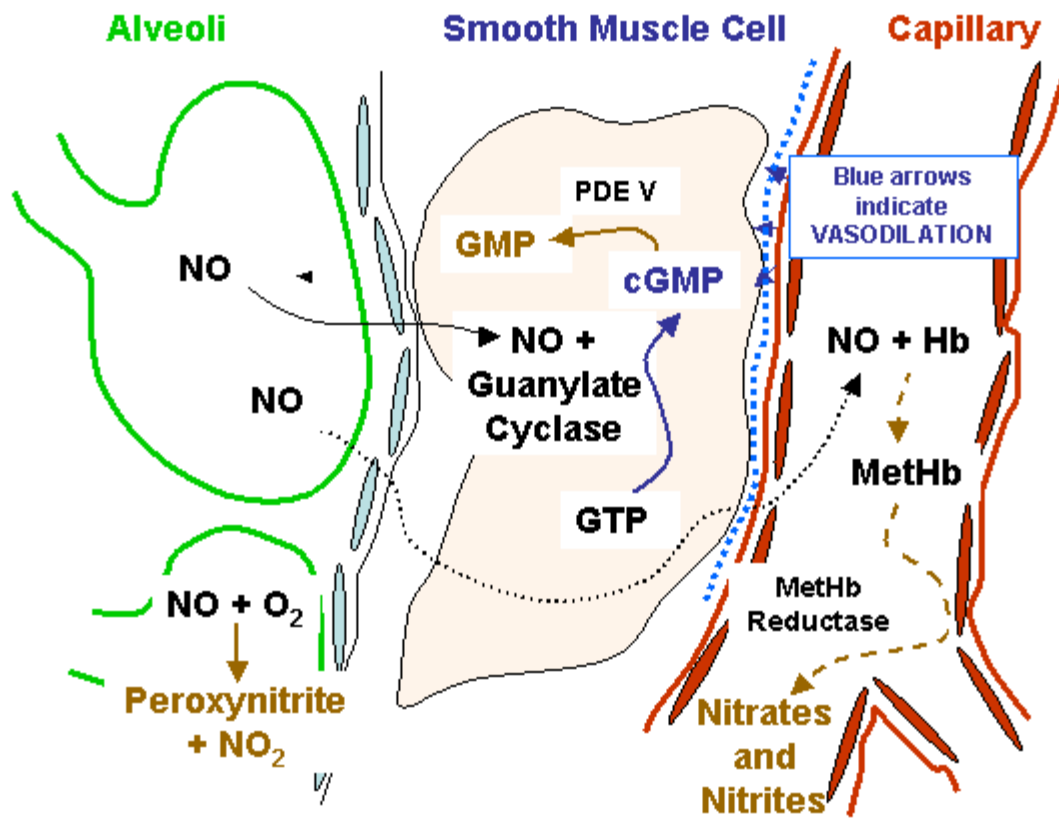
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An apparently healthy male was born vaginally to a gravida 2 African-American mother at 38 weeks' gestation. No apparent risk factors for hyperbilirubinemia are noted. He is scheduled to be discharged with his mother 25 hours after birth. Nursing notes indicate jaundice on the face and upper trunk. The infant is breastfeeding well, has passed meconium, and is voiding regularly. Following nursery protocol, transcutaneous bilirubin concentration is measured at 8.0 mg/dL (136.8 mcmol/L), which you assess for the risk of subsequent significant hyperbilirubinemia using the hour-specific bilirubin nomogram (Figure).

Of the following, the MOST appropriate plan of action at this time is to

☒ 1   consult an audiologist

2   delay discharge and repeat the bilirubin measurement in 8 to 12 hours

3   institute phototherapy

4   send the infant home after scheduling a follow-up evaluation in 1 week

5   send the infant home after scheduling a follow-up evaluation in 2 days

You selected 1, the correct answer is 2.

The bilirubin concentration measured in the infant in the vignette corresponds to the 95th percentile on the nomogram, which places the infant in the high intermediate risk category for development of severe hyperbilirubinemia. Although the infant's history presents no risk factors, hemolysis is the most common underlying reason for early hyperbilirubinemia, and incompatibility in the ABO blood grouping is responsible for most cases. Screening tests for blood group incompatibility should be ordered and the history reviewed for jaundice in the sibling or family. Because follow-up requires accurate bilirubin measurements, measuring total serum bilirubin at this time, delaying discharge, and obtaining another measurement prior to discharge would be most helpful in planning care and follow-up.

Audiology testing is not useful in determining clinical management of bilirubin at this level. Abnormal test results at this time suggest a false-positive result or congenital hearing loss. Guidelines from the American Academy of Pediatrics do not suggest phototherapy for infants at medium risk for hyperbilirubinemia if the bilirubin concentration remains below 10 mg/dL (171 mcmol/L) at 25 hours after birth. A total serum bilirubin is preferred for accuracy in serial measurements. Using total serum bilirubin is essential if phototherapy becomes necessary; skin color and transcutaneous measurements are not accurate when used in conjunction with phototherapy.

Discharging a baby who has jaundice near the 95th percentile at this age with follow-up delayed for 1 week places the child at risk for developing bilirubin levels that exceed those recommended for phototherapy and that may cause brain injury. Additionally, discharge at this age requires follow-up in 1 to 3 days for many reasons unrelated to icterus. Sending the child home with re-evaluation in 2 days without assessing the rate of bilirubin increase and the cause for the jaundice places the child at risk of developing potentially toxic bilirubin levels before being seen again.

Reference:

American Academy of Pediatrics, Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*.

2004;114:297-316

Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics*. **1999;103:6-14.**

Figure. Hour-specific nomogram for assessing bilirubin levels. Reprinted with permission from Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics*. **1999;103:6-14.**

Content Specifications:

Understand bilirubin physiology in the fetus and neonate
Know the factors associated with an increase in neonatal serum bilirubin concentrations
Understand the indications for use, the mechanism of action, the efficacy, and the dose-response relationship of phototherapy in the treatment of neonatal hyperbilirubinemia

PREVIOUS   NEXT

Nomogram for designation of risk in 2840 well newborns at 36 or more weeks' gestational age with birth weight of 2000 g or more or 35 or more weeks' gestational age and birth weight of 2500 g or more based on the hour-specific serum bilirubin values

Subcommittee on Hyperbilirubinemia, Pediatrics 2004;114:297-316

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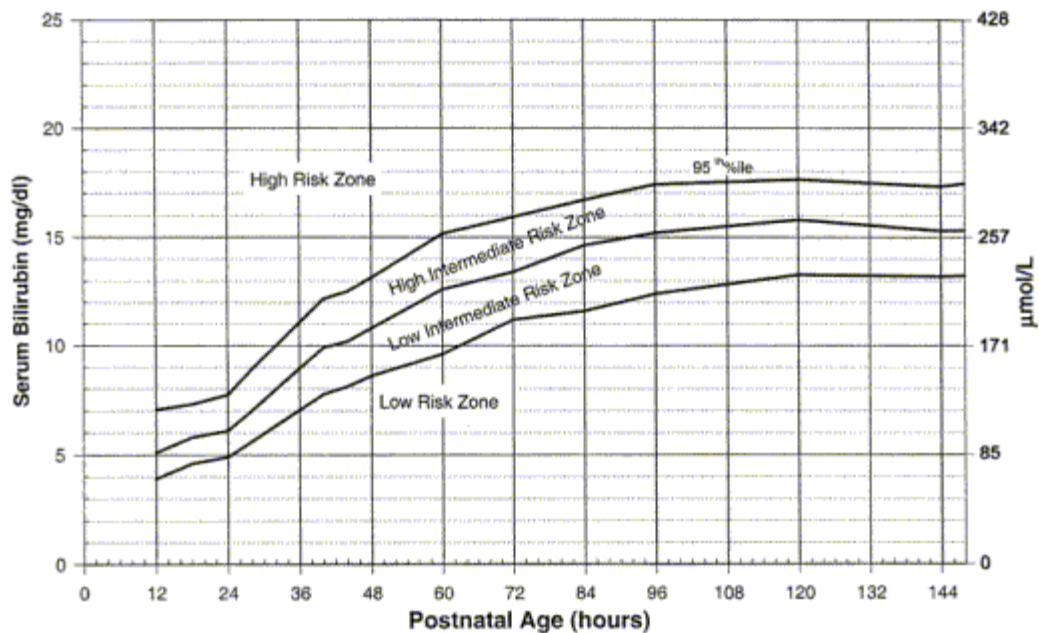
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using IE 8

A 24-year-old primiparous woman is admitted to the hospital at 32 weeks' gestation with a 1-week history of rapidly worsening hypertension and proteinuria. In your discussion with the residents and medical students regarding this case, you focus on the systemic endothelial dysfunction associated with pregnancy-induced hypertension (PIH). Specifically, you explain that binding of proangiogenic placental growth factor (PlGF) and vascular endothelial growth factor by an antiangiogenic protein, soluble fms-like tyrosine kinase 1 (sFlt1), lowers concentrations of PlGF, which causes endothelial dysfunction, followed by hypertension and proteinuria.

Of the following, the MOST accurate statement regarding urinary excretion of PlGF and its relationship to PIH is that

1. decreased urinary PlGF concentrations are noted by the end of the first trimester

2. female fetal sex results in higher urinary PlGF concentrations in PIH

3. ✗ gestational hypertension is predicted by lowered urinary PlGF concentrations in the second trimester of pregnancy

4. reduction in urinary PlGF is noted among normotensive mothers delivering small-for-gestational-age infants

5. severity of PIH correlates with the magnitude of urinary PlGF reduction

You selected **3**, the correct answer is **5**.

PIH is a common major complication of pregnancy that may result in severe maternal complications (seizures, coagulopathy, cerebral hemorrhage, renal failure) and fetal compromise (intrauterine growth restriction, preterm birth). PIH occurs in 4% of pregnancies that extend into the second trimester. Because the diagnostic signs of preeclampsia (edema, high blood pressure, proteinuria, retinal changes, and hyperreflexia) predate clinical symptoms (which may involve many organ systems), screening for PIH is a mainstay of prenatal care. Predictive testing may be useful in identifying patients before signs or symptoms arise.

The underlying systemic endothelial dysfunction manifests as hypertension and proteinuria. The only known cure for PIH is delivery of the placenta. Screening blood pressure and urinary protein concentrations are essential components of prenatal care, but the interval between the onset of PIH and the development of severe complications can be brief. Although there are no current therapeutic options for PIH that is detected early, monitoring can lead to more timely delivery and, in some cases, maternal referral to facilities better able to handle the preterm infant. Knowledge of the pathologic events of preeclampsia ultimately may result in treatments directed at these processes rather than early, emergent delivery.

Studies of angiogenic factors among pregnant women who subsequently developed PIH show elevations of sFlt1 about 5 weeks before the onset of clinical manifestations of PIH. Hypertension, proteinuria, and glomerular endotheliosis were noted among rats given sFlt1 experimentally. In the early second trimester, reduced serum concentrations of PlGF antedate the onset of clinical signs. Because PlGF is a small molecule that passes readily into the urine, reductions in urinary PlGF have been analyzed among women being followed for the development of PIH. No differences in urinary PlGF were noted until late second trimester and early third trimester, and increasing severity of PIH was associated with greater reductions in urinary PlGF excretion. For women in the lowest quartile of urinary PlGF, the odds ratio (based on urinary concentrations of PlGF) for developing PIH at less than 37 weeks' gestation was 31.3

(95% confidence interval, 5.6 to 174.7).

Urinary PlGF concentrations were unaffected by fetal sex. Mothers who manifested gestational hypertension (elevated blood pressure without proteinuria) and normotensive mothers whose infants were small for gestational age had urinary PlGF concentrations similar to those in the control group.

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Content Specification(s):

Know the effects on the fetus of mild preeclampsia and its management
Know the effects on the fetus of severe preeclampsia, including HELLP syndrome, and its management

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You are asked to determine whether preterm twin males who have identical blood types are monozygotic or dizygotic twins. You request the pathology report on the placenta.

Of the following, the MOST common type of placentation in monozygotic twins is

1   dichorionic/diamniotic with a single placenta

2   dichorionic/diamniotic with two fused placentas

3   dichorionic/monoamniotic with two separate placentas

4   monochorionic/diamniotic with a single placenta

☒5   monochorionic/monoamniotic with a single placenta

You selected **5**, the correct answer is **4**.

Determining whether twins are monozygotic or dizygotic is important for social and medical reasons. Family members have a keen interest in whether their twins are identical or fraternal. The medical reason to determine zygosity is because monozygotic twins are the perfect match if a future organ or bone marrow transplant is needed. Examining the placenta and fetal membranes determines zygosity in approximately 20% of twin pairs.

The placenta has fetal and maternal components. The fetal portion develops from the chorionic sac. The maternal portion is derived from the endometrium. The chorion is the outer fetal membrane that appears thick and opaque. The amnion is the inner fetal membrane that appears thin and nearly transparent.

Monozygotic twins are the result of a single fertilized ovum splitting during the first 2 weeks after conception. The timing of the split results in different types of placentation. The most common (70%) form of placentation in monozygotic twins is monochorionic/diamniotic, which occurs when the fertilized ovum splits between 3 and 8 days after fertilization (Fig. 1). Monochorionic twin placentas may contain vascular anastomoses that can result in twin-twin transfusion syndrome.

Dichorionic/diamniotic placentas represent the second most common form of placentation in monozygotic twins, occurring in 30% of monozygotic twins and nearly 100% of dizygotic twins. Twins that have dichorionic/diamniotic placentas always have two separate placentas that either can be separate (Fig. 2) or fused (Fig. 3). Dichorionic/diamniotic placentas occur in monozygotic twins when the zygote splits between 1 and 3 days after fertilization.

Because the amniotic cavity develops within the chorion, dichorionic/monoamniotic placentation cannot occur.

Monochorionic/monoamniotic with a single placenta is a rare form of placentation that occurs in 1% of monozygotic twins (Fig. 4). A monochorionic/monoamniotic placenta develops when the zygote splits between days 9 and 12 after fertilization. Twins that have monochorionic/monoamniotic placentation are at the highest risk for fetal demise because umbilical cords can become entangled without a separating membrane. If twinning occurs beyond 12 days after fertilization, the monozygotic pair splits only partially, which results in conjoined twins. Conjoined twins always have monochorionic/monoamniotic placentation.

When two sperms fertilize two ova, dizygotic twins result. Dizygotic twins nearly always have dichorionic/diamniotic placentation. There is a case report of monochorionic/diamniotic dizygotic twins conceived by in vitro fertilization. Dichorionic/diamniotic placentas may fuse if

implantation sites are proximate. Fused placentas can be separated easily after birth.

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Content Specification(s):

Know the types of and effects on the mother of multiple gestation pregnancy
Know the morphologic development of the placenta

PREVIOUS   NEXT

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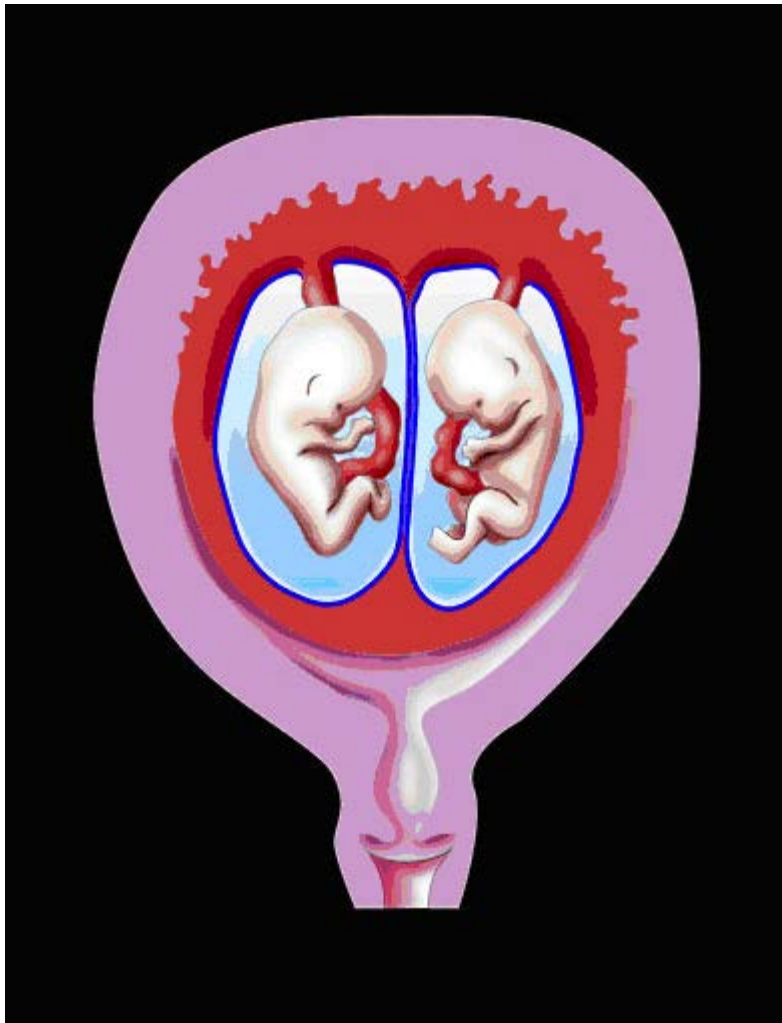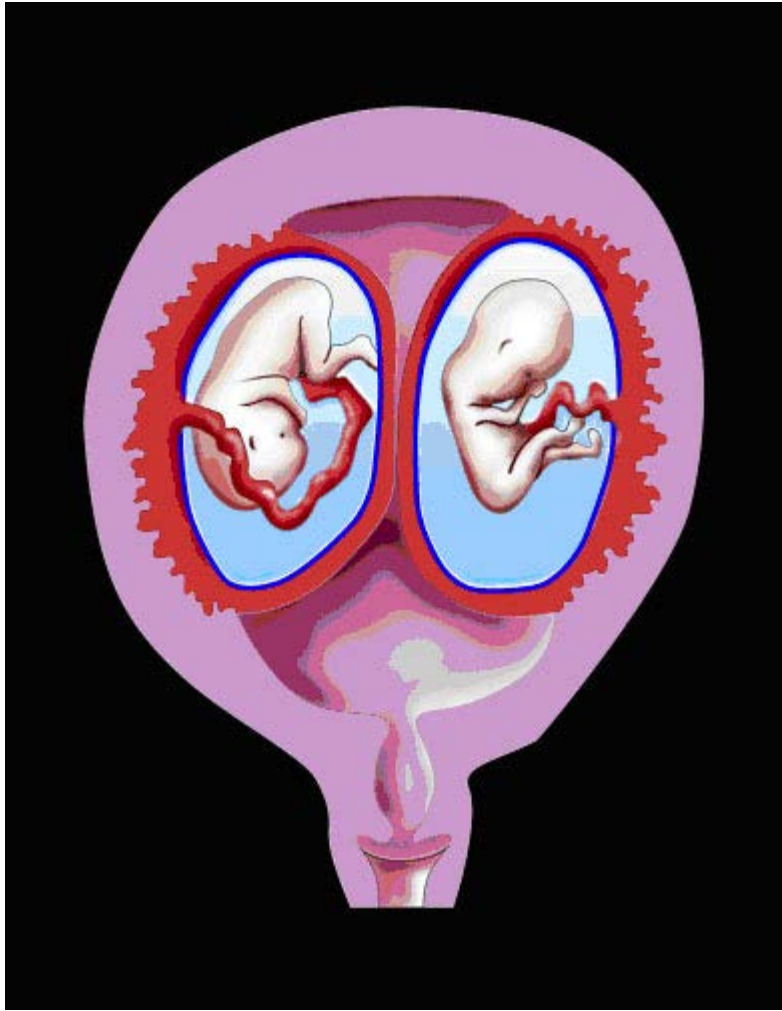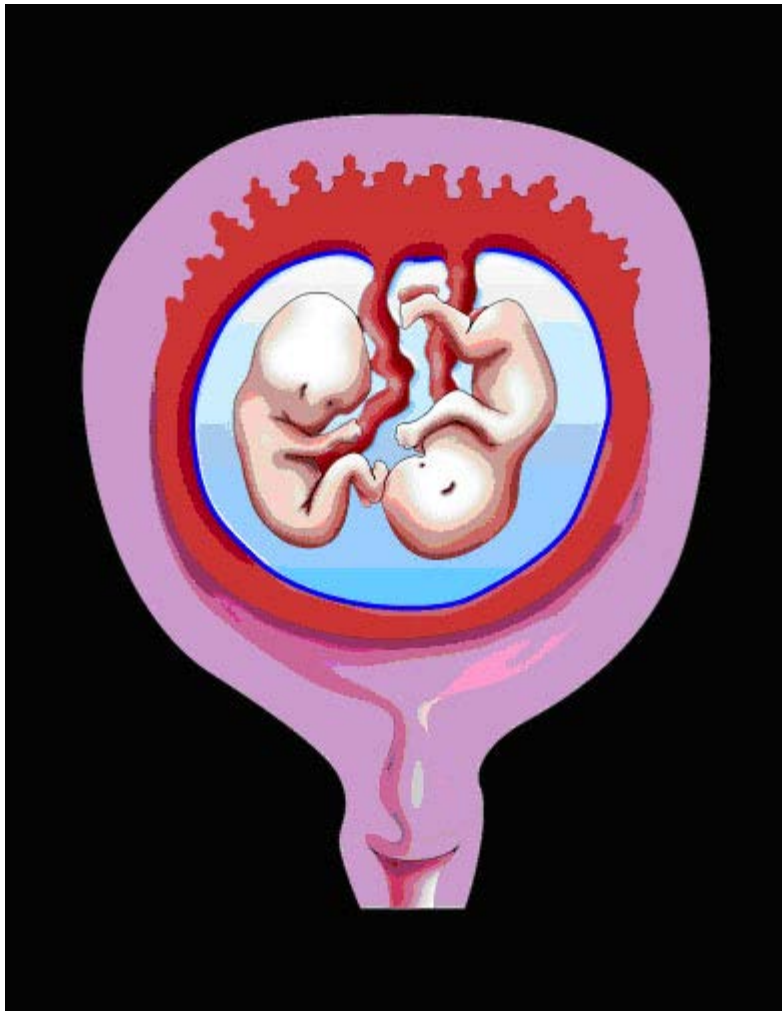
A 5-week-old Caucasian male infant who was born at 37 weeks' gestation has been receiving phototherapy with a blanket at home since his discharge at 2 days of age. Indirect bilirubin levels peaked at 18 mg/dL (308 mcmol/L) at 3 days of age and subsequently stabilized at 12 mg/dL (205 mcmol/L) after phototherapy was discontinued. Direct bilirubin levels remain less than 1 mg/dL (17.1 mcmol/L). His blood type is O-negative, and his mother's blood type is B-positive. An initial blood smear was normal, without evidence of hemolysis, and the reticulocyte count was 1% (0.01). The hematocrit at birth was 52% (0.52) and is now 44% (0.44). He is exclusively breastfed, growing appropriately, neurologically normal, and thriving. Physical examination shows scleral icterus, jaundiced skin under the diaper, and moist mucous membranes; no organomegaly, pallor, tachycardia, or other skin findings are evident. Urine is clear yellow, and stools are mushy and yellow-brown. He is the first baby for this mother, and no pregnancy, labor, or delivery complications occurred. Family history is positive for hypertension, diabetes, and neonatal jaundice in the mother and her twin brother, both of whom required phototherapy for 6 days after birth.

Of the following, the condition that is MOST likely contributing to jaundice in this infant is

1	Crigler-Najjar syndrome type I
2	Gilbert syndrome
☒ 3	Hypothyroidism
4	Lucey-Driscoll syndrome
5	Pyloric stenosis

You selected 3, the correct answer is 2.

The presence of jaundice beyond 3 weeks of age most often is associated with human milk feedings. However, more prolonged jaundice, as described for the infant in the vignette, requires additional evaluation because it may be a presenting sign for serious disease that requires urgent diagnosis or intervention (eg, biliary atresia, hypothyroidism, pyloric stenosis, cystic fibrosis). A complete history and physical examination supplemented with laboratory testing generally is sufficient to determine the diagnosis. The differential diagnosis for prolonged jaundice includes human milk jaundice, excessive bilirubin production, impaired bilirubin conjugation, increased enterohepatic circulation, and cholestasis syndromes (Table).

Gilbert syndrome is a defect in the gene for the enzyme uridinediphosphoglucuronate glucuronosyltransferase (UGT), which is responsible for conjugation of bilirubin within the hepatocyte. It affects about 6% of adults and typically presents during adolescence with mild indirect hyperbilirubinemia. This defect also has manifested in neonates who have additional icterogenic conditions. The most common polymorphism in Caucasians is an additional TA insertion in the TATAA box of the UGT 1A1 gene promotor (Figure). Homozygous individuals for the promotor defect have seven repeats-$(TA)_7TAA$ (7/7)-instead of the usual six repeats-$(TA)_6TAA$. The additional TA repeat leads to reduction in UGT activity and mild hemolysis. However, the promotor defect frequently is insufficient to cause clinical jaundice. Breastfeeding, ABO incompatibility, glucose-6-phosphate dehydrogenase deficiency, or hereditary spherocytosis in combination with the $(TA)_7TAA$ promotor defect has been associated with an increased incidence of elevated bilirubin levels in some populations of newborns. The infant described in the vignette most likely has human milk jaundice that is exacerbated by a defect in the 1A1 UGT gene (ie, Gilbert syndrome).

Genetic variations in the promotor or coding area defect of the UGT 1A1 gene, environmental factors, and the multifactorial nature of neonatal jaundice may account for the variation in hyperbilirubinemia among different newborn populations who have defects of the UGT 1A1 gene. For example, the most prevalent defect in neonates from Japan, Korea, and China involves the actual coding area of the UGT 1A1 gene (Figure). Specifically, there are missense mutations within the coding area, the most common being a G * A transition at nucleotide 211. This transition causes arginine to replace glycine at position 71. In contrast to the promotor defect in Caucasian infants, infants who have this coding area defect have higher bilirubin levels than those without the defect; additional icterogenic factors such as human milk are unnecessary to catalyze the effect, although exacerbation may occur.

Crigler-Najjar type I syndrome, like type II, is a rare disease that leads to very high levels of bilirubin soon after birth. Bilirubin encephalopathy and death may occur. Crigler-Najjar type I syndrome is due to complete absence of UGT 1A1 enzyme activity and is caused by mutations in any of the five exons coding for the UGT 1A1 enzyme (Figure). The inheritance pattern is autosomal recessive. Treatment requires exchange transfusion, phototherapy, and possibly liver transplantation. The infant in the vignette could have inherited the disease in an autosomal recessive pattern, but the bilirubin concentration stabilized at moderate levels at 5 weeks of age. In contrast, a progressive increase is seen with Crigler-Najjar syndrome whenever phototherapy is stopped.

Untreated primary hypothyroidism can be associated with prolonged jaundice in about 10% of affected newborns. Indirect hyperbilirubinemia predominates. UGT activity is low, although the mechanism is unclear. It has been speculated that the absence of thyroid hormone delays UGT and bilirubin transport development. The infant in the vignette does not demonstrate the clinical manifestations of primary congenital hypothyroidism: lethargy, hypotonia, edema, inactivity, poor feeding, cyanosis, mottled skin, coarse hair, hoarse cry, constipation, large tongue, large fontanelles, umbilical hernia, abdominal distention, or hypothermia. Of note, prolonged direct hyperbilirubinemia has been associated with central hypothyroidism and hypopituitarism.

Lucey-Driscoll syndrome (transient familial neonatal hyperbilirubinemia) is a rare familial disorder. Serum from mothers of affected infants contains high concentrations of an unidentified inhibitor of UGT that crosses the placenta to the fetus. All infants of mothers who have the inhibitor are affected. After birth, severe hyperbilirubemia occurs and may cause bilirubin encephalopathy and kernicterus. Exchange transfusion, aggressive phototherapy, and clearance of the inhibitor from the infant during the first weeks after birth resolve the hyperbilirubinemia. The infant in the vignette did not have severe hyperbilirubinemia or require exchange transfusion in the first days after birth.

Pyloric stenosis is a common disorder that is seen in 1 to 3 per 1,000 live births. Males are affected four times more often than are females. Firstborn infants also account for about 50% of those affected. Symptoms and signs may present after several weeks of age and include emesis, dehydration, metabolic alkalosis, and jaundice. Jaundice is predominately due to indirect hyperbilirubinemia and is present in 10% to 25% of infants at the time that vomiting begins. Jaundice resolves quickly after surgical intervention. UGT activity is decreased; some affected infants have the same UGT 1A1 promoter defect found with Gilbert syndrome. Because the infant in the vignette is gaining weight, thriving, and has no emesis or dehydration, pyloric stenosis is not likely contributing to the jaundice.

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Content Specification(s):

Know the pathogenesis, clinical course, diagnosis and management of human-milk jaundice. Understand the differential diagnosis, evaluation and approach to management of infants with indirect hyperbilirubinemia.

◀ PREVIOUS   NEXT ▶

Question 9 -- Table 1

Selected Causes of Jaundice Beyond 3 Weeks of Age

Human Milk Jaundice	Bilirubin Conjugation Defects	Hemolytic Defects	Cholestasis due to Hepatocellular Disorders	Cholestasis due to Ductal Disturbances
	Gilbert syndrome Crigler-Najjar syndrome type I Crigler-Najjar syndrome type II Transient familiar neonatal hyperbilirubinemia (Lucey-Driscoll syndrome) Pyloric stenosis Hypothyroidism	Erythrocyte Enzyme Defects • Glucose-6-phosphate deficiency • Pyruvate kinase deficiency and others Erythrocyte Structural Defects • Hereditary spherocytosis and others Infection • Bacterial, viral, and protozoal	Primary Hepatitis • Neonatal giant cell hepatitis • Infectious hepatitis (viral, bacterial, protozoal) Toxic Hepatitis • Bacterial sepsis or urinary tract infection • Parenteral alimentation Metabolic Disorders • Alpha-1-antitrypsin deficiency • Galactosemia • Tyrosinemia • Fructosemia • Glycogen storage disease type IV • Lipid storage diseases -- Niemann-Pick disease -- Gaucher disease -- Wolman disease Cerebrohepatorenal syndrome (Zellweger syndrome) Trisomy 18 Cystic fibrosis Familial idiopathic cholestasis (Byler disease) Hemochromatosis Idiopathic hypopituitarism	Bile plug syndrome Extrahepatic biliary atresia Alagille syndrome Intrahepatic biliary atresia Extrahepatic obstruction and choledochal cyst Hepatic or biliary tract tumors Cystic disease

Figure. Human UGT1A1 promoter, exon 1A1 and common exons 2 through 5.

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A 10-week-old female infant, whose birthweight was 690 g and estimated gestational age at birth was 26 weeks, has a systolic blood pressure of 92 mm Hg and a diastolic blood pressure of 68 mm Hg. Neonatal history is significant for initial respiratory distress managed with mechanical ventilation for 14 days, umbilical arterial catheterization for 7 days, and two courses of antimicrobial treatment for airway infection. The infant is breathing spontaneously, but she requires a fraction of inspired oxygen (Fio$_2$) of 0.42 to maintain adequate oxygen saturations. She is receiving full enteral feedings and daily oral doses of furosemide and hydrochlorothiazide. Renal ultrasonography with Doppler reveals normal renal architecture and reduced arterial blood flow to the left kidney. Findings on cranial ultrasonography are normal, as are measurements of serum electrolytes, blood urea nitrogen, and serum creatinine. You are planning treatment with an oral antihypertensive drug.

Of the following, the FIRST drug of choice for oral administration in the treatment of hypertension in this infant is

1. captopril
2. hydralazine
3. nifedipine
4. propranolol
5. spironolactone

You selected **4**, the correct answer is **1**.

The extremely low-birthweight infant described in the vignette has a clinical course and oxygen need at 36 weeks' postmenstrual age that are consistent with diagnoses of bronchopulmonary dysplasia (BPD) and renovascular hypertension. Neonatal hypertension is about two- to ninefold more common among preterm infants who have BPD than among those who have no lung disease, and its incidence varies with the severity of lung disease. Although the mechanism for hypertension in BPD remains unconfirmed, it may be related to chronic hypoxemia and its effects on peripheral vascular resistance; use of medications such as dexamethasone, xanthines, and bronchodilators and their effects on cardiovascular function; use of chronic diuretics and their effects on renal parenchyma; and chronic pulmonary hypertension with resultant cor pulmonale and its effects on salt-water homeostasis. Renovascular disorders are the most common cause for hypertension in neonates, especially in those treated with umbilical arterial catheters.

The oral drug of choice for the treatment of hypertension in the infant in the vignette is captopril, an angiotensin-converting enzyme (ACE) inhibitor. Understanding the mechanism of action of an ACE inhibitor in controlling hypertension requires an understanding of the renin-angiotensin system (Fig. 1). Renin is a proteolytic enzyme secreted by the juxtaglomerular apparatus in the kidney in response to various stimuli, principally a fall in renal perfusion pressure. Renin converts angiotensinogen, a plasma globulin synthesized in the liver, into a decapeptide, angiotensin I (Fig. 2). Angiotensin I has no appreciable activity, but is converted in the lungs by ACE to an octapeptide, angiotensin II. ACE is a membrane-bound enzyme on the surface of endothelial cells and is particularly abundant in the lung, which has a vast surface area of vascular endothelium. Angiotensin II is a potent vasoconstrictor, and its sustained action can result in vascular hyperplasia and hypertrophy. Angiotensin II is cleaved by aminopeptidase A into a heptapeptide, angiotensin III, which is cleaved further by aminopeptidase

N into a hexapeptide, angiotensin IV. Angiotensin III is a potent stimulator of adlosterone secretion, which promotes sodium and water retention; angiotensin IV stimulates the release of plasminogen activator inhibitor-1 from the endothelium, which increases blood viscosity. The actions of angiotensins, specifically angiotensin II and angiotensin III, increase blood pressure through changes in vascular tone as well as intravascular volume. ACE inhibitors exert their antihypertensive action by reversing these trends. Moreover, ACE inhibitors can suppress the vasoactive peptides bradykinin and kallidin and promote vasodilatation, which adds to the antihypertensive effect.

Captopril is one of the first ACE inhibitors used in clinical practice. Its starting oral dose is 0.01 to 0.05 mg/kg per dose administered at 8- to 12-hour intervals. The dose and the interval are adjusted according to the clinical response. Adverse effects may occur at doses higher than 0.15 mg/kg and include neurologic symptoms from decreased cerebral blood flow, oliguria from decreased renal blood flow, hyperkalemia from aldosterone suppression, and cough. The pharmacokinetic, safety, and efficacy profiles make captopril an attractive choice for single-agent treatment of neonatal hypertension.

Hydralazine is an arterial/arteriolar vasodilator whose mechanism of action remains uncertain. The starting oral dose is 0.25 to 1.0 mg/kg per dose administered at 6- to 8-hour intervals, with the dose and interval adjusted based on the clinical response. At doses higher than approximately 2.0 mg/kg, adverse effects may occur, including retention of sodium and water, reflex tachycardia, and a lupuslike syndrome. Concurrent use of a beta-adrenoceptor antagonist and a diuretic may be needed to lessen the adverse effects. Additional adverse effects of hydralazine include gastrointestinal irritation and agranulocytosis. The bioavailability of oral hydralazine is low because of its extensive first-pass metabolism in the liver and intestines. The less favorable pharmacokinetic and safety profiles of hydralazine restrict its use largely to patients who have severe hypertension that is refractory to other pharmacologic therapies.

Nifedipine is a dihydropyridine that blocks cellular entry of calcium ions by preventing the opening of voltage-gated L-type calcium channels. It exerts its antihypertensive action by inducing generalized arterial/arteriolar vasodilatation. The starting oral dose is 0.1 to 0.25 mg/kg per dose administered at 12-hour intervals. The dose is adjusted based on the clinical response. Adverse effects may be seen at doses higher than 1.5 mg/kg per dose, including reflex tachycardia and rapid, profound, and transient drops in blood pressure. Nifedipine is available in a capsule from which the contents must be drawn up in a syringe for any dose less than 10 mg, making the drug difficult to administer in neonates and inadvertent dosing errors common.

Propranolol is a beta-adrenoceptor antagonist that exerts its antihypertensive action by at least three mechanisms. First, propranolol induces a reduction in heart rate and stroke volume, with a resultant decrease in cardiac output (negative chronotropic and inotropic effects). Second, it reduces systemic vascular resistance by decreasing vasomotor tone. Third, it reduces the secretion of renin from the kidney, with consequent suppression of angiotensins. The starting oral dose is 0.25 to 0.5 mg/kg per dose administered at 6-hour intervals, and the dose is adjusted according to the clinical response. Adverse effects may be seen at doses higher than 3.5 mg/kg, including cardiac failure, hypoglycemia, and bronchoconstriction. The latter is of particular concern in infants who have significant lung disease.

Spironolactone is an aldosterone receptor antagonist that exerts its antihypertensive action by inhibiting sodium and water retention. The starting oral dose is 0.5 to 1.5 mg/kg per dose administered at 12-hour intervals, and the dose is adjusted based on the clinical response. At higher doses, adverse effects may include hyponatremia and potentially life-threatening hyperkalemia. The primary indication for spironolactone is treatment of hypokalemia associated with the use of a loop diuretic in infants who have BPD. A thiazide diuretic often is used in combination with a loop diuretic to reduce potassium loss in the urine (potassium-sparing effect). The addition of spironolactone to a combination of a loop diuretic and a thiazide diuretic, as being used for the infant in the vignette, offers little, if any, additional benefit.

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Figure 1. Renin-angiotensin system.

Figure 2. Formation of angiotensins I through IV from precursor angiotensinogen.

Content Specification(s):

Know how to manage hypertension in an infant

PREVIOUS   NEXT

Fig. 1. Renin-angiotensin system.

Angiotensinogen

C-Terminal - | V | L | L | H | F | P | H | I | Y | V | R | N | - N-Terminal

↑
Renin

Angiotensin I

| L | H | F | P | H | I | Y | V | R | N |

↑
ACE

Angiotensin II

| F | P | H | I | Y | V | R | N |

↑
Aminopeptidase A

Angiotensin III

| F | P | H | I | Y | V | R |

↑
Aminopeptidase N

Angiotensin IV

| F | P | H | I | Y | V |
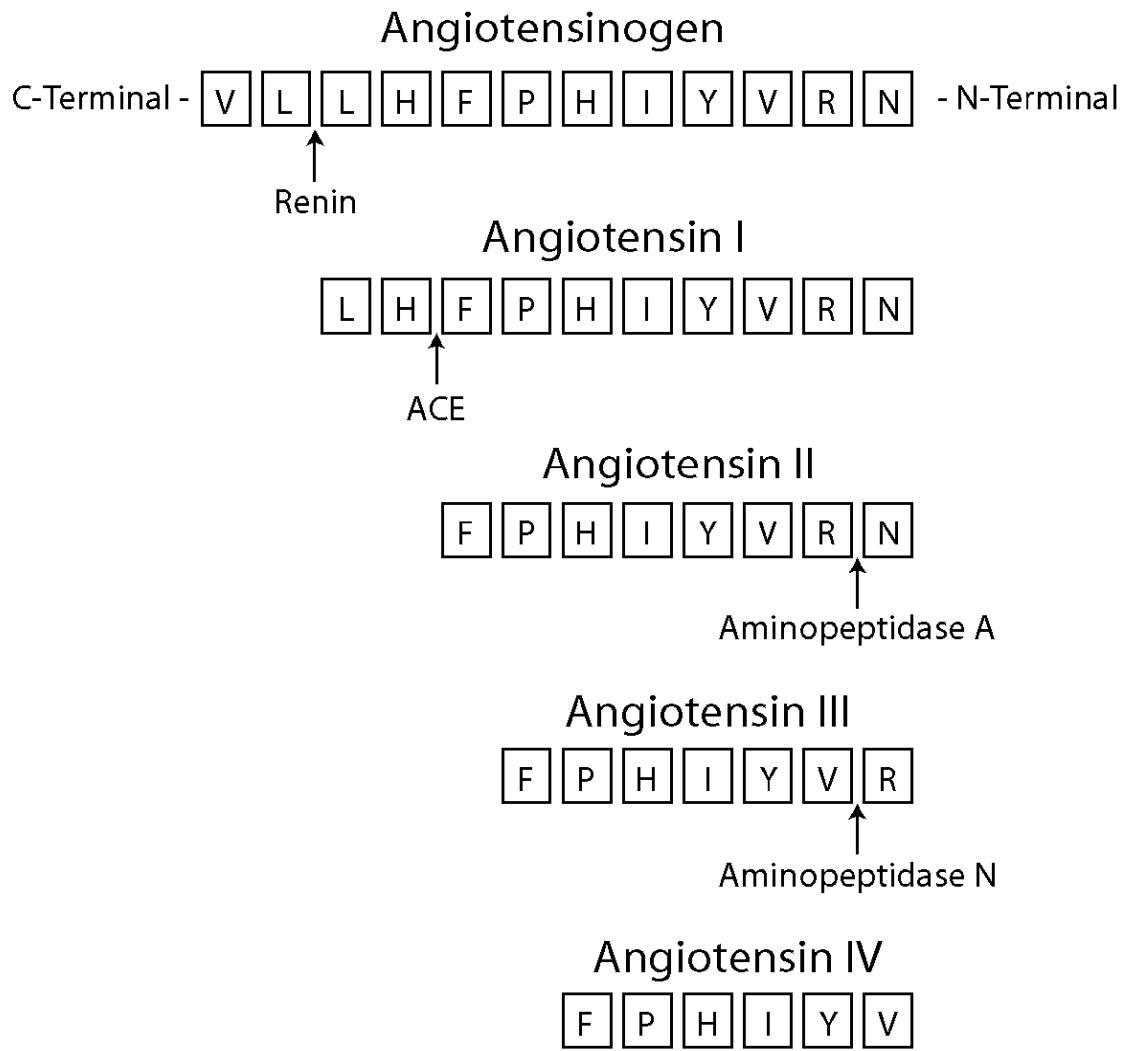
Figure 2: Formation of angiotensins I-IV from precursor angiotensinogen

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You are caring for a 7-week-old infant born at 23 weeks postconceptual age whose birthweight was 540 g. Her early course was complicated by severe respiratory failure, candidal sepsis, and multiple episodes of feeding intolerance as well as suspected necrotizing enterocolitis. She received parenteral nutrition until 40 days after birth, when full enteral nutrition was established with maternal breast milk. A chest and abdominal radiograph revealed the ribs to be osteopenic, with new fractures of the fifth and sixth thoracic ribs and bilateral healing femoral fractures. Laboratory results show: serum calcium of 10.1 mg/dL (2.5 mmol/L), alkaline phosphatase of 823 U/L, and serum phosphorous of 4.2 mg/dL (1.4 mmol/L).

Of the following, the MOST appropriate initial nutritional supplement for this infant is

☒ **1** calcium glubionate

2 human milk fortifier

3 multivitamin supplement

4 potassium phosphate

5 vitamin D

You selected **1**, the correct answer is **2**.

Osteopenia of prematurity, also referred to as metabolic bone disease or neonatal rickets, affects up to 30% of infants whose birthweights are less than 1,500 g; the incidence is inversely proportional to birthweight. Some 73% of infants whose birthweights are less than 800 g have abnormalities documented on bone radiographs. The severity ranges from mild demineralization to overt rickets and nontraumatic fractures. Calcium (Ca) and phosphorous (P) are the major inorganic constituents of bone. After 24 weeks' gestation, fetal accretion of Ca is 92 to 150 mg/kg per day and P is 59 to 85 mg/kg per day. Preterm infants miss this period of substantial mineral accretion such that an infant born at 24 weeks' gestation has only 10% to 15% of total body Ca compared with a term neonate. Other predisposing factors for osteopenia of prematurity are outlined in Table 1.

Osteopenia of prematurity is clinically asymptomatic in most cases, with radiographic changes appearing between the 6th and 12th postnatal weeks. Fractures are seen most commonly in the thoracic cage and extremities. Respiratory distress may ensue, caused by softening of the ribs and poor chest wall compliance. Craniotabes, frontal bossing, and palpable costochondral junctions (rachitic rosary) may be physical findings in more severe and prolonged cases.

The typical biochemical features of osteopenia of prematurity include a normal serum Ca concentration, low serum P level, and high serum alkaline phosphatase concentration (generally more than five times the upper adult normal reference values), as reported for the infant in the vignette. Urinary excretion of P is low or absent, and urinary Ca excretion increases as serum P concentrations decline, which suggests that P is the limiting nutrient. Serum 1,25-dihydroxyvitamin D levels are elevated, as would be expected, and return to normal with mineral supplementation, which makes this a useful marker for adequate therapy. Hyperparathyroidism typically is not present. Dual energy x-ray absorptiometry (DEXA) is the standard for whole body mineral evaluation, but the lack of portable DEXA scanning makes a plain radiograph of the wrist or humerus a practical screening tool. However, bone mineral content must decrease by 30% to 40% to appreciate changes on plain radiography.

Osteopenia of prematurity appears to be caused by insufficient provision of Ca and P rather than inadequate absorption in the gastrointestinal tract. It is difficult to attain accretion rates of

Ca and P similar to those seen in the fetus with parenteral nutrition because of limited solubility of the Ca and P salts and the high concentrations recommended (60 to 90 mg/kg per day of Ca, 47 to 70 mg/kg per day of P). Human milk is an insufficient source of Ca and P for the preterm infant, providing approximately one half to two thirds of the recommended intake. Human milk fortifier or premature infant formulas provide both additional Ca and P and represent the first step in nutritional supplementation to avoid or correct osteopenia. In some cases, even this is inadequate to correct P deficiency, and additional P supplementation is needed. For the infant in the vignette, who is being fed unfortified human milk, human milk fortifier can provide additional Ca and P most effectively. Standard cow milk formula and soy-based formulas (potential for low bioavailability of Ca and P due to phytate P binding) provide inadequate Ca and P for preterm infants. Table 2 lists sample mineral contents for the most commonly used sources of preterm infant nutrition.

Phosphate depletion and osteopenia occur rapidly in preterm infants fed unsupplemented human milk due to its low phosphate content. When hypophosphatemia is present, only limited amounts of Ca can be deposited in bone, resulting in hypercalcemia and hypercalciuria. If phosphate repletion occurs alone, it stimulates bone mineralization, leading to subnormal Ca levels ("hungry bones" syndrome). For the infant in the vignette, therefore, neither calcium glubionate nor potassium phosphate alone would be sufficient supplementation.

The standard infant formulations of multivitamins contain additional vitamin D as well as vitamins A, C, E, and K, depending on the preparation. Vitamin deficiency rarely is the cause of osteopenia in preterm infants. Supplementation of vitamin D up to 2,000 IU/d has not been effective in reducing the incidence of osteopenia. Multivitamins do not provide additional Ca or P.

Vitamin D is a fat-soluble vitamin available from dietary sources or via synthesis in the skin from cholesterol by a light-dependent process. Even the most immature infants can absorb and metabolize vitamin D within days after birth. 1,25-dihydroxyvitamin D is the most metabolically active of the more than 30 metabolites whose major physiologic action is to increase bone mineralization by increasing small bowel absorption of Ca and P. Together with parathyroid hormone, vitamin D maintains serum calcium homeostasis. Human milk contains very small amounts of vitamin D (<20 IU/L). Current recommendations suggest that a minimum of 160 to 400 IU/d is required for preterm infants. Higher doses of vitamin D have not been shown to increase bone mineralization, as measured by biochemical or radiographic differences. Vitamin D deficiency is rare in the very low-birthweight infant because of the use of supplemental vitamin D in parenteral nutrition and infant formulas.

The ideal duration of Ca and P mineral supplementation is not known, although current conservative recommendations suggest continuing full supplementation until term body size is attained, biochemical markers are normal, and radiographic evidence of healing is present. Continued use of a mineral-enriched diet has resulted in better growth and bone mineralization at 9 months of age. Osteopenia appears to be self-resolving disease, with radiographic resolution by 6 months of age, but the long-term consequences of a period of demineralization and its effect on the attainment of peak bone mass are not known. Peak serum alkaline phosphatase levels greater than 1,200 U/L have correlated with decreased body length at 18 months of age. Dental enamel hypoplasia when tooth eruption occurs also has been associated with osteopenia. Avoidance of fractures and decreased dolichocephaly may be benefits of prevention and treatment.

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Rubin LP. Disorders of calcium and phosphorus metabolism. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn*. **8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:1346-1365**

Content Specifications:

Understand the etiology, clinical manifestations, radiographic features, and approach to treatment of osteopenia of prematurity

Understand the interrelated effects of various hormones, including parathormone, calcitonin, and Vitamin D on calcium, phosphorous, and magnesium metabolism in the fetus and neonate

Recognize the relationship between the calcium and phosphorous content of parenteral nutrition solutions and osteopenia

Understand the mineral and vitamin content of infant formulas

Be familiar with the ability of human milk, infant formulas, and milk fortifiers to meet the needs of the very low-birth-weight infant

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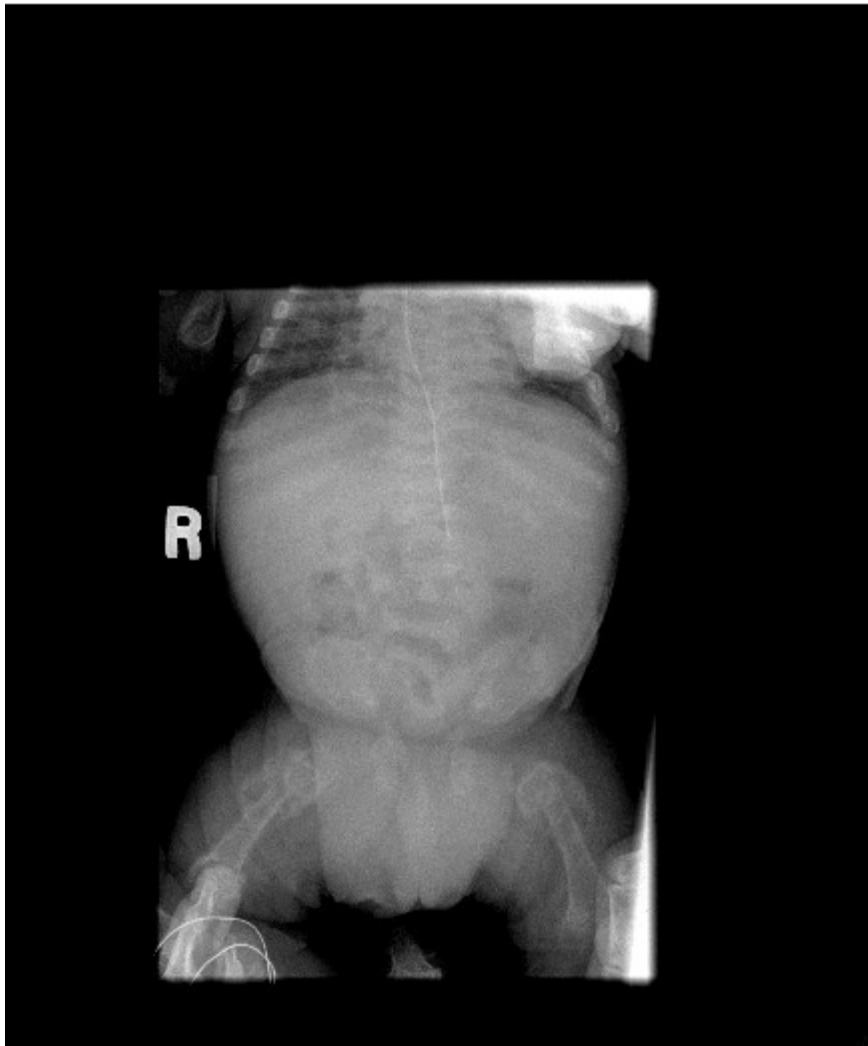
Table 1

Risk Factors for Osteopenia of Prematurity
Prematurity less than 34 weeks gestational age
Birth weight less than 1500 grams
Feedings of unsupplemented human milk
Medical complications
Delayed establishment of enteral nutrition
Prolonged parenteral nutrition
Cholestatic jaundice
Fluid restriction
Immobility
Medications
Diuretics
Dexamethasone
Sodium Bicarbinate
Theophylline

Table 2

Mineral Content of Sample Infant Formulas		
Formula	**Calcium (mg/l)**	**Phosphorous (mg/l)**
22 cal/oz premature infant formula	784 – 890	462 – 890
24 cal/oz premature infant formula	1340 – 1452	670 – 806
20 cal/oz soy based formula	709 – 710	507 – 560
20 cal/oz bovine formula	530 – 726	360 – 565
Human milk	270 – 320	130 – 150
24 cal/oz fortified human milk	1140 – 1380	590 – 776

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You are notified by the newborn screening program that a 2-week-old infant in your practice has an elevated phenylalanine level, which is confirmed by repeat testing. The mother reports that the baby is healthy and breastfeeding well.

Of the following, the MOST important first step in management of this infant is to

1. admit the baby to the hospital for further evaluation

2. consult with a metabolic geneticist or nutritionist

3. instruct the mother that she no longer should breastfeed

4. place the baby immediately on phenylalanine-free formula

5. send urine for organic acid analysis

You selected 5, the correct answer is 2.

Phenylketonuria (PKU) is an autosomal recessive inborn error of metabolism that has an incidence of approximately 1:10,000 to 1:25,000 individuals. The gene that causes PKU is well described and is mapped to chromosome 12 on the long arm. More than 240 mutations causing PKU have been defined, and carrier detection and prenatal diagnosis are available using molecular genetic testing.

Newborn screening programs for PKU initially were established based on the discovery that the early diagnosis and treatment of the disease virtually could eliminate morbidity and mortality. An elevated blood phenylalanine (PHE) concentration detected by newborn screening performed after the initiation of feeding, as described for the infant in the vignette, suggests the need for a diagnostic evaluation. However, it is important to realize that most infants in whom elevated PHE levels are identified through screening programs do not have PKU; they simply have delayed maturation of the metabolizing enzymes. Individuals who have classic PKU and continue to feed normally experience a rapid rise in serum PHE concentration to levels greater than 30 mg/dL (1,815 mcmol/L) (normal, 1 mg/dL [60.5 mcmol/L]). Some individuals have a variant termed "hyperphenylalaninemia," which also results from defective phenylalanine hydroxylase. Yet another group of individuals has biopterin deficiency; biopterin serves as a cofactor (in the form of tetrahydrobiopterin) for the formation of tyrosine from PHE.

Following the identification of an infant who has a positive newborn screening result for PKU, the most efficient next step is either to repeat the screening test or to send blood for amino acid quantitation. Because such test results are seen infrequently in general pediatric practices, it is important to consult with a metabolic geneticist. The results of the amino acid analysis allow the geneticist to distinguish among true PKU, in which the PHE level is very elevated and the tyrosine level is negligible; hyperphenylalaninemia, in which the level is elevated in the intermediate range (10 to 20 mg/dL [605 to 1,210 mcmol/L]) and there may be some tyrosine; and newborn immaturity in which the PHE level is elevated, but there is sufficient tyrosine. It is not necessary to admit the baby in the vignette to the hospital at this juncture because he is stable and is not expected to decompensate. If the mother discontinues breastfeeding and the baby does not have PKU, the opportunity to breastfeed may be lost. Phenylalanine-free formula is expensive, and 2 to 3 days of therapy while awaiting test results has no clear advantage. Finally, urine organic acid analysis is not helpful.

Once the diagnosis of PKU is confirmed, it is critical to confer with a metabolic geneticist/nutritionist and, if at all possible, to have the patient seen at a metabolic clinic.

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Therapy involves restriction of dietary PHE to the amount tolerated by the patient and regular measurement of plasma PHE concentrations. It also is important to follow plasma tyrosine concentrations because tyrosine becomes an essential amino acid in affected children.

When carefully managed and followed, individuals who have PKU have a very bright prognosis, both for health and for cognitive function. It is important to note that years ago, children were taken off their special diets at about the age of 6 years. However, it now appears best to keep affected individuals on their diets indefinitely because of measurable declines in intelligence quotient and school performance in individuals who came off the diet. Additionally, due to the potential for the severe negative impact of hyperphenylalaninemia on the embryos and fetuses of affected women, it is best to continue the diet throughout life.

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Article available online

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Available online

Content Specifications:
Understand the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of amino acids

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A term male newborn was delivered vaginally and immediately developed severe cyanosis and respiratory distress. Physical examination revealed a large-for-gestational age infant who had coarse facies, cloudy corneas, anteverted nares, cleft lip and palate, digital hypoplasia, absent nails, single transverse palmar crease, and heart sounds best heard to the right of the sternum. Breath sounds were heard only at the apex of the right lung. Despite resuscitation in the delivery room with positive pressure ventilation, oxygen, volume expansion, chest compressions, and epinephrine, the infant died. His mother had undergone amniocentesis because of advanced maternal age, and results showed a 46,XY karyotype. Four siblings are alive and well, but a fifth sibling died from severe respiratory failure following a home delivery. No autopsy or other records were available. Both parents are from a small town and are believed to be distant cousins. Fetal ultrasonography performed at 18 weeks showed a left-sided cleft lip and cleft palate. The postmortem examination is shown in Figure 1. Hirschsprung disease was evident on microscopic examination.

Of the following, the MOST likely diagnosis for this infant is

1. Beckwith-Wiedemann syndrome

2. Cornelia de Lange syndrome

3. DiGeorge sequence

4. Fryns syndrome

5. Smith-Lemli-Opitz syndrome

You selected **4**, the correct answer is **4**.

Congenital diaphragmatic hernia affects 1 to 5 in 10,000 live births. Males account for about two thirds of affected infants, most of whom are born at term. The left diaphragm is affected in 90% of cases, as seen for the infant in the vignette (Figure 1). Isolated congenital diaphragmatic hernia occurs in approximately 60% of cases; the remainder is complicated by other congenital anomalies. Cardiac anomalies predominate, although other body systems, including the brain, kidneys, bowel, or skeleton, may be involved, especially in infants who have chromosomal or multiple malformation syndromes. Such syndromes include trisomies 13 and 18, Fryns syndrome, Beckwith-Wiedemann syndrome, Cornelia de Lang syndrome, DiGeorge sequence, Ehlers-Danlos syndrome, and Marfan syndrome. The mortality associated with diaphragmatic hernia in conjunction with other congenital anomalies is about 2.4 times that for infants who have isolated diaphragmatic hernia.

The infant described in the vignette has the classic features of Fryns syndrome, a rare, autosomal recessive disorder that often presents with respiratory failure due to diaphragmatic hernia. In addition to the diaphragmatic defect, cardinal features of Fryns syndrome include digital and nail hypoplasia and coarse facies. Among the other frequent findings are brain malformations such as agenesis of the corpus callosum, Dandy-Walker malformation, hypoplasia of optic or olfactory tracts; eye abnormalities such as cloudy cornea and microphthalmia; anteverted nares; and cleft lip or palate. Other distinctive malformations of Fryns syndrome include ventricular dilatation or hydrocephalus, neuronal or cerebellar heterotopias, abnormalities of the aorta, renal cysts, dilatation of the ureters, bicornuate uterus, renal dysplasia, proximal thumbs, and broad clavicles. Some infants are large for gestational age and have a variety of gastrointestinal malformations, such as duodenal atresia, Hirschsprung disease, and imperforate anus. Polyhydramnios is a frequent feature of pregnancies when Fryns syndrome is present. Most infants who have Fryns syndrome are stillborn or die shortly after birth; those who survive have significant mental impairments.

Beckwith-Wiedemann syndrome affects about 1 in 14,000 live births. Most cases are sporadic, although familial inheritance occurs in 15% of cases. In familial cases, autosomal dominant inheritance with variable penetrance is characteristic. However, imprinting of the maternal allele at 11p15 or paternal uniparental disomy can result in an imbalance of expression of the paternal allele or underexpression of the maternal allele that leads to overgrowth and tumor formation. Characteristic findings of Beckwith-Wiedemann syndrome include macrosomia, omphalocele, macroglossia, and ear creases. Diaphragmatic hernia occasionally is a presenting feature, although eventration of the diaphragm is more frequent. Other distinctive features include organomegaly (especially adrenocortical cytomegaly), hypoglycemia, advanced bone age, and hemihypertrophy. Close follow-up for malignancy, especially Wilms tumor and hepatoblastoma, is important. Normal development often is possible if complications are avoided through interventions. The only features of Beckwith-Wiedemann syndrome exhibited by the infant in the vignette are being large for gestational age and having a diaphragmatic hernia, but the other features are more characteristic of Fryns syndrome.

Cornelia de Lange syndrome, or Brachmann-de Lange syndrome, often presents with synophrys, a thin downturning upper lip, and micromelia. Most affected infants have pre- and postnatal growth restriction, microcephaly, severe mental retardation, speech delay, feeding problems, major malformations that can include limb defects, and characteristic facial features. The facial features include arched eyebrows, synophrys, short nose with anteverted nares, long philtrum, thin upper lip, and micrognathia. Most cases of Cornelia de Lange syndrome are sporadic; nearly 50% are associated with mutations of the NIPBL gene located on chromosome 5p13. Inheritance following an autosomal dominant pattern or due to balanced chromosomal translocations has been identified. Diaphragmatic hernia only occasionally is present in this syndrome. The infant described in the vignette has a diaphragmatic defect and anteverted nares, but he is large for gestational age rather than growth-impaired, has digital nail hypoplasia rather than micromelia, and has a cleft lip/palate rather than a high-arched palate.

DiGeorge sequence is one of three disorders that involve sporadic de novo deletion of genes on chromosome 22q11.2. The other disorders are velocardiofacial syndrome and conotruncal anomaly face syndrome; collectively, they are referred to as the 22q11 deletion syndrome. Karyotyping with fluorescent in situ hybridization can identify the 22q11 deletion. This chromosomal deletion syndrome occurs in 1 in 3,000 live births, making the disorder one of the most common microdeletion syndromes. Characteristic features of the DiGeorge sequence evolve from defects in development of the thymus, parathyroids, and great vessels. The most common presentation is with symptoms associated with conotruncal congenital heart defects, hypocalcemia, or immune deficiency. Facial features include hooded eyelids, hypertelorism, overfolded ears, bulbous nasal tip, small mouth, and micrognathia. Diaphragmatic hernia, cleft palate, choanal atresia, renal agenesis, neural tube defects, imperforate anus, and hypospadias are seen occasionally. A wide range of neurodevelopmental delays, learning disabilities, and hypotonia are reported in children, but severe mental and physical impairments are unusual. The infant in the vignette has a diaphragmatic hernia, cleft palate, and coarse facial features, but none of the other features of DiGeorge sequence.

Smith-Lemli-Opitz syndrome is an autosomal recessive malformation syndrome caused by a defect in cholesterol biosynthesis. The incidence is estimated at 1 in 10,000 to 100,000 live births. The gene defect in cholesterol biosynthesis is located on chromosome 11 and results in reduced activity of 7-dehydrocholesterol (7DHC) reductase, the enzyme responsible for converting 7DHC to cholesterol. Low serum cholesterol and elevated serum 7DHC concentrations establish the diagnosis in symptomatic infants. Treatment with cholesterol supplementation has been shown to cause improvements in behavior, growth, hypotonia, developmental skills, and irritability. The distinctive features of Smith-Lemli-Opitz syndrome include anteverted nares, ptosis of the eyelids, syndactyly of second and third toes, hypospadias, and cryptorchidism. Other findings often include intrauterine growth deficiency, microcephaly, hypotonia, micrognathia, simian crease, and other renal anomalies. Occasionally, cleft palate, asymmetrically short fingers, polydactyly, flexed fingers, abnormal pulmonary lobation, and Hirschsprung disease are present. Diaphragmatic hernia is not associated with this syndrome.

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Content Specifications:

Recognize the diagnostic implications of single versus multiple anomalies

Recognize the clinical features of extrapulmonary causes of respiratory distress including diaphragmatic hernia, diaphragmatic paralysis and cord transection

Recognize the karyotype and clinical manifestations associated with common deletion syndromes

Recognize clinical features of Smith-Lemli-Opitz syndrome

Recognize clinical features of Beckwith-Wiedemann syndrome

Recognize the clinical features of and how to manage craniofacial anomalies

Recognize the clinical features of and how to manage congenital anomalies of the upper extremities such as syndactyly, polydactyly, absent clavicles, absent radius, Sprengel deformity and limb reduction
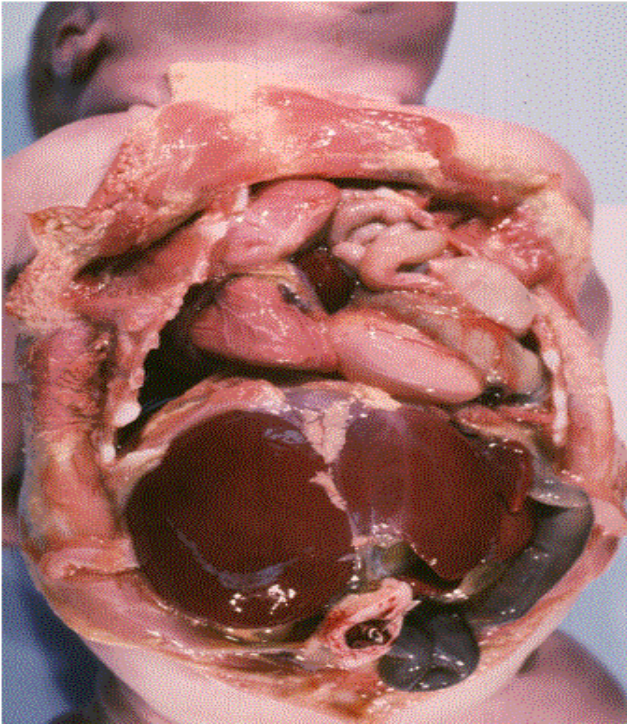
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You are caring for a 2-month-old infant who was born at 30 weeks' gestation and weighed 1,000 g at birth. At 2 weeks after birth, the infant developed severe necrotizing enterocolitis and underwent a resection of the ileum and ileocecal valve. She is estimated to have approximately 70 cm of remaining jejunum connected to a stoma. Most of the colon remains, but it is not in continuity with the small intestine. The infant has been maintained exclusively on parenteral nutrition, but you are planning to transition her to enteral feedings.

Of the following, a TRUE statement about feeding this child who has short bowel syndrome is that

1 a stool-reducing substance of 1% or greater suggests good tolerance of enteral feedings

2 bolus feedings are preferred over continuous feedings

3 cow milk protein formulas are preferred because of their decreased osmolarity

4 rectal bleeding in this patient suggests intolerance of enteral feeding

5 small bowel bacterial overgrowth is a frequent cause of feeding intolerance

You selected **5**, the correct answer is **5**.

Infants may undergo bowel resection in the neonatal period for a variety of conditions, including necrotizing enterocolitis, Hirschsprung disease, omphalocele, gastroschisis, and intestinal atresias. Ideally, infants undergoing bowel resection should receive calories enterally. However, in some cases, short- or long-term parenteral nutrition is necessary to promote health and bowel growth. Infants who have large amounts of bowel resected are at risk for developing short bowel syndrome, which is characterized by chronic diarrhea, micronutrient deficiency, and feeding intolerance. The primary determinants of the risk of short bowel syndrome are the amount of remaining bowel and whether the ileocecal valve has been resected. If the ileocecal valve has been resected, 30 to 50 cm of bowel must be present for the infant to grow enough intestine to allow weaning off parenteral nutrition. Resection of the ileum (as opposed to jejunum) leads to malabsorption of vitamin B_{12} and bile acids.

Initially, patients who undergo extensive bowel resections may have a high-output secretory diarrhea, with stool sodium levels of 80 to 100 mEq/L (80 to 100 mmol/L), and require aggressive fluid and electrolyte repletion. Once stool output and serum electrolyte concentrations are stable, enteral feeding may be attempted. Patients who have short bowel syndrome and are fed enterally may have a limited tolerance for fat and carbohydrate. Protein hydrolysates and modular formulas (in which the proportion of carbohydrate is increased gradually) often are beneficial and are preferred over intact cow milk protein formulas. Slow continuous feedings delivered by gastrostomy tube frequently are tolerated better than bolus feedings. Ostomy output may be used to determine carbohydrate tolerance. An ostomy output that equals or exceeds the amount of formula delivered implies malabsorption. In addition, a stool reducing substance of 0.25% or less suggests good tolerance of the carbohydrate, and a stool reducing substance of 1% implies malabsorption. Patients who have short bowel syndrome are at risk for bacterial overgrowth in stagnant, hypomotile loops of bowel. Bacterial overgrowth has been shown to increase feeding intolerance and decrease survival in affected infants. Therefore, periodic courses of antibiotic therapy should be considered for all infants who have short bowel syndrome.

Patients who have bowel resections often have a portion of colon that is not in continuity with the remainder of the bowel. Because this colon is not in continuity with the fecal stream, the patient may develop a condition termed diversion colitis. Diversion colitis presents with rectal

bleeding, but it does not imply feeding intolerance. The preferred treatment for diversion colitis is restoration of bowel continuity; if this is not possible, corticosteroid or short-chain fatty acid enemas may be helpful.

References:

Garcia-Careaga M, Kerner JA. Malabsorptive disorders: short bowel syndrome. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*. 17th ed. Philadelphia, Pa: WB Saunders Co; 2004;1262-1264

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Abstract available online

Content Specifications:
Understand the factors that may improve intestinal motility
Know the clinical manifestations, diagnosis, and treatment of acquired malabsorption syndrome
Understand the diagnostic procedures and approach to therapy of infectious enteritis and colitis in the neonate

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You are called to the nursery to evaluate a 1-hour-old baby who has respiratory distress and intermittent cyanosis that is relieved by crying. The nurse has been unable to pass an 8-French catheter through the right naris and has difficulty passing the catheter on the left. On physical examination, the baby is normally grown. You note right central facial nerve palsy and a lop ear malformation on the right. The genitalia are hypoplastic.

Of the following, the studies that will be MOST helpful in immediate management and diagnosis for this baby are

☒ **1** chromosome analysis, ophthalmology consultation, echocardiography

2 chromosome analysis, renal ultrasonography, ophthalmology evaluation

3 echocardiography,head computed tomography, ophthalmology evaluation

4 head ultrasonography, chromosome analysis, renal ultrasonography

5 head ultrasonography, echocardiography, ophthalmology evaluation

You selected 1, the correct answer is 3.

The infant described in the vignette has intermittent cyanosis that is relieved by crying, which is the classic presentation of choanal atresia or severe choanal stenosis. The inability to pass a catheter through the right naris of the infant confirms atresia on that side, and the difficulty passing the catheter on the left suggests stenosis on that side.

Choanal atresia occurs in about 1:8,000 infants. It is due to failure of the buccal pharyngeal membrane in the posterior nasal cavity to dissolve in the seventh week of embryogenesis, thereby preventing communication between the posterior nasal cavity and the posterior pharynx. Although crying relieves the problem, eventually the babies tire, and they become hypercarbic and can die without intervention. Evaluation using computed tomography (CT) is recommended. While awaiting CT, an oral airway should be placed. Once the diagnosis of choanal atresia is suspected, an otolaryngologist should be consulted. Sometimes it is possible to dilate the stenotic choanal passage, although this also may be accomplished surgically.

Although choanal atresia/stenosis can be an isolated condition, as many as 50% of affected children have associated abnormalities. The infant presented in the vignette has features of the CHARGE association in which C=coloboma of the eye, H=heart defect, A=atresia choanae, R=postnatal retardation of growth or development, G=genital anomalies, and E=ear abnormalities. Classically, affected individuals must have at least four of the features listed, with at least one being either choanal atresia or coloboma (Figure 6.1). It is not unusual for the children to have seventh nerve palsies (Figure 6.2), and the most common ear malformation is a lop ear (Figure 6.3). In addition to choanal abnormalities, the infant in the vignette has genital and ear anomalies.

Echocardiography is an important aspect of the immediate management of children who have CHARGE association because they are likely to have cardiac birth defects. Head CT is required to evaluate the infant for choanal abnormalities; these cannot be detected on head ultrasonography. Finally, an ophthalmology consultation is necessary even if no coloboma is seen on direct ophthalmoscopic examination because it is possible that a coloboma involves the posterior aspect of the eye, which could have significant impact on the child?s prognosis for vision. At a later point in time, chromosome analysis will be helpful because 2% of individuals who have CHARGE association have chromosome abnormalities, but this is not

useful in immediate management. Renal ultrasonography is recommended for later evaluation because children who have CHARGE association may have renal anomalies.

References:
Carey JC, Bamshad M. Genetics and dysmorphology. In: Rudolph CD, Rudolph AM, Hostetter MK, Lister G, Siegel NJ, eds. *Rudolphís Pediatrics*. 21st ed. New York, NY: McGraw-Hill; 2003:713-786

Moore KL, Persaud TVN. Human birth defects. In: *The Developing Human: Clinically Oriented Embryology*. 7th ed. Philadelphia, Pa: WB Saunders Co; 2003:157-186

<u>**Content specifications:**</u>
Recognize the incidence, clinical manifestations, and management of bilateral and unilateral choanal atresia
Know the syndromes associated with abnormalities of the eye including cranio-facial abnormalities, abnormalities of the orbit, the eyebrows, the eyelids, the eyelashes, the cornea, the iris, and the retina
Know the causes and risk factors for congenital hearing loss in the neonate
Recognize the clinical features and know how to manage craniofacial anomalies
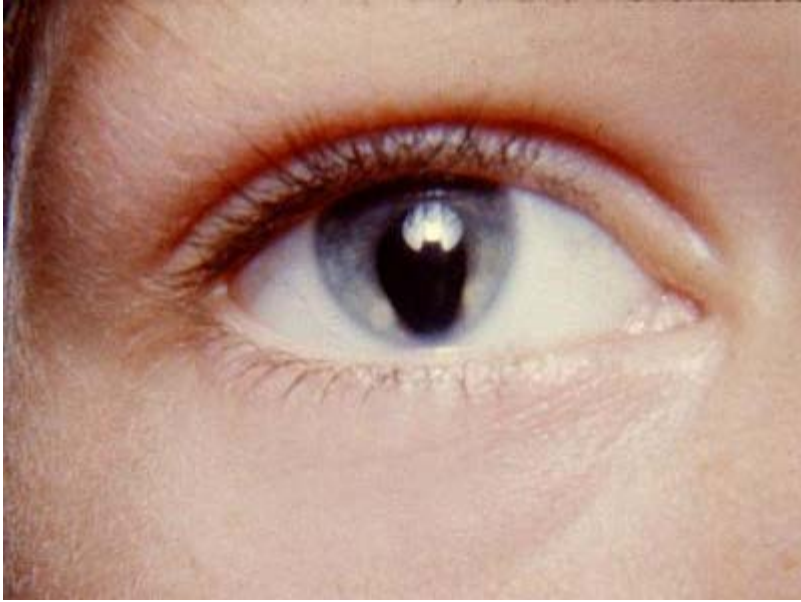
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Fig 6.2

Right peripheral seventh nerve palsy: note the inability of the infant to close the eye or open the right side of the mouth. Seventh nerve palsy often accompanies choanal atresia.(Courtesy of M Rimsza)

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Fig 6.3

A lop ear anomaly may be associated with choanal atresia. (Courtesy of M Rimsza)

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You are designing a clinical research protocol on a procedure involving neonates in the neonatal intensive care unit. The process of informed consent must be addressed in the project description. In 1979, informed consent guidelines for clinical research were published in the *Federal Register* as the Belmont Report (http://ohsr.od.nih.gov/guidelines/belmont.html). Valid consent requires that individuals giving consent be competent; understand the purpose, risks, and benefits of the research; be free of coercion; and know that they can withdraw from the research without penalty. In the case of neonates, parental consent must be obtained.

Of the following, the MOST accurate statement about informed parental consent for research is that

1 experience with enrolling their child in research makes parents less likely to enroll in subsequent studies

2 ☒ health care workers are less likely to consent for their own infants than are other parents

3 investigations involving patients' charts without consent are acceptable to parents

4 mothers and fathers are equally likely to give valid consent

5 potential risks presented to parents are less likely to be recalled than potential benefits

You selected 2, the correct answer is 5.

Obtaining a valid consent is a major tenet of research. Because neonates cannot consent for themselves, permission is sought from one or both parents to enroll their child into a clinical research project. In most instances, clinical research involves comparison among alternatives in care, with the implicit purpose of determining which is better. When an existing intervention is in common use, an innovative intervention should be compared with the existing intervention. When no effective or presumed effective drug or intervention(s) exists, a novel approach can be compared against no treatment or a placebo treatment. Investigation of a potentially improved medication or procedure should include a control group receiving the current standard (or placebo if none exists). When equipoise is present, the benefit/risk calculation is unknown, and research participants are as likely to have more risk than benefit from the intervention as from placebo or no treatment. The research protocol should be presented in a noncoercive manner that provides parents with full understanding of the benefits, risks, and nature of the treatment and allows them the freedom to withdraw. Studies of parents who have given permission for their infants to participate in research raise concern about the validity of the consent process.

Part of the informed consent process involves presentation of the potential benefits and risks of the proposed intervention or medication. Studies of informed consent have shown that parents do not recall potential risks as readily as they recall potential benefits. In a study by Ballard and associates, only 5% of parents could remember a risk associated with the protocol whereas 75% of parents could recall potential benefits. These data coincide with observations of the motives of parents to involve their child in the research: 36% cited helping their infant, and another 36% cited decreasing pain..

Parents who have enrolled their child in a research project are likely to enroll their child again if an opportunity occurs. Parents strongly believe that informed consent should be obtained for all research procedures, and that consent should be obtained before extracting research information from patient charts.

Health care workers are more likely to enroll their own infants in studies that have possible direct benefit for their child, albeit with some risk, than are other parents. Most parents trust

that physicians would not conduct research that could put an infant in real danger. Some parents and health care workers are willing to consent for their infant's participation in a study that has moderate risk and no potential for direct benefit to the infant. This observation elucidates one of the major functions of the institutional review board (IRB), which is to assure that vulnerable study participants are protected. Such willingness on the part of parents could reflect altruism, coercion or lack of understanding. Nevertheless, nontherapeutic research that involves more than minimal risk should be avoided; if contemplated, considerable IRB discussion is warranted.

Mothers are more likely to recall the purpose and potential benefits of research than are fathers.

Research will continue to require consent guided by professional, ethical, and parental standards. In the past, adhering to the process was equated with validity of consent. Recent studies raise concerns regarding the important components of the consent process.

<u>References:</u>

Ballard HO, Shook LA, Desai NS, Anand KJS. Neonatal research and the validity of informed consent obtained in the perinatal period. *J Perinatol*. 2004;24:409-415

Belmont report: ethical principles and guidelines for the protection of human subjects in research. National Commission for Protection of Human Subjects of Biomedical and Behavioral Research. Washington, DC. *Fed Reg*. April 18, 1979. Available at: http://ohsr.od.nih.gov/guidelines/belmont.html. Accessed January 2005

Singhal N, Oberle K, Darwish A, Burgess E. Attitudes of health-care providers towards research with newborn babies. *J Perinatol*. 2004;24:775-782

<u>Content Specifications:</u>

Identify when informed consent is or is not necessary

Understand which types of studies must be reviewed by the Institutional Review Board

Understand the basic criteria that must be utilized if an Institutional Review Board is to grant permission to use infants or children as subjects

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An apparently term infant who was born at home was noted to be very jaundiced by a neighbor on the fifth postnatal day. When his mother brings him to you for evaluation, he has no symptoms or clinical signs of bilirubin encephalopathy. His bilirubin concentration is 36.5 mg/dL (624.2 mcmol/L), with a direct bilirubin measurement of 1.5 mg/dL (26.7 mcmol/L). You draw blood to investigate the cause of the hyperbilirubinemia and place the infant under intense phototherapy.

Of the following, the MOST appropriate treatment plan is

1 administration of a bolus of 20 mL/kg normal saline, reassessment of bilirubin concentration in 2 hours, and initiation of exchange transfusion if the bilirubin level is not decreasing

2 administration of intravenous fluids with 10% glucose at rate of 150 mL/kg per day, reassessment of bilirubin concentration in 4 hours, and initiation of exchange transfusion if the bilirubin level is not decreasing

3 administration of salt-poor albumin (1g/kg) over the next hour, reassessment of bilirubin concentration in 4 hours, and initiation of exchange transfusion if the bilirubin level is not decreasing

4 initiation of an exchange transfusion as soon as possible

5 initiation of an exchange transfusion if the bilirubin concentration does not decrease after 4 hours of phototherapy

You selected **4**, the correct answer is **4**.

Despite the lack of clinical signs of bilirubin encephalopathy or overt kernicterus, the infant described in the vignette meets the criteria for exchange transfusion as soon as possible (ie, total serum bilirubin ≥30 mg/dL [513 mcmol/L]) (Figure). In the interim, intensive phototherapy should be maintained. Waiting for the bilirubin concentration to decrease with phototherapy can expose the child to potentially toxic levels of bilirubin. Although phototherapy causes photoisomerization of about 20% of the circulating bilirubin, there is no evidence that reliance on this therapy alone can protect the baby's brain.

Fluid bolus treatment may be indicated for management in some cases, but such treatment does not influence the decision regarding exchange transfusion. Including glucose in the infusion might be beneficial since the resultant insulin secretion will reduce free fatty acid concentrations. Free fatty acids compete for bilirubin binding sites on albumin. Infusion of salt-poor albumin to enhance the bilirubin binding capacity of the infant and increase the amount of bilirubin removed at exchange transfusion has some theoretical benefit, but it has not been demonstrated to be an alternative to exchange transfusion.

References:

American Academy of Pediatrics, Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114:297-316

Madan A, MacMahon JR, Stevenson DK. Neonatal hyperbilirubinuria. In Taeusch HW, Ballard RA, Gleason CA. *Avery's Diseases of the Newborn, 5th Ed*. Philadelphia PA. Elesevier Saunders 2005:1226-1256

Content Specification:
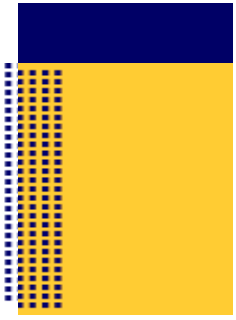
Know the indications for exchange transfusions
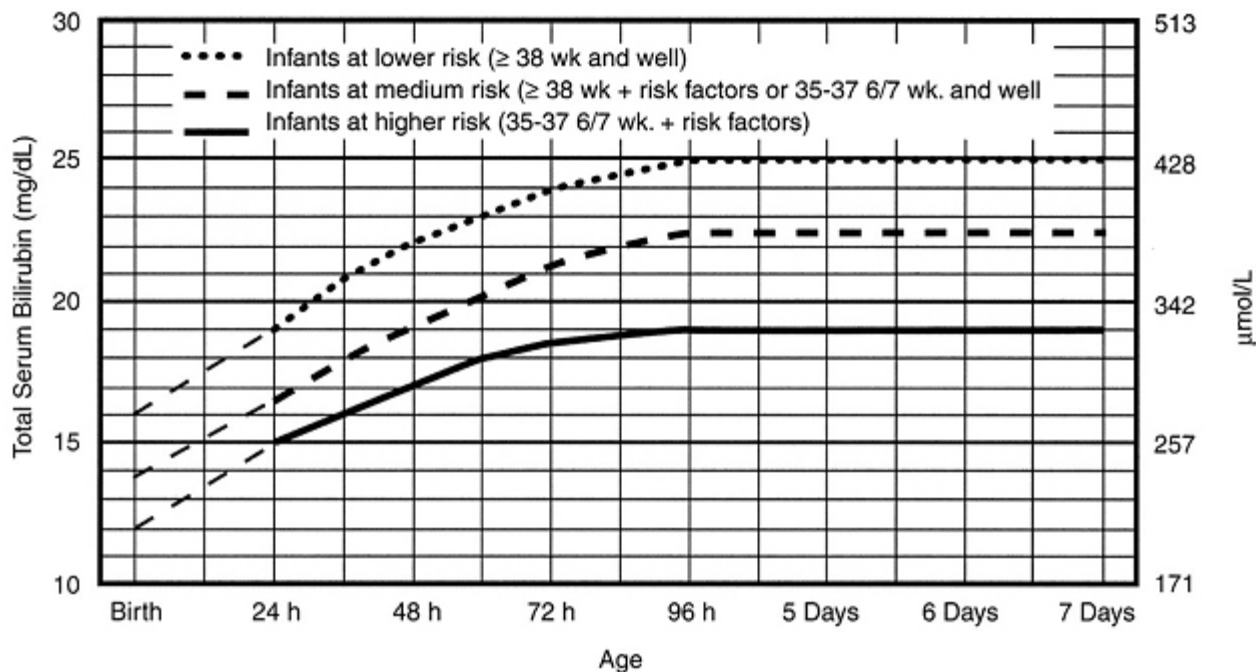
- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥5 mg/dL (85 μmol/L) above these lines.
- Risk factors - isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (See legend)
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

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A 7-week-old female infant, whose birthweight was 880 g and estimated gestational age at birth was 26 weeks, has frequent episodes of apnea and bradycardia. She is breathing spontaneously and requires a fraction of inspired oxygen (Fio_2) of 0.28 to maintain oxygen saturations above 90%. She is receiving full enteral feedings of expressed human milk enriched with a fortifier and supplemental iron, and her weight gain in the preceding 2 weeks has averaged 8.0 g/kg per day. Physical examination reveals pallor, resting heart rate of 180 beats/min, respiratory rate of 48 breaths/min, normal blood pressure, and no signs of distress. She has no evidence of hepatosplenomegaly, hemolysis, overt or occult blood loss, or sepsis. A complete blood count reveals:

- hemoglobin, 7.4 g/dL (74 g/L)
- hematocrit, 22% (0.22)
- erythrocyte count, 2.6×10^6/mcL (2.6×10^{12}/L)
- reticulocyte count, 0.4%
- normal erythrocyte indices
- platelet count, 296×10^3/mcL (296×10^9/L)
- leukocyte count, 7.8×10^3/mcL (7.8×10^9/L) with a normal differential count

Of the following, the MOST likely cause of the anemia in this infant is

1	deprivation of the transplacental supply of erythropoietin
2	enhanced clearance of erythropoietin by nonhematopoietic tissues
☒ 3	inadequate maturation of erythropoietin gene transcription
4	incomplete switch from hepatic to renal synthesis of erythropoietin
5	lack of sensitivity of erythroid progenitors to erythropoietin

You selected 3, the correct answer is 4.

The infant described in the vignette has clinical and laboratory evidence of anemia of prematurity that is hyporegenerative, normocytic, and normochromic. The principal cause of anemia of prematurity is decreased erythropoiesis from erythropoietin deficiency. Other contributing factors for the anemia include the transition from fetal to adult hemoglobin in the perinatal period (with accompanying changes in oxygen delivery to the tissues), shorter erythrocyte survival, and hemodilution associated with a rapidly increasing body mass. Deficiency of substrates, such as iron, fotate, and vitamin E, may aggravate the anemia, as may iatrogenic blood loss from repeated phlebotomy for diagnostic tests.

Erythropoietin, the primary growth factor that regulates erythropoiesis, is a 30.4-kd, 165-amino acid, glycosylated protein. Erythropoietin stimulates erythrocyte production by stimulating differentiation and proliferation and inhibiting apoptosis of erythroid progenitors. During fetal life, the primary source of circulating erythropoietin is the liver; the kidney contributes to less than 10% of the total erythropoietin pool. Renal erythropoietin synthesis increases after the 30th week of gestation, and its contribution to the total erythropoietin pool reaches about 30% at term gestation. The switch in erythropoietin synthesis from the liver to the kidney is complete by several months after birth. The erythropoietin-synthesizing cells in the kidney, located in the interstitium outside the tubular basement membrane (mostly in the inner cortex and outer medulla), are approximately 10-fold more sensitive to hypoxia than are erythropoietin-synthesizing hepatocytes in the liver. In the kidney, the increased demand for erythropoietin in response to anemia is met by a prompt increase in the number of erythropoietin-synthesizing

cells rather than by an increase in the synthesis of erythropoietin by a preset number of cells. In contrast, the proliferation of erythropoietin-synthesizing cells in the liver is much less efficient, as is the synthesis of erythropoietin. Thus, any delay in the switch in erythropoietin synthesis from the liver to the kidney, as would be expected in a preterm neonate, renders the infant susceptible to erythropoietin deficiency.

Erythropoietin does not cross the placenta; maternal and fetal erythropoiesis occur independently throughout gestation. The erythropoietin measured in the fetus reflects fetal synthesis. During fetal life, the serum erythropoietin concentration increases from approximately 4 mU/mL (4 IU/L) at 16 weeks to 40 mU/mL (40 IU/L) at term gestation. After birth, concurrent with increased oxygenation, the serum erythropoietin concentration decreases to a nadir between 4 and 6 weeks of age. Thereafter, the serum erythropoietin concentration increases steadily to reach its adult value of 15 mU/mL (15 IU/L) by about 12 weeks of age. The nadir in serum erythropoietin concentration after birth is exaggerated in preterm infants, largely as a result of immature development of the kidney. Because the fetus does not depend on maternal erythropoietin, deprivation of the transplacental supply of erythropoietin from delivery at an early gestational age does not cause erythropoietin deficiency in anemia of prematurity.

Erythropoietin exerts its biologic actions by binding to a specific cell receptor, erythropoietin-receptor (EPO-R). The EPO-R dimerizes after binding to erythropoietin, and the complex activates a cytoplasmic protein tyrosine kinase, Janus Kinase 2 (JAK 2). The activation of JAK 2 stimulates erythropoiesis. In addition to its principal distribution in the erythroid progenitors, EPO-R is present and functional in many nonhematopoietic tissues, including the liver, gastrointestinal tract, and central nervous system. The binding of erythropoietin to EPO-R is influenced largely by the degree of its glycosylation and represents the major mechanism of its clearance. Although the wide distribution of EPO-R throughout the body may result in efficient clearance of endogenous erythropoietin, such clearance is not the primary cause of erythropoietin deficiency in anemia of prematurity.

The gene encoding erythropoietin, EPO-gene, has been localized on human chromosome 7. The EPO-gene contains oxygen-sensitive sequences in a *cis*-enhancer element located in a region flanking its 3' end. The ligand for this oxygen-sensitive enhancer is a protein called hypoxia-inducible factor-1 (HIF-1), a 120-kd protein that is a heterodimeric transcription factor encoded on human chromosome 14. The binding of this protein to an 8-base pair DNA sequence within the enhancer element is regulated tightly by oxygen tension within the cell and is the physiologic regulator of erythropoietin transcription. In human fetuses, HIF-1 is expressed in the liver, kidney, brain, heart, and lung from as early as 12 weeks gestational age. Thus, unless there are genetic mutations involving the EPO-gene, the inadequacy of its transcriptional activation is not the cause of erythropoietin deficiency in anemia of prematurity.

The erythroid progenitors that are most sensitive to erythropoietin are cells in the erythroid lineage between the colony-stimulating factor erythroid and the proerythroblast. These cells express the highest density of EPO-R on their membranes and are dependent on erythropoietin for their survival, which is a prerequisite for their proliferation and maturation. The erythroid progenitors are highly sensitive to erythropoietin in infants and children, including preterm neonates. Similarly, the progenitors are sensitive to other growth factors, such as interleukin-3 and granulocyte-macrophage colony-stimulating factor, which contribute to erythropoiesis. Moreover, exogenous administration of recombinant human erythropoietin has been shown to be effective in stimulating erythropoiesis and decreasing the need for blood transfusions in preterm infants. Thus, the lack of sensitivity of erythroid progenitors to erythropoietin is not the cause of anemia of prematurity.

References:

Christensen RD, Ohls RK. Anemias unique to pregnancy and the perinatal period. In: Greer JP, Foerster J, Lukens JN, Rogers GM, Paraskevas F, Glader B, eds. *Wintrobe's Clinical Hematology*. 11th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2004:1467-1486

Dame C, Juul SE. The switch from fetal to adult erythropoiesis. *Clin Perinatol*. 2000; 27:507-526

Dessypris EN, Sawyer ST. Erythropoiesis. In: Greer JP, Foerster J, Lukens JN, Rodgers GM,

Paraskevas F, Glader B, eds. *Wintrobe's Clinical Hematology*. 11th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2004:195-216

Juul SE. Nonerythropoietic roles of erythropoietin in the fetus and neonate. *Clin Perinatol*. 2000;27:527-541

Ohls RK. The use of erythropoietin in neonates. *Clin Perinatol*. 2000;27:681-696

Content Specification(s):

Understand the normal physiology of erythropoiesis in the fetus and neonate

Understand the role of growth factors in regulating erythropoiesis in the fetus and neonate

Know the mechanisms resulting in anemia of prematurity

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A 3,200-g term male infant presents for his 1-week evaluation. The pregnancy and delivery were uneventful. His parents state that the baby has been difficult to arouse, is feeding poorly, and has been vomiting. On physical examination, the infant weighs 2,800 g, is lethargic and jaundiced, and has a palpable liver 3 cm below the right costal margin. An evaluation for sepsis has been performed and antibiotic therapy initiated. Additional laboratory results include: total bilirubin, 18 mg/dL (307.8 mcmol/L); direct bilirubin, 6 mg/dL (102.6 mcmol/L); alanine aminotransferase, 104 U/L; aspartate aminotransferase, 150 U/L; and positive urine dipstick for protein and reducing substances.

Of the following, the test that would be MOST helpful in the diagnosis of this patient is

☒ **1** Coombs test and maternal anti-Rh titer

2 examination of a blood smear for red cell morphology

3 serum amino acids and urine organic acids

4 serum galactose-1-phosphate uridyltransferase level

5 serum hepatitis B surface antigen

You selected 1, the correct answer is 4.

Direct or conjugated hyperbilirubinemia in the neonatal period may result from intrinsic liver disease or a congenital hepatobiliary obstruction. In these cases, conjugated bilirubin levels increase rapidly during the first few postnatal weeks to greater than 2 mg/dL (34.2 mcmol/L) and remain elevated. Underlying causes include bacterial or viral sepsis, nonspecific neonatal hepatitis, galactosemia and other metabolic disorders (tyrosinemia, fructosemia, Niemann-Pick disease, Gaucher disease, glycogenosis Type IV, cystic fibrosis), severe hemolysis (with inspissation of bile, which may be seen in Rh disease), biliary atresia, extrahepatic biliary obstruction, alpha-1-antitrypsin deficiency, isolated defects in hepatic bilirubin transport, and neonatal hemosiderosis. A prompt investigation should be undertaken to determine the cause of the conjugated hyperbilirubinemia because some of the causative conditions may be serious and life-threatening and have significant implications for the child?s health and future development.

The symptoms exhibited by the infant described in the vignette, coupled with their time of onset and the presence of reducing substances in the urine, suggest the diagnosis of galactosemia. Therefore, measurement of the serum galactose-1-phosphate uridyltransferase level would be the most helpful. Obtaining a Coombs test and maternal anti-Rh titer, serum amino acids and urine organic acids measurements, and a peripheral blood smear is appropriate for the evaluation of an infant who has unconjugated hyperbilirubinemia. Hepatitis B virus infection may cause conjugated hyperbilirubinemia, but the patient's age and clinical presentation are not consistent with neonatal hepatitis B infection.

References:

Karpen SJ. Update on the etiologies and management of neonatal cholestasis. *Clin Perinatol*. 2002;29:159-180.
Abstract available online

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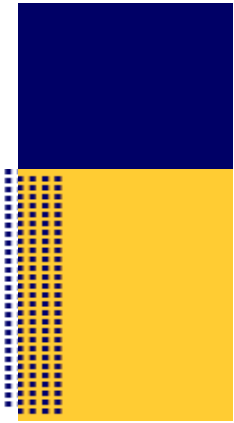
Abstract available online

<u>Content specifications:</u>
Understand the differential diagnosis, evaluation, and approach to management of mixed forms of jaundice
Understand the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of carbohydrates (excluding glucose)

PREVIOUS   NEXT

Abstract available online

<u>Content specifications:</u>

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A term male infant whose birthweight was 3.5 kg was discharged at 2 days of age with minimal visible jaundice. He went home to a family farm, and his parents did not keep scheduled appointments. When he returns for evaluation 30 days later, he appears very jaundiced and has stopped feeding vigorously. The only remarkable findings on physical examination are the jaundice and some lethargy. His weight is 4.0 kg. Laboratory findings include: total bilirubin, 32 mg/dL (547.2 mcmol/L); direct bilirubin, 0.5 mg/dL (8.6 mcmol/L); and hemoglobin, 12.5 g/dL (125 g/L).

Of the following, the MOST likely diagnosis for this infant is

1. beta-thalassemia

☒ 2. congenital hypothyroidism

3. Crigler-Najjar syndrome

4. Dubin-Johnson syndrome

5. Gilbert disease

You selected 2, the correct answer is 3.

Crigler-Najjar syndrome is an autosomal recessive disorder characterized by a complete absence of activity of the enzyme bilirubin-uridine diphosphate-glucuronyl transferase A1A, leading to severe unconjugated hyperbilirubinemia, as reported for the infant in the vignette. The condition is rare, with approximately 50 known cases in the United States. Intensive phototherapy can prevent the high bilirubin levels that can occur in this syndrome. Arias syndrome (Crigler-Najjar type 2) results from a depressed, but not absent, activity of the enzyme. Patients who have this condition have lower levels of bilirubin, often respond to phenobarbital, and may have exacerbations during infection or stress.

Beta-thalassemia results from a defect in the genes that code for the beta chain of the hemoglobin molecule. This condition presents in the latter half of the first year after birth because newborns have significant levels of fetal hemoglobin. Neonatal jaundice is not a presenting sign.

Congenital hypothyroidism may be associated with jaundice, usually presenting as prolonged clinical jaundice, but usually not with unexpectedly high levels of bilirubin. Other symptoms of hypothyroidism, including growth failure, hoarse cry, and slow feeding, were not noted in the infant in this vignette. Hypothyroidism does not present with early, rapidly rising bilirubin levels.

Dubin-Johnson syndrome is due to defects in the human canalicular multispecific organic ion transporter protein that is required for transfer of conjugated bilirubin across the canalicular membrane. Nonpruritic jaundice associated with conjugated hyperbilirubinemia is noted in the teen years.

Gilbert syndrome results from an abnormality in the activity of the bilirubin-uridine diphosphate-glucuronyl transferase enzyme. An abnormality in the promoter region of the gene has been identified. Affected patients have serum bilirubin concentrations that range from normal to about 6 mg/dL (102.6 mcmol/L). Severely elevated bilirubin levels in infancy are not consistent with this diagnosis alone, although Gilbert syndrome can exacerbate jaundice in infants with other underlying problems in bilirubin metabolism, especially those with increased bilirubin production.

References:

American Academy of Pediatrics, Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. **2004;114:297-316**

Anand MK, Mishark KJ. eMedicine: Dubin-Johnson syndrome. Available at: www.emedicine.com/med/topic588.htm. Accessed January 2005

Cao A, Galanello R. Beta-thalassemia. Available at: www.genetests.org/query?dz=b-thal. Accessed January 2005

Mukherjee S. eMedicine: Gilbert syndrome. Available at: www.emedicine.com/med/topic870.htm. Accessed January 2005

Pigazzi A, Ravelli S. eMedicine: Criglar-Najjar syndrome. Available at: www.emedicine.com/med/topic476.htm. Accessed January 2005

Content Specifications:

Know the factors associated with an increase in neonatal serum bilirubin concentrations

Understand the differential diagnosis, evaluation, and approach to management of infants with indirect hyperbilirubinemia

You are teaching medical students how to perform a neurologic examination in a newborn. The discussion focuses on the evolution of primitive reflexes through gestational development and infancy.

Of the following, the EARLIEST primitive reflex to appear during human gestation is the

1. crossed extension reflex

2. Moro reflex

3. palmar grasp reflex

4. rooting reflex

5. tonic neck reflex

You selected 3, the correct answer is 3.

Primitive neonatal reflexes, also called primary integrated reflexes, are transitory developmental phenomena that appear according to a predictable timetable during gestation and disappear during infancy. The most frequently elicited reflexes are: Moro reflex; palmar and plantar grasp reflex; placing and stepping reflex; rooting, sucking, and swallowing reflex; tonic neck reflex; and crossed extension reflex. Others include Galant's trunk incurvation reflex, finger extension reflex, and head traction reflex. These highly stereotypical patterns of automatic movement are elicited by specific sensory stimuli and controlled by subcortical neuronal pathways. Some of the reflexes can be elicited as early as during the 25th week of gestation; most are fully present at birth in term neonates. These reflexes become difficult to elicit after the first half of infancy when cortical inhibition emerges and voluntary muscle activity replaces the reflex movements. Delayed appearance of the reflexes during gestation and persistence of the reflexes beyond the anticipated age for their disappearance are indicators of potential central nervous system dysfunction.

The palmar grasp reflex is one of the earliest primitive neonatal reflexes to appear during human gestation. The reflex is elicited by stroking with a finger the palmar surface of the infant's hand, which results in flexion of the fingers in a grasping motion. This reflex can be elicited, albeit weakly, as early as at 26 weeks of gestational age, is stronger at 32 weeks, and is strong enough to allow the examiner to lift the infant from the bed at 37 weeks. The palmar grasp reflex begins to fade at 2 months of age and disappears by 4 months with the development of a voluntary grasp.

To elicit the crossed extension reflex, one leg is held firmly in extension and the sole of the foot is rubbed. The reflex is observed in the opposite (free) leg in three successive phases: initial flexion (withdrawal), subsequent extension and fanning of the toes, and, in its fully developed form, adduction of the free leg toward the stimulated side as if to push away the stimulus. This reflex is absent at 26 weeks of gestational age, can be elicited in its partial form (only flexion) at 30 weeks, and is complete at 34 weeks. The crossed extension reflex disappears by about 2 months of age.

The Moro reflex can be elicited by startling the infant. The most effective and reproducible method for startling is to create a sensation of falling by sudden dropping of the head in relation to the trunk. With the infant held in supine position, the head is allowed to fall a few centimeters, rapidly but gently, in the examiner's hands. The reflex is observed in two successive phases. The infant's first response is a spreading motion in which the arms are abducted and extended with hands opened. The spreading motion is followed by a clutching motion in which the arms are adducted and flexed over the trunk with fists closed, often

accompanied by an audible cry. The Moro reflex is absent at 26 weeks of gestational age, can be elicited in its partial form (only spreading motion) at 30 weeks, is complete but variable (spreading with or without clutching motion) at 34 weeks, and is fully developed at 38 weeks. The reflex begins to fade at 2 months of age and disappears by 4 months.

In addition to being an index of gestational maturation, the Moro reflex can be useful in other clinical settings. An absent or depressed Moro reflex often accompanies severe illness, especially kernicterus and general depression of the central nervous system or a disorder of motor function. An exaggerated Moro reflex may be a manifestation of narcotic withdrawal or moderately severe hypoxic-ischemic encephalopathy. An asymmetric Moro reflex is seen with brachial plexus palsy and with trauma to the clavicle, humerus, or shoulder joint.

The rooting reflex is elicited by stroking with a finger the upper or lower lip or either corner of the infant's mouth, which results in the infant turning the head, searching for the finger, and attempting to suck. Sucking tends to reinforce the rooting; a recent feeding tends to suppress it. The rooting reflex tests the integrity of the sensory pathways of the trigeminal nerve and of the motor pathways of the trigeminal, facial, and hypoglossal nerves. This reflex is absent at 26 weeks of gestational age, can be elicited with long patency at 30 weeks, and is fully developed at 34 weeks. The reflex disappears by 4 months of age.

To elicit the tonic neck reflex, the infant is placed in a supine position with the head in the midline, and the head is turned slowly to one side. This maneuver results in extension of the arm on the side to which the head is turned and flexion of the arm on the opposite side. The lower limbs respond similarly, but less strikingly. Ultimately, the infant assumes a "fencing" posture. The tonic neck reflex is one of the latest primitive neonatal reflexes to appear during human gestation. It appears at 35 weeks of gestational age, is most prominent at 2 months after birth, and disappears by 6 months of age.

<u>References:</u>

Brett EM, Kaiser AM. Neurology of the newborn. In: Brett EM, ed. *Pediatric Neurology*. 3rd ed. Edinburgh, Scotland: Churchill Livingstone; 1997:1-24

Fenichel GM. The neurological consultation. In: *Neonatal Neurology*. 3rd ed. New York, NY: Churchill Livingstone; 1990:1-16

Rennie JM. Assessment of the neonatal nervous system. In: Rennie JM, Roberton NRC, eds. *Textbook of Neonatology*. 3rd ed. Edinburgh, Scotland: Churchill Livingstone; 1999:1203-1213

Volpe JJ. Neurological examination: normal and abnormal features. In: Neurology of the Newborn. 4th ed. Philadelphia, Pa: WB Saunders; 2001:103-133

Zafeiriou DI. Primitive reflexes and postural reactions in the neurodevelopmental examination. *Pediatr Neurol*. 2004;31:1-8

<u>Content Specifications:</u>

Know the normal integrated (primitive) reflexes that are present in the newborn infant, such as Moro, tonic neck, rooting, and grasping

Know the normal pattern of development of primitive (primary or integrated) reflexes in premature and term infants and through infancy (e.g. grasp, asymmetric tonic neck reflex, tonic labyrinthine)
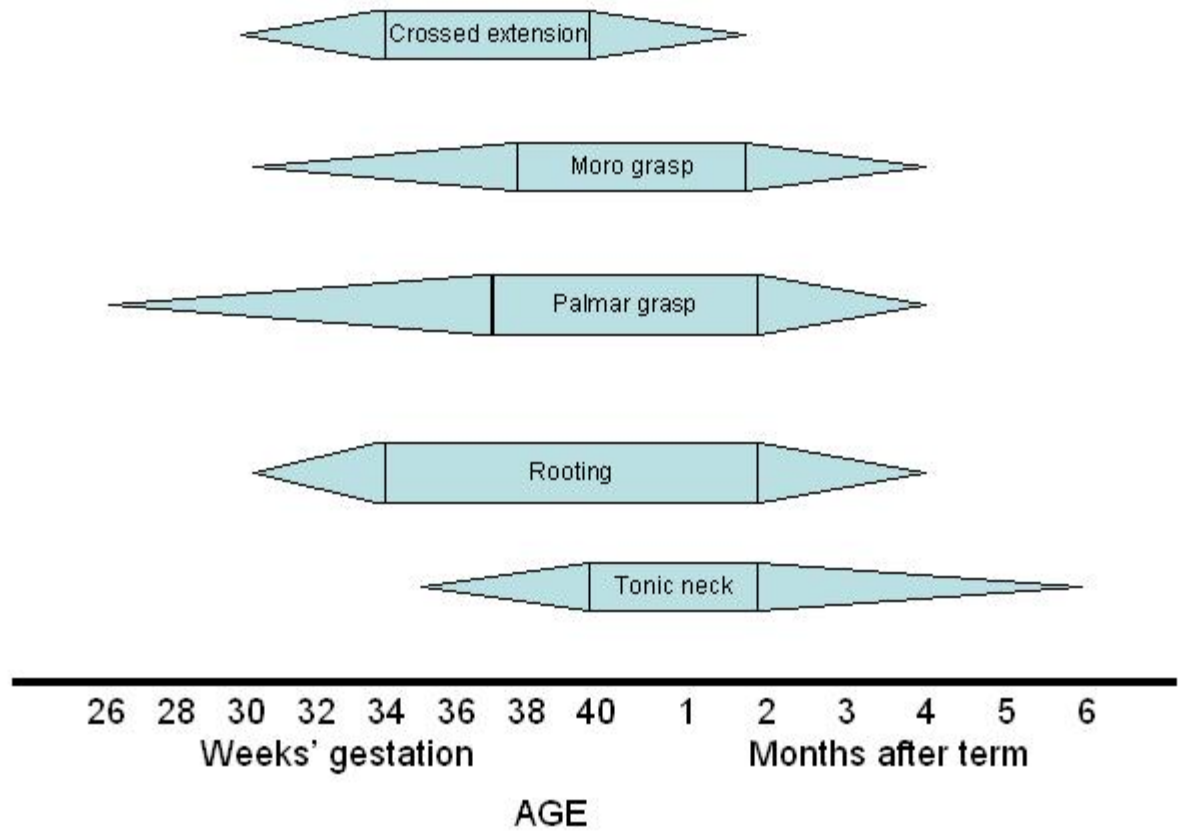
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NeoReviewsPlus

May 05 | Questions | Assessment Summary | CME Credit Expired | ▶

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You are reviewing with medical students the case of a term infant who developed overwhelming group B streptococcal (GBS) sepsis. In the course of your discussion, you examine the role of complement in host defense.

Of the following, the MOST accurate statement regarding the complement system is that

1. activation of complement via the alternative pathway is dependent on type-specific antibodies

2. C1q is the complement component that plays a central role in chemoattraction

3. C3b is the complement component that plays a central role in opsonization

4. ☒ gram-positive bacteria can be lysed by the membrane attack complex

5. most fetal complement components are acquired transplacentally

You selected 4, the correct answer is 3.

The complement system consists of approximately 35 serum or membrane proteins that interact in a cascade similar to the clotting cascade. The functions of the complement system in host defense include opsonization of microorganisms, cytolysis of susceptible bacteria, and release of potent anaphylotoxins and chemoattractants.

The complement cascade can be activated via the classic, lectin, or alternative pathway. The classic pathway (animation 1) is considered antibody-dependent and is activated when type-specific antibodies combine with an antigen. The lectin and alternative pathways are considered nonspecific or antibody-independent. The lectin pathway (animation 2) is triggered by microbial polysaccharides. The alternative pathway (animation 3) is triggered by other "foreign" surface structures, such as bacterial cell membranes, viral envelopes, and hemodialysis and oxygenator membranes.

Upon activation, complement proteins act sequentially to form an enzyme cascade. Each step generates a proteolytic enzyme that cleaves subsequent components. The cascade permits amplification of the system. Deposition of a single C3b fragment on the surface of a microorganism can generate the cleavage of thousands of later-acting complement components. This powerful amplification system is controlled by at least 10 negative regulating proteins.

C3 is the pivotal component of the complement cascade. Activation of any of the three pathways results in the cleavage of C3 to C3a and C3b. C3a is an anaphylotoxin that causes vasodilation and increases vascular permeability at the site of inflammation. C3b plays the central role in opsonization and enhances the uptake of microorganisms into phagocytic cells via complement receptors.

Microbial polysaccharides or bacterial cell membranes activate the complement system via the lectin and alternative pathways. These pathways are particularly important in newborns because they are antibody-independent. Newborns who lack maternally derived type-specific anti-GBS immunoglobulin (Ig) G rely on these pathways to generate C3b to opsonize GBS.

The classic complement pathway is activated when antibody-antigen complexes cleave C1 to C1q, C1r, and C1s. C1q is the fragment that binds to the Fc portion of IgM or IgG to trigger the cascade. C5a is the proteolytic fragment of C5 that plays the central role in chemoattraction of phagocytes. Although an influx of phagocytes is beneficial in host defense, it may be detrimental in neutrophil-induced lung injury associated with extracorporeal life support, postischemic reperfusion injury, and acute respiratory distress syndrome.

The membrane attack complex (MAC) is formed after activation of the terminal components of the complement cascade: C5 through C9. The MAC assembles on the bacterial cell membrane, creates a hole in the membrane, and directly kills some gram-negative bacteria by osmotic lysis. Gram-positive organisms, such as GBS, are protected against complement lysis by the presence of their peptidoglycan cell walls.

Complement components cannot be passed transplacentally. The fetal liver is the primary site of production for complement proteins. Complement components have been detected as early as 5 weeks of gestation, and concentrations increase with increasing gestational age. By 26 weeks of gestation, C3 concentrations are approximately 66% of adult concentrations. Term infants have approximately 75% of adult concentrations. Extrahepatic synthesis of complement occurs by a number of cells, including monocytes, macrophages, type II pulmonary epithelial cells, fibroblasts, and astrocytes. Extrahepatic production of complement proteins may be important at local sites of inflammation.

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Content Specifications:

Know the consequences of defects in the complement system

Know the role of complement in host defense

PREVIOUS   NEXT

Classical Complement Pathway Animation

Classical Complement Pathway
The classical complement pathway is activated when the Y-shaped antibodies attach to bacterial surfaces. This leads to cleavage of C1, C2 and C4 to form C3 convertase, which in turn cleaves C3 into C3a and C3b. C3b is the pivotal protein in the complement cascade. Binding of C3b to the bacterial surface will activate C5 through C9 forming the membrane attack complex. The membrane attack complex kills some bacteria by osmotic lysis.

Close

Lectin Complement Pathway Animation

LECTIN COMPLEMENT PATHWAY
The main constituent of the Lectin complement Pathway is the plasma protein mannose-binding-ligand. Mannose-bindin-ligand recognizes mannose on bacterial surfaces and directly cleaves C3. Binding of C3 to the bacterial surface will activate C5 through C9 forming the membrane attack complex which can kill some bacteria by osmotic lysis.

Close

Alternative Complement Pathway Animation

ALTERNATIVE COMPLEMENT PATHWAY

C3 can be activated in the alternative complement pathway independently of antibody. There are some activator surfaces on some bacteria that can result in cleavage of C3 and covalent attachment of C3b to the bacterial surface. When C3b covalently attaches to an activator surface then factor B can associate with C3. The factor B plus C3 complex further amplified by factor D such that additional C3 molecules can attach to the bacterium. This in turn can activate C5 through C9, the membrane attack complex, which can kill some bacteria by osmotic lysis.

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A term infant has rhizomelic shortening of the arms and legs, a disproportionately long trunk, trident hands, midfacial hypoplasia, and a prominent forehead (frontal bossing) (Figure). Radiographic examination shows caudal narrowing of the interpedicular spaces. Parents have average-stature.

Of the following, the MOST appropriate recurrence risks for the parents and for the son when he becomes a father are:

1   25% for the parents; less than 1% for the son

2   50% for the parents; less than 1% for the son

3   less than 1% for the parents; 25% for the son

4   less than 1% for the parents, 50% for the son

5   50% for the parents; 50% for the son

You selected 4 , the correct answer is 4 .

The infant has the cardinal features of achondroplasia, a non-lethal form of chondrodysplasia. Achondroplasia is an autosomal dominant condition in which approximately 80% of affected individuals have a de novo gene mutation. Frequency is estimated at 1 case per 15,000-40,000 births. Since the condition shows complete penetrance, the average-stature parents of children who have achondroplasia have a low recurrence risk, estimated to be less than 1%, although parental germline mosaicism has been reported rarely. Of interest, de novo gene mutations are associated with advanced paternal age (>35 to 40 y). Even in the absence of advanced paternal age, de novo mutations are inherited exclusively from the father, apparently due to a gene change during spermatogenesis.

More than 99% of individuals who have achondroplasia have one of two point mutations (G1138A or G1138C) in the fibroblast growth factor receptor 3 (FGFR$_3$) gene at chromosome 4p16.3. The genetic dysfunction results in decreased endochondral ossification, inhibited proliferation of chondrocytes in growth plate cartilage, decreased cellular hypertrophy, and decreased cartilage matrix production. The likelihood that the child of a person who has achondroplasia will be affected is 50% if his or her partner is not affected. However, when counseling the couple described in the vignette, it is important to point out that little people often choose to marry other little people. Should their son choose to marry a woman who has achondroplasia, their risk for having a child who has homozygous achondroplasia (inheriting two copies of the unusual gene) is 25%, and this is a lethal condition. Of the remaining three possible outcomes, two children would be affected with achondroplasia, and one would not inherit the unusual gene.

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Content specifications:

Know the clinical features and know how to manage skeletal dysplasias, such as achondrogenesis, achondroplasia, chondrodermal dysplasia, epiphyseal dysostosis, osteogenesis imperfecta, hypophosphatasia, etc

Demonstrate understanding of inheritance patterns and recurrence risks for autosomal dominant disorders

Rimoin DL, Connor JM, Pyeritz RE, eds. *Emery and Rimoinís Principles and Practice of Medical Genetics*. 4th ed. New York, NY: Churchill Livingstone; 2002

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One year after delivering her second infant by cesarean delivery because of placenta previa, a woman becomes pregnant for the third time. Her first child was delivered vaginally at term. She expresses an interest in delivering this third infant vaginally and inquires about the pregnancy outcomes of vaginal birth after cesarean (VBAC) section for mothers and infants.

Of the following, the MOST accurate statement regarding VBAC is that

1. augmentation of labor produces a rate of uterine rupture similar to that following spontaneous onset of labor

2. increasing numbers of mothers previously delivered by cesarean section are delivering vaginally

☒ 3. neonates delivered by VBAC incur a lower risk of stillbirth, neonatal death, or hypoxic-ischemic encephalopathy

4. successful vaginal delivery in the past improves the potential for successful VBAC

5. uterine rupture during a trial of labor occurs only in the presence of a classic uterine incision

You selected 3, the correct answer is 4.

Cesarean births now occur in about 26% of pregnancies, up from 4% in 1950 and 5% in 1970. Noting that 98% of women who delivered by cesarean section subsequently delivered by repeat cesarean section, goals were set in the 1980s to encourage VBAC and to reach a VBAC rate of 35% by the year 2000. By 1996, the rate had reached 28.6%. Due to reports of higher perinatal mortality and increased numbers of uterine rupture associated with trials of labor, the VBAC rate decreased to 12.6% by 2002. Overall, VBAC is associated with more perinatal risk (odds ratio [OR], 1.96; 95% confidence intervals [CI], 1.73 to 2.22]) than elective repeat cesarean delivery, but statistical analyses reveal that approximately 588 elective cesarean deliveries are needed to avert each severe adverse perinatal outcome. Some mothers and physicians consider this risk acceptable to attempt vaginal delivery; others do not.

Detailed outcomes of VBAC were reviewed from 19 academic medical center hospitals involved in a study of VBAC from 1999 through 2002. These centers followed the guidelines of the American College of Obstetricians and Gynecologists that required immediate availability of emergency cesarean section during trials of labor in women attempting VBAC. Among the factors associated with successful VBAC were previous vaginal delivery and previous VBAC. Mothers who had smaller infants were more likely to undergo a trial of labor after cesarean section.

The overall risk for uterine rupture among women undergoing a trial of labor was about 5 to 7 per 1,000 deliveries. After previous cesarean section, women who entered labor spontaneously had less chance of uterine rupture than did women whose labor either was induced (OR, 2.86; CI, 1.75 to 4.67) or augmented with oxytocin, prostaglandins, or both (OR, 2.42; CI, 1.49 to 3.93). Women delivered by elective cesarean section without labor evidenced uterine rupture in 1.6 per 1,000 deliveries in one study, and "uterine dehiscence" was described among 0.5% of 15,000 women delivering by elective cesarean section in a second study. Although data regarding maternal complications have been inconsistent, the most recent analysis by Landon and associates found elective cesarean section to be associated with a lower rate of endometritis and blood transfusion, with no difference in needs for hysterectomy or in maternal death. Overall, a trial of labor presents a greater chance (OR, 1.95; CI, 1.73 to 2.22) for adverse maternal events than does elective repeat cesarean section.

As noted previously, after a peak VBAC rate of 28% in 1996, the rate dropped to 12.6% in 2002, resulting in fewer women delivering by VBAC in recent years. Due to the declining rate of trial of labor during the projected 3-year study period for the previously cited multicenter study, an

additional year was added to obtain sufficient data to analyze perinatal outcomes associated with VBAC.

The risk to the infant for stillbirth, neonatal death, or hypoxic-ischemic encephalopathy (HIE) was significantly greater (OR, 2.72; CI, 1.49 to 4.97) among infants whose mothers underwent a trial of labor. Of 12 cases of HIE, 6 followed spontaneous onset of labor, 2 followed augmentation, and 4 followed induction of labor. Seven of the 12 were associated with uterine rupture, and two of the 12 infants died in the neonatal period. The incidence of neonatal death from uterine rupture was 0.1 to 0.4 deaths per 1,000 trials of labor. The overall perinatal mortality rate among women undergoing trials of labor was 4 per 10,000 deliveries contrasted to 1.4 per 10,000 deliveries among women undergoing elective cesarean section delivery in the multicenter trial.

The risk for uterine rupture during the trial of labor was 0.7% if the previous cesarean section was performed via a low transverse uterine incision. A low vertical incision was associated with a 2% risk, and classic, inverted T, or J incision types were associated with a 1.9% risk in the series by Landon and associates. The incidence of uterine rupture was 4% to 9% with classic or T-shaped incisions, 1% to 7% with low vertical incisions, and 0.2% to 1.5% with low transverse incisions.

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Content Specifications:

Know the indications for cesarean delivery

Know the maternal and fetal/newborn complications of cesarean delivery

Know the advantages of, indications for, and complications of vaginal delivery

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You are asked to see an infant who has a bilateral port wine stain (Figure 1) on the upper right side of the face. The parents request advice on removing the lesion.

Of the following, your BEST recommendation is

1. an explanation that there is no effective therapy

2. consecutive cryotherapy treatments

☒ 3. repeated dermabrasion treatments

4. sequential pulsed dye laser treatments

5. staged surgical excision

You selected 3, the correct answer is 4.

Port wine stain (PWS) (also called nevus flammeus (NF) or dermal capillary malformation or venulocapillary malformation) occurs among 0.3-0.5% of newborns in the United States. PWS is the most common type of vascular malformation. The name derives from the dark red color that develops as the lesions mature. PWS must be differentiated from nevus flammeus neonatorum which applies to telangiectatic areas on the glabella, nose, upper lip, eyelids and/or occipital area of the scalp. These lesions go by terms such as salmon patch, stork bite, angel kiss, nevus simplex, NF nuchae, medial telangiectatic nevus, and medial NF. These conditions occur more commonly, affecting 42% of white and 31% of black infants. With the exception of the occipital lesions, these lesions lighten and resolve in the first two years of life. In contrast, PWS grows commensurate with the child and shows no tendency to involute.

The vascular-specific (585-nm) pulsed (450-msec) dye laser (Figure 2)

is the treatment of choice for port wine stains. The procedure is relatively painless when topical anesthetics are used, and adverse effects are minimal. The response of the lesions to treatment depends on the age of the patient at initiation of therapy and the size of the port wine stain. Treatment in the first year of life, beginning as early as the second week of life, may elicit a better response although some studies showed no benefit to very early treatment.

Younger patients who have small lesions are more likely to experience complete removal.

For patients who have facial port wine stains, the possibility of the Sturge-Weber syndrome should be considered. The Sturge-Weber syndrome (leptomeningeal angiomatosis) is the association of a PWS involving the facial portion (V-1 branch) of the trigeminal nerve with central nervous system vascular malformations involving the ipsilateral leptomeninges. Approximately 8% of port wine stains involving a unilateral V-1 (first branch of the trigeminal nerve) dermatome are associated with ocular or central nervous system involvement. The risk triples if the V-1 involvement is bilateral. Individuals with SWS may have involvement of the V-2 (maxillary) and/or V-3 (mandibular) branches, but involvement of V-2 or V-3 without V-1 involvement is not consistent with SWS. NF or PWS affecting an extremity (85% leg) with associated varicose veins and ipsilateral tissue hypertrophy occurs in the Klippel-Trenaunay syndrome. PWS may be seen also in Parkes-Weber, Cobb, and Wyburn-Mason syndromes.

Cryotherapy is inappropriate for the patient described in the vignette because of the recognized complications of postoperative pain, hypopigmentation, atrophic scarring, and inadvertent nerve injury. Both dermabrasion and surgical excision involve the inherent risk of significant scarring and infection. None of these treatments is appropriate for PWS.

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Content specification:

Know how to manage port wine stain

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A normal-appearing male was delivered at 38 weeks' gestation. He is scheduled to be discharged with his mother at 25 hours after birth. During the night, nurses had noted facial icterus at 19 hours after birth, at which time a transcutaneous bilirubin concentration was 5.7 mg/dL (97.5 mcmol/L). Repeat transcutaneous bilirubin concentration at 25 hours is 8.3 mg/dL (141.9 mcmol.L). His mother reports that the infant's older brother also was jaundiced after birth. Using the hour-specific bilirubin nomogram (Figure), you note the pattern of his hyperbilirubinemia and keep him in the hospital for testing and treatment.

Of the following, the MOST likely cause for this infant's jaundice is

1. Gilbert disease

2. hemolytic disease

3. inadequate feeding

4. physiologic jaundice

5. sepsis

You selected 5, the correct answer is 2.

The bilirubin concentration for the infant described in the vignette increased 2.6 mg/dL (44.5 mcmol/L) in 5 hours or more than 0.5 mg/dL per hour (8.6 mcmol/L per hour), which strongly suggests that excess bilirubin production is the underlying cause of the jaundice. Hemolytic disease is the most common cause of early and rapid increases in serum bilirubin. When the transcutaneous bilirubin concentration increases rapidly, confirmation of the bilirubin value in the serum as well as testing for blood group incompatibilities, reticulocytosis, and anemia is indicated. Although the bilirubin level for the infant in the vignette has not reached the usual threshold for treatment, this rapid of an increase is a reasonable indication for the early use of intensive phototherapy, for which total serum bilirubin testing is the only appropriate measure of therapeutic effect.

Gilbert disease is caused by a congenital defect in the promoter region of the glucoronyl transferase 1A1 gene, resulting in mildly impaired conjugation. Bilirubin synthesis is not excessive, and early or rapidly rising levels cannot be attributed to this condition.

Inadequate feeding may accentuate bilirubin levels by enhancing the role of the enterohepatic circulation of bilirubin. When inadequate feeding is associated with decreased intestinal motility, glucuronidases in the intestines convert conjugated bilirubin back to the unconjugated form, which is resorbed into the bloodstream and may contribute to bilirubin concentrations. Such jaundice does not start early, and an excessively rapid increase in bilirubin is not common; rather, a delayed peaking and persistent icterus are more common.

Physiologic jaundice is a diagnosis of exclusion. When jaundice occurs early and bilirubin rises rapidly, pathologic mechanisms such as hemolysis must be explored. Among term infants, physiologic jaundice becomes evident after 24 hours of age, peaks by postnatal days 3 to 5, is characterized by bilirubin levels remaining below those requiring treatment, and no longer is evident by 7 to 10 days of age.

Although jaundice may accompany sepsis, rarely is it the sole presenting sign of infection. When present with infection, the jaundice tends to be prolonged and, in some types of infection, conjugated bilirubin concentrations are elevated.

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Figure. Hour-specific nomogram for assessing bilirubin levels. Reprinted with permission from Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics*. **1999;103:6-14.**

Content Specifications:

Understand the differential diagnosis, evaluation, and approach to management of infants with indirect hyperbilirubinemia

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You are called to the newborn nursery to evaluate a 1-day-old baby who is irritable, tremulous, and has been feeding poorly. On physical examination, you note that the term baby weighs 2,200 g (<5th percentile), and her head circumference is 31 cm (<5th percentile). She is hirsute, has fifth finger clinodactyly, and has hypoplastic nails on her hands and feet. Her facial features are swollen, and her eyelids are edematous due to face presentation at delivery.

Of the following, the baby's features are MOST likely due to prenatal exposure to

1 alcohol

2 lithium

3 retinoic acid

4 ☒ tobacco

5 valproic acid

You selected **4**, the correct answer is **1**.

The combination of being small for gestational age with microcephaly, hirsutism, fifth finger clinodactyly (Figure 1), hypoplastic nails (Figure 2), and irritability and tremulousness described for the infant in the vignette is strongly suggestive of fetal alcohol syndrome (FAS). FAS is a constellation of physical and behavioral features that can be appreciated in a percentage of babies who were exposed to alcohol during the first trimester of pregnancy. FAS is a major public health problem; it is estimated that 1:500 babies born in the United States has FAS, making it the most common preventable cause of mental retardation. Among babies born to heavy drinkers, the incidence of FAS is about 4%. Many more infants suffer negative effects from prenatal alcohol exposure.

To meet the diagnostic criteria for FAS, affected individuals must have abnormalities in three different areas: physical formation, growth, and neurodevelopment. Affected infants often are irritable and tremulous. However, tremulousness is self-limited and disappears within the first few months after birth. The children are thin, with very little subcutaneous fat, and tend to remain so throughout childhood. They also have prenatal-onset microcephaly and impaired linear growth. Neurodevelopmentally, the children have a variety of difficulties ranging from increased risk for sensorineural hearing loss and strabismus to learning deficits, especially in arithmetic, and a wide variety of behavior difficulties. Physical abnormalities, in addition to growth retardation, include short palpebral fissures (Figure 3), midface hypoplasia, smooth philtrum, narrow and smooth upper vermilion border, joint anomalies, altered palmar creases, fifth finger clinodactyly, small distal phalanges and fingernails, and heart defects.

Prenatal exposure to lithium during the first trimester of pregnancy increases the risk for Ebstein anomaly in the fetus.

Retinoic acid embryopathy results from prenatal exposure to isotretinoin from the 15th day after conception through the end of the first trimester. Isotretinoin interferes with neural crest cell migration and can result in defects of central nervous system development, severe ear anomalies, conotruncal heart defects, and abnormalities of the thymus.

Children born to women who smoke cigarettes during pregnancy are at increased risk for reduced birthweight; the likelihood of a birthweight of less than 2,500 g is increased significantly for the offspring of women who smoke more than 10 cigarettes per day. There is

also an increased risk for cleft palate in babies exposed prenatally to cigarette smoke who have a particular genetic polymorphism. There also may be an increased risk for cleft lip, and studies have shown that children exposed to cigarette smoke in utero are at increased risk for asthma in later life and may be at increased risk for some cancers.

Valproic acid embryopathy is associated most commonly with neural tube defects, and although some facial abnormalities may overlap with those of FAS, the children are not hirsute, and they are not small for gestational age.

References:

American Academy of Pediatrics Committee on Substance Abuse and Committee on Children With Disabilities. Fetal alcohol syndrome and alcohol-related neurodevelopmental disorders. *Pediatrics*. 2000;106:358-361. Abstract available online at http://pediatrics.aappublications.org/cgi/content/abstract/106/2/358, article available online for subscription or fee only

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Shepard TH. *Catalog of Teratogenic Agents*. 10th ed. Baltimore, Md: Johns Hopkins University Press; 2001

Content specifications:

Know the developmental consequences of maternal substance abuse, such as cocaine, heroin, alcohol, and tobacco, on the fetus, infant, and child

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Figure 2

Hypoplastic nails are a feature of the fetal alcohol and fetal hydantoin syndromes. (Courtesy of M Rimsza)

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A newborn is brought to the NICU from the delivery room due to multiple physical anomalies. On examination, you note a cleft positioned diagonally across the face. (Figure 1) On the right hand, there are distal amputations of index and middle fingers, absent ring finger, and constriction noted on the little finger. complete 2,3 syndactyly of the fingers, with distal hypoplasia and small nails on fingers 4 and 5. (Figure 2)

Of the following, the MOST likely cause of these abnormalities is

1	amnion rupture
2	chorionic villus sampling at 9 weeks' gestation
3	factor V Leiden deficiency
4	phenylhydantoin exposure
☒ 5	prenatal cocaine exposure

You selected 5, the correct answer is 1.

The newborn described in the vignette has features of amnion rupture sequence (also called "amniotic band sequence"). Although there is ongoing discussion about the factors that precipitate amnion rupture, it generally is believed to be a sporadic event that most likely occurs prior to 12 weeks' gestation, before the amnion and chorion are fused. Following rupture, the fetus can become entangled in or swallow strands of amniotic tissue, resulting in various disruptive outcomes, including clefts, constriction rings, amputations, pseudosyndactyly, and secondary deformations due to a combination of directly tethering normal tissue migration and an increase in local pressure, producing cellular ischemia and apoptosis. Animal data suggest that these clefts can occur later in fetal development during a period of facial growth rather than during the period of primary facial morphogenesis. Careful examination of the membranes at delivery may be diagnostic. Similarly, careful examination of the newborn before he or she is bathed may reveal adherent strands of tissue at sites of disruption. (Figure 3)

Although amnion rupture sequence may be apparent based on the presence of constriction rings or adherent bands of tissue, there are several other diagnostic possibilities, especially when there are absent or partially absent digits. However, these entities would not produce a facial cleft, as described for the infant in the vignette. Chorionic villus sampling performed prior to 10 weeks' gestation has been shown to be associated with transverse terminal limb defects similar to those caused by amniotic bands. Prenatal exposure to phenylhydantoin is associated with hypoplasia of the nails and distal phalanges as well as a number of other potential abnormalities. Factor V Leiden thrombophilia, an autosomal dominant condition that predisposes affected women to miscarriage, has an unclear role in fetal limb deficiency. In case reports, prenatal cocaine exposure has been described in association with terminal transverse limb reduction defects.

References:

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Content specifications:

Recognize the consequences of the amniotic band syndrome

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A female newborn, who weighs 2,100 g, is delivered by repeat cesarean section at term. In the delivery room, the infant has cyanosis, a respiratory rate of 74 breaths/min, unlabored respirations, and a grade III/VI harsh systolic murmur at the right sternal border. Blow-by oxygen elicits no improvement in color or respiratory distress. Oxygen saturations in the right hand and foot are both 83%. Peripheral pulses are equal, precordium is quiet, breath sounds are clear, and the liver is palpable at 1 cm below the right costal margin. Additional physical findings include a head circumference of 31 cm, micrognathia with U-shaped cleft palate, small low-set and malformed right pinna, epicanthal folds that continue as long infraorbital creases bilaterally, hirsutism, absent left forearm, hypoplastic right thumb, broad chest, and small lumbar meningomyelocele. The maternal history is significant for hypertension, seizures, depression, and diabetes. These conditions were well-controlled with labetolol, nifedipine, valproic acid, fluoxetine, and insulin. Maternal hypertension had been treated with enalapril until the pregnancy was diagnosed at 11 weeks' gestation. Fetal karyotype was 46,XX, and results of fetal ultrasonography performed at 20 weeks' gestation were reported as normal.

Of the following, the MOST likely cause for the congenital anomalies in this infant is

☒ 1	enalapril
2	fluoxetine
3	labetalol
4	nifedipine
5	valproic acid

You selected **1**, the correct answer is **5**.

The congenital anomalies described for the infant in the vignette are characteristic of fetal valproate syndrome or valproic acid embryopathy. Valproic acid crosses the placenta and is teratogenic to the fetus when given during embryogenesis. The mechanism for teratogenicity is unknown, although a number of gene disturbances that may account for the teratogenicity of valproic acid have been identified recently. Neural tube defects (3% of cases), congenital heart disorders (26%), limb reduction defects (62%), and characteristic facial features are described in this disorder. The facial features include long infraorbital fissures, small and broad nose, small ears, wide philtrum, and micrognathia. Additional findings include intrauterine growth restriction; microcephaly; and genital, skin, and pulmonary abnormalities. Abnormalities of the brain, eye, kidney, and auditory systems occur less frequently. Death in infancy is seen in 12% of affected infants, developmental delays in 20%, and mental retardation in 9%.

Enalapril is an angiotensin-converting enzyme (ACE) inhibitor that readily crosses the placenta. During fetal life, renal perfusion and glomerular plasma flow are low, and it has been proposed that high levels of angiotensin II are required to maintain glomerular filtration and urine production during states of low renal perfusion. Therefore, when ACE inhibitors are used during pregnancy, especially during the second and third trimesters, fetal urine production may be impaired, causing oligohydramnios. Intrauterine growth restriction, fetal compression defects (oligohydramnios sequence), neonatal renal failure, and hypotension may occur. Neonatal renal failure may be prolonged because ACE inhibitors are excreted through the kidney. Hypocalvaria and incomplete skull ossification have been reported in animal studies and some case reports. It is hypothesized that the combination of oligohydramnios, fetal hypotension, and uterine compression impair ossification of the calvaria. These effects are not found with short-term use of ACE inhibitors during the first trimester of pregnancy. Congenital anomalies other than intrauterine growth restriction, hypocalvaria, and deformation effects associated with

oligohydramnios are not associated consistently with ACE inhibitors.

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) used for treatment of depression. Nearly 20% of pregnant women are taking fluoxetine or another SSRI. Animal and human studies have not shown a consistent relationship between fluoxetine and major congenital anomalies. Some investigators have suggested an increase in the risk for spontaneous abortions, minor anomalies, prematurity, and transient neonatal withdrawal symptoms with fetal fluoxetine exposure, although these findings have not been confirmed by well-controlled studies. Furthermore, adverse maternal events due to untreated depression must be considered when prescribing an antidepressant.

Labetalol is a combined alpha- and beta-adrenergic blocking drug used to treat hypertension during pregnancy. It crosses the placenta, with cord blood concentrations about 50% of those in maternal blood. Despite relatively high fetal concentrations of labetalol, no major congenital anomalies have been reported when the fetus is exposed during the first trimester, although information is limited. Intrauterine growth restriction and premature labor due to labetalol have been suggested, but not confirmed. On rare occasions, neonates may have transient hypotension or bradycardia. Neonatal hypoglycemia has not been reported with labetalol, although it is associated with other beta-blocking agents (propranolol, atenolol). Interestingly, labetalol may reduce the incidence of respiratory distress syndrome due to $beta_2$ adrenoceptor agonist activity and a resultant increase in surfactant production.

Nifedipine is a calcium channel blocker. Calcium channel blockers have been used during pregnancy to treat premature labor and hypertension. They inhibit calcium entry into the cell and release from intracellular stores, thereby reducing myometrial contractility and smooth muscle tone. Nifedipine use during the second and third trimesters has not been associated with fetal or neonatal effects. Calcium channel blockers theoretically could disrupt many developmental events when used during embryogenesis because many of these events are calcium-dependent. Animal fetuses exposed to pharmacologic levels of nifedipine demonstrate growth restriction and deformities of the digits, ribs, and palate. However, no congenital anomalies have been reported in humans.

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Jeanty P, Silva SR. Fetal valproic acid exposure syndrome. Available at: www.TheFetus.net. Accessed January 2005

Kozma C. Valproic acid embryopathy: report of two siblings with further expansion of the phenotypic abnormalities and a review of the literature. *Am J Med Genet*. 2001;98:168-175

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Content Specifications:

Know the effects on the fetus of maternal chronic hypertension and its treatment

Know the effects of maternal seizure disorders and their management on the fetus
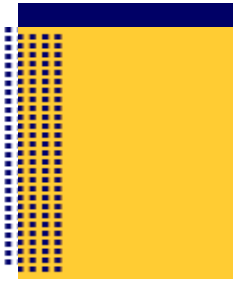
Know the normal and abnormal embryologic development of the heart and great arteries and the factors affecting these.

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You are teaching medical students how to manage fluid-electrolyte balance in newborns. The discussion focuses on body water distribution and body fluid composition during fetal and postnatal development in humans.

Of the following, the ONLY body fluid compartment that increases as percentage of body weight during fetal and postnatal development is

1   extracellular fluid

☒ 2   interstitial fluid

3   intracellular fluid

4   plasma fluid

5   total body water

You selected **2**, the correct answer is **3**.

The body water distribution is shown in **Figure 1**. The total body water is distributed in two main compartments: intracellular fluid contained within the cells and extracellular fluid contained outside the cells. The cell membrane separates these two compartments. The extracellular fluid is divided further into two subcompartments: plasma fluid contained within the vascular bed and interstitial fluid contained outside the vascular bed. The capillary membrane separates these two subcompartments.

The extracellular fluid (both plasma and interstitial fluid) is rich in sodium and chloride, whereas the intracellular fluid is rich in potassium and organic phosphate. Among the cations, calcium is located mainly in the extracellular compartment, whereas magnesium is largely in the intracellular compartment. Among the anions, bicarbonate is located mainly in the extracellular compartment, whereas proteinate (anionic protein) is largely in the intracellular compartment. The plasma and interstitial fluid are similar in composition except for proteinate, which is contained largely in the plasma. In case of fluid loss or gain, the concomitant loss or gain of electrolytes can be anticipated, if the body water compartment undergoing the change can be identified. For example, hyponatremia and hypochloremia resulting from loss of sodium and chloride can be anticipated with exclusive loss of extracellular fluid.

The body water distribution changes progressively during fetal and postnatal development (**Figure 2**). At 8 weeks of gestational age, the fetal body is approximately 95% water with the remainder being composed of salts, minerals, hydrocarbons, and proteins. The total body water constitutes approximately 90% of fetal body weight at 16 weeks of gestational age, 85% at 24 weeks, 80% at 32 weeks, and 70% at term gestation. The somewhat rapid decrease in total body water in the last 8 weeks of gestation is attributed to accretion of largely water-free fat during late gestation. The total body water continues to decline during infancy, reaching approximately 60% of body weight at 1 year of age. The total body water in lean adults is approximately 55% of body weight.

The extracellular fluid (plasma and interstitial fluid) decreases progressively with advancing gestation (**Figure 2**). The extracellular fluid constitutes approximately 70% of fetal body weight at 16 weeks of gestational age, 60% at 24 weeks, 50% at 32 weeks, and 38% at term gestation. Much of this decrease in extracellular fluid is attributed to a decline in interstitial fluid volume, whereas the plasma fluid volume remains relatively constant at approximately 5% throughout fetal life. The extracellular fluid continues to decline in infancy, reaching approximately 25% of body weight at 1 year of age. The extracellular fluid in lean adults is approximately 20% of

body weight.

The intracellular fluid is the only body fluid compartment that increases as percentage of body weight with advancing gestation (Figure 2). The intracellular fluid constitutes approximately 20% of fetal body weight at 16 weeks of gestational age, 25% at 24 weeks, 30% at 32 weeks, and 32% at term gestation. The intracellular fluid continues to increase in infancy, reaching approximately 35% of body weight at 1 year of age. The intracellular fluid in lean adults is about the same at 35% of body weight.

In summary, the changes in body water distribution during human gestation expressed as percentage of body weight are characterized by a progressive decrease in total body water content; a progressive decrease in extracellular fluid, specifically interstitial fluid; and a proportionate gain in intracellular fluid. These body fluid changes make the newborn, particularly one born prematurely, vulnerable to fluid-electrolyte imbalance, largely resulting from the loss of extracellular fluid and its constituents. A better understanding of the composition of these body fluids and their flux will facilitate fluid electrolyte management of these infants.

References:

Brace RA. Fetal extracellular fluid and lymphatic function. In: Brace RA, Hanson MA, Rodeck CH, eds. *Fetus and Neonate: Physiology and Clinical Applications: Body Fluids and Kidney Function.* Vol 4. Cambridge, England; Cambridge University Press: 1998;57-68

Friis-Hansen B. Body water composition in children: changes during growth and related changes in body composition. *Pediatrics.* 1961;28:169-178

Lorenz JM. Fetal and neonatal body water compartment volumes with reference to growth and development. In: Polin RA, Fox WW, Abman SH, eds. *Fetal and Neonatal Physiology.* 3rd ed. Philadelphia, Pa: WB Saunders: 2004;1351-1356

Content Specification:

Understand the changes in body water distribution and body fluid composition during fetal and postnatal development.

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Figure 1

TOTAL BODY MASS

Plasma Interstitial

EXTRACELLULAR | INTRACELLULAR

| TOTAL BODY WATER | SOLIDS

BODY WATER DISTRIBUTION

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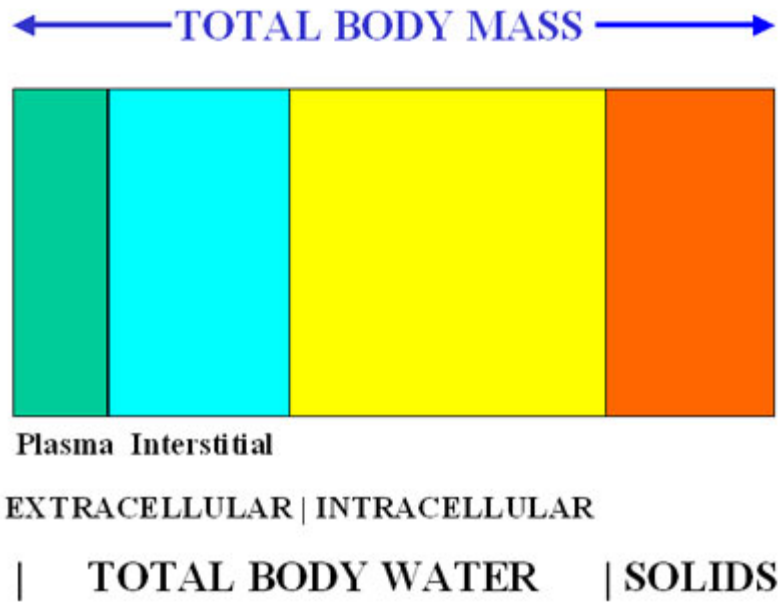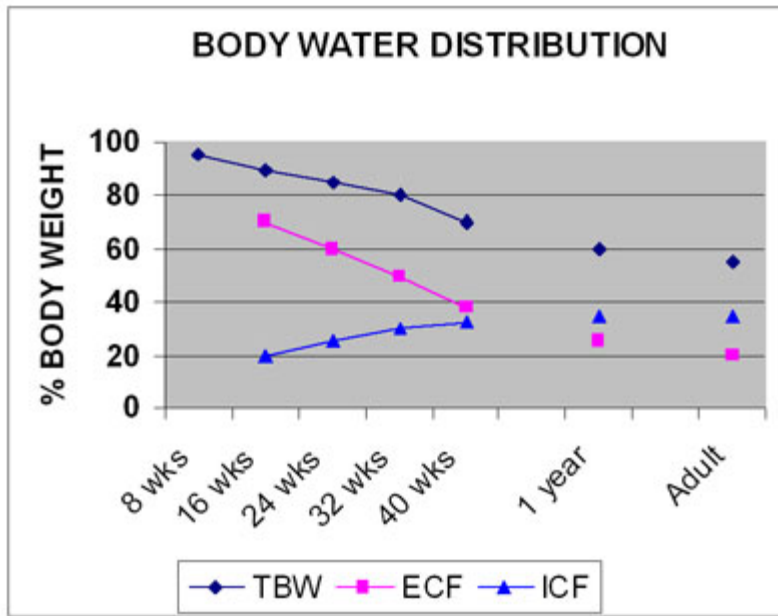
You care for a boy who has severe hemophilia A (factor VIII deficiency). His mother tells you that she is 6 weeks pregnant and is interested in prenatal testing for this condition. Family history reveals that the mother has a brother who also is affected.

Of the following, the MOST reasonable next step is to suggest

1. amniocentesis at 14 to 18 weeks' gestation

2. chorionic villus sampling at 10 to 12 weeks' gestation

3. DNA testing on her son or brother

4. fetoscopy with fetal blood sampling at 18 weeks' gestation

5. linkage analysis for her family

You selected 3, the correct answer is 3.

Before pursuing prenatal genetic testing for any condition, it is critical to know what information must be gathered. The mother of the boy described in the vignette is an obligate hemophilia carrier because both her brother and her son are affected. However, it is important to know which, if any, factor VIII gene mutation is detectable in the family. Therefore, the most appropriate next step is to send blood from an affected family member for mutational analysis.

The factor VIII gene, located at the tip of the long arm of the X chromosome at Xq28, is very large. Many changes within the gene can cause hemophilia A. Hemophilia occurs in 1 of 5,000 males born, 85% of which are Hemophilia A. One of the most common, a gene inversion, occurs in approximately 45% of individuals who have severe disease; 50% to 90% of remaining individuals have a detectable mutation. If there is no detectable mutation, linkage analysis is available, but this typically requires multiple affected and unaffected family members.

Once a gene mutation or linkage is established, a woman can choose the method of prenatal testing she prefers. Chorionic villus sampling has the advantage of providing results earlier in the pregnancy than amniocentesis, but it may confer a higher risk to the fetus (depending on the experience of the practitioner).

Fetoscopy is not the test of choice because it confers too great a risk to the fetus, and it overlaps with amniocentesis with respect to time of sampling.

Of note, molecular genetic testing also is available for factor IX deficiency (hemophilia B) and identifies disease-causing mutations in more than 95% of affected individuals.

References:

Johnson MJ, Thompson AR. Hemophilia A. *GeneReviews*. Seattle, Wash: Children's Health System and University of Washington; 2003. **Available online**.

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Rimoin DL, Connor JM, Pyeritz RE, eds. *Emery and Rimoin's Principles and Practice of Medical Genetics*. 4th ed. New York, NY: Churchill Livingstone; 2002

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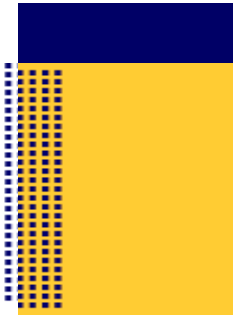
Content specifications:

Understand the inheritance pattern of the common factor deficiencies

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A term female infant was delivered vaginally to a gravida 2 26-year-old Hispanic mother 12 hours after rupture of membranes. Her Apgar scores were 7 and 9 at 1 and 5 minutes, respectively. She is breastfeeding well, has passed meconium once, and has had wet diapers before each feeding. On physical examination at 25 hours of age, faint facial icterus is apparent. The transcutaneous bilirubin concentration is 5.1 mg/dL (87.2 mcmol/L). You assess the bilirubin level using the hour-specific bilirubin nomogram (**Figure**).

Of the following, the MOST appropriate plan of action at this time is to

☒ **1** consult an audiologist

2 delay discharge and repeat bilirubin measurement in 8 to 12 hours

3 institute phototherapy

4 send the infant home after scheduling a follow-up evaluation in 1 week

5 send the infant home after scheduling a follow-up evaluation in 2 days

You selected 1 , the correct answer is 5 .

The bilirubin concentration for the infant described in the vignette corresponds to the lowest risk zone on the nomogram for the development of subsequent significant hyperbilirubinemia. Guidelines from the American Academy of Pediatrics suggest follow-up of low-risk infants in 1 to 3 days. Although the icterus was distributed solely to the face, a clinical estimation of jaundice based on the distribution is not sufficiently reliable to determine the subsequent course of action, which is why transcutaneous bilirubin measurement was obtained. The relationship between results of the transcutaneous testing and total serum bilirubin for the infant in the vignette is such that laboratory confirmation of the transcutaneous value is not warranted. Although the bilirubin concentration places her in the low-risk zone and her term birth, female sex, not being the first child, and good feeding all suggest low risk, discharge at this age mandates a follow-up in 1 to 3 days.

Hearing would not be expected to be affected by this level of jaundice, and normal test results do not contribute to management. In many states, hearing testing is routine before discharge, but normalcy on this test is not a reliable criterion on which to base bilirubin management. Delaying discharge is not indicated for an infant at this low risk level. Follow-up at 1 to 2 weeks may be appropriate for the child discharged at 4 to 5 days of age, but many other concerns other than bilirubin call for early reassessment of babies discharged at 25 hours of age. Although phototherapy may be considered benign, its use for an infant whose bilirubin concentrations are at the level described in the vignette incurs expenses and parental anxiety not commensurate with the risk of hyperbilirubinemia.

References:

American Academy of Pediatrics, Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114:297-316.

Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics*. 1999;103:6-14.
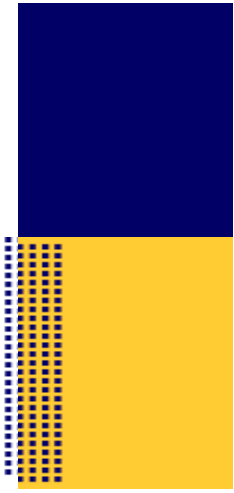
Figure. Hour-specific bilirubin nomogram for assessing bilirubin levels. Reprinted with permission from Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics*. 1999;103:6-14.

Content Specifications:

Understand bilirubin physiology in the fetus and neonate

Know the factors associated with an increase in neonatal serum bilirubin concentrations

PREVIOUS   NEXT

Nomogram for designation of risk in 2840 well newborns at 36 or more weeks' gestational age with birth weight of 2000 g or more or 35 or more weeks' gestational age and birth weight of 2500 g or more based on the hour-specific serum bilirubin values
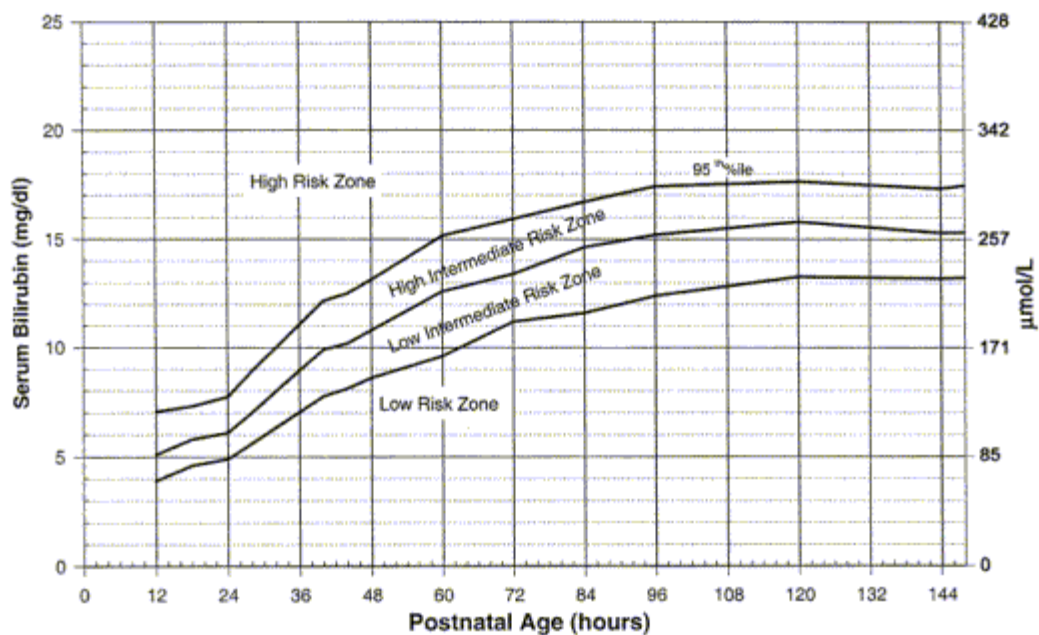
Subcommittee on Hyperbilirubinemia, Pediatrics 2004;114:297-316

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A 32-year-old woman received a single embryo by in vitro fertilization. Ultrasonographic examination confirmed twin females with a single placenta, a two-layered dividing membrane between the fetal sacs, and no projection of placental tissue into the dividing membrane. Genetic amniocentesis in the second trimester confirmed both fetuses to be 46,XX. At 25 weeks' gestation, ultrasonographic examination showed discordant fetal growth, oligohydramnios associated with the smaller twin, and polyhydramnios with the larger twin.

Of the following, the treatment that MOST directly addresses the underlying cause of this condition is

1. amnioreduction

2. cord occlusion by bipolar diathermy

3. laser coagulation of placental vascular anastomoses

4. microseptostomy

5. termination of pregnancy

You selected 3, the correct answer is 3.

Because the twin gestation described in the vignette resulted from implantation of a single embryo, it is nearly certain that the twins are identical. Twinning occurs in 0.8% of single embryo implantations. Approximately 70% of identical twins are monochorionic. In multiple-gestation pregnancy, prematurity, monochorionicity, and growth restriction contribute most to fetal and neonatal health risks. Monochorionic twins have a perinatal mortality rate of 26%.

Although all monochorionic (and rarely dichorionic) twins have vascular anastomoses and some degree of twin-twin transfusion, about 15% have sufficient blood transfer from arteriovenous anastomoses to result in the clinical syndrome of mid-trimester discordance in fetal size and amnionic fluid volumes known as the twin-twin transfusion syndrome. The exact incidence of this syndrome is not known because twin-twin transfusion may result in the death and subsequent resorption of one twin in the first trimester, an entity called "vanishing twin syndrome." In 70% of monochorionic twin pregnancies, arteries from one twin enter placental cotyledons drained by veins going to the other twin. In most situations, bidirectional arterioarterial anastomoses compensate for the arteriovenous shunting. Studies have demonstrated that a paucity of arterioarterial connections combined with a number of deep arteriovenous connections is associated with twin-twin transfusion syndrome. The donor twin develops uteroplacental insufficiency and hypovolemia; the recipient twin develops hypervolemia, with resultant cardiac dysfunction from right ventricular dilatation and tricuspid regurgitation, as well as a 9% risk for right ventricular outflow obstruction due to hypertrophy. Twin-twin transfusion noted before 26 weeks' gestation and left untreated is associated with up to 90% perinatal mortality and a significant risk of developmental abnormalities among the surviving infants. The severity of the syndrome is assessed by a scoring system developed by Quintero and associates:

Stage 1   Abnormal amnionic fluid levels only, urinary bladder of donor twin filled

Stage 2   Collapsed urinary bladder in oliguric donor twin

Stage 3   Abnormal Doppler flow in umbilical artery or ductus venosus in either twin

Stage 4   Hydrops in either twin

Stage 5   Intrauterine death of either twin

Among the therapeutic options presented, laser coagulation of aberrant blood vessels on the placental surface most directly influences the arteriovenous anastomoses that are the underlying cause of the syndrome. Because selective fetoscopic laser coagulation involves the combination of fetoscopy, laser therapy, and experience with placental vascular anatomy, its use requires experience in appropriate patient selection as well as in the technique itself. In one study by Senat and associates, 142 women who had twin-twin transfusion presenting between 16 and 26 weeks' gestation with polyuric polyhydramnios in the recipient twin and oliguric oligohydramnios in the donor twin were randomized to either amnioreduction or laser vascular occlusion performed percutaneously. Greater survival and a reduced incidence of neurologic impairment were noted among the infants of mothers treated with laser compared with those treated with amnioreduction. Survival to 28 days after birth was 76% for infants in the laser group and 56% for infants in the serial amnioreduction group. The relative risk (RR) of death of both fetuses was 0.63 (95% confidence interval [CI], 0.25 to 0.93) with laser treatment, and survival without neurologic complications was 52% in the laser cohort compared with 31% in the amnioreduction group. Even with laser therapy, only 36% of the pregnancies resulted in two surviving infants. Factors still needing elucidation in this procedure include identification of clinically relevant anastomoses using vascular tracers, identification of deeper anastomoses that cannot be seen with the fetoscope, and underlying poor placentation in the donor fetuses. In situations associated with the death of one twin in utero, the relative risk for cerebral lesions in the surviving twin was reduced (RR 0.2; 95% CI, 0.05 to 0.85) among fetuses in the laser group.

Amnioreduction is directed at effects of the twin-twin transfusion syndrome rather than at its cause. The therapeutic goals are to reduce polyhydramnios, thereby decreasing the risk of preterm delivery, and to reduce pressure on the fetal surface of the placenta, thereby improving fetal hemodynamics. Amnioreduction is more readily available, simpler, and safer than fetoscopy and laser coagulation, and an initial trial of amnioreduction may prevent disease progression in 20% of cases. In one investigation, Quintero stage 1 or 2 disease treated with laser was associated with greater fetal mortality (odds ratio [OR], 2.7), but in Quintero stage 3 or 4 disease, the affected fetuses had reduced mortality (OR, 0.4) with laser treatment. In two large registries of twin-twin transfusion syndrome, amnioreduction has been associated with 60% fetal survival, although the data from these registries are not directly comparable to the data from the population presenting at 15 to 26 weeks' gestation in the laser coagulation study.

In cases in which fetal death is likely, cord occlusion by bipolar diathermy may protect the surviving fetus from the complications of hypotension associated with agonal intertwin transfusion. However, this treatment does not affect the placental vascular anastomoses underlying the twin-twin transfusion syndrome.

Connecting the two amniotic sacs by microseptostomy attempts to balance the amnionic fluid volumes between the two fetuses. Similar to amnioreduction, microseptostomy may reduce the impact of polyhydramnios and may increase the intravascular volume of the donor twin by promoting fetal swallowing, but it does not improve the circulatory imbalance between the fetuses.

Termination of pregnancy may be presented as an option when the fetus develops signs of a worsening condition, such as hydrops, critical pulmonary outflow obstruction, grade 3 or 4 intracranial hemorrhage, porencephaly, or hydrocephaly, in spite of therapy. In the laser/amnioreduction comparison study, 11 of 70 women randomized to the amnioreduction group eventually elected termination of pregnancy for one or more of the above reasons. None of the 72 women in the laser group electively terminated the pregnancy.

References:

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Fisk NM, Tan TYT, Taylor MJO. Stage-based treatment of twin-twin transfusion syndrome. *Am J Obstet Gynecol*. 2004;190:1490.

Malone FD, D'Alton ME. Multiple gestation: clinical characteristics and management. In: Creasy RK, Resnik R, eds. *Maternal-Fetal Medicine: Principles and Practice*. 5th ed. Philadelphia, Pa:

Saunders; 2004:513-536.

Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin-twin transfusion syndrome. *J Perinatol*. 1999;19:550-555.

Senat MV, Deprest J, Boulvain M, Paupe A, Winer N, Ville Y. Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. *N Engl J Med*. 2004;351:136-144.

<u>Content Specification</u>:

Understand the implications and complications of multiple gestation, such as cord problems, twin-twin transfusion, "stuck twin," conjoined twins, etc.

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A 7-day-old term female infant remains in the neonatal intensive care unit because of episodes of hyperpnea alternating with spells of apnea of up to 25 seconds. Physical examination reveals a healthy child who has nystagmus of both eyes that is unassociated with the respiratory variations.

Of the following, the test that is MOST likely to establish the correct diagnosis is

☒ **1** electroencephalography

2 magnetic resonance imaging of the brain

3 MECP2 gene testing for Rett syndrome

4 molecular genetic testing for spinal muscular atrophy

5 urine toxicology screen

You selected 1, the correct answer is 2.

Apnea is defined as not breathing or cessation of airflow in and out of the lungs. If airflow ceases because respiratory effort has stopped, the condition is termed central apnea, referring to the absence of drive from respiratory centers in the central nervous system. When airflow ceases because of occlusion of the upper airway, the condition is known as obstructive apnea. Hyperpnea is deeper and more rapid respirations than normal, and tachypnea is simply rapid breathing.

Of these breathing patterns in an infant, central apnea may be the most ominous or life-threatening. The differential diagnosis includes prematurity, increased intracranial pressure, shunt malfunction, Chiari malformation, myelodysplasia, meningoencephalitis, ischemia, trauma, achondroplasia, the rare congenital central hypoventilation syndrome (Ondine curse) (ie, intact voluntary but not automatic control of breathing), and Joubert syndrome.

Joubert syndrome is an autosomal recessive disorder that is characterized by agenesis of the cerebellar vermis and sometimes other brain anomalies such as brainstem hypoplasia. Episodic apnea alternating with hyperpnea may appear shortly after birth, as in the child described in the vignette. Eye movement disorders, including nystagmus, disruption of rapid eye movements (ie, hypometric saccades), and oculomotor apraxia, may occur, as might retinal dystrophy. Magnetic resonance imaging of the brain establishes the diagnosis.

If the apnea and nystagmus occurred simultaneously, electroencephalography would be useful to exclude a subtle seizure. Such is not the case in the vignette.

MECP2 gene testing is appropriate for an older child who exhibits hand wringing, loss of development, and later episodic hyperpnea, which are suggestive of Rett syndrome.

Genetic testing for spinal muscular atrophy is indicated for a baby who has profound hypotonia and areflexia. A urine toxicology screen can aid in excluding intoxication in any child who has respiratory and eye movement abnormalities, but the child probably would not appear otherwise healthy.

References:

American Academy of Pediatrics Committee on Fetus and Newborn. Apnea, sudden infant death syndrome, and home monitoring. *Pediatrics*. 2003;111:914-917. Article available online at http://pediatrics.aappublications.org/cgi/reprint/111/4/914.pdf

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Carroll JL, Marcus CL, Loughlin GM. Disordered control of breathing in infants and children. *Pediatr Rev.* **1993;14:51-65**

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Ewig J, Shelov SP. In brief. Respiratory conditions predisposing children to disordered sleep. *Pediatr Rev.* **1992;13:116**

Content specification:

Understand the pathophysiology of apnea of prematurity.

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A 32-hour-old term female infant develops respiratory distress. On physical examination, she has midfacial hypoplasia, short philtrum, low-set ears, and retrognathia. Her respiratory rate is 76 breaths/min, she has a grade 2/6 systolic heart murmur, and she is jittery. Her 3-year-old sister has recurrent viral infections and persistent oral thrush. A complete blood cell count reveals: hemoglobin, 20 g/dL (200 g/L); hematocrit, 60% (0.60); platelet count, 160x10^3/mcL (160x10^9/L); and total leukocyte count, 7.6x10^3/mcL (7.6x10^9/L), with a differential count of 70% neutrophils, 3% band forms, 8% lymphocytes, 8% monocytes, and 11% eosinophils. Ionized calcium is 2.8 mg/dL (0.70 mmol/L). Echocardiography reveals an interrupted aortic arch.

Of the following, the MOST likely diagnosis for the infant and her sister is

1. Bruton agammaglobulinemia

2. Chédiak-Higachi disease

☒ 3. chronic granulomatous disease

4. DiGeorge syndrome

5. Wiskott-Aldrich syndrome

You selected **3**, the correct answer is **4**.

The infant described in the vignette has clinical features and laboratory findings consistent with the diagnosis of DiGeorge syndrome (DGS). DGS occurs when the third and fourth pharyngeal pouches fail to differentiate into the thymus and parathyroid glands by the sixth week of gestation. The facial anomalies are due to abnormal development of the first arch. The syndrome is the result of a deletion on the long arm of chromosome 22. The deletion, known as the DGS critical region, is located on band 22q11.2 and can be transmitted in an autosomal dominant inheritance pattern or from an unbalanced translocation from an unaffected parent. DGS is diagnosed by high-resolution chromosomal analysis with fluorescent in situ hybridization probe for the 22q11 deletion.

Cardiac defects occur in 50% to 90% of patients who have DGS. The most common defects are conotruncal anomalies such as the type B interrupted aortic arch [coarctation of aorta figure from Neopix], right aortic arch, bicuspid aortic valve, truncus arteriosis, and tetralogy of Fallot. Other potential cardiac anomalies include membranous ventricular septal defects, atrial septal defects, aberrant right subclavian artery, and the absent pulmonary vein syndrome.

Characteristic facies of DGS may not be apparent at birth but become more pronounced with aging. The classic phenotype includes midface hypoplasia, velopharyngeal insufficiency (such as cleft soft palate), narrow palpebral fissures with hypertelorism, long face, shortened philtrum (fish-mouth), low-set posteriorly rotated ears, and retrognathia.

Approximately 25% of affected patients have clinically significant immune deficiency because of thymic hypoplasia. The degree of immune deficiency depends on the amount of thymic tissue present. Thymic aplasia is rare; most patients have "partial DGS" with thymic hypoplasia. Patients who have DGS usually exhibit mild lymphopenia. Low numbers of T cells can be quantified by flow cytometry, and generally there are decreased numbers of CD3$^+$, CD4$^+$, and CD8$^+$ T cells. The numbers of B cells and natural killer cells usually are normal. Patients who have complete DGS are susceptible to opportunistic infections with organisms such as *Pneumocystis carinii* as well as viral and fungal infections. Graft versus host disease can develop from nonirradiated blood transfusions.

Parathyroid gland hypoplasia in DGS results in hypoparathyroidism and hypocalcemia. Because approximately 10% to 20% of patients develop seizures due to hypocalcemia, calcium supplementation may be required.

Bruton agammaglobulinemia (BA), also known as X-linked agammaglobulinemia, is associated with the development of recurrent infections because of absent circulating B cells and low levels of all immunoglobulin isotypes. The infections, caused by pyogenic bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae,* develop after maternal immunoglobulin (Ig) G concentrations wane at 6 to 9 months of age. BA only occurs in males and is not associated with cardiac defects, hypocalcemia, or facial abnormalities.

Chédiak-Higashi syndrome (CHS) is characterized by oculocutaneous albinism and recurrent infections. The immunodeficiency is due to abnormal lysosomal granule function. Giant lysosomal granules, seen in neutrophils, cannot fuse with phagosomes, and ingested bacteria are not killed. CHS is an autosomal recessive disorder. The genetic defect has been localized to chromosome 1q42-43. CHS usually is fatal by 30 months of age. The lack of oculocutaneous albinism or abnormal neutrophils in the infant in the vignette, and the viral and fungal rather than bacterial recurrent infections in her sister rule out this diagnosis.

Chronic granulomatous disease (CGD) is an inherited disorder in which phagocytic cells (neutrophils and macrophages) can ingest but cannot kill certain microorganisms. Phagocytes of affected patients have an impaired ability to assemble the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. The incidence of CGD is 1 per 200,000 individuals. Most affected patients present in early childhood with recurrent skin infections, suppurative lymphadenitis, or pneumonia. They also may develop granulomas of the skin or gastrointestinal tract; osteomyelitis; and perianal, hepatic, or splenic abscesses. Affected patients do not have cardiac abnormalities, facial dysmorphology, or hypocalcemia.

Wiskott-Aldrich syndrome (WAS) is an X-linked immunodeficiency characterized by recurrent bacterial sinopulmonary infections, eczema, and thrombocytopenia. Recurrent infections are due to low IgM and IgG concentrations and a lack of antibody production against polysaccharides. Decreased numbers of CD8$^+$ T cells result in elevated CD4/CD8 ratios. WAS may present with recurrent bleeding from thrombocytopenia before the development of recurrent infections. Episodes of recurrent otitis media begin at 3 to 8 months of age, as maternal IgG levels diminish. Pneumonia and meninigitis caused by encapsulated bacteria such as *S pneumoniae* and *H influenzae* and life-threatening varicella and herpes simplex infections may develop. Eczema may be mild or severe and may be associated with milk or food allergies.

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Content Specifications:

Understand the DiGeorge anomaly.

Be aware of the clinical features and differential diagnosis of neonates with immune deficiency.

Understand the pathophysiology, including genetics, of a neonate with a left sided cardiac obstructive lesion.

Recognize the karyotype and clinical manifestations associated with the common deletion syndromes.

Understand the etiology and clinical manifestations of neonatal hypocalcemia.
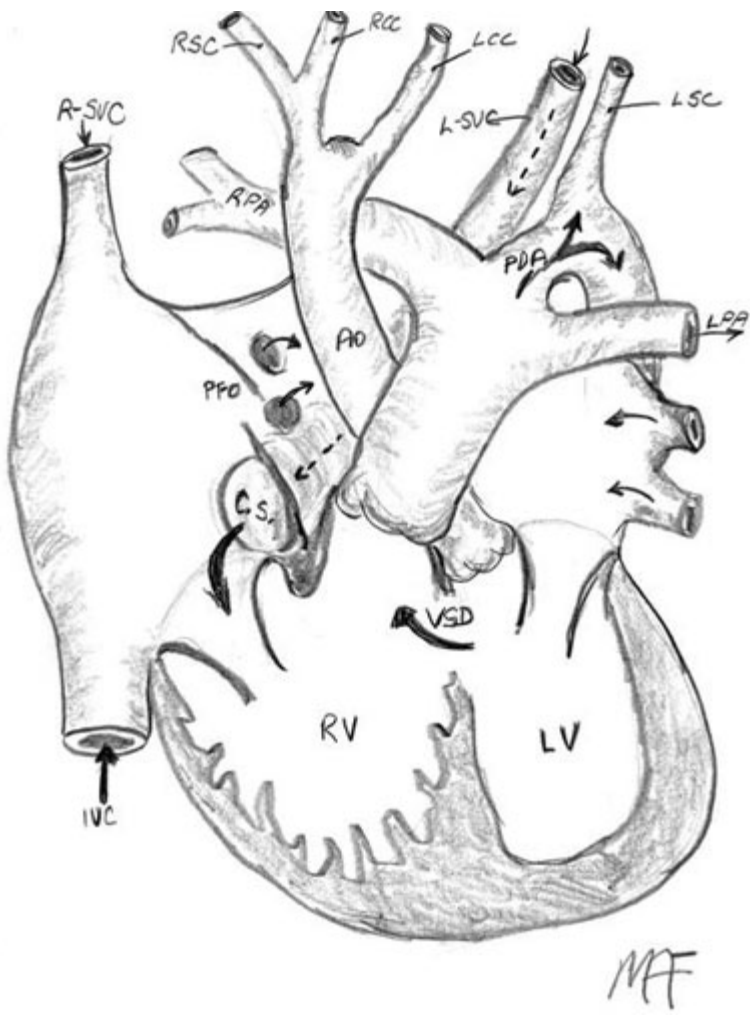
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A 6-month-old male infant presents with a 3-day history of rhinorrhea, decreased appetite, and a temperature of 101.5°F (38.6°C). On physical examination, the child. A male infant delivered at term and went home with his mother. His family physician has been discussing his course with you since 3 weeks of age, at which time he was noted to have neutropenia on a complete blood count (CBC) done when he presented with a runny nose.   His CBCs have consistently documented peripheral white blood cell counts ranging from 2.4 to 3.0 x 10^3/mcL (2.4 to 3.0 x 10^9/L) with absolute neutrophil counts of less than 400 cells/mcL (0.4 x 10^9/L). A bone marrow biopsy at 4 months of age demonstrated granulocytopenia with normal numbers of platelet, erythroid, and myeloid precursors. At 6 months of age, he appears happy and playful and has rhinorrhea and no other focal findings. Besides the occasional cold, he has had no other infections.

Of the following, the management strategy that is MOST appropriate is

1	allogeneic bone marrow transplant
2	intravenous immunoglobulin
☒ 3	prophylactic antibiotic therapy
4	recombinant human granulocyte colony-stimulating factor
5	symptomatic supportive care

You selected 3, the correct answer is 5.

Neutropenia is defined as an absolute decrease in the number of circulating neutrophils in the bloodstream. Chronic neutropenia is defined as having an absolute neutrophil count (ANC) of less than 500/mcL (0.5 x 10^9/L) for more than 6 months. The neutropenia may be persistent or cyclic and benign or serious. Chronic idiopathic neutropenia of childhood is a nonfamilial disorder in which neutrophil counts range from less than 500/mcL (0.5 x 10^9/L) to 1,000/mcL (1 x 10^9/L). The risk of infection is proportional to the degree of neutropenia. Bone marrow examination (BME) reveals an adequate number of platelet, erythroid, and myeloid precursors. As noted for the infant in the vignette, children who have the mild form of the disease usually do not experience serious complications with infection. Familial chronic benign neutropenia is an autosomal dominant condition among western Europeans, Africans, and Jewish Yeminites. Non-familial chronic benign neutropenias may be associated with mild infections. In this condition, the ANC may respond to stresses from infections, corticosteroids, and catecholamines. Treatment is symptomatic; prophylactic antibiotic therapy is not recommended. Intravenous immunoglobulin has been used in selected cases of severe autoimmune neutropenia, but it is costly and has not been proven to improve outcome in patients who have chronic idiopathic neutropenia.

Cyclic neutropenia is a rare disorder characterized by regular, periodic oscillations in the number of circulatory neutrophils and has associated cyclic clinical manifestations. The cyclic oscillations in bone marrow function result in a regular periodicity of neutropenia, with intervals ranging from 14 to 36 days between episodes. Each episode may last 3 to 10 days. During the neutropenic phase, patients may develop fever, malaise, oral ulcers, stomatitis, pharyngitis, and lymphadenopathy. More serious infections, such as pneumonia, mastoiditis, and sepsis, may occur, and up to 10% of patients die from complications of infectious diseases. The diagnosis is made by serial neutrophil counts, obtained over 6 to 8 weeks to establish periodicity, and BME. BME during periods of neutropenia may show granulocytic hypoplasia or an apparent arrest of maturation. Treatment is symptomatic. Use of recombinant human granulocyte colony-

stimulating factor (GCSF) has marked benefit in these patients by reducing the duration of neutropenia and greatly decreasing the risk of infections.

Severe congenital neutropenia (infantile genetic agranulocytosis of Kostmann) is a rare autosomal recessive disorder characterized by a failure of terminal differentiation of the myeloid precursors. The ANC is usually less than 300/mcL (0.3×10^9/L). BME reveals developmental arrest at the promyelocyte or myelocyte stage. Monocytosis is prominent, and serum immunoglobulin concentrations are normal or elevated. The typical clinical presentation is an acute, life-threatening infection occurring within the first few postnatal months. Common pathogens include *Staphylococcus aureus, Escherichia coli*, and *Pseudomonas* sp. Recombinant human GCSF therapy results in decreased numbers of neutrophils and substantial decreases in infectious complications. Bone marrow transplantation can correct the disorder partially or completely.

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Shin DD, Goodwin JE. Neutropenia. Emedicine. Available at: http://www.emedicine.com/med/topic1640.htm. Accessed February 26, 2005.

Content specifications:

Recognize the causes and consequences of alterations in number and distribution of neutrophils.

Understand the differential diagnosis of neonatal leukopenia.

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On a television news magazine program, a female business student declared, "I plan to be super fit, super in shape when I'm 40, 50. And if I'm physically able to do it, then I will have a child at 55." The number of first births (per 1,000 women) at ages 35 to 39 increased by 36% in the decade 1991 through 2001, with 263 births reported among women 50 to 54 years of age. You are preparing a presentation on the implications of delayed childbearing on perinatal outcomes.

Of the following, the MOST accurate statement regarding delayed childbearing is that

1. fertility declines linearly from menarche to menopause

2. hypertensive complications decrease with advancing maternal age

3. in vitro fertilization with donor eggs reduces fetal risk of aneuploidy among older women

4. paternal age is a major influence on miscarriage rates among older women

5. stillbirth rates remain stable over the childbearing years

You selected 4, the correct answer is 3.

As the combination of careers, available reproductive options, and control over health outcomes becomes an increasingly powerful influence on childbearing, more women are exploring the potential for delayed motherhood. Using techniques of in vitro fertilization with eggs donated by women in their 20s or 30s, many women in their 40s and 50s can become pregnant. Once pregnancy is established, the risks of miscarriage and chromosomal abnormalities are consistent with the age of the donor. Studies on human trisomies regardless of the chromosome involved have found them to originate with errors in maternal meiosis I (separation of homologous chromosomes). Because meiosis I is initiated in the fetal ovary and is completed at ovulation many years later, age-related influences on the meiotic process (degradations of meiotic proteins) are more influential with advanced maternal age. Thus, older women who undergo in vitro fertilization with younger eggs have a reduced risk of fetal aneuploidy.

Among women trying to conceive, the rate of childbearing is stable at greater than 400 pregnancies per 1,000 women per year until about 30 years of age. Thereafter, the rate decreases rapidly and nonlinearly, reaching fewer than 50 pregnancies per 1,000 women older than 45 years of age. Advanced maternal age is associated with deterioration in the quality of ova, which results in both reduced fertility and increased chromosomal abnormalities.

Women in their 40s experience twice the rate of hypertensive complications of pregnancy compared with younger women. These complications contribute to the increased risk of delivering a small-for-gestational age or preterm infant noted among women older than 40 years of age.

Advanced paternal age is associated with an increased risk for autosomal dominant conditions such as achondroplasia and Marfan syndrome due to new genetic mutations, but it is not a major influence on maternal miscarriage rate. Miscarriage is a major contributor to the progressive decline in fertility with age, rising from a rate of 10% at 20 years of age to more than 90% among women older than 45 years of age. Karyotyping after miscarriage demonstrates a chromosomal abnormality in two thirds of pregnancies lost before 20 weeks' gestation.

Stillbirth, fetal death after 20 weeks of pregnancy, increases from 4 per 1,000 pregnancies among women in their 20s to 10 per 1,000 pregnancies among women older than 40 years of age. Although uncommon, the stillbirth rate is approximately 10 times the risk of sudden infant

death syndrome.

<u>References</u>:

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Lamb NE, Hassold TJ. Nondisjunction-a view from ringside. *N Engl J Med*. **2004;351:1931-1934**

Preconceptual counseling. In: Cunningham FG, Gant NF, Leveno KJ, Gilstrap LC, Hauth JC, Wenstrom KD, eds. *Williams Obstetrics*. **21st ed. New York, NY: McGraw-Hill; 2001:203-220**

<u>Content Specification(s):</u>

Understand organ and integrated physiology of maternal adaptation to pregnancy and know the normal changes in physiologic variables and in laboratory values.

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A term newborn experiences generalized tonic-clonic seizures 1 hour after birth. The vaginal delivery was unremarkable, and Apgar scores were 9 at both 1 and 5 minutes. The pregnancy was notable for the mother reporting that the "baby had hiccups." Except for the ongoing seizures, physical examination results are normal, and the baby boy is afebrile. Despite full dosing of intravenous fosphenytoin and phenobarbital, the seizures continue.

Of the following, the MOST likely cause of the child's seizures is

1. Aicardi syndrome

2. benign familial neonatal seizures

3. hypoxic-ischemic encephalopathy

❌ 4. nonketotic hyperglycinemia

5. pyridoxine dependency

You selected 4, the correct answer is 5.

Neonatal seizures are defined as seizures that occur during the first month after birth (principally during the first few days). Neonatal seizures can manifest, in order of decreasing incidence, as generalized tonic (primarily preterm infants), multifocal clonic (primarily term infants), focal clonic (term more often than preterm infants), or myoclonic (both term and preterm infants). Myoclonic seizures may presage infantile spasms. More frequent than any of these seizure types are subtle seizures, that is, behaviors and movements that may not be appreciated as seizures (eg, horizontal eye deviation, color change, apnea, drooling, sucking, lip smacking, and swimming or pedaling movements). Once neonatal seizures are identified, determining their cause is key to treating the underlying condition and, in some instances, to halting the seizures.

The infant described in the vignette has typical findings for autosomal recessive pyridoxine dependency. Fewer than 100 cases have been reported. Seizures related to this condition commence in utero (often mistaken as fetal hiccups). After birth, the seizures continue as generalized clonic seizures refractory to fosphenytoin and phenobarbital. Pyridoxine is a coenzyme for glutamic acid decarboxylase that converts glutamic acid to the inhibitory transmitter gamma amino butyric acid. For infants suspected of having pyridoxine-dependent seizures, 100 mg of pyridoxine should be administered intravenously during simultaneous electroencephalography to determine whether the electrical tracing normalizes. Affected individuals require lifelong treatment with pyridoxine. Untreated patients usually die with seizures, and although early treatment may be life-saving, most survivors have mental retardation. Whether earlier treatment leads to better intellectual function is controversial.

Aicardi syndrome is a form of cerebral dysgenesis in a females characterized by agenesis of the corpus callosum and coloboma of the iris. Deterioration of higher brain functions follows a period of normal development. Severe dementia, autism, loss of purposeful use of the hands, jerky truncal ataxia, seizures and acquired microcephaly may follow. Due to its exclusive appearance in females, a dominant defect on the X chromosome leading to lethality in males and affected females is suspected.

Benign familial neonatal convulsions (BFNC) is an autosomal dominant disorder characterized by 10 to 20 seizures per day commencing around the third postnatal day that usually are self-resolving. This child's age at seizure onset and refractoriness to anticonvulsants are not typical of benign familial neonatal seizures. BFNC has been related to loci on 20Q in most families and

on 8Q in another. Resultant mutations in potassium channel proteins have been identified in most families and one family has abnormalities in the acetylcholine alpha-4 receptor unit. Frequent seizures and certainly status epilepticus should be treated. Due to the resolution of BFNC in the first few weeks of life, Phenobarbital is the drug of choice. Fosphenytion may be appropriate for control of status, but not for longer term treatment. Valproic acid is not suggested. In spite of the potassium channel abnormality, the seizures resolve early in infancy. Long-term follow-up reveals normal development, although and 11% risk for later seizures is noted.

The timing of the postnatal seizures and the likelihood of ongoing seizures in utero (the "hiccups") over time are not likely features of hypoxic-ischemic encephalopathy. Of note, some cases of pyridoxine dependency have been confused with birth asphyxia in the neonatal period.

Nonketotic hyperglycinemia manifests seizures days or weeks after birth, often in an infant who is obtunded or exhibits development delay.

When confronted with neonatal seizures, the clinician must be familiar with the wide range of possible causes: hypoxia-ischemia, trauma, hemorrhage, infection (eg, congenital infections with *Toxoplasma gondii*, rubella, cytomegalovirus, or herpesvirus), cerebral dysgenesis, and metabolic disorders (eg, hypercalcemia in DiGeorge syndrome, urea cycle defect, propionic acidemia, methylmalonic acidemia, maple syrup urine disease, or nonketotic hyperglycinemia). Delineation of the cause requires the combination of careful history, complete physical examination, testing, and response to interventions. Neonatal seizures do not necessarily predict epilepsy (ie, an ongoing seizure disorder). Although neonatal seizures are the best predictor of future neurologic damage, most infants who have these seizures do well. There is little evidence that transient seizures damage the newborn cortex. Neonatal seizures have virtually no relationship to later epilepsy unless the child has suffered sufficient damage to the brain to manifest later evidence of cerebral palsy. More than 50% of children who have neonatal seizures do not develop epilepsy.

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<u>Content specifications:</u>

Understand the spectrum of clinical seizures in the newborn infant.

Understand the differential diagnosis and evaluation of neonatal seizures.

Understand the management and prognosis of neonatal seizures.
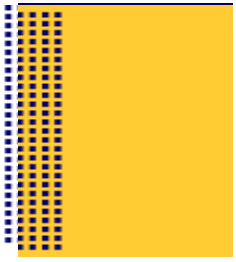
Education Module Learner

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A term female infant is admitted from the delivery room after resuscitation due to respiratory distress. She was delivered vaginally to a 38-year-old primigravida woman in whom fetal ultrasonography demonstrated a large nuchal translucency measurement and moderate bilateral pleural effusions, and a fetal karyotype showed three copies of chromosome 21. At birth, the infant exhibited no hydrops, congestive heart failure, or congenital heart disease.

Of the following, the pathophysiologic consideration that MOST likely caused the pleural effusions in the infant is

1	increased pulmonary venous pressure
☒ **2**	increased systemic venous pressure
3	maldevelopment of the lymphatic system
4	perforation of the parietal pleura
5	thoracic duct injury

You selected 2, the correct answer is 3.

The pleural space lies between the parietal pleura of the chest wall and visceral pleura of the lungs. Normally, little fluid accumulates in the pleural space because production of pleural fluid by both parietal and visceral pleura is matched by reabsorption through lymphatics located in the connective tissue lying immediately below the pleural surface. Fluid does accumulate when the balance between pleural fluid filtration and absorption is altered. Filtration pressure increases when systemic venous pressure and pulmonary venous pressure are elevated and when permeability increases due to infection. Pleural fluid absorption and clearance are decreased when systemic venous pressure obstructs drainage of the thoracic duct into the venous circulation or there is congenital obstruction of thoracic vessels with lymphatic fistula formation into the pleural space. Treatment of the hydrothorax and chylothorax includes expectant management, use of formulas containing medium-chain triglycerides (decreases thoracic duct flow), withholding of oral feedings, direct needle or thoracostomy drainage, pleuroperitoneal shunt drainage, or continuous infusion of somatostatin.

The infant described in the vignette has trisomy 21, which was suggested antenatally by the combination of elderly maternal age and wide nuchal translucency in the fetus on prenatal ultrasonography and confirmed on the fetal karyotype. Infants who have trisomy 21 are known to have malformations in the lymphatic system that may cause fetal and neonatal pleural effusions. Similar lymphatic abnormalities occur in infants who have Turner and Noonan syndromes.

Increased pulmonary and systemic venous pressure may occur with congestive heart failure, hydrops, congenital anomalies of the lymphatic system, or mechanical obstruction of the thoracic duct with central venous catheters or thrombi. The visceral pleura is drained by the pulmonary veins, and the parietal pleura is drained by systemic veins. Increased pressure in either of these venous systems can obstruct venous drainage, increase venous pressure, and result in increased filtration pressure by the visceral and parietal pleura. If lymphatic clearance cannot compensate for increased pleural fluid production, pleural effusion develops. Heart failure, hydrops, or mechanical obstruction of the thoracic duct that could increase pulmonary and systemic venous pressures were not present in the infant in the vignette.

Direct perforation of the parietal pleura by a central venous catheter or diffusion of hypertonic solutions from central catheters into the pleural space also can cause pleural effusions with

intravenous fluids in neonates. Pericardial effusion and tamponade occasionally accompany pleural effusions caused by these mechanisms. Acute decompensation may require immediate pleural or pericardial drainage.

Thoracic duct injury may occur following cardiothoracic surgery (eg, for congenital heart disease, congenital diaphragmatic hernia, ductus arteriosus), extracorporeal membrane oxygenation, or deep insertion of thoracostomy tubes. Unilateral and bilateral pleural effusions may result from drainage of lymphatic fluid directly into the pleural space.

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Weisman L, Hansen TN. Acute, acquired lung diseases. In: *Contemporary Diagnosis and Management of Neonatal Respiratory Diseases*. 3rd ed. Newtown, Pa: Handbooks in Health Care Co; 2003:90-151

Content Specification:

Understand the pathophysiology and recognize the clinical, radiographic and laboratory manifestations of hydrothorax/chylothorax.

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A 7-day-old female who was born at an estimated gestational age of 24 weeks, has experienced weight loss that exceeds 15% of birthweight. Although her skin appears well keratinized, it has poor turgor. She is breathing spontaneously in room air with ambient humidity of 70% and is receiving intravenous nutrition along with trophic enteral feeds. She has received neither indomethacin nor diuretics. Her serum electrolytes are: sodium 158 mEq/L (158 mmol/L), potassium 4.6 Eq/L (4.6 mmol/L), and chloride 116 mEq/L (116 mmol/L). Her serum osmolality is 328 mOsm/kg (328 mmol/kg H_2O). Her urine output is 5.8 mL/kg per hour and urine osmolality 70 mOsm/kg. A lack of effect of the hormone arginine vasopressin (AVP) is suspected.

Of the following, the MOST likely cause of lack of effect of AVP in extremely preterm infants is

1. inadequate secretion of AVP from posterior pituitary

2. lack of AVP receptors in distal nephron and collecting duct

3. lack of production of cyclic AMP after AVP binding to its receptor

4. lack of water channel proteins, aquaporins, in the kidney

5. metabolic degradation of AVP by cysteine aminopeptidase

You selected 4, the correct answer is 3.

The preterm infant in this vignette has clinical and biochemical evidence of hypernatremic dehydration. Although excessive transepidermal water loss is a common cause of hypernatremic dehydration in the first few days after birth in such infants, the high urine output and low urine osmolality as well as the increased concentrations of serum electrolytes and high serum osmolality in the infant in this vignette suggest a lack of action of the hormone arginine vasopressin (AVP). The most likely cause of inaction of AVP in preterm infants is the lack of production of cyclic adenosine monophosphate (cAMP) after AVP binding to its receptor. A review of AVP metabolism from its synthesis to its degradation may facilitate our understanding of this hormonal abnormality in preterm infants.

AVP, also called the antidiuretic hormone in most vertebrate species, is the major determinant of renal water excretion and, therefore, plays a central role in the maintenance of water balance. Synthesis of the AVP precursor occurs principally in the hypothalamic neurons of the supraoptic and paraventricular nuclei. AVP, produced by cleavage of its precursor, is stored as neurosecretory granules in the posterior pituitary. The secretion of AVP is regulated by the osmolality of plasma. In healthy adults, a plasma osmolality in excess of 284 mOsm/kg initiates the release of AVP from the posterior pituitary. In humans, extremely high concentrations of AVP are present in cord arterial blood samples from term as well as preterm newborns, indicating active fetal production of AVP. Plasma AVP concentrations are increased in the human fetus by many stimuli, such as hypoxia, acidemia, hemorrhage, infection, umbilical cord compression, hypotension, and increased plasma osmolality. Postnatally, pulmonary conditions, such as pneumothorax or atelectasis, and cardiac conditions associated with stretching of the left atrium are accompanied by increased release of AVP. Thus, inadequate secretion of AVP from the posterior pituitary is not the limiting factor accounting for the lack of action of AVP in preterm infants.

The effects of AVP are mediated by two major classes of receptors, V_1 and V_2. The V_1 receptor is distributed widely in tissues including vascular smooth muscle, liver, platelets, and cerebrum. The V_2 receptor, more specific for the antidiuretic response, is found principally in the kidney; the specific sites include the medullary thick ascending limb of the loop of Henle and the collecting duct. In sheep, the fetal kidney is replete with V_2 receptors with binding

characteristics similar to those in the adult kidney. Likewise, the fetal kidney in humans is replete with V_2 receptors. Thus, the lack of AVP receptors in the distal nephron and the collecting duct is not the limiting factor for the lack of effect of AVP in preterm infants.

Located on the basolateral membranes of the cells of the collecting duct, the V_2 receptors, when occupied by AVP, initiate a cascade of intracellular events. These events begin with activation of adenylate cyclase for generation of cyclic AMP from adenosine triphosphate (ATP), which is followed by phosphorylation of protein kinases. The stimulation of protein kinases results in the translocation of cytoplasmic water channels (aquaporins) to the apical membrane of the cells of the collecting duct. The net result is an increase in water permeability of the collecting duct. The other renal site of AVP action is the medullary thick ascending limb of the loop of Henle, which possesses the AVP-sensitive adenylate cyclase. Upon activation of adenylate cyclase, sodium is transported actively into the renal interstitium, which generates a hypertonic interstitial renal medulla and increases the osmotic water gradient across the collecting duct, resulting in augmentation of its antidiuretic action. In newborn rats, the adenylate cyclase response to AVP is low (approximately 25% of adult response) and does not reach maturity until about 30 days after birth. The adenylate cyclase response to AVP is immature in human neonates, particularly preterm infants. Thus, the lack of production of cyclic AMP after AVP binding to its receptor from immaturity of the adenylate cyclase is the limiting factor that accounts for the lack of effect of AVP in preterm infants.

Aquaporins are water channel proteins required for the translocation of water across cellular membranes. Of the 4 aquaporins described, aquaporin 1 (AQP-1) has a wide distribution throughout the body. In the kidney, AQP-1 is present in the thin descending limb of the loop of Henle and the proximal tubule. Aquaporin 2 (AQP-2) is located exclusively in the cortical and medullary cells of the collecting duct. Aquaporin 3 (AQP-3), likewise, is present principally in the cells of the collecting duct. Aquaporin 4 (AQP-4) is distributed widely in the brain, not the kidney. The ontogeny of only AQP-1 and AQP-2 has been studied. In humans, AQP-1 is detected at 14 weeks' gestational age and is present in significant amounts in the proximal tubule by 17 weeks and in the thin descending limb of the loop of Henle by 24 weeks. The ontogeny of AQP-2 in the collecting duct is similar. Thus, the lack of aquaporins in the kidney is not the limiting factor for the lack of action of AVP in preterm infants.

AVP circulates in the blood unbound to proteins. The half-life of AVP in the blood is approximately 5 to 15 minutes. The metabolic fate of AVP molecules is three-fold. First, the AVP involved in the actions mediated by adenylate cyclase is metabolized in the target tissue. Second, much of the AVP in the blood binds avidly to circulating platelets. And third, only a small percentage of AVP molecules undergoes enzymatic cleavage. A cysteine amniopeptidase, called vasopressinase, which can degrade AVP, has been described during pregnancy and the immediate postpartum period. This enzyme derived from the placental syncytiotrophoblast is not likely to be present at 7 days of age. Thus, rapid enzymatic degradation of AVP is not the limiting factor for the lack of effect of AVP in preterm infants.

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<u>Content Specifications:</u>

Understand the specific hormonal factors that influence water balance in neonatal life

Understand the effects of arginine vasopressin (antidiuretic hormone) on sodium and water balance

Understand the impact on water requirements of renal and metabolic fluid disorders that arise because of endocrine dysfunction in infants

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A pediatrician asks you to consult on an 18-hour-old infant born at 37 weeks' gestation. The infant had been delivered vaginally 27 hours after membrane rupture. Group B streptococcus status is unknown. The child's axillary temperature is 37.7°C (99.8°F). Review of the local culture results over the years suggests that there is a 1 in 30 chance that her blood culture, taken 16 hours after birth, would be positive. Laboratory data reveal an elevated serum C-reactive protein (CRP) value. In your experience, the sensitivity of the serum CRP to predict a positive blood culture is 0.90, with a specificity of 0.69. The mother asks you how likely the blood culture is to be positive.

Of the following, the positive predictive value (PPV) of an elevated serum CRP is CLOSEST to

1	0.03
❌ **2**	0.05
3	0.09
4	0.12
5	0.15

You selected **2**, the correct answer is **3**.

The positive predictive value (PPV) can be calculated from the following equation:

PPV = [(SEN) x (Ch)] / [(SEN) x (Ch) + (1 - SPE) x (1 - Ch)]

*Ch = overall chance of disease in the population under study, in this case the chance of a positive blood culture

*PPV = Positive predictive value

*SEN = sensitivity, the proportion of those with the disease who test positive

*SPE = specificity, the proportion of those with no disease who test negative

Applying the numbers from the vignette:

PPV = (0.90) x (1/30) / [(0.90) x (1/30) + (1-0.69) x (1-(1/30))]

PPV = 0.09

Direct formulas are not always easily available or remembered. Alternatively, it is useful to diagram questions involving sensitivity and specificity with the following table in mind:

	Disease	**No Disease**	
Test Positive	A (true positive)	B (false negative)	PPV = A / (A+B)

Test Negative	C (false negative)	D (true negative)	NPV = D / (C+D)
Column Total	Ch = (A+C)	(1-Ch) = (B+D)	
	SEN = A / Ch	SPE = D / (1-Ch)	

*NPV = Negative predictive value

Given the information from the vignette, the above diagram can be filled in with:

SEN = 0.90

SPE = 0.69

Ch = 1/30 = 0.033

(1-Ch) = 29/30 = 0.97

	Disease	**No Disease**	
Test Positive	A	B	PPV = A / (A+B)
Test Negative		D = (1 - Ch) - B	
Column Total	0.033	(1-Ch) = 0.97	
	SEN = 0.90	SPE = 0.69	

What remains of the original question is to find A and B, then compute PPV from them.

Because SEN = A / Ch, rearrangement gives A = SEN x Ch = 0.90 x 0.033 = 0.03.

Similarly, SPE = D / (1-Ch), giving D = SPE x (1-Ch) = 0.69 x 0.97 = 0.67. To get B out of this, remember that (1-Ch) = (B+D), or B = (1-Ch) - D = 0.97 - 0.67 = 0.30

Finally, PPV = A / (A+B) = 0.03 / (0.03+0.30) = 0.09, the preferred answer.

A single CRP value obtained at the time of initial evaluation for sepsis has a low sensitivity. This is likely due to a delay in the initial rise. After the first day, it has promise because of its high NPV, allowing a negative test to contribute to the decision as to when to stop treatment. Other blood tests used in the evaluation of suspected sepsis may have low PPVs but still may be useful due to high NPVs. For example, the immature-to-total neutrophil ratio (I/T ratio) of less than 0.20 gives PPVs of 0.11 to 0.51 in various studies, but has useful NPVs of 0.99 to 1.0. These high NPVs help in combining tests to form various "sepsis screens," which may include

combinations of I/T ratio, absolute leukocyte count, erythrocyte sedimentation rate, haptoglobin, interleukin 6, and CRP. These screens may help support decisions regarding management of sepsis.

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Content specifications:

Know how to define and calculate specificity and sensitivity

Know how to define and calculate positive and negative predictive value

Understand the laboratory features of sepsis

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You are asked to resuscitate a 24-weeks' gestation male infant in the delivery room.   He was born preterm despite maternal treatment with magnesium sulfate for severe pregnancy-induced hypertension. Maternal serum magnesium concentration is 6.5 mg/dL (2.7 mmol/L).   His mother was given betamethasone 48 hours before delivering vaginally.

Of the following, the intervention MOST likely to be needed to stabilize this infant is

1	bag-mask ventilation
☒ 2	chest compressions
3	continuous positive airway pressure
4	surfactant
5	tactile stimulation

You selected 2, the correct answer is 1.

Bag-mask ventilation of the lungs is the most likely intervention required to stabilize the extremely low birthweight infant in the vignette.   Ventilation of the lungs is the most important intervention during neonatal resuscitation, because respiratory distress and apnea are the most frequent reasons for cardiopulmonary decompensation after birth.   This observation is especially true in this extremely low birthweight infant, who likely will have apnea due to hypermagnesemia.   Maternal and neonatal magnesium concentrations often are similar, because magnesium readily crosses the placenta.   Other neonatal complications of hypermagnesemia include hypotonia, ileus, delayed passage of meconium, and, after prolonged fetal exposure, meconium obstruction.

Chest compressions usually are not required in neonates who need resuscitation.   Initiation of ventilation is associated most often with a rapid rise in heart rate.   This improvement in heart rate may be followed by improved color, tone, and spontaneous respiratory efforts.   In the extremely low birthweight infant in this vignette, apnea may persist for hours.   After initial stabilization of vital signs with bag-mask ventilation, mechanical ventilation likely will be needed.

Continuous positive airway pressure (CPAP) is an alternative respiratory support strategy in infants who are breathing spontaneously with acceptable vital signs. In the infant in this vignette, apnea associated with extreme prematurity and hypermagnesemia is likely.   Therefore, a period of positive pressure ventilation before spontaneous breathing occurs should be anticipated. In addition, the delivery room use of CPAP to provide respiratory support after initial resuscitation steps has been suggested in large case series to reduce the need for mechanical ventilation in the delivery room, bronchopulmonary dysplasia, and other complications of prematurity. Although more than half of infants less than 28 weeks' gestation may not require intubation and mechanical ventilation in the delivery room, within the first days after birth, 80% will require mechanical ventilation.   Whether a delay in initiation of mechanical ventilation with delivery room CPAP is safe and effective compared to delivery room intubation and positive pressure ventilation is unknown.   Randomized clinical trials to answer this question are in progress.

Surfactant administration in this infant likely will be needed, because more than 80% of infants born at 24 weeks' gestation receive surfactant within hours of birth. Surfactant administration before the first breath was hypothesized to improve dispersion of surfactant throughout the lung.   It does not appear that outcomes are different if extremely preterm infants receive

surfactant before the first breath or after initial resuscitation and stabilization. Therefore, a commonly accepted practice is to initiate and support breathing first, then administer surfactant if a surfactant deficiency is evident.

Tactile stimulation is one of the initial steps in resuscitation of newborn infants. Extreme prematurity and hypermagnesemia-associated apnea make it likely that positive pressure ventilation will be required. After initial brief tactile stimulation with drying and positioning, positive pressure should be initiated with a bag and mask. Prolonged attempts at tactile stimulation probably will not be effective in the infant in this vignette and may be associated with injury to the skin.

References:

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Content Specifications:

Understand the proper approach to airway management in the delivery room

Know the indications for assisted ventilation in the delivery room

Understand the indications, techniques and potential complications of chest compression

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A 28-year-old schoolteacher has had several pupils miss school after developing a facial rash about one week following several days of mild headache, low-grade fever, and runny nose for which most did not miss school. The Health Department has notified the school of an outbreak of Fifth Disease in the community. The teacher is 16 weeks' pregnant and inquires whether she should be concerned. At this time, she is asymptomatic.

Of the following, the recommendation MOST appropriate at this time is

1. cordocentesis

2. fetal ultrasound

3. maternal antibody concentrations

4. reassurance ✗

5. termination of pregnancy

You selected 4, the correct answer is 3.

Fifth Disease is caused by infection with Parvovirus B19. Susceptibility to infection and its effects depend on the patient's age, immune status, hematological stability, and prior exposure. Infection during childhood is common, with one-half of 15-year-olds having antiparvoviral antibodies, although most do not recall a specific illness suggestive of Fifth Disease. Most elderly individuals have antibodies. Of infected individuals, 25% remain asymptomatic; 50% report nonspecific symptoms, such as fever, coryza, myalgia, headache, nausea, or mild diarrhea; and 25% experience the classic rash (in children) or arthralgia (more common in adults). The illness has two phases: approximately one week after exposure, the nonspecific symptoms occur and last two to three days. After approximately a week symptom-free, the rash (when seen) occurs.

The virus is spread by respiratory droplets and is resistant to heat and common solvent detergents, resulting in a 20% to 30% infection risk among susceptible individuals, as in a common classroom or household. Among pregnant women, incidence of acute Parvovirus B19 infection overall is about 3.5%, but schoolteachers experience a 16% risk, and child care workers and homemakers have a 9% risk. Viremia occurs about 6 days (range 4 to 14 days) after exposure and is present until cleared by the antibody response, at which time the characteristic skin rash and/or arthralgia may occur. The skin rash is characterized by "slapped cheek" appearance on the face and reticulated appearance on the trunk and extremities. The skin rash is transient, although it may recur with sun exposure, temperature change, or emotional stress for several weeks. The arthralgia typically resolves within a few weeks. The skin rash and arthralgia are believed to be mediated by viral-immunoglobulin complex, and their appearance signifies that the patient no longer is infectious. Except in rare instances, exposure results in immunity, detectable by early elevation of specific Immunoglobulin M (IgM) followed by Immunoglobulin G (IgG) antibodies that confer lifetime immunity.

Patients who have increased erythropoiesis (such as in sickle cell anemia) may develop a transient aplastic crisis if infected with Parvovirus B19. Because the virus attacks erythroid progenitor cells, the aplastic crisis occurs during the period of viremia, with erythrogenesis becoming re-established once the antibody response clears the viremia, allowing the erythroid line to recover. Patients with impaired immunity may develop a chronic infection with persistent anemia. Although a period of red-cell aplasia (detectable by a drop in reticulocyte count and 1 gm/dL drop in hemoglobin concentration) usually occurs in normal individuals, the brief viremia and long red-cell life span protect against severe anemia. In susceptible pregnant women, the

virus may cross the placenta and affect the fetus, primarily by attacking erythrogenic precursors and the myocardium, resulting in risk of fetal death from anemia, hydrops, and myocardiopathy.

For the schoolteacher in the vignette, measurement of maternal antibodies to Parvovirus B19 is the most appropriate first step in addressing her concern. The presence of IgG antibodies indicates prior infection and immunity, present in 35% to 53% of pregnant women tested, and can result in reassurance. The presence of IgM antibodies indicates acute infection. Seroconversion results in vertical transmission 30% of the time. Testing for viral DNA in amniotic fluid can be done to make the diagnosis in utero. Risk to the fetus depends on gestational age. In the first 20 weeks of pregnancy, the risk of fetal death ranges from 13% in the first trimester to 9% between 13 and 20 weeks' gestation, and <1% after 20 weeks. Detection of acute maternal infection at <20 weeks' gestation should be managed by counseling the schoolteacher regarding the low risk of adverse outcomes. The virus is not considered teratogenic, therefore termination of pregnancy would not be recommended. Intravenous immunoglobulin has not been shown to be beneficial in pregnant women with Parvovirus B19 infection.

Because the virus attacks the red blood cell line of the fetus, fetal anemia and/or hydrops may occur. The risk for fetal hydrops is a function of gestational age, occurring among 4.4% of pregnancies <32 weeks and among 0.8% >32 weeks. Hydrops fetalis usually occurs between 2 and 5 weeks after maternal infection, although hydrops after 8 weeks has been reported. After 20 weeks' gestation, ultrasonography performed weekly to evaluate for fetal hydrops is recommended for at least 8 weeks. Presence of early signs of hydrops mandates continued surveillance. About one-third of cases will resolve spontaneously and result in a healthy infant. If signs of severe hydrops are noted (fetal edema, ascites, pleural or pericardial effusions), fetal hematocrit by percutaneous umbilical blood sampling (cordocentesis) is recommended. Measurement of peak systolic velocity in the middle cerebral artery by Doppler also may be used to assess fetal anemia. Severe fetal anemia with hydrops can be treated by intrauterine blood transfusion. Survival among fetuses treated with intrauterine transfusion is approximately 85%. Lesser degrees of involvement may require emergent delivery room management, including ventilatory support, exchange transfusion with packed red blood cells, removal of pleural or peritoneal fluid, and care in a neonatal intensive care unit. Optimally, such infants should be delivered at a Level III facility experienced in these techniques. Long-term studies show no developmental sequelae from intrauterine Parvovirus B19 infection.

References:

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Jordan JA. Clinical manifestations and pathogenesis of human Parvovirus B19 infection. Available at www.uptodate.com [requires subscription]. Accessed March 28, 2005.

Kwon KT. eMedicine: Pediatrics, fifth disease or erythema infectiosum. Available at www.emedicine.com/emerg/topic378.htm. Accessed April 15, 2005.

Riley LE, Fernandes CJ. Parvovirus B19 infection during pregnancy. Available at www.uptodate.com. [requires subscription]. Accessed March 28, 2005.

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Content Specifications:

Understand the epidemiology, pathogenesis, and prevention of perinatal Parvovirus infections

Understand the clinical manifestations, diagnostic criteria, and treatment of perinatal Parvovirus infections

Understand the complications of perinatal Parvovirus infections
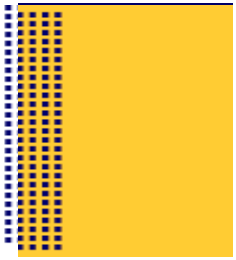
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You are asked to consult with a woman who is 26 weeks' pregnant with twin male fetuses. The prenatal ultrasound fails to demonstrate a dividing membrane between the twins.

Of the following, the complication of twin pregnancy MOST likely to develop in this woman is

1 acardiac twinning

☒ 2 conjoined twins

3 twin-to-twin transfusion

4 umbilical cord entanglement

5 vanishing twin syndrome

You selected 2, the correct answer is 4.

Absence of a dividing membrane, as described in the vignette, confirms that this woman is pregnant with monozygotic twins with monoamniotic placentation. Monozygotic twins may have three different types of placentation: diamniotic/dichorionic (Figure 1) diamniotic/monochorionic (Figure 2), or monoamniotic/monochorionic (Figure 3). Monoamniotic/monochorionic placentation, the rarest type, occurring in <1% of monozygotic twins, has the highest rate of complications.

Umbilical cord entanglement (Figure 4) is the most likely because there is no amniotic membrane separating the fetuses. Fetal mortality rate in monoamniotic twins is approximately 40%, primarily due to umbilical cord entanglement with subsequent vessel occlusion. True knots in the umbilical cord have been diagnosed as early as 10 weeks' gestation. Although fetal demise from cord entanglement and occlusion can happen throughout gestation, the incidence is highest during early pregnancy, when space between the twins is greatest and more fetal movement occurs. Intensive fetal surveillance of monoamniotic twins should occur from the period of fetal viability until delivery. Because entangled umbilical cords can tighten during labor, cesarean delivery may be considered.

Acardiac twinning, known also as twin reversed arterial perfusion (TRAP) sequence, is a rare complication of monozygotic twins. Acardiac twinning occurs when one monozygotic twin has an absent or rudimentary heart and is usually acephalic. The incidence of acardiac twinning is 1% of monochorionic twins or 1 in 35,000 live births. The cause of acardiac twinning is early development of an arterial-to-arterial anastomosis between the umbilical arteries of twins. The normal donor (pump) twin provides circulation for itself and the recipient (perfused) twin through umbilical artery to umbilical artery anastomosis at the placental surface. The term "reversed perfusion" is used because blood enters the acardiac twin through the umbilical artery and exits through the umbilical vein. Cardiac failure can occur in the donor twin because of excessive demands from the TRAP sequence, especially if the acardiac twin is larger than the pump twin. The diagnosis of acardiac twins is made by fetal ultrasound

Conjoined twins, which occur in approximately 1 in 50,000 live births, are the result of incomplete division of monozygotic twins 13 to 15 days after conception. Conjoined twins always have monoamniotic placentation. Conjoined twins are classified based on the site of attachment into five types: thoracopagus (75% of conjoined twins), pygopagus (20%), ischiopagus (5%), craniopagus (<1%) and omphalopagus (<1%). Prenatal diagnosis usually is made by an ultrasound that reveals conjoined fetuses in a single sac.

Twin-to-twin transfusion syndrome is a complication of monochorionic placentation in which

arterial-to-venous shunts develop in the placenta and preferential blood flow occurs from one twin to the other. Vascular communications are present in almost all monochorionic placentas; clinically significant twin-to-twin transfusion occurs in <5% of monochorionic gestations. Because all monoamniotic twins also have monochorionic placentas, the twins described in the vignette are at risk to develop twin-to-twin transfusion. However, the likelihood of umbilical cord entanglement is greater than twin-to-twin transfusion syndrome in monoamniotic twins.

The vanishing twin syndrome occurs with the identification of a multifetal gestation with subsequent demise and disappearance of one (or more) fetus(es). The frequency of the vanishing twin syndrome is difficult to ascertain because it usually occurs early in pregnancy. Vanishing twin syndrome has been diagnosed more frequently since the use of ultrasound in the first trimester. In vitro fertilization techniques have improved the understanding of vanishing twin syndrome because these pregnancies are monitored, and the number of implanted fertilized eggs is known.

In vanishing twin syndrome, there may be complete reabsorption of a fetus, formation of a fetus papyraceus (ie, a "mummified" or compressed fetus), or development of a subtle abnormality on the placenta, such as a cyst, subchorionic fibrin, or amorphous material.

The fetal loss is usually asymptomatic for the pregnant woman, but may be associated with modest vaginal bleeding. It is estimated that 5% of pregnant women who have first-trimester vaginal bleeding are experiencing a vanishing twin. Because the woman in the vignette is 26 weeks' pregnant, a fetal demise with subsequent reabsorption makes vanishing twin syndrome unlikely.

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Zach TL, Pramanik A, Ford SP. eMedicine: Multiple births. Available at: http://www.emedicine.com/ped/topic2599.htm. Accessed May 26, 2005.

Content Specifications:
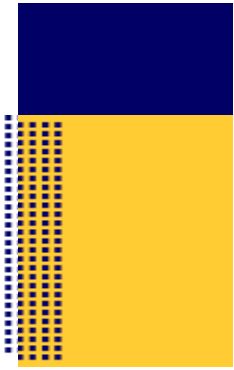
Know the types of and effects on the mother of multiple gestation pregnancy

Know the morphologic development of the placenta

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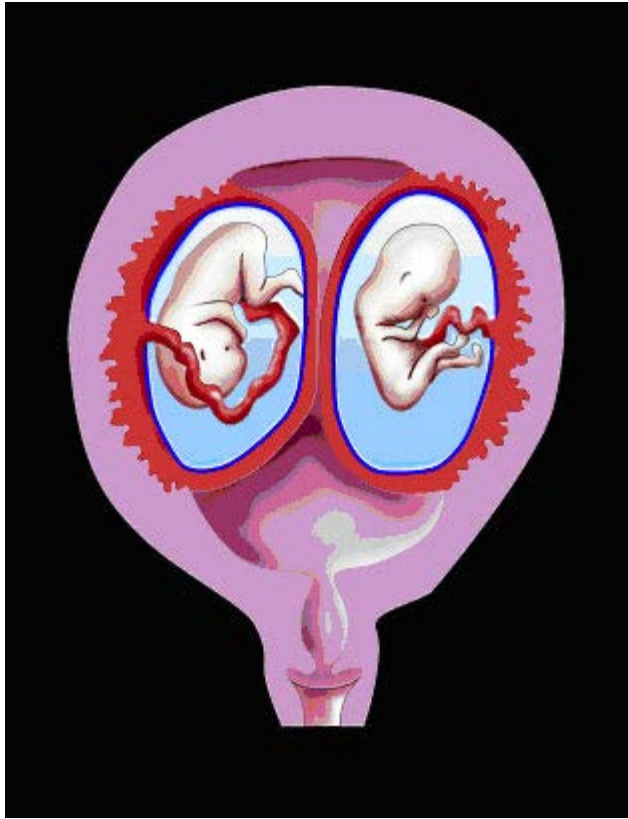
Figure 2

Figure 2. Diamniotic/monochorionic placenta.
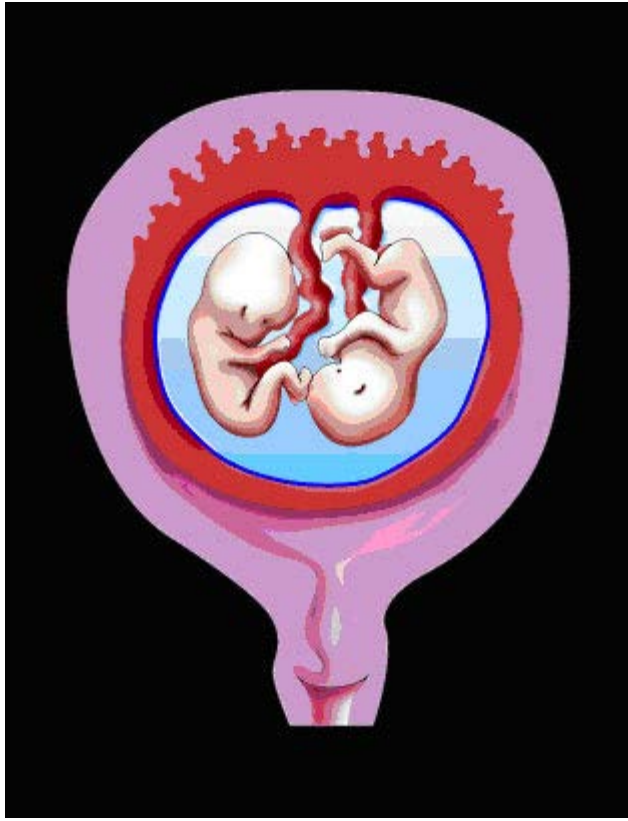
Figure 4

Figure 4. Umbilical cord entanglement in monoamniotic twins.

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In 1994, Tholl and associates published a meta-analysis of 10 randomized controlled studies of the use of phenobarbital to prevent intraventricular hemorrhage in preterm infants. They concluded that "the data suggest that prenatal phenobarbital was beneficial." In 1997, Shankaran and associates published a large randomized multicenter trial of antenatal phenobarbital on intracranial hemorrhage in preterm infants involving more than 600 pregnancies. Shankaran and associates found no decrease in the risk of intracranial hemorrhage or early death. Subsequent analyses and reviews confirm that antenatal phenobarbital is not effective in preventing intracranial hemorrhage in preterm infants.

Of the following, the MOST likely explanation for the discrepancy between a positive meta-analysis and a negative large clinical trial is

1. bias in the publication rate for smaller studies

2. bias of the investigator(s) conducting the meta-analysis

3. changes in clinical practice over time

4. erroneous inclusion of studies with disparate designs in meta-analysis

5. pooling of bias inherent in individual studies magnifying bias in meta-analysis

You selected 5, the correct answer is 1.

Meta-analysis is the statistical technique that pools the results of several small clinical trials to increase the reliability of the estimated effect of a treatment. In theory, if the studies selected for meta-analysis are close enough in design (including patient selection and exclusion, treatment method, and outcome variables), the result should be equivalent to those of a single large multicenter randomized trial. However, a landmark article by LeLorier and associates described 12 large randomized clinical trials that were preceded in the medical literature by meta-analyses of groups of similar small clinical trials. These trials were similar in populations studied, therapeutic interventions, and at least one major outcome. A total of 40 outcomes were considered in their analysis of the 12 large trials. They examined the odds ratios and 95% confidence limits for these outcomes and their preceding meta-analyses. Considering the large randomized trial as the gold standard, the authors concluded that meta-analyses would have led physicians to either reject useful therapies (known as a type II error) or adopt ineffective ones (type I error) in approximately 1 in 3 cases. This discrepancy was seen equally with peer-reviewed meta-analyses that tended to recommend a new therapy (positive meta-analysis) and those that reported no statistical advantage of a therapy (negative meta-analysis).

The most likely explanation for the discrepancy between a positive meta-analysis and a negative large clinical trial is bias in the publication rate for smaller studies. Bias occurs in several ways. First, clinical investigators doing a small or pilot project resulting in no statistical difference between groups might not finish the project or submit it for publication. To be convincing and to avoid a type II error (rejecting a useful treatment), more subjects are needed, making it harder to complete than a positive trial. Second, small studies that show no benefit of a new therapy tend <u>not</u> to be selected for presentation at national meetings or to be published by journals as often as small positive studies. Another source of bias has been found when the authors of a meta-analysis limit the search for studies to publications in English.

Peer review and adherence to the rules underlying meta-analysis tend to weed out bias in those meta-analyses that are published. Bias of the investigator(s) conducting the meta-analysis and erroneous inclusion of studies with disparate designs, therefore, are less likely to contribute to the discrepancies between a positive meta-analysis and a subsequent negative trial.

It has been speculated that when the original meta-analysis is negative and is followed by a convincing large clinical trial that shows that the treatment is effective, then changes in clinical practice over time have had an influence on the effectiveness of the treatment. In contrast, in the vignette a positive meta-analysis has been followed by a negative large trial; in this circumstance, changes in practice over time are unlikely to explain the discrepancy.

The bias that might contaminate small individual studies actually might influence the outcomes of those studies in either a positive or a negative direction, making it more likely that pooled biases would be smaller rather than magnified. Thus, pooling of bias inherent in individual studies magnifying bias in meta-analysis is unlikely to explain the discrepancy in their results.

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Content Specifications:

Understand alpha (type I) and beta (type II) errors

Understand the use of confidence intervals

Define and calculate odds ratios

Know how to calculate the rate of events and adverse effects in clinical trials

PREVIOUS   NEXT

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You are called to see a 3.5-kg child born 20 minutes ago. The child has cyanosis, despite receiving 100% oxygen, and is in shock. Clinical examination reveals poor pulses, mottled appearance, oxygen saturation (SpO_2) 40%, and blood pressure 35/25 mmHg. The mother, whose prenatal care was not provided locally, tells you that some sort of congenital heart disease was suspected several months ago, but she cannot remember any specifics. You immediately start prostaglandin E_1 (PGE_1) at 0.1 mcg/kg per minute by intravenous route and call for an emergency echocardiogram. Over the next 20 minutes, the child worsens, with SpO_2 of 30% and blood pressure of 30/20 mmHg.

Of the following, the MOST likely explanation for this child's deterioration is

1 hypoplastic left heart syndrome with restricted atrial septum

2 interrupted aortic arch

3 total anomalous pulmonary venous return with obstruction of the common pulmonary vein

4 transposition of the great arteries with ventricular septal defect

☒ **5** viral myocarditis

You selected 5, the correct answer is 1.

Prostaglandin E_1 (PGE_1) often is used in infants suspected to have ductus-dependent congenital heart disease. PGE_1 is believed to exert its actions by two mechanisms: by activating adenylate cyclase in the vascular smooth muscle cells of the ductus arteriosus, thereby inhibiting the sensitivity of the contractile proteins to calcium; and by opening potassium channels to hyperpolarize the muscle cells, thereby reducing muscle tone. Due to its half-life of minutes, PGE_1 is given by constant infusion at doses of 0.01 to 0.4 mcg/kg per minute. Acute adverse effects include fever, apnea, hypotension, hypertonia, and irritability. Long-term adverse effects may include renal insufficiency, hypoglycemia, hypocalcemia, hyperostosis, obstructive gastropathy, thrombocytopenia, and seizures. Maternal inhibition of prostaglandin synthesis by chronic nonsteroidal anti-inflammatory drugs is associated with premature ductal closure and persistent pulmonary hypertension of the newborn.

Clinical deterioration once PGE_1 is started can be a useful sign of conditions in which there is obstruction to the pulmonary veins or to left atrial outflow. These conditions include total anomalous pulmonary venous return with pulmonary vein obstruction (TAPVR-PVO), hypoplastic left heart syndrome with restrictive atrial septum (HLV-RAS), mitral atresia with restrictive foramen ovale, and transposition of great arteries (TGA) with intact ventricular septum. Without the "pop-off" through the foramen ovale or atrial septal defect, pressure builds up in the left atrium and pulmonary veins to quickly cause pulmonary congestion, and markedly decreased pulmonary flow. The fully opened ductus would worsen the pulmonary overload.

Interrupted aortic arch usually presents as shock or congestive heart failure in the first fortnight. More than half the time, it is associated with a microdeletion of chromosome 22 and the DiGeorge syndrome. These children are dependent on a patent ductus arteriosus for blood flow to the descending aorta. Such a case would be expected to benefit from PGE_1 infusion.

TAPVR-PVO usually presents with cyanosis and tachypnea, often initially diagnosed as a primarily pulmonary problem. Delayed presentation until after age 12 hours helps differentiate it from respiratory distress syndrome. Physical findings, including murmurs, thrills or hyperactive pulses, seldom are found. Drainage often is below the diaphragm into the inferior vena cava.

TAPVR-PVO is difficult to find by echocardiogram, especially in the prenatal period; it is unlikely that the mother would have been warned about it.

HLV-IAS could present as in the vignette and fail to respond to PGE_1. The small size of the left ventricle would have been seen on prenatal echocardiogram and mentioned to the mother, as in the vignette. The severe obstruction to left-atrial outflow requires rapid palliation (atrial septostomy) or surgical intervention. Most other causes of left-sided obstruction should improve with PGE_1, including critical aortic stenosis, coarctation of the aorta, interrupted aortic arch, and HLV with atrial septal defect.

TGA with ventricular septal defect is likely to present with a higher SpO_2 than in the vignette. Improvement rather than deterioration is expected with PGE_1; the better mixing between the two parallel circulations would give even higher saturations.

Viral myocarditis might present with shock but would be unlikely to produce such low SpO_2 levels. The peripheral vasodilatation caused by PGE_1 might even help cardiac function by reducing afterload. Most cases should resolve over two months into either adequate cardiac function, or failure and death. It is unlikely that this was the problem the mother was told about prenatally.

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<u>Content Specifications</u>:

For therapeutic drugs commonly used in the neonate, know the indications for their use, clinical effects, pharmacokinetics, adverse effects, and toxicity

Recognize the clinical features of a neonate with a left-sided cardiac obstructive lesion

Formulate a differential diagnosis of a neonate with a left-sided cardiac obstructive lesion

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A term male infant evaluated in your nursery has a large anterior fontanel (5 cm x 4 cm), occipito-frontal circumference 37 cm, deep-set eyes, flat nasal bridge, cleft lip and palate, midface hypoplasia, pointed chin, bilateral transverse palmar creases, hypotonia, sacral dimple, cyanosis, and systolic heart murmur. Family history is not contributory, and both parents are healthy. This is the first infant for these parents. Chest radiograph shows cardiomegaly, and echocardiogram shows Ebstein anomaly and large patent ductus arteriosus. Karyotype is normal. Fluorescence in situ hybridization (FISH) analysis for subtelomeric microdeletions demonstrates a terminal deletion at chromosome 1p36.

Of the following, the outcome MOST likely to develop in this infant is

1	asthma
☒ 2	diabetes mellitus
3	leukemia
4	mental retardation
5	renal failure

You selected 2 , **the correct answer is** 4 .

Telomeres are the "protective" caps at the ends of each chromosome and are highly conserved in all vertebrate species ([Figure 1](#)). These protective caps are composed of a repeating DNA sequence (TTAGGG) and can reach a length of 15,000 base pairs. Telomeres function to protect chromosomes from losing base pairs (genes and other genetic material) during cell replication. They also prevent chromosomes from adhering to one another during mitosis. During each cell division, 25 to 200 base pairs are lost from the telomere. The chromosome is shortened, or eroded, with each cell division until a "critical length" is reached, at which additional cell division is no longer possible. In other words, the cells in which the telomeres have reached this critical length have aged and prepared for programmed cell death, or apoptosis. Telomerase, or telomere terminal transferase, is an enzyme that adds TTAGGG sequences to the end of existing chromosomes. Telomerase activity is low in most of the body's somatic cells but is active in fetal tissues, adult germ cells, and tumor cells. Telomere and telomerase research are important to understand the biology of aging and cancer.

The base pair sequences adjacent to the telomeric repeats are called subtelomeres ([Figure 2](#)). This area of each chromosome is highly polymorphic and rich in repetitive DNA elements (subtelomeric repeats) and genes. Base pair rearrangements, duplications, and deletions in the subtelomeric region have been associated with microscopically visible chromosome abnormalities (4p-, Wolf-Hirschorn; 5p-, cri du chat; 22q11.2-, DiGeorge/Velocardiofacial; 7q-, Williams; 17p-, Miller-Diecker; 15q-, Prader-Willi/Angelman; 9p-, 13q- and 18p- syndromes). In addition, submicroscopic subtelomeric abnormalities (<2 to 3 Mb) found only with newer cytogenetic and molecular techniques, such as subtelomeric fluorescence in situ hybridization (FISH), spectral karyotyping, multiplex FISH telomere integrity assays, automated fluorescent genotyping, and comparative genomic hybridization, also have been associated with multiple malformation syndromes and mental retardation. The incidence of subtelomeric abnormalities is not well established. However, in as many as 5% of infants who have multiple malformations and 5% of children who have mental retardation, the clinical outcome may be related to subtelomeric chromosomal abnormalities.

In nearly half of neonates who have multiple anomalies, the abnormalities are not explained using routine chromosome analysis, amino and organic acid analysis, physical examination by

an experienced geneticist, and history. It is estimated that subtelomeric testing will establish a diagnosis in approximately 5% of these infants. Subtelomeric testing currently is considered as a second tier of tests for neonates who have multiple congenital anomalies, dysmorphic facial features, and intrauterine growth restriction in which a diagnosis is not otherwise explained.

The infant in this vignette has a contiguous gene deletion of chromosome 1p36 (ie, monosomy 1p36 -- see figures 3, 4, 5, and 6). The incidence of de novo monosomy for 1p36 has been estimated at 1 in 10,000 newborns. Parental chromosomal translocation is estimated to account for 1 in 30 of these patients; therefore, parental testing is indicated. This infant likely will have moderate to severe mental retardation and severe developmental delay, both commonly found in many of the syndromes caused by submicroscopic subtelomeric abnormalities. Hypotonia, large anterior fontanel, prominent forehead, deep-set eyes, depressed nasal bridge, midface hypoplasia, pointed chin, cleft lip and palate, ear asymmetry, and facial dysmorphism characterize this syndrome. Hydrocephalus occurs occasionally. Ebstein anomaly, a rare congenital heart malformation, appears to be represented disproportionately in this syndrome, although other congenital heart defects, especially patent ductus arteriosus, also are found. Ebstein anomaly, large anterior fontanel/hydrocephalus, cleft lip/cleft palate and facial dysmorphism should raise suspicion for this subtelomeric disorder. Later complications include growth failure, seizures, sensorineural hearing loss, visual abnormalities, and a variety of musculoskeletal, genitourinary, and miscellaneous features. Asthma, diabetes mellitus, leukemia, and renal failure are not reported in this syndrome.

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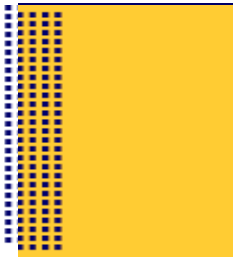
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Content Specifications:

Recognize the karyotype and clinical manifestations associated with the contiguous gene disorders

Recognize the karyotype and clinical manifestations associated with the microdeletion syndromes

PREVIOUS   NEXT

Figure 1. Telomere and Subtelomeric Region of Chromosome 1
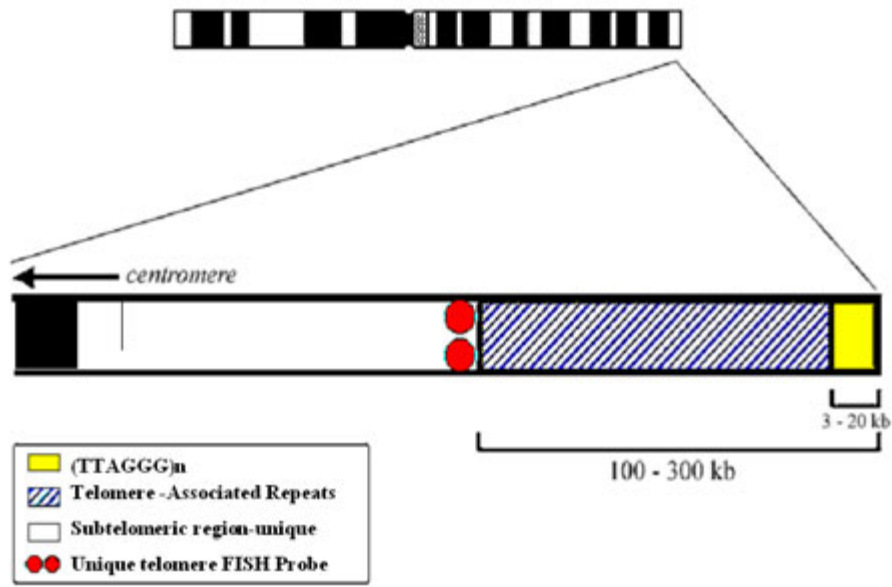
Figure 2. Subtelomeric Microdeletion of Chromosome 1
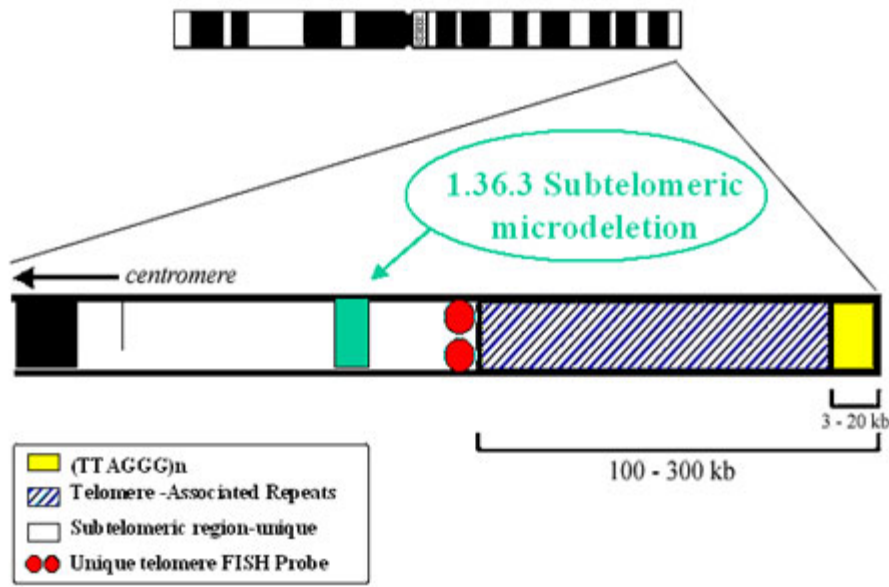
Figure 3. Newborn with 1p36.3 microdeletion

Figure 4. Newborn with 1p36.3 microdeletion

Figure 5

Figure 5. Newborn with 1p36.3 microdeletion

Close

Figure 6

Figure 6. Newborn with 1p36.3 microdeletion

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As part of your collaboration with maternal-fetal medicine, you have prenatal consultations with women in the high-risk clinic, some of whom have a history of congenital heart disease. Many of the mothers' concerns revolve around the risk of congenital heart disease in their children.

Of the following, the maternal cardiac lesion MOST likely to be associated with congenital heart disease in an offspring is

1 anomalous pulmonary venous connection

2 atrioventricular septal defect

3 Ebstein anomaly of the tricuspid valve

4 tetralogy of Fallot

5 transposition of the great arteries

You selected **2**, the correct answer is **2**.

Children of parents who have a history of congenital heart disease (CHD) have an increased risk of having CHD. The overall risk ranges from 2.7% to 10.7% among different studies. In a study by Gill et al of 6,640 patients referred for fetal echocardiography based on family history, recurrence was noted 2.7% of the time and was similar for fetuses whose index case was the mother, the father, or another sibling . One population-based survey by Whittemore et al found a 10.7% risk among offspring, and a British collaborative study by Burn et al found that risk for offspring was 4.1% and 2.1% for siblings. The latter study found recurrence higher after maternal CHD (5.7%) than after paternal CHD (2.2%).

Although series and overall population data help in establishing some degree of increased risk, family history may refine your counseling. If CHD is part of a syndrome or chromosomal abnormality, recurrence risk of the underlying condition best reflects prognosis. If no genetic syndrome is recognized, the overall recurrence rate is 7%. If the cardiac anomaly is isolated, recurrence varies with the lesion and the severity of the lesion in the proband (more severe lesions have higher recurrence). In most studies, maternal CHD was more likely to recur than paternal. Recurrence is increased further if other first-degree relatives are affected.

Recurrence risk varies according to the specific anomaly of the affected parent. In the Gill et al fetal echocardiography study, a parent who had atrioventricular septal defect had a 7.8% risk, whereas a 10% risk was noted by Burn et al. These data are contrasted to lower risks for Ebstein anomaly (6%), anomalous pulmonary venous connection (3.7%), and tetralogy of Fallot (3.8%). Whereas no recurrences were noted with maternal d-transposition in the study by Burn et al, earlier reports found the risk to be in the 5% range. Recurrence risks for various lesions are noted in the Table. Recurrence rates vary considerably due to the relatively small numbers in most series, suggesting these rates be used to convey increased risk rather than to provide a more exact estimate.

If an offspring does have CHD, the risk for concordant CHD (having the same lesion as the parent) varies by the lesion as well. Ventricular septal defect has the highest concordance rate (55%), followed by hypoplastic left heart (33%), and coarctation of the aorta (13%).

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Content Specifications:

Know the effects of maternal cardiac disease and its treatment on the fetus

Understand the pathophysiology, including genetics, of a cyanotic neonate

Understand the pathophysiology, including genetics, of a neonate with a left-to-right shunt lesion

Understand the pathophysiology, including genetics, of a neonate with a left-sided cardiac obstructive lesion

Understand the pathophysiology, including genetics, of a neonate with a right-sided cardiac lesion

PREVIOUS   NEXT

Table

Table: Recurrence risk to offspring of mothers with congenital heart disease

Lesion	Recurrence risk-offspring(%)	Reference(s)
Aortic stenosis	1.2, 5-11.5	Driscoll, Hoffman
Atrial septal defect	4-14	Hoffman
Atrioventricular septal defect	5-10, 10	Hoffman, Burn
Coarctation of aorta	3-8	Hoffman
Double outlet right ventricle	4	Hoffman
Ebstein anomaly	5, 6	Hoffman, Perloff
Hypoplastic left heart	5-13.5	Hoffman
Hypoplastic right heart	5	Hoffman
Patent ductus arteriosus	3-11	Hoffman
Pulmonic stenosis (valvular)	6-9, 2.8	Hoffman, Driscoll
Single ventricle	5	Hoffman
Tetralogy of Fallot	4, 3.1	Hoffman, Burn
Total anomalous pulmonary venous return	5	Hoffman
Transposition (d)	5	Hoffman
Truncus arteriosus	7.7	Hoffman
Ventricular septal defect	4-22, 2.9	Hoffman, Driscoll

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A 4-hour-old male newborn, whose birthweight is 700 g and whose estimated gestational age is 24 weeks, is placed in a radiant warmer. His axillary temperature is 36.8°C, and the ambient humidity around the infant is 80%. He is receiving intravenous fluids through an umbilical arterial catheter and assisted ventilation with a conventional mechanical ventilator. He is not receiving any enteral feeds at this time. You are estimating the fluid intake required to maintain an appropriate water balance in this infant.

Of the following, the PRINCIPAL determinant of water balance in this infant is

1	respiratory water output
2	stool water output
3	transepidermal water output
☒ 4	urinary water output
5	water output through sweat

You selected **4**, the correct answer is **3**.

Water balance is determined as water intake minus water output. The components of the water balance are shown in the **Figure**. The intake in the assessment of water balance is determined by exogenous intake of water and endogenous production of water (water of oxidation), largely produced through metabolism of carbohydrate, fat, and protein. The exogenous intake of water can be controlled with the rate of fluid administration, whereas the water of oxidation is relatively difficult to influence and is estimated at 10 mL/kg per day in a preterm infant whose metabolic status is normal. The output in the assessment of water balance is determined by insensible water output (transepidermal and respiratory), urinary water output, stool water output, and water output through sweat. One additional component that can be included in output is growth water retention, which represents water deposited in body tissues during growth; it is estimated at 10 mL/kg per day in a preterm infant whose growth is normal. Because water of oxidation and growth water retention affect the water balance nearly equally in opposite directions, these components may be omitted in the assessment of water balance.

The principal determinant of water balance in the preterm infant described in this vignette is transepidermal water output, which represents evaporative water loss from the skin to the ambient air by diffusion. The rate of evaporation is directly proportional to the concentration gradient of water between the skin and the ambient air, and it is inversely proportional to the resistance to diffusion of water both in the skin and the ambient air. Mathematically, this relationship can be expressed as:

$$E = [Pvs - Pva] / [Rs + Ra]$$

in which: E represents evaporation rate; Pvs, water vapor density of skin; Pva, water vapor density of ambient air; Rs, resistance of skin to diffusion of water; and Ra, resistance of ambient air to diffusion of water. The transepidermal water loss (TEWL) is excessive in the preterm infant largely because of skin immaturity and large surface area of the skin relative to body weight. The immaturity of the skin is reflected in the lack of development of stratum corneum and its keratinization. Although keratinization begins as early as 18 weeks' gestation in the human fetus, the neonatal epidermis is extremely thin at 24 weeks, and the stratum corneum is barely visible. The stratum corneum is not developed fully until 34 weeks' gestation. The TEWL in an infant born at 24 weeks' gestation is estimated at 140 mL/kg per day at an ambient humidity of 50% in the first 2 days after birth. It decreases significantly by

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postnatal day 3 to approximately 100 mL/kg per day and by postnatal day 28 to approximately 50 mL/kg per day. The TEWL in an infant born at 32 weeks' gestation is estimated at 12 mL/kg per day, similar to that observed in a term infant.

In addition to gestational age and postnatal age, the key infant variables that influence TEWL include body temperature and posture. A high body temperature increases TEWL by inducing peripheral vasodilatation, and assumption of an extended (spread-eagled) posture, rather than a flexed fetal posture, can augment TEWL by increasing the exposed skin surface area. The key environmental variables that influence TEWL include ambient humidity and heat source. In infants born at 26 weeks' gestation or less, a reduction in ambient humidity from 60% to 20% can increase TEWL by as much as 100%, whereas maintenance of ambient humidity above 90% can minimize TEWL. A radiant heat source can increase TEWL by 50% to 200%. Likewise, exposure to phototherapy can increase TEWL by as much as 30%. The environmental approaches that can be implemented to decrease TEWL include control of air currents and application of skin barriers. Circumferential placement of plastic walls around the infant can reduce TEWL by decreasing air turbulence. Topical application of water-impermeable skin barriers, such as soft paraffin or emollient ointments, can reduce TEWL.

Respiratory water output represents evaporative water loss from the respiratory epithelium to the ambient air during ventilation. It accounts for approximately one-third of the total insensible water loss. The rate of evaporation is directly proportional to the concentration gradient of water between the expired air and the inspired air as well as to the minute ventilation, and inversely proportional to the body surface area. Mathematically, this relationship can be expressed as:

$$E = [(P_e - P_i) \times V_{[DC1]}] / [60A],$$

in which E represents evaporation rate; P_e, water vapor density of expired air; P_i, water vapor density of inspired air; $V_{[DC2]}$, minute ventilation (product of tidal volume and respiratory rate); 60, factor to convert time to seconds; and A, body surface area. The key variables that influence respiratory water loss include humidity of ventilated gases and minute ventilation. An increase in relative humidity of inspired gases can decrease respiratory water loss. Conversely, any lung disease associated with an increased respiratory rate and/or tidal volume can increase respiratory water loss.

Stool water output in neonates is estimated at 5 to 10 mL/kg per day, which is approximately one-tenth of urinary water output. The stool water output is increased in breast-fed infants, in conditions such as diarrhea and malabsorption, and with exposure to phototherapy. The stool water output is decreased in infants whose enteral feedings are not established, as in the infant in this vignette.

Urinary water output in neonates is estimated at 50 to 100 mL/kg per day, assuming normal renal function. The volume of water excreted in the urine is influenced by the renal solute load and the ability of the kidney to concentrate or dilute the urine. The renal solute load is determined by dietary intake of solute (potential renal solute load) minus sparing effect of growth (actual renal solute load). The potential renal solute load can be estimated from dietary intake as follows: 5.7 mOsm per gram of protein; 1 mOsm each per milliequivalent of sodium, potassium, and chloride; and 1 mOsm per 30 mg of phosphorus. The actual renal solute load can be estimated by subtracting from potential renal solute load 1 mOsm per each gram of weight gain. Typical potential renal solute load in neonates is calculated to be approximately 30 mOsm/kg per day. Typical actual renal solute load in rapidly growing neonates is calculated to be approximately 15 mOsm/kg per day. A urine osmolality between 75 and 300 mOsm/kg is desirable in neonates as it indicates that renal concentrating and diluting mechanisms are not being stressed. Within the typical range of urine solute excretion (7.5 - 15.0 mOsm/kg per day) and within the desirable range of urine osmolality (75 - 300 mOsm/kg), the required water loss in the urine is between 50 and 100 mL/kg per day.

In contrast to term neonates, preterm infants sweat later in the postnatal period, sweat at fewer body sites, sweat less, and require a higher degree of thermal stimulus for the sweating response. Water output through sweat, therefore, is minimal in preterm neonates and may be omitted in the assessment of water balance.

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Hammarlund K, Sedin G. Transepidermal water loss in newborn infants: III. Relation to gestational age. *Acta Paediatr Scand.* 1979;68:795-801.

Modi M. Management of fluid balance in the very immature neonate. *Arch Dis Child Fetal Neonatal Ed.* 2004;89:F108-F111.

Roy RN, Sinclair JC. Hydration of the low birth-weight infant. *Clin Perinatol.* 1975;2:393-417.

Saigal S, Sinclair JC. Urine solute excretion in growing low-birth-weight infants. *J Pediatr.* 1977;90:934-938.

Content Specifications:

Recognize environmental and other factors that increase insensible water loss (IWL)

Know therapeutic interventions that can be used to lower IWL

Be aware of the influence of gestational age on water requirement

Be aware of the influence of thermal environment on water requirement

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[DC2]inser dot over v
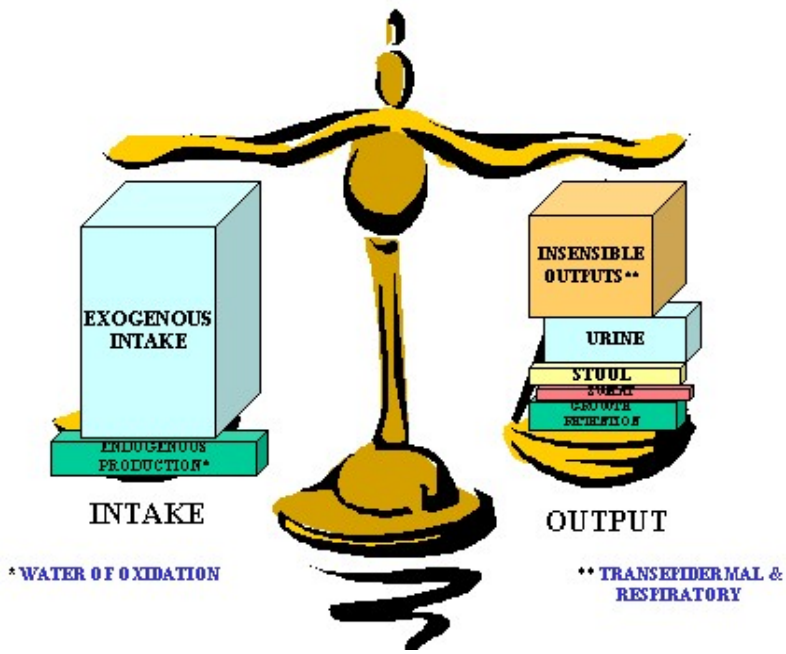
EXOGENOUS
INTAKE

ENDOGENOUS
PRODUCTION*

INTAKE

* WATER OF OXIDATION

INSENSIBLE
OUTPUTS **

URINE

STOOL

SWEAT

GROWTH
RETENTION

OUTPUT

** TRANSEPIDERMAL &
RESPIRATORY

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A 26-weeks'-gestation premature infant is receiving mechanical ventilation for respiratory distress syndrome in your NICU. The infant likely will be subjected to multiple noxious interventions over the ensuing days. Pursuant to the recommendations of the American Academy of Pediatrics, a pain score using the Premature Infant Pain Profile (PIPP) is recorded along with vital signs. You are considering a continuous intravenous infusion of morphine for pain prevention..

Of the following, the MOST likely outcomes from continuous prophylactic morphine infusion versus episodic pain treatment are:

1 pain scores reduced moderately and no effect on incidences of death, severe intraventricular hemorrhage (IVH), or periventricular leukomalacia (PVL)

2 pain scores reduced moderately plus reduced incidences of severe IVH and PVL

3 pain scores reduced substantially and no effect on incidences of death, severe IVH, or PVL

4 pain scores reduced substantially plus reduced mortality

5 pain scores reduced substantially plus reduced incidences of severe IVH and PVL

You selected 5 , the correct answer is 1 .

The American Academy of Pediatrics issued a joint statement with the Canadian Paediatric Society entitled "Prevention and Management of Pain and Stress in the Neonate," recommending to a) evaluate and reduce the stress and pain experienced by neonates, b) use environmental as well as pharmacological methods to reduce pain and stress, c) use analgesics with known pharmacokinetics and dynamics in the neonate, and d) develop and implement pain management policies in neonatal units. Preliminary information from small studies indicated that continuous prophylactic morphine infusions might reduce mortality, intraventricular hemorrhage (IVH), and periventricular leukomalacia (PVL) in infants such as the one in this vignette. A large, multicenter, randomized trial, the NEOPAIN Trial, was carried out to evaluate these early findings.

The NEOPAIN trial enrolled 898 preterm infants between 23 weeks' gestation and 32 weeks' gestation who were intubated prior to age 72 hours and had been ventilated for less than 8 hours before enrollment. Infants were randomized to morphine or placebo infusions. They received a loading dose (100 mcg/kg infused over 1 hour for the morphine group) followed by a continuous infusion of drug or placebo. The infusion was continued for up to 14 days. This trial demonstrated a modest reduction in the pain score (8 for the morphine group, 8.77 for controls, p=0.0034). There was no statistical difference between groups for mortality or in the incidences of severe IVH (grades III and IV) or PVL.

The NEOPAIN Trial suggests that a protocol-based approach for pain control among all ventilated preterm neonates might not be appropriate because of the marked variability of the population. Instead, a more targeted use of powerful analgesics to prevent severe pain is recommended. Long-term effects of routine continuous morphine analgesia would be important to know but have not been assessed so far.

References:

American Academy of Pediatrics Committee on Fetus and Newborn, Committee on Drugs, Section on Anesthesiology, Section on Surgery, Canadian Paediatric Society Fetus and Newborn

Committee. Prevention and management of pain and stress in the neonate. *Pediatrics.* 2000;105:454-461

Anand KJS, Hall RW, Desai N, et al, for the NEOPAIN Trial Investigators Group. Effects of morphine analgesia in ventilated preterm neonates: primary outcome from the NEOPAIN randomised trial. *Lancet.* 2004;363:1673-1682

Stevens V, Johnston C, Petryshen P, Taddio A. Premature infant pain profile: development and initial validation. *Clin J Pain.* 1996;12:13-22.

Content Specification:

Know the importance, recognition, and management of neonatal pain

PREVIOUS   NEXT

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In the delivery room, you begin resuscitation of a term female infant who has apnea, bradycardia, and hypotonia. No meconium was present in the amniotic fluid. You have positioned, dried, and suctioned the nose and mouth as well as provided tactile stimulation. However, her heart rate is 50 beats per minute. You begin positive pressure ventilation (PPV) with a bag and mask.

Of the following, the MOST important clinical indicator of adequate ventilation is

1. chest rise

❌ 2. color

3. heart rate

4. muscle tone

5. skin perfusion

You selected 2, the correct answer is 3.

The most important step in resuscitation of the depressed, newly born infant (heart rate <100 beats per minute, apnea or gasping respiration, hypotonia) is ventilation of the lungs. The most important response to positive pressure ventilation (PPV) is an immediate rise in heart rate. The infant in the vignette is expected to have a rapid rise in heart rate after ventilation is established. Evidence for interventions during neonatal resuscitation often is limited to comparative animal studies and consensus of opinion. Evidence that supports the heart rate response as the most important clinical indicator of response to PPV is based on animal experiments performed during the early 1960s (Figure). In these cardiorespiratory studies, changes in heart rate, breathing, and blood pressure were recorded. A rapid heart rate increase after initiation of bag and mask ventilation is followed by a gradual blood pressure increase and subsequent spontaneous respiration. Heart rate response as the most important clinical indicator of adequate ventilation is different from the frequently taught concept that chest rise is most important. Avoiding the risks associated with large tidal volume ventilation (pneumothorax and bronchopulmonary dysplasia) is an important goal that favors heart rate increase as the preferred indicator of response to PPV.

Chest rise during PPV is an indication that ventilation of the lungs is occurring. With inadvertent overventilation, the risks of volutrauma and barotrauma causing pneumothorax or initiating bronchopulmonary dysplasia in very preterm infants has caused clinicians to reassess the physiologic responses to, and technique of, ventilation with a resuscitation bag. Therefore, these risks of PPV and data from animal experiments indicate that a rapid heart rate increase, rather than chest rise, is a better indicator of adequate ventilation.

Mucus membrane color is an immediate clinical indicator of oxygenation. It follows that color will change from cyanotic to pink during the first minutes after birth in the healthy, spontaneously breathing newborn. Likewise, during PPV of an infant with bradycardia, apnea, and hypotonia, this transition to pink occurs only after ventilation of the lung with gas and establishment of cardiac output to the pulmonary and systemic circulations, both primary factors in oxygen delivery to tissues. In the neonate, heart rate appears to be more important than stroke volume to increase cardiac output.

Improved muscle tone is a sign that oxygen delivery to the brain has improved. Improved skin perfusion, on the other hand, is a sign that oxygen delivery to other organ systems also has improved. Resolution of hypotonia and improved skin perfusion are expected to follow

improvements in heart rate, establishment of lung volume and ventilation of the lung in the infant in the vignette.

References:

Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease in low birth weight infants preventable? *Pediatrics.* 1987;79:26-30

Boyle DW. Initial ventilation strategies during ventilation of the newborn in the delivery room [2005 International Consensus on CPR and ECC Science with Treatment Recommendations Web site]. C2005 Evidence Evaluation Worksheets, Neonatal Life Support. Available at http://www.americanheart.org/presenter.jhtml?identifier=3026625 Accessed Jan. 25, 2005

Dawes GS. *Birth asphyxia, resuscitation and brain damage.* Chicago, IL: Year Book Medical Publisher Inc. 1968:141-159

Kattwinkel J, ed. *Textbook of Neonatal Resuscitation American Academy of Pediatrics and American Heart Association.* 4th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2000:1.1-1.22

Van Marter LJ, Allred EN, Pagano M, et al. Do clinical markers of barotrauma and oxygen toxicity explain interhospital variation in rates of chronic lung disease. *Pediatrics.* 2000;105:1194-1201

Heart Rate, Blood Pressure and Breathing after Asphyxia
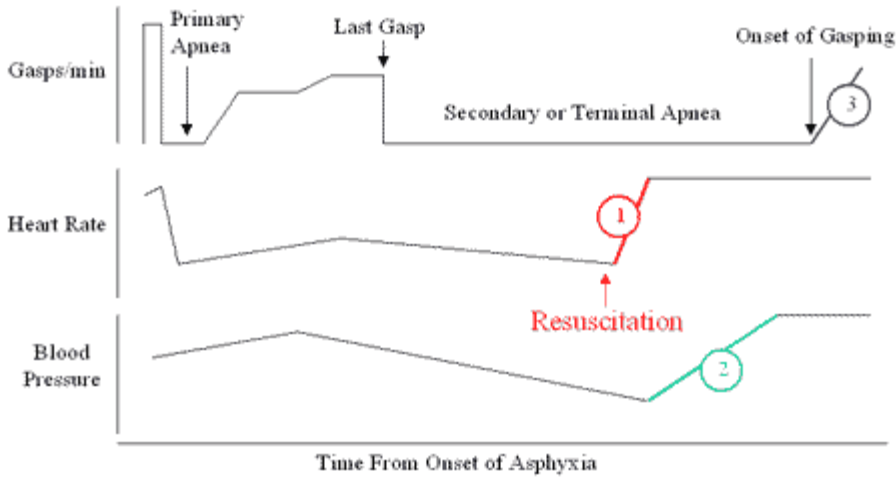
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A 760-g female infant was born after 26 weeks' gestation to a 33-year-old woman who was admitted in preterm labor with uterine tenderness and a low-grade fever. The mother was treated with antibiotics (but not gentamicin) as well as a full course of betamethasone before a cesarean delivery due to poor fetal tolerance of labor. The infant had poor tone at birth and received Apgar scores of 1 and 7 at 1 and 5 minutes, respectively. Because of an abnormal white blood cell count and the chest radiograph consistent with congenital pneumonia, a 7-day course of ampicillin and gentamicin was initiated. The initial gentamicin dose of 5 mg/kg was given intravenously over 30 minutes. Gentamicin concentrations were measured 30 minutes after the end of the first 30-minute infusion and 24 hours later. The respective values were 16.3 mcg/mL and 5.1 mcg/mL. Upon receiving these values, you calculate the volume of distribution (V_d) and the elimination half-life ($t_{1/2}$) to decide on future dosing.

Of the following, the PREFERRED dose of gentamicin for this infant is:

1	2.6 mg/kg every 48 hours
✗ 2	2.6 mg/kg every 60 hours
3	4.2 mg/kg every 72 hours
4	5 mg/kg every 48 hours
5	5 mg/kg every 72 hours

You selected **2**, the correct answer is **1**.

It is important to individualize gentamicin dosing if it is planned for more than a few days, because there is considerable variation in the volume of distribution and the rate of drug elimination among patients in general and sick premature infants in particular. Peak and trough values that are regularly too high can lead to nephrotoxicity and ototoxicity. On the other hand, concentrations that are too low may be inadequate to treat the infection. Published guidelines for starting gentamicin were followed in this vignette, but confirmation via peak and trough concentrations is important for safe dosing. The same guidelines recommend that peak concentrations be maintained between 5 and 12 mcg/mL and trough concentrations between 0.5 and 1 mcg/mL.

The volume of distribution (V_d) is a theoretical volume of diluent that would be needed to obtain the observed rise in drug concentration after a known dose. In the vignette, the infused dose (D) of 5 mg/kg (or 5000 mcg/kg) resulted in a peak concentration (C_p) of 16.3 mcg/mL. The mathematical expression for V_d is seen in the formula:

$$V_d = \frac{D}{C_p} = \frac{5000\ mcg/kg}{16.3\ mcg/ml} = 306.75\ ml/kg$$

Because the volume of distribution is a theoretical one, it does not represent a specific fluid or body space. In the case of a drug like digoxin, where cardiac receptors bind much of the dose, the apparent V_d greatly exceeds the size of the infant.

One should readjust the dose in this vignette to produce a peak concentration around the midpoint of the recommended range (ie, 8.5 mcg/mL). The V_d could be used to calculate a new dose, but this is not needed because V_d would be represented on both sides of the equation

and would cancel out. Instead, a simple proportion can be used (Figure 2).

The preferred dosing interval then can be determined by calculating the constant of elimination (k_{elim}) and the half-life ($t_{1/2}$). The half-life is defined as the time it takes for the drug concentration to fall to half of its previous value. Two ways can be used to estimate $t_{1/2}$, given peak and trough values. First, one could simply plot the concentrations versus time. Gentamicin, however, is eliminated from the body primarily through glomerular filtration, and the amount leaving the body per hour is proportional to its concentration. This produces an exponential curve when plotted on linear paper (ie, first-order kinetics) and two points alone would be inadequate to reproduce the whole curve. To transform the excretion rate into a straight line, the logs of the concentrations are plotted against time. This can be accomplished without calculations by using semi-log paper (see references and Figure 3) and finding the time at which the initial concentration falls to half. The second way is through mathematics. The mathematical formulae are seen in figure 4.

In our vignette, gentamicin concentration will reach the recommended trough concentration of 0.5 to 1 mcg/mL around 60 hours after the 5 mg/kg dose. When the lower dose (2.6 mg/kg) is given, it will take about 48 hours for the concentration to return to these values (Table).

References:

Chambers HF. The aminoglycosides. In: Hardman JG, Limbird, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 10th ed. New York, NY: McGraw Hill; 2001:1219-1238

The following links, accessed March 2, 2005, give details about V_d and $t_{1/2}$ and provide a semi-log plot for printing:

http://www.rxkinetics.com/pktutorial/2_4.html

http://www-users.med.cornell.edu/~spon/picu/calc/halfcalc.htm

http://www.csun.edu/~vceed002/ref/measurement/data/graphpaper/4-cycle_semi-log.pdf

Young TE, Mangum B. *Neofax: A Manual of Drugs Used in Neonatal Care.* 16th ed. Raleigh, NC: Acorn Publishing; 2003:4-35

Content Specifications:

Understand the factors involved in the distribution of a drug (ie, factors influencing peak serum concentrations of a drug)

Understand the mechanisms by which various drugs are excreted

Understand basic pharmacokinetics and basic pharmacokinetic definitions, including the basic definitions of linear (single compartment) and nonlinear (multiple compartment) pharmacokinetics

Understand the definitions of drug dose, serum concentrations, and volume of distribution, and how these values are related mathematically

Know how to calculate a drug dose to achieve a specific serum concentration

Know how to use serum drug concentrations to adjust the dosing regimen of a drug eliminated by first-order kinetics

Understand the definitions of drug half-life, elimination rate constant, and clearance, and know how these values are related mathematically
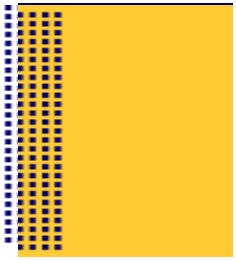
Figure 2

Figure 2: Calculating dose from trial peak value

$$\text{Dose (desired)} = \frac{\text{Dose (trial)} \times \text{Peak (desired)}}{\text{Peak (trial)}} = \frac{5 \text{ mg/kg} \times 8.5 \text{ mcg/ml}}{16.3 \text{ mcg/ml}} = 2.6 \text{ mg/kg}$$

Figure 3: Hand drawing of semi-log plot of peak and trough concentrations. T1/2 is indicated.
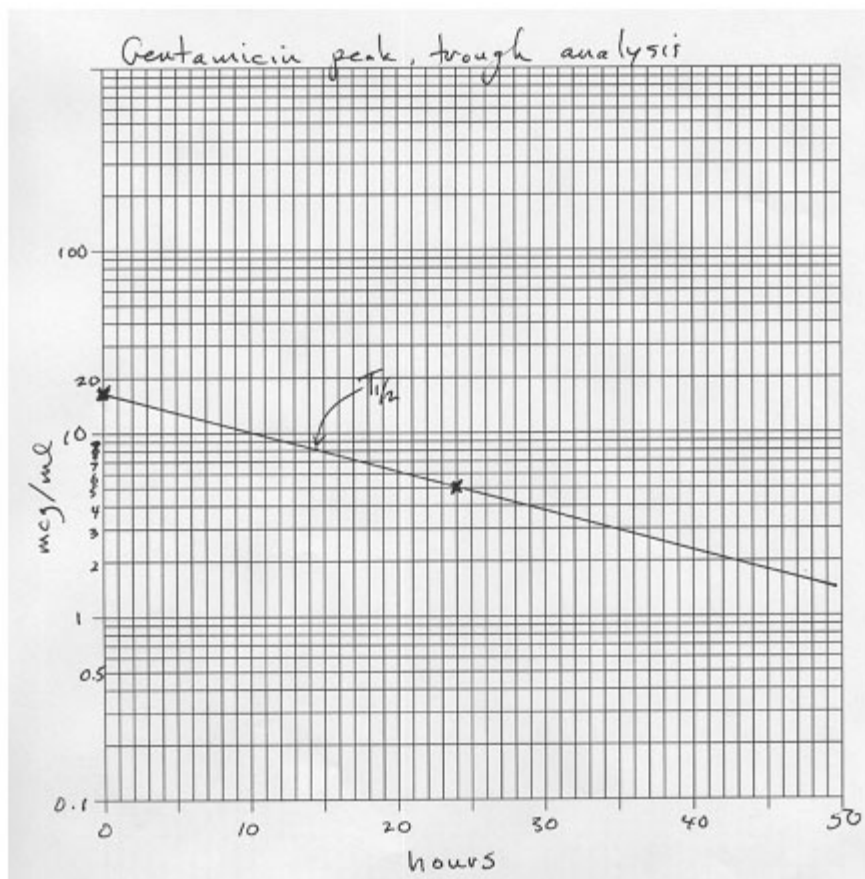
Figure 4. Calculating the $t_{1/2}$ from peak and trough values

$$k_{elim} = \frac{\ln(C_{peak}) - \ln(C_{trough})}{t_{interval}} = \frac{2.79 - 1.63}{24 \text{ hrs.}} = 0.048$$

$$t_{1/2} = \frac{0.693^*}{k_{elim}} = 14.4 \text{ hrs.}$$

$$^* \ 0.693 = \ln(2)$$

Table: Time course of drug elimination starting at the two peak values:
8.5 mcg/ml (desired) and 16.3 mcg/ml (observed) given t1/2 = 14.4 hours

Half-lives	Hours*	Gentamicin Conc. (mcg/ml)	
0	0	8.5	16.3
1	14.4	4.3	8.2
2	28.8	2.1	4.1
3	43.2	1.1	2.0
4	57.6	0.5	1.0
5	72.0	0.3	0.5
6	86.4	0.1	0.3

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A 37-year-old woman with three normal children opts for chorionic villus sampling due to advanced maternal age.   An abnormal chromosomal pattern is noted.

Of the following, the chromosomal pattern MOST likely to result in early fetal loss is:

1. monosomy X (45, X)

2. triploidy (69)

3. trisomy 16 (47, +16)

4. trisomy 18 (47, +18)

5. trisomy 21 (47, +21)

You selected 5, the correct answer is 3.

Although never seen among live newborns, trisomy 16 is the most prevalent of the autosomal trisomies noted among abortuses. Of the 50% of spontaneous abortuses found to have chromosomal abnormality, about one-half have an autosomal trisomy. Autosomal trisomy is a major contributor to increased pregnancy loss associated with advanced maternal age. Most trisomies result from errors in maternal meiosis (stage 1). Trisomies involving every autosome except chromosome 1 have been documented in abortuses. Prognosis depends on the specific chromosome involved, with uniform early loss with trisomy 16.

Monosomy X is noted in 19% of chromosomally abnormal abortuses. Some 99% of 45, X embryos will succumb in the first or early second trimester; 1% of embryos survive and present with the Turner syndrome phenotype (short stature, shield chest, webbed neck, hypoplastic nails, short 4th metacarpal, cubitus valgus, lymphedema, ovarian dysgenesis, and congential heart abnormalities). This pattern is not associated with advanced maternal age and is thought to result from anaphase lag during meiosis or mitosis.

Triploidy results from the embryo receiving a full set of extra chromosomes. Diandric triploidy is the more common variant (90%), resulting from fertilization of a single egg by two sperm or by a diploid sperm. In this variant, fetal size is mildly restricted, fetal head size is normal or slightly microcephalic, and the placenta is large with partial hydatidiform mole. Digynic triploidyresults from fertilization of a diploid ovum. This variant is less common (10%), results in a severely growth restricted macrocephalic fetus, and is associated with a small, noncystic placenta. Although most triploid fetuses die in utero, occasional live births occur (mostly digynic) with death coming in early infancy. Long-term survival has not been reported. No data support an increased recurrence risk in subsequent pregnancies.

Trisomy 18 occurs in 1 in 5,500 live births, making it the second most common autosomal trisomy detected in live births. Three quarters of affected infants are female. As with the other autosomal trisomies, it is associated with advanced maternal age, and 90% are due to meiotic nondisjunction. Translocation trisomy 18 is rare. Neonatal mortality is high and infant mortality is 90% to 95%. Survivors have severe developmental retardation. Recurrence risk for subsequent fetuses is estimated at 1%, but less than 1% of subsequent live-born siblings will be affected due to early fetal loss of many trisomy 18 embryos.

Trisomy 21 is the most commonly detected autosomal trisomy among midtrimester amniocenteses and live-born infants, occurring in 1 in 730 live births. Of trisomy 21 fetuses detected early in gestaion, one-third survive to term. Nondisjunction during maternal meiosis underlies 95% of cases, and 5% result from abnormal spermatogenesis.

References:

Down syndrome (Trisomy 21). In: *Smith's Recognizable Patterns of Human Malformation.* 5th ed. Philadelphia, Pa: Saunders; 1997:8-13

Hsu LY. Cytogenetic abnormalities in the embryo, fetus and infant. Available at http://www.uptodate.com (subscription required). Accessed March 28, 2005

Petrozza JC, O'Brien B. eMedicine: early pregnancy loss. Available at http://www.emedicine.com/med/topic3241.htm. Accessed April 15, 2005

Singh D, Singh JR. eMedicine: prenatal diagnosis for congenital malformations and genetic disorders. Available at http://www.emedicine.com/oph/topic485.htm. Accessed April 15, 2005

Triploidy syndrome and Diploid/Triploid Mixoploidy syndrome. In: Jones KL. *Smith's Recognizable Patterns of Human Malformation.* 5th ed. Philadelphia, Pa: Saunders; 1997:30-31

Trisomy 18 syndrome. In: Jones KL. *Smith's Recognizable Patterns of Human Malformation.* 5th ed. Philadelphia, Pa: Saunders; 1997:14-15

XO syndrome. In: Jones KL. *Smith's Recognizable Patterns of Human Malformation.* 5th ed. Philadelphia, Pa: Saunders; 1997:81-83

Content Specifications:

Understand the implications of a prenatal diagnosis of sex chromosome aneuploidy for the long-term developmental outcome of an infant

Know fetal and placental manifestations of triploidy

PREVIOUS   NEXT

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You are viewing the autopsy of a term male infant who died six days after birth. He was admitted for cyanosis secondary to persistent pulmonary hypertension. The infant was born by emergent cesarean section for severe fetal bradycardia; amniotic fluid was meconium-stained. Cyanosis at birth was treated with 100% oxygen, high-frequency oscillation, inhaled nitric oxide and sedation. Pre- and postductal SaO_2s were 76%. Chest radiograph showed a mildly enlarged heart and dark lung fields. Echocardiogram two hours after birth was reported to show right-to-left shunting at the atrial level, bowing of the ventricular septum into the left ventricle, right ventricular hypertrophy and tricuspid valve jet indicative of suprasystemic pulmonary arterial pressure. The study was abbreviated because of worsening hypoxemia (SaO_2, 63%).

Transfer arrangements were made for extracorporeal membrane oxygenation (ECMO), which was initiated emergently upon arrival in your neonatal intensive care unit. Within minutes, perfusion worsened, pulse pressure narrowed to less than 5 torr and blood pressure measured in an umbilical arterial catheter fell to 31 mmHg. Repeat echocardiogram indicated poor biventricular function and findings not visualized previously. The infant's parents requested withdrawal of ECMO, and the infant died within minutes.

Gross inspection of the heart revealed a small hypertrophied right ventricle, thickened and nodular coronary arteries, dimples on the epicardial surface (consistent with ventriculocoronary sinusoidal connections), and absent coronary artery origins from the proximal aorta.

Of the following, the autopsy diagnosis MOST likely to be confirmed in this infant is:

1. pulmonary atresia with intact ventricular septum

2. total anomalous pulmonary venous return

3. transposition of the great arteries

4. tricuspid atresia with ventricular septal defect

5. truncus arteriosus

You selected 5, the correct answer is 1.

The infant in the vignette is most likely to have pulmonary atresia with intact ventricular septum (PA-IVS). This condition accounts for only 1% to 3% of all congenital heart defects, although it is one of the more frequent defects that presents as cyanosis in neonates. A variable spectrum of findings is included in this disorder, with two predominant pathophysiologic patterns categorized as either Type I or Type II. Type I pulmonary atresia with intact septum is characterized by the association of abnormal ventriculocoronary sinusoidal connections, abnormal coronary artery anatomy, atretic pulmonary valve, competent tricuspid valve, small hypertrophied right ventricle with suprasystemic pressure and, in some cases, right ventricular-dependent coronary artery circulation. Type II is characterized by anomalous tricuspid valve and insufficiency, retrograde blood flow through the right atrium and atrial septal defect, and a normal or dilated, thinned, low-pressure right ventricle. Type II may be associated with hydrops fetalis and fetal loss when severe tricuspid insufficiency is present in utero.

Type I PA-IVS is anticipated in the repeat echocardiogram and autopsy of the infant in the vignette. In Type I, myocardial dysfunction or infarction occurs due to venous blood supplying an abnormal coronary circulation; this is worsened with unloading of the right ventricular pressure head that drives coronary perfusion. Right ventricular pressure was acutely decreased during initiation of ECMO in the infant in this vignette. This coronary artery steal phenomenon is better understood by tracing the circulation of venous blood from the hypertrophic blind right

ventricle in patients with Type I PA-IVS. Suprasytemic pressure in the blind right ventricle functions to force venous blood into intramyocardial sinusoids that anastomose with the coronary artery circulation. The high blood flow through the coronary arteries induces morphologic changes characterized by endothelial irregularity, stenosis and obstruction. Coronary artery blood then flows into the coronary veins, coronary sinus and right atrium. From the right atrium, venous blood flows through the anomalous tricuspid valve back into the hypertrophic right ventricle thereby completing a circular pattern of blood flow. This pattern does not include flow through the lung. The result is desaturated blood flowing through the coronary circulation. If the anomalous coronary circulation is only perfused by right ventriculocoronary sinusoids and not supplemented from a source of oxygenated blood (left to right shunt through an atrial septal defect or patent foramen ovale), a high risk for myocardial ischemia exists.   This ischemic risk is increased because of coronary artery stenosis and obstruction.

In the infant in the vignette, the cause for cyanosis was thought to be persistent pulmonary hypertension of the newborn due to a history of fetal distress, meconium-stained amniotic fluid, cyanosis and suggestive echocardiographic evidence. However, the infant developed severe myocardial dysfunction soon after beginning venoarterial extracorporeal membrane oxygenation (VA ECMO). Myocardial dysfunction after initiation of VA ECMO most often is due to myocardial stun, the mechanism of which is unknown. Myocardial stun is also more common during venoarterial rather than venovenous cardiopulmonary bypass. The mechanism for the rapid onset of myocardial dysfunction in the infant in this vignette with PA-IVS is an acute reduction in driving pressure and blood flow into the right ventricular-dependent coronary circulation during ECMO initiation. This acute decrease in coronary blood flow in a coronary circulation already compromised by perfusion with poorly saturated venous blood precipitated severe myocardial dysfunction; in the infant in this vignette, the ischemia was considered lethal, and additional cardiovascular interventions were not undertaken.

This case is unusual but demonstrates the value of echocardiography before ECMO initiation. Although the clinical history and abbreviated initial echocardiogram suggested persistent pulmonary hypertension of the newborn, persistent low oxygen saturations and unresponsiveness to interventions, including ECMO, indicated that congenital heart disease was possible. ECMO also is used to stabilize some critically unstable infants with congenital heart diseases before surgical treatment. Most of these cardiac anomalies do not have right ventricular-dependent coronary blood flow so are not at high risk for myocardial ischemia when right ventricular pressure is reduced. Type I PA-IVS is also an uncommon form of congenital heart disease as is a right ventricular-dependent coronary circulation. The odds of this condition being present in the infant in this vignette are low. Although valuable, echocardiography may not identify ventriculocoronary sinusoidal connections and right ventricular-dependent coronary flow unless the sinusoidal connections are large. Cardiac catheterization often is required to establish this diagnosis as well as the coronary anatomy. The infant in this vignette was in extremis on arrival, so ECMO was initiated emergently before repeat echocardiography and catheterization could be performed.

Total anomalous pulmonary venous return, transposition of the great arteries, tricuspid atresia with ventricular septal defect and truncus arteriosus are congenital heart lesions that most often present as cyanosis during the neonatal period. None of these disorders is associated with right ventriculocoronary sinusoidal connections, coronary artery stenosis and obstruction and right ventricular-dependent coronary circulation. Therefore, none of these would be found on echocardiography or autopsy in the infant in this vignette.

An example of PA-IVS , demonstrated by right ventricular injection of dye during a cardiac catheterization of a child with pulmonary atresia and intact ventricular septum, is demonstrated on the video clip. Pause or slow the clip to notice retrograde filling of coronary vessels immediately after right ventricular injection in the lower right quadrant at the beginning of the clip. During the remainder of the clip, coronary vessels continue to be filled from the right ventricular-coronary connections (sinusoids in the right ventricular wall).

References:

Baschat AA, Love JC, Stewart PA, Bembruch U, Harman CR. Prenatal diagnosis of

ventriculocoronary fistula. *Ultrasound. Obstet Gynecol.* 2001;18:39-43

Freedom RM, Nykanen DG. Pulmonary atresia and intact ventricular septum. In: Allen HD, Clark EB, Gutgesell HP, Driscoll DJ, eds. *Moss and Adam's Heart Disease in Infants, Children, and Adolescents.* 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001:845-863

Joffe G, Izquierdo LA, Del Valle GO, et al. Pulmonary valve atresia with intact ventricular septum, Type 1. Available at http://www.thetetus.net/page.php?id=62. Accessed April 8, 2005.

*Videoclip compliments of Robert Darragh, M.D., Indiana University School of Medicine.

Content Specifications:

Plan appropriate management for a neonate with a right-sided cardiac lesion and understand the potential adverse effects of specific therapeutic approaches

Understand the pathophysiology, including genetics, of a neonate with a right-sided cardiac lesion

Recognize the lab and radiographic findings of an infant with a right-sided cardiac lesion

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A 3-day-old male infant, whose birth-weight was 720 g and estimated gestational age at birth 24 weeks, has evidence of periventricular-intraventricular hemorrhage on cranial ultrasonography (Fig. 1). At 4 weeks of age, the infant has a bulging anterior fontanel, slight separation of cranial sutures, and a gain in head circumference of 1.2 cm during the preceding week. A cranial ultrasonograph reveals slowly progressive ventricular dilatation (Fig. 2).

Of the following, the MOST appropriate treatment for prevention of hydrocephalus and need for ventriculo-peritoneal shunt in this infant is the use of:

1. carbonic anhydrase inhibitor

2. cerebrospinal fluid drainage

3. head wrapping

4. intraventricular fibrinolytic therapy

5. osmotic agent

You selected 2, the correct answer is 2.

Periventricular-intraventricular hemorrhage (PIVH) is classified, as suggested by Papile, into 4 grades based on its severity. In grade I, the hemorrhage is localized to the germinal matrix region in the thalamocaudate groove and does not extend into the ventricular cavity (Fig. 3). In grade II, the hemorrhage extends into the ventricular cavity, covers less than 50% of the ventricular area, and does not cause ventricular distension (Fig. 4). In grade III, the hemorrhage extends into the ventricular cavity, covers more than 50% of the ventricular area, and causes ventricular distension (Fig. 1). And in grade IV, the hemorrhage extends beyond the ventricular cavity into the brain parenchyma (Fig. 1). The risk of death increases with the severity of PIVH and so does the risk of post-hemorrhagic hydrocephalus among the survivors. The mortality rates in PIVH are approximately 5% in grade I, 10% in grade II, 20% in grade III, and 50% in grade IV. Among the survivors, the rates of post-hemorrhagic hydrocephalus needing ventriculo-peritoneal shunt are approximately 5% in grade I, 20% in grade II, 55% in grade III, and 80% in grade IV. The infant in this vignette, who has grade III PIVH in the left cerebral hemisphere and grade IV PIVH in the right cerebral hemisphere, is at substantial risk for the development of post-hemorrhagic hydrocephalus. The symptoms and signs of increased intracranial tension and the cranial ultrasonographic evidence of slowly progressive ventricular dilatation at 4 weeks of age in this infant suggest that spontaneous resolution of ventricular dilatation is unlikely and treatment for prevention of post-hemorrhagic hydrocephalus is warranted.

The most appropriate treatment for persistent and slowly progressive ventricular dilatation that does not resolve spontaneously within about 4 weeks of the occurrence of PIVH is the institution of cerebrospinal fluid (CSF) drainage. The rationale behind this treatment is that removal of blood products by early and repeated drainage of CSF may prevent or ameliorate the occlusion of arachnoid granulations to allow CSF absorption. Additionally, intermittent decompression of the ventricles from CSF drainage may improve cerebral blood flow and, at least temporarily, arrest the progression of ventricular dilatation to allow for the natural healing to occur. One of the methods of CSF drainage is the institution of sequential lumbar punctures. To be effective, the presence of communication between the ventricles and the lumbar subarachnoid space is critical. Also, a sufficient volume of CSF - estimated at approximately 10 mL/kg body weight - needs to be removed at each procedure. The frequency and duration of lumbar punctures are determined by the volume of CFS removed at each procedure, clinical evaluation of the infant for symptoms and signs of increased intracranial tension, cranial ultrasonographic evaluation of ventricular size, and other factors including the

stability of the infant during the procedure. The typical frequency of lumbar punctures is once at 24 hour intervals, and the typical duration is 2-3 weeks. The complications associated with sequential lumbar punctures include meningitis, ventriculitis, epidural abscess, vertebral osteomyelitis, and intraspinal epidermoid tumor. The latter is associated with the use of unstyletted needles while performing lumbar punctures. A large, multicenter, randomized trial, performed in mid-1980s, has shown a significant reduction in neuromotor disability among preterm infants who had PIVH with brain parenchymal involvement treated with sequential lumbar punctures as compared with those treated conservatively and expectantly. According to Volpe, sequential lumbar punctures performed under optimal conditions may prevent the development of post-hemorrhagic hydrocephalus and the need for ventriculo-peritoneal shunt in approximately 2/3rds of the survivors of PIVH with persistent and slowly progressive ventricular dilatation.

An alternative method of CSF drainage is the placement of a ventricular access device. This device is a small, flat-bottomed reservoir attached to a ventricular catheter. The reservoir is placed on the surface of the skull under the galea of the scalp. Percutaneous puncture of the reservoir with sequential aspiration of CSF serves to keep the ventricular system decompressed. The ventricular access device is used commonly as a temporizing measure pending the placement of a ventriculo-peritoneal shunt. The latter may be delayed to allow for infant growth as well as for clearance of CSF protein and cellular debris.

Head wrapping involves compression of the head by application of a tight bandage. Although historically documented, this approach does not have a sound rationale as a means for prevention of post-hemorrhagic hydrocephalus and is no longer implemented in clinical practice.

The rationale behind the use of a carbonic anhydrase inhibitor is that suppression of CSF production induced by this drug may control CSF accumulation and prevent or ameliorate ventricular dilatation. The carbonic anhydrase inhibitor, acetazolamide, causes a 50% reduction in CSF production, and when used in combination with a diuretic such as furosemide, can induce a nearly complete cessation of CSF production. The dosage of acetazolamide used in clinical trials has been100 mg/kg/d, and that of furosemide 1.0 mg/kg/d. The total duration of treatment has been 6 months. The complications of this treatment include metabolic acidosis and nephrocalcinosis. The furosemide promotes hypercalciuria by inhibiting renal tubular reabsorption of calcium, and the acetazolamide promotes precipitation of calcium salts in the renal tubules by inducing alkalinization of urine. The beneficial effect of acetazolamide in prevention of post-hemorrhagic hydrocephalus has not been established. On the contrary, a large, multicenter, randomized trial has shown a greater need for ventriculo-peritoneal shunt and increased neurodevelopmental disability among preterm infants treated with acetazolamide and furosemide as compared with those treated with sequential lumbar punctures. Thus, carbonic anhydrase inhibitor treatment as a means for prevention of post-hemorrhagic hydrocephalus following PIVH cannot be recommended.

The CSF following PIVH is low in plasminogen activity and has high concentrations of plasminogen activator inhibitor, conditions that are conducive to clot formation. Additionally, the CSF following PIVH has high concentrations of transforming growth factor-beta (TGF-beta), the key mediator of deposition of extracellular matrix proteins within the ventricular system, especially along the basal cisterns. The fibrosis induced by TGF-beta can result in chronic obstruction and progressive hydrocephalus. Intraventricular fibrinolytic therapy, as a means to dissolve the clot, restore CSF circulation, and prevent TGF-beta- induced chronic fibrosis, is sound in its rationale. Moreover, by way of its direct action at the site of the clot, the intraventricular approach for administration of a fibrinolytic agent is reasonable. The fibrinolytic agents used in clinical trials have included urokinase, streptokinase, and tissue plasminogen activator (TPA). Most recently, a small, nonrandomized, preliminary trial using historic controls has shown the feasibility of a closed system of ventricular irrigation with TPA. In this trial, human recombinant TPA was injected in a dose of 0.5 mg/kg body weight via a reservoir or anterior ventricular catheter into the cerebral ventricle and left for 8 hours before irrigation for 72 hours with a fluid containing electrolytes and antibiotics. Although the results are promising, the therapeutic benefit is small and the risk is unacceptably high. The treatment is highly invasive, labor-intensive, and expensive, and it carries the risks of iatrogenic injury, serious infection, bleeding, and fluid-electrolyte abnormalities. Thus, in the absence of

supportive data from properly controlled, multicenter trials, intraventricular fibrinolytic therapy as a means for prevention of post-hemorrhagic hydrocephalus following PIVH cannot be recommended.

The rationale behind the use of an osmotic agent is based on the inverse relation between serum osmolarity and CSF formation. A 1% increase in serum osmolarity results in a 15% decrease in CSF production. The osmotic agents used in clinical trials have included isosorbide and glycerol. The dosage of either of these agents has been 8.0 g/kg/d in 4 divided doses. The total duration of treatment has been 3 months. The complications of treatment with an osmotic agent include fluid-electrolyte abnormalities, alterations in glucose homeostasis, and diarrhea and vomiting. Much of the experience with the use of the osmotic agent has involved small clinical trials of treatment of infantile hydrocephalus. The treatment has been used mostly as a temporizing measure pending the placement of a ventriculo-peritoneal shunt. The experience with the use of the osmotic agent as a means for prevention of post-hemorrhagic hydrocephalus in preterm infants is limited.

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Content Specifications:

Understand the proposed mechanisms, clinical features, and diagnosis of periventricular-intraventricular hemorrhage

Understand the treatment and long-term consequences of periventricular-intraventricular hemorrhage

Understand the treatment of hydrocephalus

PREVIOUS   NEXT
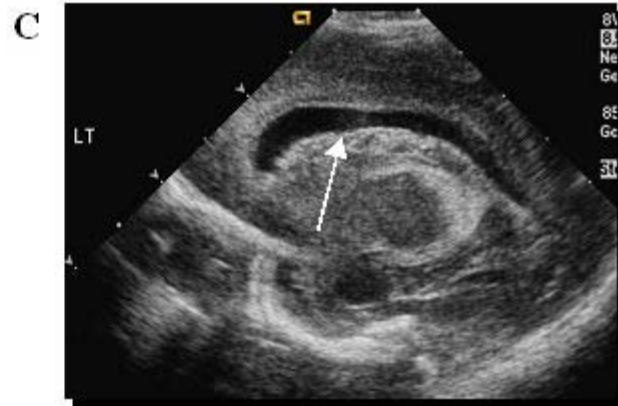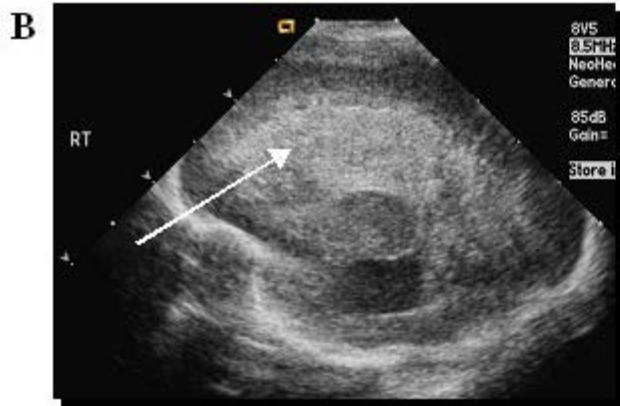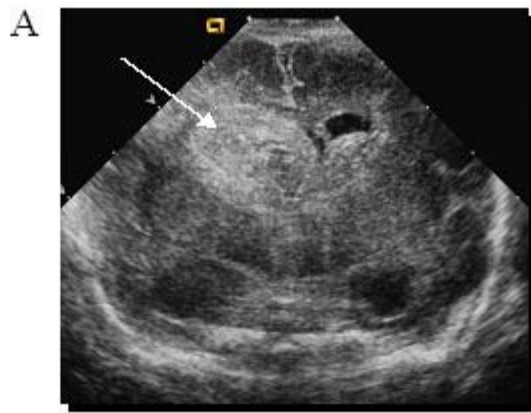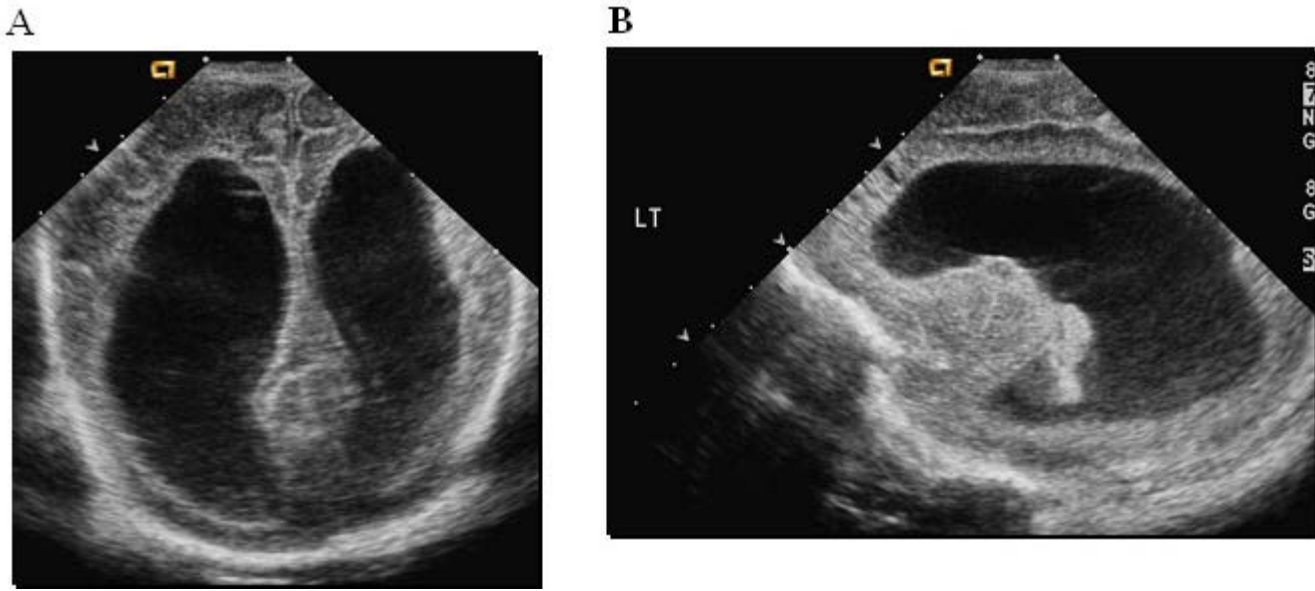
Figure 2

Figure 2: Coronal (panel A) and sagittal (panel B) views on cranial ultrasonography show ventricular dilatation.
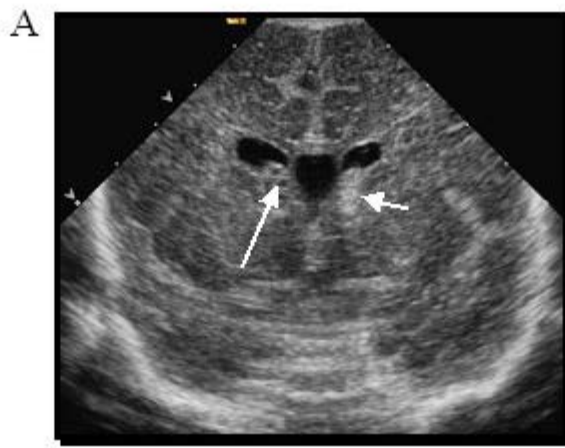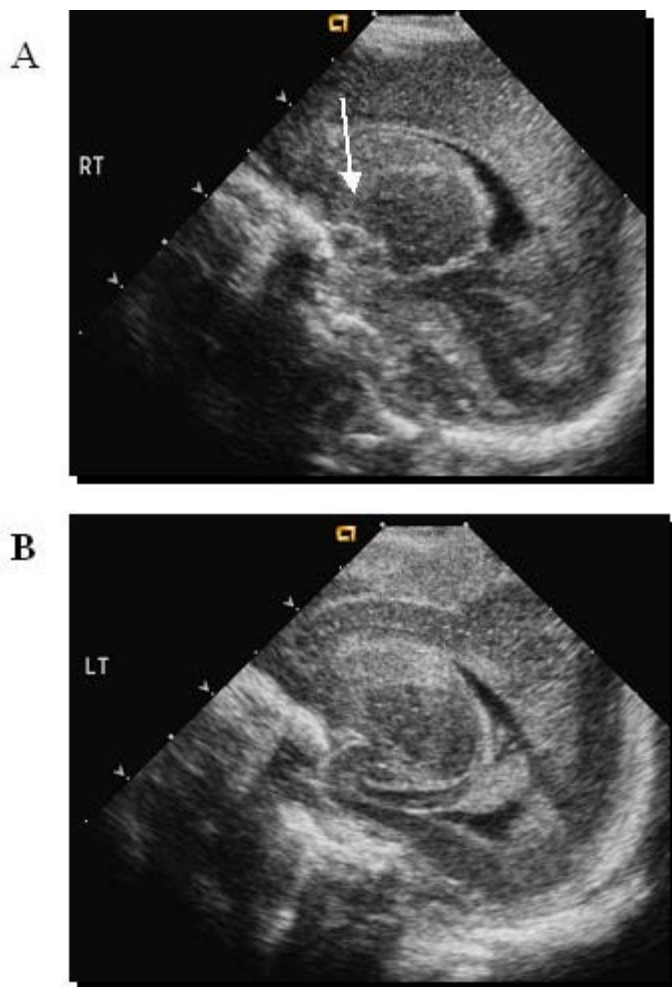
Figure 4

Figure 4: Coronal (panel A) and sagittal (panel B) views on cranial ultrasonography show grade II periventricular-intraventricular hemorrhage.

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A 4-hour-old term male infant has persistent drooling. The infant attempted to bottle-feed and immediately choked and spit. The pregnancy was complicated by polyhydramnios. A tracheoesophageal abnormality is suspected.

Of the following, the MOST likely tracheoesophageal abnormality is:

1. esophageal atresia with a distal and a proximal tracheoesophageal fistula

2. esophageal atresia with a distal tracheoesophageal fistula

☒ esophageal atresia with a proximal tracheoesophageal fistula

4. esophageal atresia without a tracheoesophageal fistula

5. tracheoesophageal fistula without esophageal atresia

You selected 3 , the correct answer is 2 .

Congenital esophageal atresia (EA) with or without a tracheoesophageal fistula (TEF) is a common congenital anomaly with an incidence of 1 in 3,000 live births. Newborns with EA may present in the delivery room with either a sonorous "seal-bark" cry because of associated tracheomalacia or within the first few hours after birth with excessive oral secretions. Feeding an infant with EA will cause spitting and choking, and aspiration pneumonia can occur. Reflux of gastric secretions through a distal TEF also can cause aspiration pneumonia. Diagnosis of EA is suspected by failure to pass an orogastric tube beyond 10 cm to 11 cm from a term infant's lips. Chest radiography confirms the position of the orogastric tube in the proximal esophageal pouch.

From 30% to 60% of infants with EA and TEF have associated anomalies, including cardiac (25%), genitourinary (15%), skeletal (14%), and intestinal atresias (13%). The VACTERL association (vertebral defects, anorectal abnormalities, cardiac defects, TEF, renal abnormalities, limb defects) occurs in approximately 10% to 25% of cases.

Embryologic development of the trachea and esophagus is a complex process. During week four of gestation, the embryo is C-shaped, and the primitive (primordial) gut is divided into the foregut, midgut, and hindgut. The trachea and esophagus are formed from the foregut. The trachea develops from the laryngotracheal tube, which buds off the ventral surface of the foregut. The tracheoesophageal septum separates the foregut into tracheal and esophageal tubes. The esophagus rapidly elongates with growth of the embryo. The lumen of the esophagus becomes obliterated by the proliferation of endodermal lining cells. During week eight of gestation, endodermal cell death re-establishes the esophageal lumen. Failure of the tracheoesophageal septum to divide into the esophagus and trachea at week four of gestation, or failure of recanalization of the esophagus during week eight of gestation results in various types of EA and TEF.

Polyhydramnios may develop because the fetus with EA cannot swallow amniotic fluid. Significant polyhydramnios may lead to premature delivery in approximately 30% of cases. Because the fetus may derive some nutritional benefit from swallowed amniotic fluid, newborns with EA may be small for gestational age.

The most common tracheoesophageal abnormality (86%) is EA with a distal TEF (Fig. 1). The proximal esophagus ends blindly in the superior mediastinum at the third or fourth thoracic vertebra. The distal esophagus usually enters the posterior wall of the trachea 1 cm to 2 cm above the carina. The proximal esophageal pouch and the distal TEF may overlap or be

separated widely. Because the distal TEF allows some amniotic fluid to flow from the trachea to the gastrointestinal tract, polyhydramnios only occurs in approximately 33% of pregnancies with this type of EA.

EA with distal and proximal TEF, also known as a double TEF, is a rare (<1%) tracheoesophageal abnormality (Fig. 2). This type of malformation may be misdiagnosed as the more common EA with a distal TEF. If the small proximal TEF is unrecognized, then recurrent respiratory infections will occur. Preoperative endoscopy permits recognition of the double fistula and complete repair at the initial operation.

EA with a proximal TEF is another rare (2%) tracheoesophageal abnormality (Fig. 3). The TEF usually is located 1cm to2 cm above the distal end of the esophageal pouch. Polyhydramnios occurs nearly 100% of the time because no distal fistula is present.

Isolated EA without a TEF (Fig. 4), occurs in 7% of tracheoesophageal abnormalities. The proximal esophageal segment usually ends in the posterior mediastinum near the second thoracic vertebra. Unlike EA with distal TEF, infants without a distal TEF have a flat, gasless abdomen. A wide gap usually divides the upper and lower esophageal segments, making primary anastomosis difficult. Isolated EA without a TEF may be the result of failure of recanalization of the esophagus during week eight of gestation.

TEF without EA, also known as H-type TEF (Fig. 5), comprises 4% of tracheoesophageal abnormalities. Infants with H-type TEF may have intermittent choking episodes in the newborn period. More commonly, patients with H-type TEF present later in life, even into adulthood, with chronic cough, recurrent pneumonia, or reactive airway disease. This form of TEF is the most difficult to diagnose because the fistula may not be identified by routine contrast swallow studies. Esophagoscopy or bronchoscopy may be necessary to visualize the TEF.

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Content Specifications:

Know the morphogenesis of the gastrointestinal (GI) tract and factors that lead to congenital malformations

Know how to recognize and evaluate an infant with excessive gastric contents and hydramnios
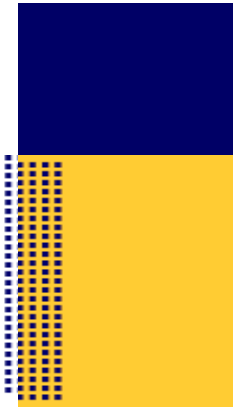
Know how to diagnose polyhydramnios, its significance, and the management of pregnancy when polyhydramnios is diagnosed

Plan appropriate management for an infant with airway obstruction, such as vascular rings, choanal atresia, and tracheal abnormalities

Recognize the clinical features of VATER association

PREVIOUS   NEXT
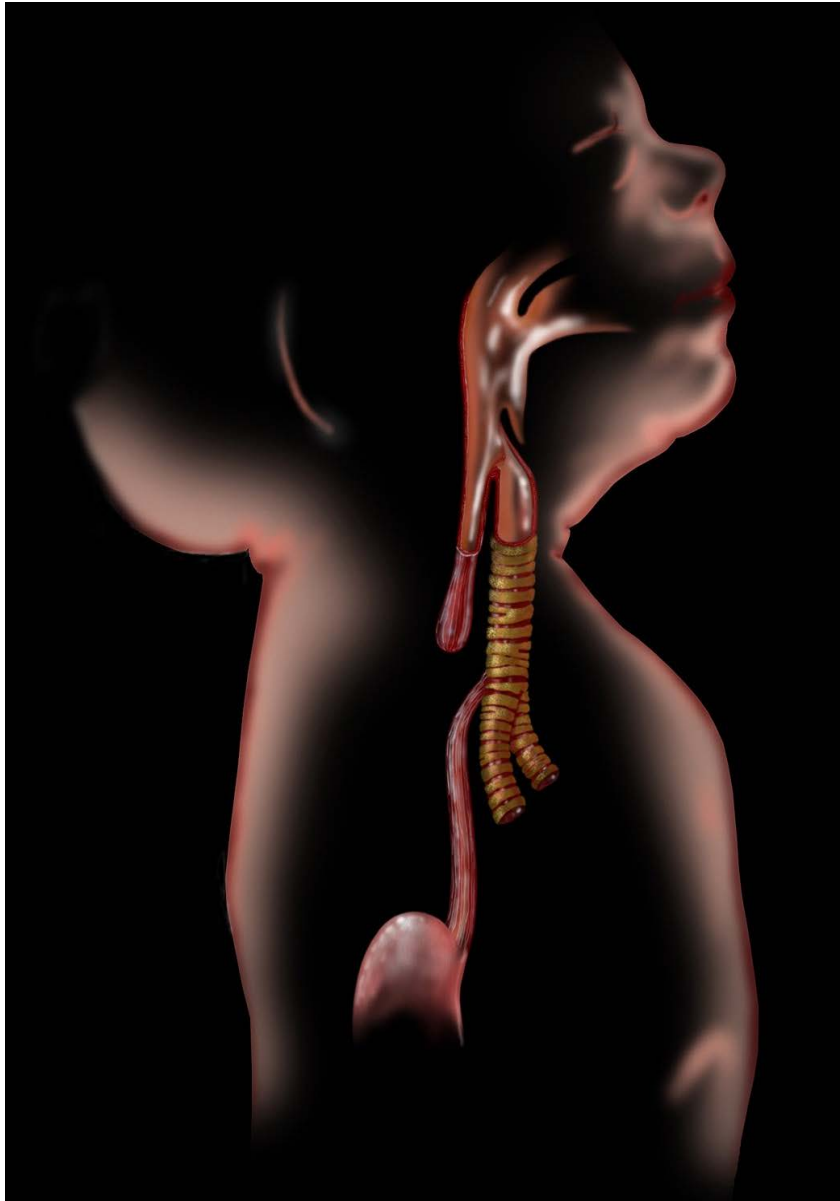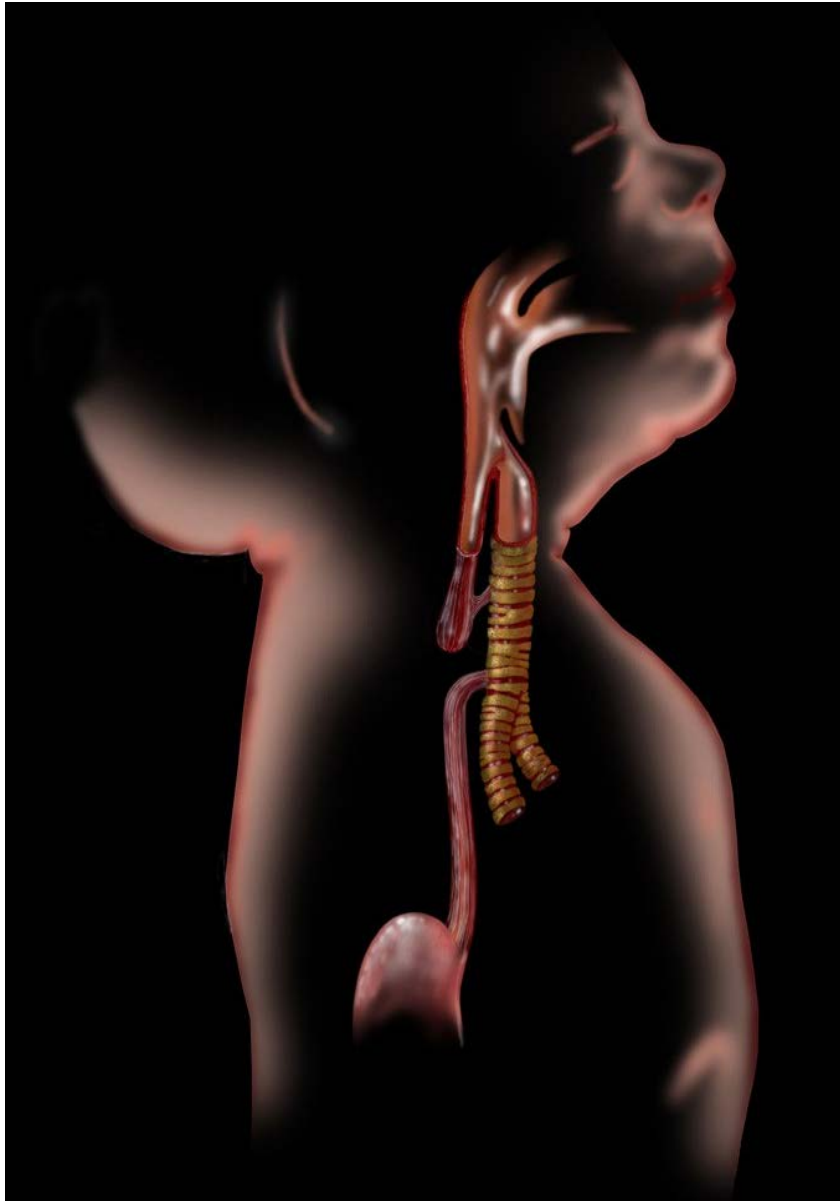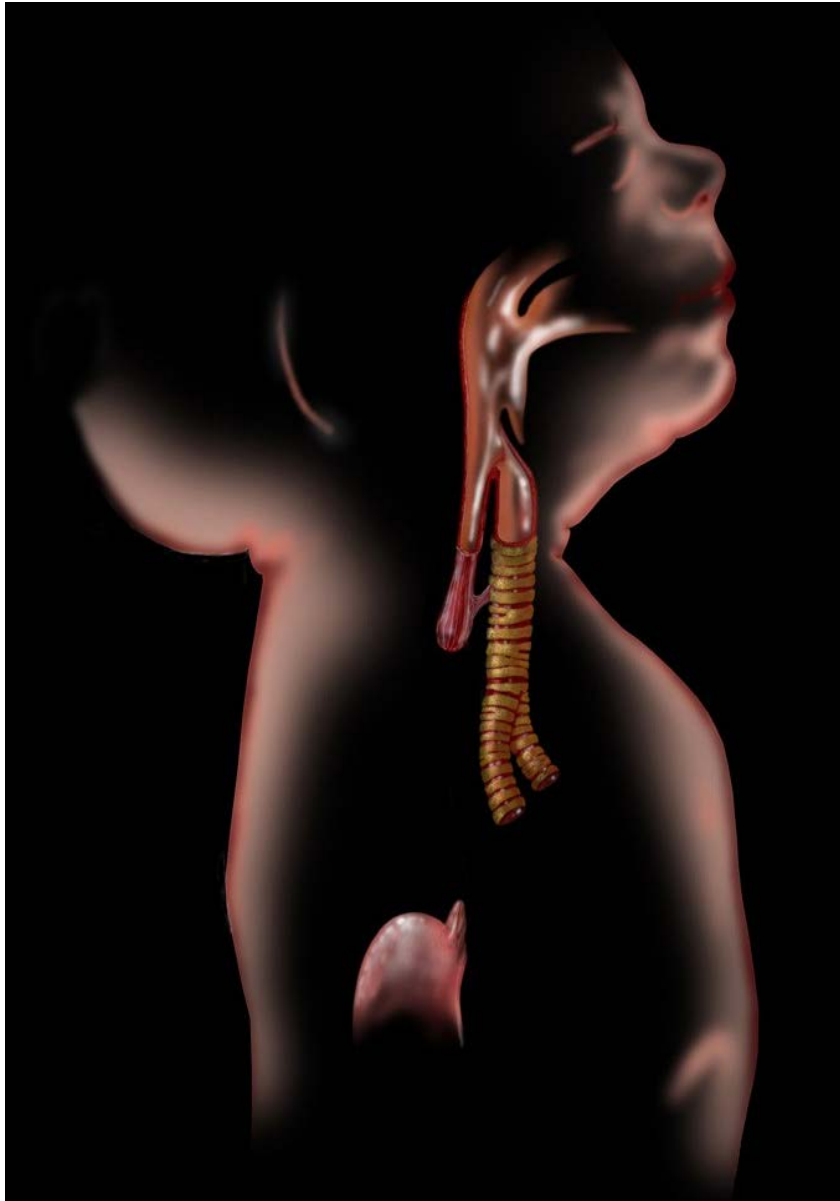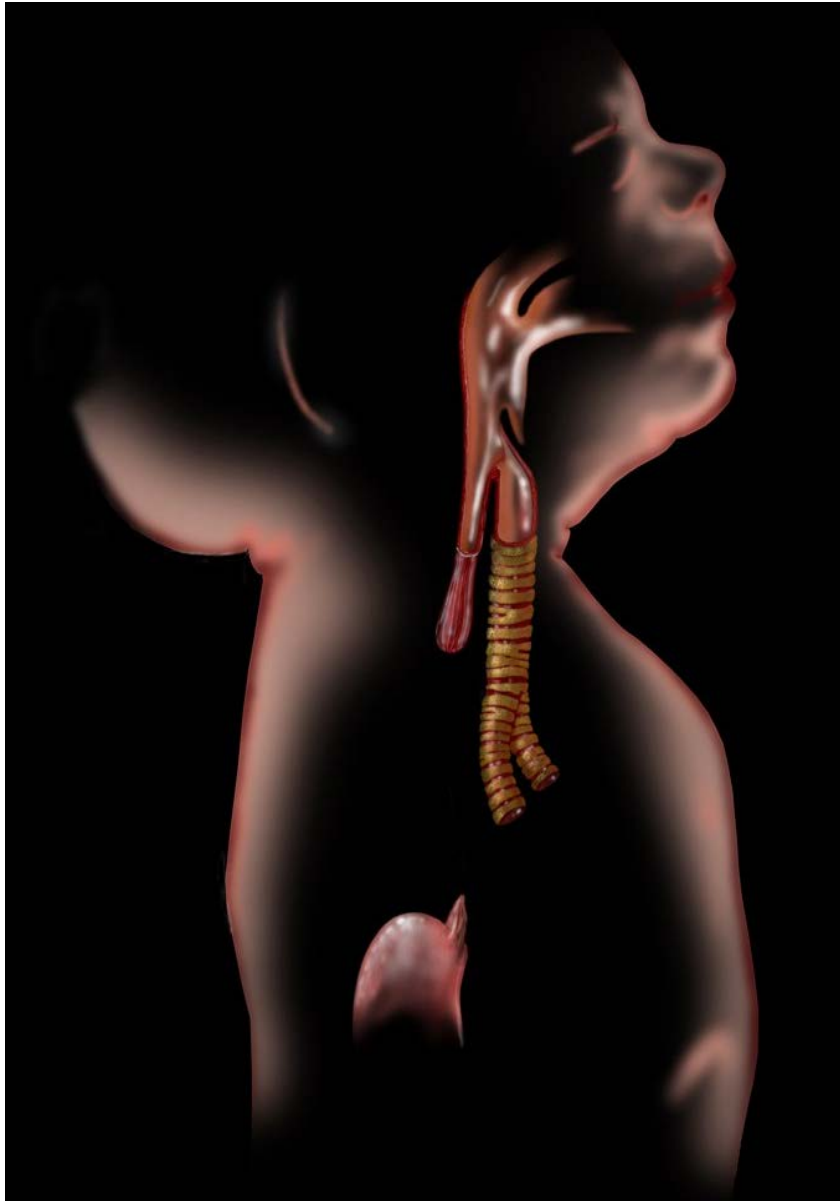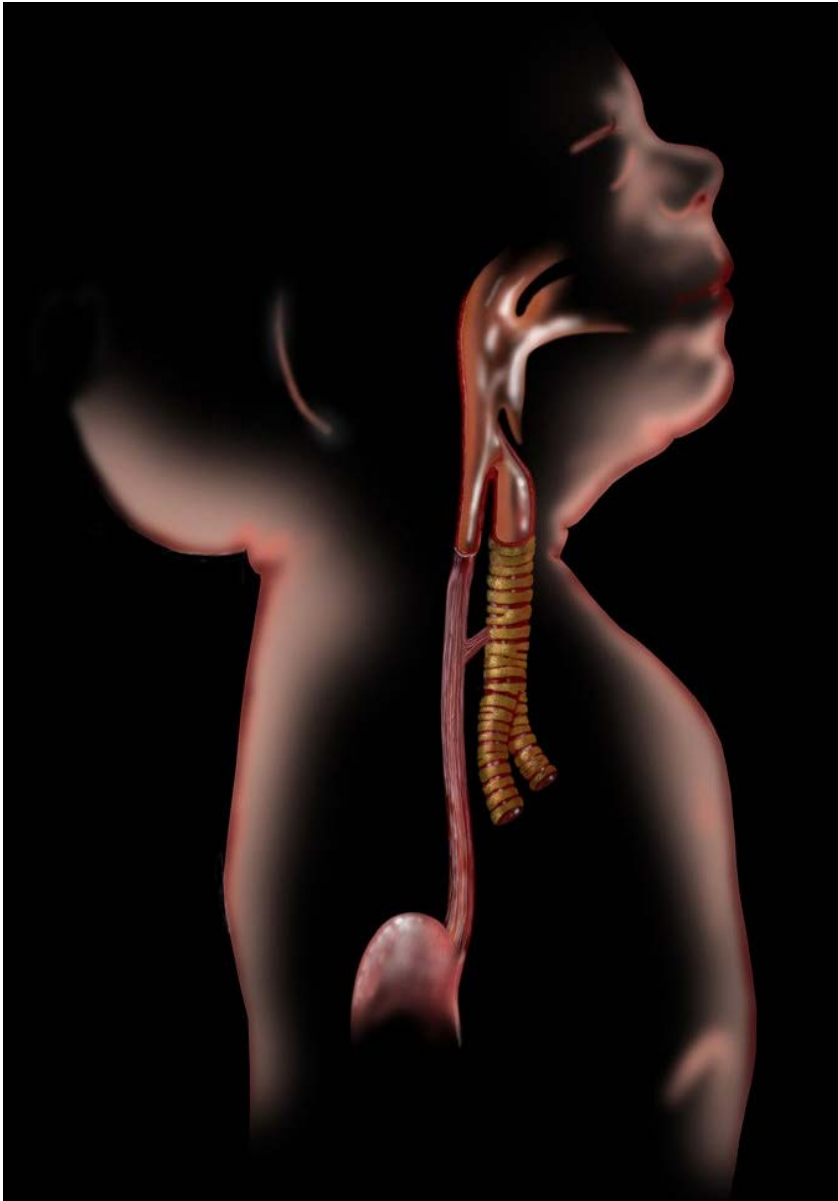
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Cesarean delivery of 33-week twins, both male, is necessary due to severe preeclampsia unresponsive to treatment since presenting four hours ago. The mother was a fraternal, or dizygotic, twin. She conceived the month after stopping oral contraceptive therapy. Sonographic evaluation shows dichorionic, diamnionic twins with discordant growth. Twin A is estimated to weigh 1750 grams and twin B to weigh 1125 grams. Hydramnios has been present since 18 weeks in Twin B. While preparing for resuscitation and stabilization of these infants, you are discussing information about twin gestations with the pediatric residents and nurse practitioners.

Of the following, the TRUE statement regarding twinning is:

1   dichorionic, diamniotic placentas indicate that the twins are dizygotic

2   malformations occur more frequently in twin pregnancies complicated by transient hydramnios during the second trimester

☒ 3   monozygotic twins are phenotypically identical

4   most twins deliver at term

5   women who themselves are dizygotic twins have a greater chance for having dizygotic twins than fathers who themselves are dizygotic twins

You selected 3, the correct answer is 5.

Twin pregnancies account for the majority of multifetal pregnancies. In the United States, the number of twin births has increased by more than 50% between 1980 and 1997, whereas singleton births rose by 6%. This disproportionate increase has been attributed to an increase in pregnancies achieved with artificial reproductive therapy. Twins account for approximately 1 in 94 naturally occurring pregnancies. However, they also account for a large share of fetal, neonatal and maternal pregnancy complications. Fetal and neonatal complications include higher rates of perinatal mortality, congenital malformations and twin-twin transfusion syndrome. Maternal complications include a two-fold risk of preeclampsia, postpartum hemorrhage and maternal death.

Twin gestations result from fertilization of two separate ova (dizygotic or fraternal) or from a single fertilized ovum that divides into two structures capable of developing into separate individuals (monozygotic or identical). Dizygotic twins result from fertilization of two ova during the same ovulatory cycle, ie, they are two separate offspring who share the same time and place in which to develop into two individuals. Dizygotic twins account for approximately two-thirds of all twins, monozygotic twins for about one-third.

Dizygotic twinning is determined in part by the family history.. Mothers who themselves are dizygotic twins have a 1 in 58 chance of a twin conceptus; this is a two-fold greater chance than fathers who themselves are dizygotic twins. This has been hypothesized to be due to an autosomal dominant gene that increases the number of follicles that can produce ovum for fertilization by prolonging the effect of follicle stimulating hormone (FSH). The mechanism may be an increase in synthesis and release of FSH or increased receptor sensitivity to FSH, or both. This same mechanism also may account for the increased chance of twinning soon after discontinuing oral contraceptives, when a rebound release of endogenous pituitary gonadotropin occurs. The influence of race, age, weight and fertility also may be due to prolonged FSH effect. Research is ongoing to test this hypothesis.

Dichorionic, diamniotic placentas may indicate either monozygotic or dizygotic twins.

Monochorionic or monoamnionic placentas indicate monozygosity. However, dichorionic, diamniotic placental structures also occur in monozygotic twins if division of the fertilized ovum occurs before the inner cell mass (morula) is formed and the outer layer of the blastocyst is committed to chorion development. This usually occurs within 72 hours of fertilization. In contrast, a diamniotic, monochorionic twin pregnancy will occur if division of the developing morula and chorion occurs between four and eight days after fertilization. This occurs when the inner cell mass and chorionic structures are committed but amniotic differentiation has not committed so that two amniotic sacs form. Monoamniotic, monochorionic placentas develop when the inner cell mass, chorionic structures and amniotic structures have committed to a direction of differentiation before division occurs; this happens eight days or more after fertilization. In rare instances when division occurs even later, after the embryonic disk is formed, conjoined twins result, because separation is nearly always incomplete.

Monozygotic twins may or may not be phenotypically identical. This is dependent on the amount of tissue that accompanies division of the fertilized ovum. Differences in tissue allocation during division can result in discordant growth and development. The discordant growth of the twins in the vignette raises suspicion for monozygosity and associated complications of cord entanglement, congenital anomalies and twin-twin transfusion syndrome. Discordancy for genetic mutations or gene expression and, in female fetuses, different patterns of lyonization, can produce different phenotypes in monozygotic twins. Congenital malformations are particularly more common in monozygotic twins compared to singletons; major malformations occur in 2% and minor malformations in 4% of twins. These anomalies result from defects during the twinning process itself (eg, conjoined twins, neural-tube defects, sirenomelia, holoprosencephaly), vascular accidents due to interchange of blood flow and emboli through vascular anastomoses (eg, microcephaly, hydranencephaly, intestinal atresia, aplasia cutis or limb amputation) or deformations due to crowding (eg, talipes equinovarus, hip dislocation). One clinical clue to the presence of malformations is the presence of hydramnios persisting throughout pregnancy. Both twins in the vignette should be evaluated for congenital malformations, especially twin B, whose course has been complicated by hydramnios.

Twin gestations account for about 12% of all spontaneous conceptions, but only approximately 14% of these survive to term. A greater risk of spontaneous abortion occurs with twins, especially if monochorionic. Interestingly, in some twin pregnancies, one of the twins is lost before the second trimester; this is referred to as the "vanishing twin" and occurs in 21% to 63% of spontaneous twin pregnancies. At the time of delivery, there is usually no evidence of the lost fetus.

<u>References:</u>

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Multifetal Pregnancy. In: Cunningham FG, Gant NF, Leveno KJ, et al, eds. *Williams Obstetrics*. 21st ed. New York, NY: McGraw Hill. Available at <u>http://online.statref.com/document.aspx?fxid=3&docid=1</u>. Subscription required. Accessed April 17, 2005

<u>Content Specification:</u>

Understand the implications and complications of multiple gestation, such as cord problems, twin-twin transfusion, "stuck twin," conjoined twins, etc.

Education Module Learner

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A term male infant has a strong family history of recurrent infections. His 3-year-old brother has frequent otitis media, sinusitis, pneumonia, and chronic diarrhea that began 6 months after birth. A maternal uncle had multiple bouts of pneumonia and died of lymphoma at 12 years of age. The 3-year-old brother's quantitative serum immunoglobulins are immunoglobulin (Ig) G = 0 mg/dL (normal mean ± SD 929±228 mg/dL), IgA = 0 mg/dL (93±27 mg/dL), and IgM = 400 mg/dL (56±18 mg/dl).

Of the following, the MOST likely mechanism for the aberrant Ig synthesis by B cells in this family is abnormal:

1. B-cell differentiation into isotype switched IgA-secreting plasma cells

2. B-cell polyclonal expansion triggered by Epstein Barr Virus (EBV)

3. maturation of pro-B cells into pre-B cells

4. postnatal timing of T helper cell regulation of plasma cell maturation

5. T helper cell regulation of Ig isotype switching

You selected 5, the correct answer is 5.

Immunoglobulin (Ig) synthesis by B cells is an intricate, highly regulated process. Aberrations in B-cell maturation or T-cell regulation result in abnormal Ig synthesis and defects in host defense.

B-cell lymphopoiesis first occurs in the fetal liver at 7 weeks' gestation. By 12 weeks' gestation, the bone marrow becomes the major site of B-cell production for the remainder of fetal and postnatal life. Common lymphoprogenitor cells (Figure) differentiate into either pro-B cells or trilineage cells (progenitors for T cells, natural killer cells, and dendritic cells). Pro-B cells differentiate into pre-B cells, immature B cells, and then mature B cells within the bone marrow in an antigen-independent process.

The ontogeny of the B cell can be monitored by the expression of developmentally regulated genes. Pro-B cells express cell markers, such as CD19, that are specific to the B-cell lineage. Pro-B cells undergo Ig gene rearrangements to become pre-B cells. Pre-B cells express the *mu* heavy chain of IgM in the cytoplasm. Pre-B cells generate clonal diversity through rearrangement of heavy and light chain genes. After heavy and light chain gene rearrangement occurs, pre-B cells exit the cell cycle and become immature B cells, which express surface Ig of the same isotype that is to be secreted.

Each B cell is genetically programmed to encode a surface Ig that acts as a specific receptor for a particular antigen. After release from the bone marrow, mature B cells migrate into lymphoid tissues until the B cells recognize the specific antigen for their surface Ig receptor. After antigenic stimulation, mature B cells, with the assistance of T helper cells, multiply and differentiate into plasma cells. Plasma cells synthesize thousands of Ig molecules per second. The Ig molecule secreted by a plasma cell has the same binding specificity as the surface receptor Ig molecule on its precursor B cell.

B cells produce five Ig isotypes (IgG, IgA, IgM, IgE, and IgD). Igs have a basic unit structure of two light chains and two heavy chains. Ig isotype is determined by the structure of the heavy chain. Thus, IgM has heavy chain m, IgG has heavy chain g, IgA has heavy chain á, IgE has heavy chain e, and IgD has heavy chain d. Immature B cells produce IgM only. Mature B cells switch from IgM to other isotypes by gene recombination. Each terminally differentiated plasma cell is derived from a specific B cell that produces Ig of just one isotype.

The switch of Ig isotype from IgM to IgG, IgA, or IgE is antigen-driven and requires signaling between CD40 on the B-cell surface with CD40 ligand present on the surface of T cells. The isotypes produced are regulated further by cytokines. Interleukin (IL)-10 and transforming growth factor-b promote IgA, and IL-4 stimulates IgE synthesis.

The family described in the vignette has X-linked hyper-IgM syndrome (HIgM). HIgM is a life-threatening disorder that results in extremely elevated IgM concentrations and low concentrations of other Ig isotypes (IgG, IgA, and IgE). HIgM occurs in approximately 1 in 1 million live births.

Males with HIgM develop recurrent sinopulmonary infections and chronic diarrhea between 6 months and 12 months of age as maternally derived IgG wanes. Frequent sinopulmonary infections with polysaccharide encapsulated bacteria, such as *Haemophilus influenza*, *Streptococcus pneumoniae,* and *Moraxella catarrhalis,* result in chronic cough and bronchiectasis. The gastrointestinal tract becomes infiltrated with IgM-producing B cells. Intractable diarrhea, caused by Cryptosporidium, rotavirus, Giardia, or Campylobacter, results in malnutrition and cachexia. The host defense system in HIgM is compromised further by IgM autoantibodies to neutrophils, which cause neutropenia that leads to mouth and perianal ulcers. Patients with HIgM have high rates of malignancies, particularly lymphomas and gastrointestinal adenomas. The mean age at death from HIgM is 11.7 years; only 20% survive to 25 years of age.

Abnormal T helper cell regulation of B-cell Ig isotype switching is the mechanism for HIgM. In HIgM, B cells can initiate the immune response by producing IgM but cannot make the isotype switch from IgM to synthesis of IgG, IgA, or IgE. HIgM is due to a mutation in the gene for the CD40 ligand on T cells. T cell CD40 ligand must bind to CD40 receptors on B cells for the Ig heavy chain class isotype switch to occur. The absence of CD40 ligand on T cells interrupts B-cell activation.

Abnormal B-cell differentiation into isotype-switched IgA-secreting plasma cells is the mechanism for selective IgA deficiency. Patients with IgA deficiency have near total absence of serum IgA (<10mg/dL, 0.1 g/L) with normal concentrations of IgG, IgM, IgE, and IgD. IgA deficiency is the most common immunodeficiency (1in 700 whites). Lack of IgA increases the risk of respiratory, gastrointestinal, and genitourinary infections.

Abnormal B-cell polyclonal expansion triggered by EBV is the mechanism for X-linked lymphoproliferative disease (XLP), also referred to as Duncan disease. Affected males are healthy until an EBV infection triggers fulminant, frequently fatal infectious mononucleosis, B-cell lymphomas, hepatitis, aplastic anemia, or hypogammaglobulinemia. The median age of onset is 5 years, and 70% die by 10 years of age. XLP is caused by a mutation in the SH2D1A gene at Xq26-27. This gene encodes the signaling lymphocyte activation molecule-associated protein (SAP). In patients with XLP, the lack of SAP leads to uncontrolled cytotoxic T-cell response to EBV and polyclonal B-cell expansion.

Abnormal maturation of pro-B cells into pre-B cells is the mechanism for Bruton X-linked agammaglobulinemia (XLA). The bone marrow of males with XLA has normal numbers of CD19+ pro-B cells but severely decreased numbers of the cytoplasmic m-positive pre-B cells. Because of a mutation in B-cell cytoplasmic tyrosine kinase gene, pre-B cell maturation does not occur. Patients with XLA have no B cells in their blood or lymphoid tissue, and their sera contain only small amounts of IgG and no IgA, IgM, IgE, or IgD.

Abnormal postnatal timing of T helper cell regulation of plasma cell maturation is the likely mechanism for transient hypogammaglobulinemia of infancy (THI). Transplacental transfer of IgG begins at 8 weeks' gestation. By 30 weeks' gestation, IgG concentration in fetal serum is approximately 50% of the maternal concentration. IgG is transported actively across the placenta during the last trimester of pregnancy. Term infants have serum IgG concentrations that equal or exceed those of the mother. Significant amounts of IgG are not made by the infant until 2 to 3 months of age. Because maternally derived IgG is catabolized with a 30-day half-life, a physiologic IgG nadir occurs at 3 to 6 months of age. In THI, there is delayed production of IgG that prolongs and accentuates the IgG nadir. Patients with THI develop recurrent otitis media and bronchitis between 6 months and 2 years of age. In THI, IgG concentrations normalize by 2 to 6 years of age. The precise mechanism of THI is not known. These patients

have normal numbers of circulating B cells; however, their lymph nodes exhibit a marked reduction in the number of plasma cells. A transient abnormality in T helper cell function involving the terminal differentiation of B cells to plasma cells is the most likely cause of THI.

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Rosen FS. Primary immunodeficiency. In: Roitt I, Brostoff J, Male D, eds. *Immunology*. 6th ed. Edinburgh, Scotland: Mosby; 2001:303-305

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Shigeoka AO. eMedicine: X-linked immunodeficiency with hyper IgM. Available at http://www.emedicine.com/ped/topic2457.htm. Accessed March 2005

Turner M. Antibodies. In: Roitt I, Brostoff J, Male D, eds. *Immunology*. 6th ed. Edinburgh, Scotland: Mosby; 2001:65-86

Content Specifications:

Know the various factors (specific host defense mechanisms) that affect the normal development of the human immune system and their timing

Know the normal immunoglobulin pattern in the newborn infant

Understand the origin, maturational process, and regulation of leukopoiesis during development

Understand the function of B-lymphocytes

Know the function of immunoglobulins

Understand the consequences of immunoglobulin deficiencies

Ontogeny of B cells
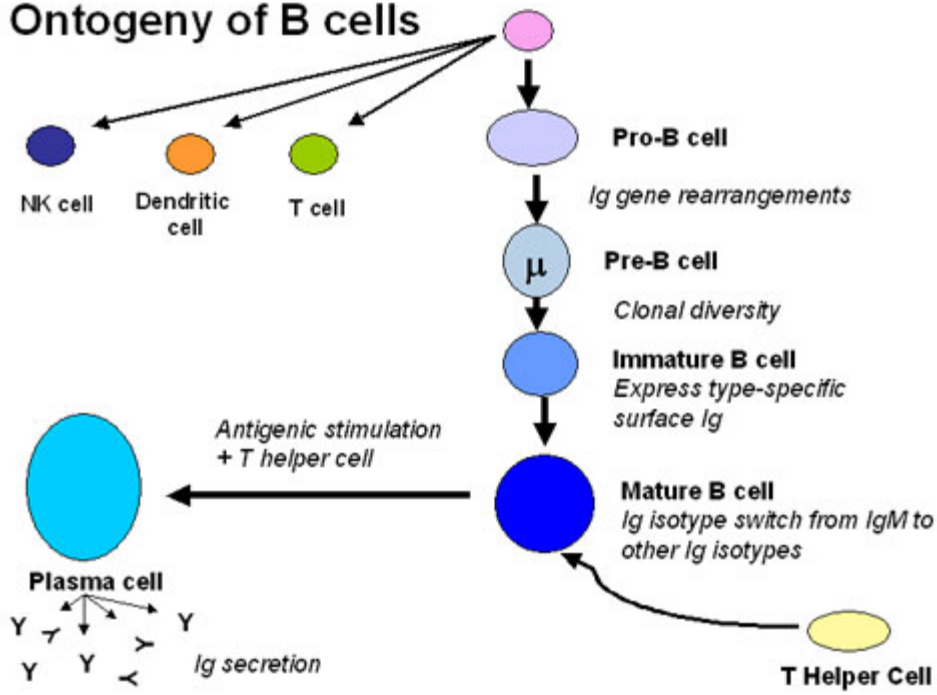
Pro-B cell

Ig gene rearrangements

μ Pre-B cell

Clonal diversity

Immature B cell
Express type-specific surface Ig

Mature B cell
Ig isotype switch from IgM to other Ig isotypes

NK cell

Dendritic cell

T cell

Antigenic stimulation + T helper cell

Plasma cell

Y Y Y Y Y *Ig secretion*

T Helper Cell

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You are called to the delivery room to evaluate a male infant because of an abnormality of the lower abdomen. You see the following on physical examination:

Otherwise, he looks normal.

Of the following, the MOST likely associated anomaly in this infant is:

1. anal atresia

2. congenital heart disease

3. cryptorchidism

4. inguinal hernia

5. ureteropelvic junction obstruction

You selected 4, the correct answer is 4.

The infant in this vignette has exstrophy of the bladder, which is seen more often in boys than in girls (male to female ratio, 2.5 to 1). Clinical features include an open bladder area, inferiorly displaced umbilicus, and diastasis of the pubis. Presence of an omphalocele, intestinal opening into the exposed bladder mucosa, and absence of an anal opening are characteristic of cloacal exstrophy, a more extensive and severe condition.   The defects in exstrophy occur due to

failure of migration of infraumbilical mesenchyme about the 6th to 7th week of development, resulting in continued contact between the bladder portion of the cloaca and the overlying ectoderm. More extensive mesodermal deficiency results in cloacal exstrophy. Infraumbilical mesenchyme gives rise to the lower abdominal wall, genital tubercles, and pubic rami. Its lack results in breakdown of the cloacal membrane as in other areas where mesoderm does not separate ectoderm from endoderm, such as the mouth, anus, and urogenital areas. Exstrophy of the bladder is more common among first-born children, and it is rarely seen among African Americans. Parents having an infant with bladder exstrophy have a 1 in 275 chance for exstrophy or epispadias in a future infant. Children of affected individuals experience a 1 in 70 risk.

The anomaly most associated with exstrophy of the bladder in male infants is inguinal hernia. The prevalence of inguinal hernia is estimated at 80% in male infants, and only 10% in female infants.

Anal atresia is not commonly seen with the exstrophy/epispadias combination as seen in the vignette. Children with the more extensive mesenchymal deficiency associated with cloacal exstrophy have anal atresia and often have a prolapsed segment of ileum coming from the cecal

portion of the exposed cloacal membrane. Fecal and urinary continence should be expected with bladder exstrophy after reconstructive surgery. In contrast, patients with cloacal exstrophy rarely achieve either urinary or fecal continence.

Congenital heart disease is not prevalent among infants with bladder exstrophy.

Cryptorchidism usually is not seen with bladder exstrophy. The lesion often results in lateral displacement of the scrotum due to the widened pubic tubercles, but the testes are usually retractile and will not require orchidopexy.

Ureteropelvic junction abnormalities are not seen often with exstrophy. Vesicoureteral reflux is common due to the short course of the ureter through the bladder wall in exstrophy. Renal agenesis is rare. In contrast, exstrophy of the cloaca is associated frequently with upper urinary tract anomalies, such as agenesis, multicystic kidney, pelvic kidney, and ureteral duplication. Females have bifid uterine horns and duplicated, short or atretic vaginas.

References:

Exstrophy of the bladder sequence. In: Jones KL, ed. *Smith's Recognizable Patterns of Human Malformation.* 5th ed. Philadelphia, Pa: Saunders; 1997:626-7

Exstrophy of cloaca sequence. In: Jones KL, ed. *Smith's Recognizable Patterns of Human Malformation.* 5th ed. Philadelphia, Pa: Saunders; 1997:628-9

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Yerkes EB, Rink RC. eMedicine: exstrophy and epispadias. Available at http://www.emedicine.com/ped/topic704.htm. Accessed April 15, 2005

Content Specifications:

Recognize the clinical manifestations of anatomic abnormalities of the urinary tract in infants

Know how to diagnose specific anatomic abnormalities of the urinary tract in infants

Know the recommended supportive and corrective treatment of anatomic abnormalities of the urinary tract in infants

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Questions | Assessment Summary | CME Credit Expired ▶

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A 21-day-old male, whose birthweight was 820 g and estimated gestational age at birth was 26 weeks, has the following serum electrolytes: sodium 125 mEq/L (125 mmol/L), potassium 5.4 mEq/L (5.4 mmol/L), chloride 95 mEq/L (95 mmol/L), and bicarbonate 20 mEq/L (20 mmol/L). During the last week, he has averaged caloric intake of 90 kcal/kg per day, sodium intake of 2.8 mEq/kg per day, and weight gain of 15 g/kg per day. He is breathing spontaneously in room air and has received neither indomethacin nor diuretics. His serum creatinine is 0.4 mg/dL (30.5 mmol/L). His urine measurements are: output 86 mL/kg per day, sodium 72 mEq/L, and creatinine 6 mg/dL.

Of the following, the hormone/vasoactive peptide whose dysfunction is MOST likely to account for the serum electrolyte abnormalities in this infant is

1. aldosterone
2. arginine vasopressin
3. atrial natriuretic peptide
4. catecholamine
5. cortisol

You selected 5, the correct answer is 1.

The preterm infant in this vignette has evidence of late hyponatremia. Typically, the serum sodium concentration in this disorder is less than 130 mEq/L (130 mmol/L) and the postnatal age at the time of manifestation is 2 weeks to 6 weeks. The hyponatremia is attributed to a negative sodium balance in which the sodium output, largely through urine, exceeds sodium intake. A rapid weight gain associated with growth, not water retention, may be accompanied by increased accretion of sodium in the tissues and may exaggerate hyponatremia.

The urine sodium output can be estimated from the urine output and urine sodium concentration, assuming that the sodium excretion in the urine is uniform throughout the day. Using the equation:

Urine sodium output (mEq/kg per day) = [Urine sodium concentration (mEq/L) x urine output (mL/kg per day)] ÷ 1000,

and assuming zero losses of sodium in the stool and sweat, the total sodium output in the infant in this vignette is estimated at 6.2 mEq/kg per day. With a sodium intake of 2.8 mEq/kg per day, the sodium balance is negative, with a calculated deficit of 3.4 mEq/kg per day. Additionally, the weight gain in this infant, assuming no water retention, suggests that that sodium accretion in the tissues may be contributing to hyponatremia.

The high urine sodium output is reflected in the elevated renal fractional excretion of sodium (FE_{Na}), which is calculated using the equation:

FE_{Na} (%) = [urine Na (mEq/L) x serum creatinine (mg/dL)] ÷ [serum Na (mEq/L) x urine

creatinine (mg/dL)] x 100.

The FE_{Na} varies inversely with gestational age, ranging in the first 2 days after birth from >5% in neonates of gestational age 27 weeks or younger to 1% in those born at term. The FE_{Na} also varies inversely with postmenstrual age, ranging at 2 weeks after birth from approximately 1% in infants 27 weeks or younger by gestational age to 0.2% in those born at term. The FE_{Na} in the infant in this vignette is calculated at approximately 3.8%.

A review of renal absorption of sodium may facilitate our understanding of late hyponatremia in preterm infants. In the kidney, the proximal tubule receives an ultrafiltrate of plasma from the glomerulus and reabsorbs all of the filtered glucose and amino acids along with most of the chloride and bicarbonate. Much of the reabsorption of sodium is mediated by an energy-consuming transporter, Na/K-ATPase, located on the basolateral membrane of the tubular cell, and by specific ion transporters, located on the apical membrane. Of the net reabsorption of sodium in the nephron, approximately 70% occurs in the distal half of the proximal tubule, mediated by an Na/H exchanger and a Cl/OH exchanger; 25% in the thick ascending limb of the loop of Henle, mediated by an Na/K/2Cl cotransporter; 5% in the distal tubule, mediated by an Na/Cl cotransporter; and 1% in the collecting duct, mediated by a Na channel. The factor that limits the reabsorption of sodium in the nephron and promotes its excretion in the urine is not any structural or functional deficiency of Na/K-ATPase or other ion transporters, but the lack of their abundance in the neonatal kidney, particularly in preterm infants.

The most likely cause of late hyponatremia from excessive urine loss of sodium in preterm infants is the lack of renal tubular response to aldosterone. Aldosterone is produced by zona glomerulosa of the adrenal cortex. Angiotensin II, a product of the renin-angiotensin system, is the major secretogogue involved in regulating aldosterone secretion in response to changes in sodium intake or fluid volume. Aldosterone induces reabsorption of sodium and excretion of potassium largely by regulating the permeability of sodium in the distal tubule and collecting duct. In the fetus, angiotensin II is a poor stimulus for aldosterone secretion. In contrast, birth causes a marked increase in renin, angiotensin II, and aldosterone concentrations in both term and preterm neonates. However, the immaturity of proximal tubular function in the preterm infant limits the responsiveness of the proximal tubule to reabsorption of sodium, thereby increasing the load of sodium presented to the distal tubule and collecting duct. The lack of abundance of Na/K-ATPase and other ion transporters limits the responsiveness of the distal nephron to aldosterone, particularly in the presence of increased load of sodium from the proximal tubule. The net result is natriuresis.

Arginine vasopressin (AVP), the antidiuretic hormone, is the major determinant of renal water excretion. AVP is synthesized in its precursor form in the hypothalamic neurons of the supraoptic and paraventricular nuclei. AVP, produced by cleavage of its precursor, is stored in the posterior pituitary, and its release is regulated by the osmolality of plasma. AVP induces reabsorption of water largely by regulating the water permeability of the collecting duct. Excess of AVP results in retention of water and dilutional hyponatremia. In the fetus, AVP production is active as indicated by high concentrations of AVP in cord arterial blood. After birth, AVP production in both term and preterm neonates can be increased in response to hypoxia, acidemia, hemorrhage, infection, central nervous system disease, pulmonary complications, and cardiac conditions. The absence of such factors in the infant in this vignette makes it unlikely that high AVP concentrations were the cause of late hyponatremia.

Atrial natriuretic peptide (ANP) is produced in the cardiac atria. The major stimulus for ANP secretion is increased cardiac atrial wall tension, resulting from acute or chronic fluid volume expansion, congestive heart failure, and other conditions associated with increased intra-atrial pressure. ANP induces diuresis and natriuresis by at least two mechanisms. The afferent arteriolar dilatation and efferent arteriolar constriction in the glomerulus induced by ANP increases glomerular filtration of fluid and electrolytes, including sodium. The tubular contribution to natriuresis by ANP involves the collecting duct and may be mediated by

inhibition of the action of angiotensin II. In the human fetus, ANP is detected as early as 10 weeks' gestational age. The circulating concentrations of ANP increase throughout gestation and during the first 7 to 10 days after birth. Although high ANP concentrations are seen in preterm neonates, particularly those with lung disease, the renal diuretic and natriuretic response to ANP in these infants is blunted. Possible reasons for this include low renal perfusion pressure in the neonatal kidney, and inhibition of ANP effect by high circulating concentrations of angiotensin II and aldosterone. Thus, the late hyponatremia of prematurity is unlikely to be caused by ANP abnormalities.

Catecholamines, both neuronally derived and locally produced in the renal parenchyma, are increased markedly in concentration in the first few hours after birth and under stressful conditions thereafter. The renal sympathetic nerve activity, mimicked by catecholamines, reduces renal sodium excretion by limiting the increase in the glomerular filtration rate that occurs in the early neonatal period and by promoting the reabsorption of sodium in the tubules. Likewise, cortisol, a glucocorticosteroid hormone, enhances tubular reabsorption of sodium by promoting the maturation of ion transporters, specifically Na/H exchanger in the distal segment of the proximal tubule. Thus, neither catecholamines nor cortisol has been linked to the pathogenesis of late hyponatremia of prematurity.

<u>References:</u>

Baum M, Quigley R. Ontogeny of renal sodium transport. *Semin Perinatol.* 2004;28:91-96

Baylis PH. Vasopressin and its neurophysin. In: DeGroot LJ, ed. *Endocrinology.* 3rd ed. Philadelphia, Pa: WB Saunders; 1995:406-420

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Feld LG, Corey HE. Renal transport of sodium during early development. In: Polin RA, Fox WW, Abman SH, eds. *Fetal and Neonatal Physiology.* 3rd ed. Philadelphia, Pa: WB Saunders; 2004:1267-1278

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Mortensen RM, Williams GH. Aldosterone action. In: DeGroot LJ, ed. *Endocrinology.* 3rd ed. Philadelphia, Pa: WB Saunders; 1995:1668-1676

Wintour EM. Alcorn D, Rockell MD. Development and function of the fetal kidney. In: Brace RA, Hanson MA, Rodeck CH, eds. *Fetus and Neonate: Physiology and Clinical Applications: Body Fluids and Kidney Function.* Vol 4. Cambridge, England: Cambridge University Press; 1998:3-56

<u>Content Specifications:</u>

Understand the production sites and actions of various types of vasoactive peptides that affect renal function

Understand the etiology of electrolyte abnormalities in the neonate
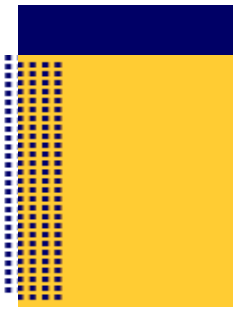
Recognize the clinical and laboratory manifestations of electrolyte abnormalities in the neonate

Know how to calculate renal clearance

PREVIOUS   NEXT

NeoReviewsPlus

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A term infant was delivered yesterday to a 25-year-old primiparous kindergarten teacher. Mother reports that she has had a runny nose and fever beginning one day prior to delivery, and today she notes reddish papules on her face and trunk, some of which have become vesicles. She now remembers sending one of her pupils home from school about 10 days ago upon discovering a similar rash, and she later learned that he had chicken pox. She does not recall having had chicken pox herself. Examination of the infant is normal.

Of the following, the treatment MOST indicated for the infant at this time is

1	acetaminophen
☒ **2**	acyclovir
3	amantadine
4	varicella attenuated live-virus vaccine
5	varicella-zoster immune globulin

You selected **2**, the correct answer is **5**.

Maternal varicella has varied effects on the fetus and newborn depending on the timing of the infection. Infection early in pregnancy--between 8 weeks and 20 weeks--can result in congenital varicella syndrome with skin lesions, ocular defects, hypoplasia of limb, bone and muscle, and central nervous system lesions. The risk is greatest between 13 weeks and 20 weeks, when a 7% risk of congenital varicella is reported. Of note, herpes zoster during pregnancy is not associated with the varicella syndrome. During midpregnancy, varicella may be more severe in the pregnant woman, with an increased risk of varicella pneumonitis. Fetal varicella may occur, but stigmata of the congenital varicella syndrome would not be expected.

Varicella-zoster immune globulin (VZIG) should be given to infants born to mothers whose symptoms presented in the interval from five days before to two days after delivery. Approximately 24% to 50% of infants so exposed will develop clinical disease, and, of these, 20% to 30% may die. This treatment will not prevent the infant from developing varicella, but it will lessen severity of the disease. Nevertheless, 15% of treated infants may develop severe infection. VZIG lengthens the incubation period to 28 days, rather than 21 days, after exposure. VZIG also is indicated for hospitalized premature infants >28 weeks' gestation exposed to varicella whose mothers have not had varicella as well as to all exposed preterm infants <28 weeks' gestational age.

Acetaminophen is commonly used for analgesia and fever reduction among infants. There is some evidence that its use may prolong varicella. It has no role for the asymptomatic infant, as in the vignette.

Acyclovir may be helpful in the treatment of infants with severe varicella. It should be started early in the illness, during the period of viral replication, which extends to about 72 hours after the rash appears. For this infant, no symptoms have appeared, and this treatment is not indicated.

Amantadine has specific antiviral activity against influenza A viruses. It is not indicated in this situation.

Varicella attenuated live-virus vaccine is not indicated for pregnant women. One dose of this vaccine results in seroconversion of 97% of the 1- to 12-year-old children for whom it is recommended. Two doses, one month to two months apart, are needed for unvaccinated

adolescents or adults. Postpartum use, if implemented, among seronegative women is estimated to potentially eliminate one-half of chickenpox cases.

References:

Baley JE, Toltzis P. Viral infections. In: Fanaroff AA, Martin RJ. (eds). Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant. 7th ed. St. Louis, Mo.: Mosby; 2002:755-802

Infections. In: Cunningham FG, Gant NF, Leveno KJ, et al. . Williams Obstetrics. 21st ed. New York: McGraw-Hill; 2001:1461-84

Laartz BL. eMedicine: Viral infections and pregnancy. Available at http://www.emedicine.com/med/topic3270.htm. Accessed April 15, 2005

Speer ME. Varicella-zoster infection in the newborn. Available at http://www.uptodate.com [subscription required]. Accessed March 28, 2005

Content Specification:

 Know the treatment of herpes simplex and varicella zoster

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After a series of difficult deliveries, your staff has the impression that cord blood acidosis is worse at night than by day. The pH values of 100 nighttime deliveries were compared with 100 daytime deliveries, with respective medians of 7.20 and 7.24.

Of the following, the statistical test that will BEST indicate whether the medians are statistically different is the

☒ 1	chi-square
2	Fischer exact
3	Kruskal-Wallis
4	Mann-Whitney
5	Student *t*

You selected 1, the correct answer is 4.

Inferences about pH data in this vignette are best made using the Mann-Whitney test, due to the data being ordinal and non-Gaussian.

Data analysis starts with a null hypothesis. The burden is on the data to show a significant difference, to demonstrate a pattern, and to reject the null hypothesis. Statistical tests are designed to estimate the probability *(P)* that the pattern observed was merely a chance occurrence and that the null hypothesis is accepted. In much biologic and medical work, if the observed data show a pattern that has less than a 5% chance of being a random occurrence, then the null hypothesis is rejected and the pattern is considered significant.

In that case, there still is a small chance that there really is no pattern, and that the analyst is making a mistake by declaring there is. This is called a type 1 error, and the type I error rate is denoted as alpha (*a*). If the *P*-value found after applying a statistical test is less than the agreed-upon significant *a*, the analyst concludes there is less of a chance of a type I error.

Similarly, if the null hypothesis is accepted when there truly is a pattern, this is a type II error, whose rate is beta (*b*). The power of a study, or 1-*b*, is important when a data set does not suggest a pattern. The important question then is, "What is the chance that there might indeed be a hidden pattern?" The answer is the *b* of the study. The smaller the *b* (and so the greater the power), the less the chance that a true pattern was not detected. The most likely cause of a type II error is a small sample size. Beta estimates, then, become critical in study design. Sample sizes often are computed based on estimates and previous studies using an á of 5% and a *b* of 20%.

The type of statistical test used depends on the nature of the variables measured. One way of classifying variables is to group them as continuous, categorical, or ordinal. Continuous variables can be identified further as normal (Gaussian) or non-normal. A Gaussian distribution is expected to have a symmetric, bell-shaped frequency curve with a median that matches the mean and equal distribution around the central tendency.

Student *t* test often is considered for continuous and normal (parametric) data, such as height, hemoglobin concentration, or gastrointestinal transit times. The mathematics is based on the Gaussian bell-shaped curve. The Student *t* test is used to compare two groups of equal variance. Other tests in this class include the paired *t* test, the Welsh test, and the parametric analysis of variance (ANOVA) tests. Because so many variables in nature are Gaussian, this class of tests is the most frequently used. However, this test is not valid for nonGaussian data

in this vignette.

Categorical variables give discrete data that can be pigeonholed, such as eye color, gender, or death. These data often can be analyzed using chi-square or Fisher exact tests. The decision to use one or the other is governed by the sample size and the minimum expected number in each pigeonhole. The Fisher exact test is used for smaller sample sizes than in the vignette.

If the variables studied are not normal but still can be put in order from smallest to largest, all is not lost. Example variables include pain scales, pH values, and free-throw success rates. These variables often have interval scale problems: the importance of a difference between pain scores of 2 and 3 is not the same as the difference between 9 and 10. Because pH is based on log-transformed data, it suffers from this interval problem: the clinical importance of the difference between 7.30 and 7.40 is not the same as the difference between 7.10 and 7.20.

Although the specific parameters measured might not be appropriate inputs for the tests mentioned previously, their rank or order relative to one another can be used in nonparametric tests. The Mann-Whitney test takes the measured values for two groups and combines them into one ordered list. The two groups then are separated, but only the rank order of each item in the master list is used. These derived ranks in each group are summed, and a statistic is extracted that indicates whether these rank sums are significantly different between the two groups. The test is not dependent on scale or most other transformations of the initial measured values. The Mann-Whitney test is not based on Gaussian distribution assumptions, so it can be used without assuming that the observed natural phenomenon is distributed normally. For example, Figure 1 shows the calculation of "Ucalc" comparing 2 groups, each having 6 pH values. Ucalc is then entered into the table of Mann-Whitney critcal values (Figure 2) to determine statistical significance. To answer the staff questions referred to in the vignette, the 200 pH values obtained should be analyzed in this manner.

The Kruskal-Wallis test is similarly useful for ordinal data but is used when there are three or more groups being compared. It does not say, of itself, which group is the most different, just that a significant difference exists somewhere among all the groups.

Because all parametric data can be ordered, why not always use nonparametric testing? As appealing as it may seem to have to remember fewer tests, the nonparametric tests generally are less powerful and more likely to miss finding a pattern that is truly there (type II error). Some authors believe that this objection can be overcome by slightly larger sample sizes (greater power), but most believe that if a parametric test is applicable, it should be used.

References:

Bland M. *Introduction to Medical Statistics.* 3rd ed. Oxford, England: Oxford University Press; 2001:210-229, 257-267

Swinscow TD, Campbell MJ. *Statistics at Square One.* 10th ed. London: BMJ Books; 2001:135-144

Zar JH. *Biostatistical Analysis.* 4th ed. Upper Saddle River, NJ: Prentice Hall; 1999:161-176, 486-515

Content specifications:

Understand the null hypothesis

Understand type I (alpha, *a*) and type II (beta, *b*) errors

Understand the importance of calculations of power

Distinguish the differences between categorical, ordinal, and continuous variables
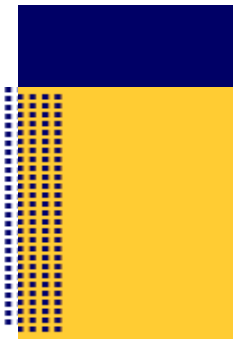
Know when to apply a parametric test (eg chi-square test, Fisher exact test, Student *t* test, analysis of variance (ANOVA), etc)

Know when to use a nonparametric test (eg signed rank test, rank sum test, etc)

PREVIOUS   NEXT

Table: Mann-Whitney U Computation Example

Compare two groups of pH values.

Ho (null hypothesis) = Group 1 and Group 2 are not different

	Group 1	Master List Ranking	Group2
	7.29	1	
	7.28	2	
		3	7.27
	7.25	4	
	7.23	5	
	7.22	6	
	7.2	7	
		8	7.17
		9	7.14
		10	7.11
		11	7.1
		12	7.09
Rank Sum		Sum1=25	Sum2=53
	n1=6		n2=6

$C1 = n1n2 + n1(n1+1)/2 - Sum1$
$= 6*6 + 6*7/2 - 25$
$= 32$

$C1' = n1n2 + n2(n2+1)/2 - Sum2$
$= 6*6 + 6*7/2 - 53$
$= 4$

$C2 = n1n2 - C1$
$= 6*6 -32$
$= 4$

$C2' = n1n2 - C1'$
$= 6*6 -53$
$= 32$

Ucalc = larger of C1 or C2 (which equals larger of C1' or C2') = 32

Ucritical(6, 6, 0.025) = 31 (from special table), therefore reject Ho.

Larger	Smaller	Significance level						
n_1	n_2	0.2	0.1	0.05	0.02	0.01	0.002	0.001
3	2	6						
3	3	8	9					
4	2	8						
4	3	11	12					
4	4	13	15	16				
5	2	9	10					
5	3	13	14	15				
5	4	16	18	19	20			
5	5	20	21	23	24	25		
6	2	11	12					
6	3	15	16	17				
6	4	19	21	22	23	24		
6	5	23	25	27	28	29		
6	6	27	29	**31**	33	34		

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You are asked to consult on a term female infant with a strong family history of recurrent infections that develop in childhood due to an inherited primary immunodeficiency syndrome. There are equal numbers of affected males and females in the family.

Of the following, the primary immunodeficiency disorder MOST likely to occur in both males and females is

1 Bruton agammaglobulinemia

2 Chédiak-Higashi syndrome

☒ 3 Duncan disease

4 Hyperimmunoglobulin M syndrome

5 Wiskott-Aldrich syndrome

You selected **3**, the correct answer is **2**.

Immunodeficiency disorders can be classified as primary or secondary. Primary immunodeficiency disorders are genetically determined conditions that result in increased susceptibility to infections. Secondary immunodeficiency disorders are the result of aging, infections, malnutrition, or medications.

More than 100 primary immunodeficiency disorders have been described. There is a 5-to-1 male-to-female sex predominance for primary immunodeficiency disorders that present in childhood, because many are due to X-linked recessive mutations (Figure). Among the primary immunodeficiency disorders in this vignette, only Chédiak-Higashi syndrome (CHS) affects both males and females, whereas the rest of the syndromes are X-linked and affect only males.

CHS is characterized by recurrent infections, excessive bleeding, and partial oculocutaneous albinism. The hallmark of CHS is giant lysosomal granules seen in neutrophils, melanocytes, neural Schwann cells, hepatocytes, renal tubular cells, and gastric mucosa. Defective melanization of melanosomes causes partial oculocutaneous albinism. Children with CHS have light skin and silvery hair. Photophobia is caused by loss of iris pigmentation. Progressive neurologic deterioration, characterized by weakness, ataxia, neuropathies, and seizures, develops if the infant survives until late childhood.

The immunodeficiency is due to abnormal lysosomal granule function. The giant lysosomal granules in neutrophils cannot fuse with phagosomes, and ingested bacteria are not killed. Recurrent skin infections, pyoderma, and subcutaneous abscesses caused by *Staphylococcus aureus* are common. CHS usually is fatal by 30 months of age due to infection, bleeding or secondary lymphoma.

CHS is an autosomal recessive disorder with equal numbers of affected males and females. The genetic defect has been localized to chromosome 1q42-43. The CHS protein is important in the synthesis and maintenance of storage and secretory lysosomal granules.

Bruton agammaglobulinemia (BA), also known as X-linked agammaglobulinemia, is associated with the development of recurrent infections because of absent circulating B cells and low levels of all immunoglobulin isotypes. The infections, caused by pyogenic bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae,* develop after maternal immunoglobulin (Ig)G concentrations wane at 6 to 9 months of age. BA is due to a mutation in

B-cell tyrosine kinase gene mapped to position Xq22. This kinase is necessary for pro-B-cell maturation into pre-B cells. The bone marrow of males with BA has normal numbers of pro-B cells but severely decreased numbers of pre-B cells. Patients with BA have no B cells in their blood or lymphoid tissue, and their sera contain only small amounts of IgG and no IgA, IgM, IgE or IgD.

Duncan disease, also referred to as X-linked lymphoproliferative disease (XLP), is due to abnormal B-cell polyclonal expansion triggered by Epstein Barr virus (EBV). Affected males are healthy until an EBV infection triggers fulminant, frequently fatal infectious mononucleosis, B-cell lymphomas, hepatitis, aplastic anemia, or hypogammaglobulinemia. The median age of onset is 5 years, and 70% die by age 10 years. XLP is caused by a mutation in the SH2D1A gene at Xq26-27. This gene encodes the signaling lymphocyte activation molecule-associated protein (SAP). In patients with XLP, the lack of SAP leads to uncontrolled cytotoxic T-cell response to EBV and polyclonal B-cell expansion.

HyperIgM syndrome (HIgM) is a life-threatening, X-linked, inherited disorder that results in extremely elevated IgM concentrations and low concentrations of other Ig isotypes (IgG, IgA, and IgE). Males with HIgM develop recurrent sinopulmonary infections and chronic diarrhea between 6 months and 12 months of age as maternally derived IgG wanes. Frequent sinopulmonary infections with *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* result in chronic cough and bronchiectasis. The gastrointestinal tract becomes infiltrated with IgM-producing B cells. Intractable diarrhea caused by *Cryptosporidium*, rotavirus, *Giardia*, or *Campylobacter* results in malnutrition and cachexia. Patients with HIgM have high rates of malignancies, particularly lymphomas and gastrointestinal adenomas. The mean age at death from HIgM is 11.7 years; only 20% survive to 25 years of age.

In HIgM, B cells can initiate the immune response by producing IgM but cannot make the isotype switch from IgM to synthesis of IgG, IgA, or IgE. HIgM is due to a mutation in the gene for the CD40 ligand on T cells. T-cell CD40 ligand must bind to CD40 receptors on B cells for Ig heavy chain class isotype switch to occur. The absence of CD40 ligand on T cells interrupts B-cell activation. The abnormal gene for HIgM is localized to Xq26.

Wiskott-Aldrich syndrome (WAS) is an X-linked immunodeficiency characterized by recurrent bacterial sinopulmonary infections, eczema, and thrombocytopenia. Recurrent infections are due to low IgM and IgG concentrations and a lack of antibody production against polysaccharides. Decreased numbers of $CD8^+$ T cells result in elevated CD4/CD8 ratios. WAS may present with recurrent bleeding from thrombocytopenia before the development of recurrent infections. Episodes of recurrent otitis media begin at age 3 months to 8 months as maternal IgG levels diminish. Pneumonia and meningitis caused by encapsulated bacteria such as *S pneumoniae* and *H influenzae* and life-threatening varicella and herpes simplex infections may develop. Eczema may be mild or severe and may be associated with milk or food allergies. The WAS gene is localized on Xp11.23, and it encodes the WAS protein (WASP). *WASP* appears to regulate actin polymerization in hematopoietic cells, but its exact function has not been elucidated.

References:

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Male D. Cell migration and inflammation. In: Roitt I, Brostoff J, Male D, eds. *Immunology*. 6th ed. Edinburgh, Scotland: Mosby; 2001:307-308

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Shigeoka AO. eMedicine: X-linked immunodeficiency with hyper IgM. Available at http://www.emedicine.com/ped/topic2457.htm. Accessed April 2005

Content Specifications:

Know how to diagnose hypopigmentation, including albinism, phenylketonuria, Chédiak-Higashi syndrome, tuberous sclerosis, partial albinism, and Waardenburg syndrome

Recognize the clinical features associated with X-linked disorders

Demonstrate understanding of inheritance patterns and recurrence risks for X-linked recessive disorders

Understand the consequences of immunoglobulin deficiencies

Be aware of the clinical features and differential diagnosis of neonates with immune deficiency

Be aware of the prognosis for neonates with common immune deficiencies

Understand the etiologies and pathophysiologies of neonatal thrombocytopenia and thrombocytosis

PREVIOUS   NEXT

**Gene location of
primary immunodeficiency
disorders on X chromosome**
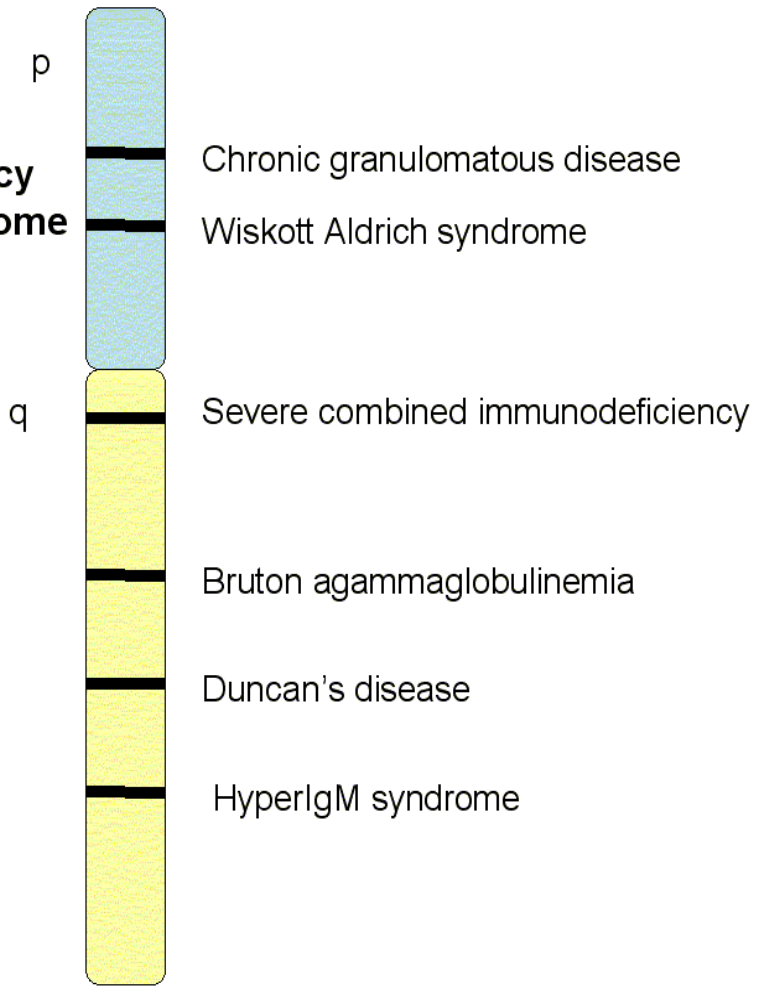
p

Chronic granulomatous disease

Wiskott Aldrich syndrome

q

Severe combined immunodeficiency

Bruton agammaglobulinemia

Duncan's disease

HyperIgM syndrome

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A 3,500-g female newborn is delivered active but cyanotic at a mountain hospital at an altitude of 8,000 feet. Sepsis is not suspected. At the age of one hour, she has oxygen saturation by pulse oximetry (SpO2) in the right upper extremity of 89% in ambient oxygen of 100%. An arterial blood gas (ABG) from right radial artery reveals partial pressure of oxygen (PaO2) of 323 mmHg, an oxygen saturation (SaO2) of 100%, and a total hemoglobin of 17 gm/dL. Methylene blue is given, 3.5 mg intravenously, without effect.

Of the following, the BEST explanation for the discordance between SpO2 and SaO2 in this case is

1	congenital porphyria
2 ☒	glucose-6-phosphate-dehydrogenase deficiency
3	hemoglobin M disorder
4	high-altitude effect
5	machine-error in the pulse oximeter

You selected **2**, the correct answer is **3**.

The best explanation for the findings in the infant in this vignette is congenital methemoglobinemia due to hemoglobin M disorder.

Abnormalities of hemoglobin (Hgb) structure can affect how the four oxygen molecules bind reversibly to each Hgb tetramer. Changes in either the alpha chain or the beta chain of the Hgb molecule can affect oxygen binding. For example, Hgb Kansas has a low affinity for oxygen, while Hgb Yakima has a higher affinity.

In Hgb M disorder, one of seven known single substitutions causes the four heme iron atoms of each Hgb molecule to stay oxidized in the ferric +3 state instead of the ferrous +2 state. This makes oxygen bind almost irreversibly to the molecule, and oxygen exchange cannot take place. Even with the oxygen attached, Hgb M will be dark-colored. With normal Hgb, it takes 5g/dL (50 g/L)of deoxygenated hemoglobin to visually detect cyanosis. Hgb M will present as cyanosis with as little as 1.5 g/dL (15 g/L). If the alteration is in the gamma chains, the disorder is transient. If the alteration is in the alpha or beta chains, the disorder is lifelong. The homozygous state is not viable. The diagnosis is confirmed by Hgb electrophoresis. Patients are asymptomatic except for cyanosis. There is no treatment for Hgb M disorder.

Machine error in the pulse oximeter does not account for the discordance between SpO2 and SaO2. A pulse oximeter measures the pulsed absorbance above baseline at 660 nm for Hgb and 940 nm for oxyhemoglobin (HgbO2), and calculates the ratio Hgb/HgbO2. A ratio of 0.43 in one model of pulse oximeter corresponds to SpO2 of 100%, and a ratio of 1.0 gives SpO2 of 85%. Hgb M absorbs equally at both wavelengths, giving a ratio closer to 1.0, thus overestimating the true ratio of Hgb/HgbO2. This is reflected as a lower SpO2 on the pulse oximeter despite a higher SaO2 computed from the arterial blood gas (ABG). Remember, the ABG machine usually does not measure oxygen saturation but instead computes it assuming that normal Hgb is present.

Co-oximetry analyzes at four or more wavelengths and can provide percentages of Hgb, HgbO2, MetHgb, and Hgb-Carbon monoxide. Some ABG machines include co-oximetry, but usually co-oximetry needs to be ordered separately.

Another cause of congenital methemoglobinemia is deficiency of NADH-methemoglobin

(MetHgb) reductase. MetHgb is made constantly in small amounts from normal Hgb by the oxidation of heme iron. Homeostasis is preserved by NADH-MetHgb reductase. A rare autosomal-recessive deficiency in this enzyme allows accumulation of MetHgb. Treatment is with intravenous methylene blue at a dose of 1 mg/kg, and an improvement in SpO_2 is expected within two hours. Lack of a response, as in the infant in this vignette, suggests a hemoglobin M disorder, although glucose-6-phosphate-dehydrogenase (G6PD) deficiency cannot be ruled out.

G6PD deficiency is an X-linked disorder of red cells that leads to low levels of reduced glutathione, making the cells susceptible to oxidant stress and resulting in hemolysis. Given an oxidative stress, such as infection, vitamin C, or fava bean ingestion, deficiency of G6PD would not allow the red cells to make adequate amounts of NADPH with which to reduce MetHgb in the methylene blue reaction. It is possible that G6PD deficiency could have contributed to higher MetHgb levels in the vignette, but, in the absence of sepsis or anemia, this is less likely on the first day of life than Hgb M disorder.

The porphyrias are a group of disorders of the heme biosynthetic pathway. Congenital porphyria is an autosomal recessive decrease in uroporphyrinogen cosynthase resulting in accumulation and hypersecretion of brown porphyrins into the amniotic fluid, urine, and skin. Although infants may be affected by anemia, presentation usually is delayed until adulthood. Oxygen saturation is not affected.

Altitude affects the oxygen tension in the alveolus (PaO_2) via the alveolar gas equation:

$$PaO_2 = FiO_2(B-47) - (PaCO_2/R)+F$$

in which FiO_2 = fraction of inspired O_2, B = barometric pressure in mmHg, 47 represents vapor pressure of water at 37° C, $PaCO_2$ = alveolar CO_2 (estimated by blood PCO_2), R = respiratory quotient (volume of CO_2 made / O_2 used, usually 0.8), and F = fudge factor.

For the first 10,000 ft, barometric pressure will decrease about 23 mmHg for every 1,000 ft above sea level. At sea level in room air, the inhaled oxygen tension (first term in the above equation) would be 149 mmHg versus 111 mmHg at 8,000 feet. Computing from the above equation, the PaO_2 will decrease from 99 mmHg to 61 mmHg. Acclimatization strategies include hyperventilation to reduce the second component in the equation, polycythemia to increase oxygen-carrying capacity, and increased 2,3-diphosphoglycerate to shift the $HgbO_2$ dissociation curve to the right, facilitating oxygen delivery. None of these adaptations explains this discordance in oxygen saturations in the vignette.

References:

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Jensen LA, Onyskiw JE, Prasad NG. Meta-analysis of arterial oxygen saturation monitoring by pulse oximetry in adults. *Heart Lung.* 1998;27:387-408

Mentzer WC, Glader BE. Erythrocyte disorders in infancy. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn.* 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:1180-1214

Sassa S. The porphyrias. In: Behrman RE, Kliegman RM, Jensen HB, eds. *Nelson Textbook of Pediatrics.* 17th ed. Philadelphia, Pa: Elsevier Saunders; 2004:495-504

West JB. *Respiratory Physiology: The Essentials.* 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2000;119-122

Content Specifications:

Understand and be able to interpret the various techniques for assessing lung function,
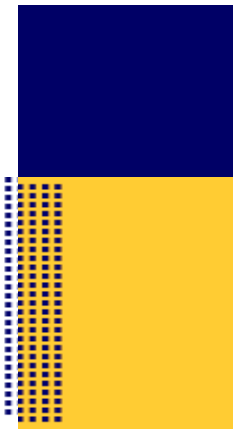
including arterial blood gas measurements and noninvasive methods for estimating arterial oxygenation

Know what determines alveolar gas composition (ie, ability to predict the effects of changes in altitude on oxygenation)

Understand the laboratory features of neonatal hemoglobinopathies

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You are asked to recommend a surfactant product to your hospital's Pharmacy and Therapeutics Committee.

Of the following, the surfactant product MOST likely to be excluded from the formulary is

1	beractant
2	calfactant
3	colfosceril
☒ **4**	lucinactant
5	poractant alfa

You selected 4 , the correct answer is 3 .

Surfactant replacement for infants with surfactant deficiency reduces mortality, severity of illness, and incidence of pneumothorax and pulmonary interstitial emphysema. Both natural and synthetic surfactants have proven efficacious in randomized, placebo-controlled trials.

First-generation synthetic surfactants, such as colfosceril, artificial lung expanding compound, and pumactant, contain dipalmitoylphosphatidylcholine as the principal surface active agent. They contain no surfactant protein or peptide mimics of surfactant protein activity (Table). Chemical agents were added to reproduce the spreading functions of the surfactant proteins. When compared to natural surfactants derived from bovine or porcine sources (alveofact, beractant, bovine lipid extract surfactant, calfactant, poractant alfa), these first-generation synthetic surfactants performed less effectively than natural surfactants.

Second-generation synthetic surfactants, such as, lucinactant, recombinant surfactant protein C surfactant, also contain dipalmitoylphosphatidylcholine as the primary surface active agent and either a surfactant protein or peptide that mimics surfactant protein C or B activity (recombinant surfactant protein C or sinapultide, respectively). Lucinactant has proven clinical superiority over colfosceril palmitate, a first-generation synthetic surfactant, for reducing the incidence of bronchopulmonary dysplasia and the combined outcome of death or bronchopulmonary dysplasia by 36 weeks' postmenstrual age. When compared to natural surfactants (eg, beractant, poractant alfa), no significant differences in clinical outcome were reported.

Additional studies with second-generation synthetic surfactants are needed. The efficacy trials of lucinactant were hampered by early trial closure, limited statistical power, trial design questions, and limited information on the metabolic fate of product components. Recombinant surfactant protein C surfactant has been studied in vitro and in vivo in animal models and adults with Acute Respiratory Distress Syndrome (ARDS). Although in vitro and animal studies have been promising, clinical trials in adults with ARDS have not shown significant benefit at the doses studied. Clinical trials in neonates with surfactant deficiency have not been reported.

Second-generation synthetic surfactant products offer promising therapies, but additional information about safety and efficacy still is needed. However, because second-generation surfactants and natural surfactants outperform first-generation synthetic surfactants, first-generation surfactants no longer are preferred. Therefore, colfosceril is the most likely of the surfactant products to be excluded from the formulary. Colfosceril does have some advantages compared to other products. It does not need refrigeration, special mixing, or a warming cradle

before use. When refrigeration and preparation equipment are not available, colfosceril remains an acceptable option.

Natural surfactants and lucinactant appear to result in similar clinical outcomes. Factors driving the development of synthetic surfactants include reduced transmission of microbes, reduced exposure to animal proteins, and ability to manufacture large quantities of surfactant with consistent content. On the other hand, there has been no evidence that the natural surfactants have been associated with microbe transmission or caused immunologic illness. Manufacturing practices also have allowed for consistency in natural surfactant composition.

Natural surfactants also have been evaluated in comparison trials and found equally effective. No major differences in outcomes make one product superior to the others.

<u>References</u>:

Moya FR. A multicenter, randomized, masked, comparison trial of lucinactant, colfosceril palmitate and beractant for the prevention of respiratory distress syndrome among very preterm infants. *Pediatrics.* 2005;115:1018-1029

Sinha SK, Lacaze-Masmonteil T, Soler AV, et al. A multicenter, randomized, controlled trial of lucinactant versus poractant alfa among very premature infants at high risk for respiratory distress syndrome. *Pediatrics.* 2005;115:1030-1038

Spragg RG, Lewis JF, Walmrath HD, et al. Effect of recombinant surfactant protein C-based surfactant on the Acute Respiratory Distress Syndrome. *N Engl J Med.* 2004;351:884-892

Suresh GK, Soll RF. Exogenous surfactants. In: Goldsmith JP, Karotkin EH, eds. *Assisted Ventilation of the Neonate.* 4th ed. Philadelphia, PA: Saunders; 2003:329-344

<u>Content Specification</u>:

Understand the management of respiratory distress syndrome (RDS), including surfactant replacement.

| ◄ PREVIOUS | NEXT ► |

Table: Surfactant Preparations

	Generic Name	Preparation	PL and Protein	PL Dose mg/kg	Dose ml/kg	Comments
Natural	Beractant	Bovine lung mince	DPPC, PG, SP-B, SP-C	100	4.0	Refrigerate, Protect from Light Warm by standing at room temp x 20 min or x 8 min Do Not Shake, Swirl to mix
	Calfactant	Calf (bovine) lung extract	DPPC, SP-B, SP-C	105	3.0	Refrigerate, Protect from Light Do Not Shake, Swirl to mix
	Poractant alfa	Porcine lung mince	DPPC, SP-B, SP-C	200	2.5	Refrigerate Do Not Shake, Gently turn vial upside-down until uniform
Synthetic	Colfosceril Palmitate	DPPC + Hexadecanol + Tyloxapol	DPPC no protein	67.5	5.0	No refrigeration Mix thoroughly with preservative-free sterile
	Lucinactant	Sinapultide (KL-4) DPPC, POPG Palmitic acid	DPPC, POPG Palmitic Acid Sinapultide	175	5.8	Refrigerate Warming Cradle Agitate
	Recombinant Surfactant Protein C	Lusupultide (rSP-C) DPPC, POPG Palmitic Acid, Calcium chloride	DPPC, POPG Palmitic acid rSP-C	50	1.0	Clinical studies in ARDS did not improve outcomes Dosing from ARDS studies, not neonatal studies

PL, phospholipid; SP-B(or C), surfactant protein B(or C); PG, phosphatidylglycerol; POPG, palmitoyl-oleoyl phosphatidylglycerol; rSP-C, recombinant protein C; KL-4 peptide, SPB mimic

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A recent article by Tiffany and associates reported the two-year outcomes for 16 consecutive infants presenting with either central nervous system (CNS) and/or disseminated neonatal herpes simplex infections. These infants were treated with two years of continuous oral acyclovir therapy after completion of the standard parenteral acyclovir therapy (60 mg/kg per day divided into 3 doses over 21 days). Target minimum peak serum acyclovir concentrations were >2 mcg/mL for the first 3 patients and >3 mcg/mL for all others. They found no severe adverse effects of the prolonged acyclovir therapy.

At the end of treatment, 11 of 16 (69%) had Bayley mental scores in the normal range, 11 of 14 (79%) had normal motor scores, and 5 of 16 had some developmental delay though only 1 was considered severe. None had died. These results compare favorably to previous large series in which 49% to 75% of infants with CNS or disseminated herpes simplex infection died or developed moderate to severe disabilities.

Acyclovir therapy has been associated with severe thrombocytopenia and neutropenia. Aplastic anemia has not been reported as a consequence of this drug.

In considering whether prolonged oral acyclovir therapy should be recommended, you are concerned that the small number of subjects does not allow an adequate estimate of safety. To make a recommendation about use of this therapy, you would like to be 90% certain that serious adverse effects will not occur. You estimate that risk from the information in the vignette.

Of the following, the HIGHEST incidence of adverse effects that still could occur, given the data from this study, is

1	2%
☒ 2	10%
3	25%
4	50%
5	90%

You selected **2**, the correct answer is **3**.

In the interpretation of clinical trial data, we are most familiar with the type I (*a*) error, the chance of finding a difference between groups that isn't really true. We generally accept an *a* error of 5% (ie, p <0.05). This means that we will reject the null hypothesis (ie, that there is no actual difference between groups) when the probability that the difference we observed could have occurred by chance alone is less than 5%. The type II (*b*) error is defined as the probability that one is reporting no difference between groups (ie, accepting the null hypothesis) when a real difference actually exists. The power to detect a true difference is defined as 1-*b*. Therefore, a *b*-error of 0.1 is the same as saying you have a power of 90% to detect a difference between groups. The larger the sample size, the smaller the *b*-error. On the other hand, the smaller the difference you are seeking, the larger the sample size you will need.

In this vignette, even a 2% incidence of a potentially fatal adverse effect, such as aplastic anemia, would be an important risk to weigh against the potential benefits of long-term drug treatment. Given an acceptable *a*-error of 0.05 and a *b*-error of 0.1 (90% power), 16 subjects would have the power to rule out an incidence of an adverse effect at 50% but could miss an adverse event risk of 25%. This is based on the assumption that the control group would have

an incidence approaching zero (Table). One would not want to recommend a treatment if the incidence of a potentially severe or fatal complication might be as high as 25%. In this case, more safety data is needed to better estimate the ratio of benefit versus risk. This is why large multicenter trials are so important, and why small studies, in general, should not dictate clinical care.

The table was constructed using the formula for estimating sample size in cases where the outcome is expressed in incidences or proportions. The formula for calculating sample size per group (n) depends on the values selected for *a* and *b* as well as the population incidence of the outcome you are measuring (p), which (in most cases) is assumed equal to the control sample incidence (p_c). In addition, the expected or sought-after difference between the two incidences ($\bar{\delta}$) and the resultant treatment incidence (p_t) is used in the calculation. The formula uses the Z-scores for *a* and *b* rather than the raw values. Z represents a number of standard deviations away from the population mean and can be found in standard tables. The formula is:

$$n = \left[\frac{Z_\alpha \sqrt{p(1-p)} - Z_\beta \sqrt{p_t(1-p_t) + p_c(1-p_c)}}{\delta} \right]^2$$

References:

American Academy of Pediatrics. Herpes simplex. In: Pickering LK, ed. *Red Book: 2003 Report of the Committee on Infectious Diseases.* 26th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2003:344-353

Inference on Proportions. In: Colton T. *Statistics in Medicine.* Boston: Little Brown and Co; 1974:151-188

Tiffany KF, Benjamin DK Jr, Palasanthiran P, O'Donnell K, Gutman LT. Improved neurodevelopmental outcomes following long-term high-dose oral acyclovir therapy in infants with central nervous system and disseminated herpes simplex disease. *J of Perinatol.* 2005;25:156-161

Content Specifications:

Understand the null hypothesis

Understand type I alpha (*a*) and type II beta (*b*) errors

Determine the importance of calculations of power

Identify and evaluate the efficacy of study designs commonly used in clinical research

Know how to evaluate the rate of events and adverse effects in a clinical trial

PREVIOUS   NEXT

Table

Increased Incidence of an Adverse Event over Control (%)	Subjects Needed/Group (b - Error = 0.1 Power = 90%)	Subjects Needed/Group (b - Error = 0.2 Power = 80%)
50	9	6
25	26	19
12.5	60	43
10	77	56
5	163	118
2	421	304
1	850	614

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As part of your collaboration with maternal-fetal medicine, you have prenatal consultations with women in the high-risk clinic, some of whom have a history of congenital or acquired heart disease. Maternal heart disease may influence a woman's tolerance to pregnancy, growth and development of the fetus, and tolerance for delivery and the postpartum period.

Of the following, the MOST significant predictor of maternal or fetal complications among pregnant women with congenital heart disease is

1. arrhythmia
2. coagulopathy
3. cyanosis
4. Eisenmenger syndrome
5. functional classification

You selected **4**, the correct answer is **4**.

Many women reach the child-bearing years after diagnosis and treatment for congenital heart disease. In most cases, careful management allows for pregnancy with no long-term adverse effects after delivery. Overall, pregnancy among women with congenital heart disease is associated with increased pregnancy loss, increased pregnancy complications (especially cardiac), higher cesarean section rate, and premature birth.

Tolerance for pregnancy varies depending on the specific cardiac lesion and its effects on cardiac and respiratory physiology in the individual patient. A number of factors influence the tolerance to pregnancy. Major hemodynamic changes during pregnancy include blood pressure decrease mediated by a decrease in peripheral vascular resistance starting in early gestation and reaching a low point in the second trimester, and increase in intravascular volume peaking in the first half of the third trimester. Cardiac output increases 30% to 50% during pregnancy, with half of this increase occurring by 8 weeks' gestation. The rise in cardiac output during early pregnancy is due to increased stroke volume, whereas the rise in cardiac output during later pregnancy is due to higher heart rate. Labor and delivery is associated with marked increase in cardiac output, up to a 50% increase by the end of the second stage of labor. Dramatic volume shifts occur with delivery: physiologic transfusion follows the release of venocaval obstruction and contraction of the uterus; and blood loss at delivery and postpartum can deplete blood volume. Any of these changes may be compromised by maternal congenital heart disease.

Maternal cardiac disease is associated with an increased cesarean section rate. The cesarean section rate for fetal distress, failure to progress, breech or prior cesarean delivery is not increased, but some procedures are performed due to maternal risks associated with labor. Neonatal complications are increased (odds ratio 2.3, 95% confidence intervals 1.4 - 4). In a controlled study, 15% of infants of mothers with congenital heart disease delivered at <37 weeks' gestation as compared to 5% among controls. Some 6% had either intraventricular hemorrhage, delivery at <34 weeks' gestation, or fetal/neonatal death contrasted with 2% in the control group. Of mothers whose cardiac disease was not part of a recognized syndrome, 8% of their infants had congenital heart disease.

The congenital cardiac condition most threatening to pregnant women and their fetuses is

pulmonary hypertension associated with Eisenmenger syndrome. Patients with pulmonary hypertension secondary to a nonrestrictive ventricular septal defect have right to left shunting, which is exacerbated by the decrease in systemic vascular resistance of pregnancy, resulting in worsening cyanosis because afterload is required to control the right to left shunt. Tolerance to pregnancy is poor, with increased susceptibility to spontaneous abortion, preeclampsia, intrauterine growth impairment, prematurity, and postpartum hemorrhage. From 20% to 40% of these pregnancies end in spontaneous abortions. Prematurity and fetal growth restriction complicate 50% of cases, and fewer than 25% of pregnancies go to term. Perinatal mortality ranges from 8% to 28%. Tolerance to labor is particularly poor, and most maternal deaths occur postpartum. As increases in systemic vascular resistance occur during labor secondary to uterine contractions and maternal effort, abrupt drops in cardiac output may result in maternal syncope, sometimes fatal. This complication is particularly troublesome in patients with Eisenmenger syndrome because of the dependence of cardiac output on adequate preload. The combination of these factors has resulted in maternal mortality of 30% to 50% for Eisenmenger syndrome, with most deaths due to thromboembolism, volume depletion, and preeclampsia. In spite of the risks of labor, cesarean section delivery offers a worse prognosis. Most experts believe that Eisenmenger syndrome is a contraindication to pregnancy. In the absence of Eisenmenger syndrome, pulmonary hypertension is not an independent predictor of risk due to its association with left heart obstruction or poor functional status, both of which are ominous signs during pregnancy.

Adverse consequences from arrhythmias are not major risk factors for either mother or fetus in most situations. Atrioventricular nodal reentrant tachycardia is the most common supraventricular tachycardia among women, pregnant or not. In the absence of structural heart disease, maternal or fetal problems are unusual. If structural heart disease is present, hemodynamic instability may result. Atrioventricular reentrant supraventricular tachycardia is less common but more likely to be symptomatic because of the rapidity of the heart rate. Approximately 25% of patients with Ebstein anomaly have accessory conduction pathways commonly associated with hemodynamic deterioration due to tachycardia. Other arrhythmias are unusual among pregnant women unless they are associated with cardiac structural abnormalities or previous cardiac surgery. Most antiarrhythmic medications are able to be used in pregnancy, but data on the individual medications should be obtained before use. Radiofrequency ablation is not recommended during pregnancy because of the associated need for fluoroscopy and radiation exposure. Women on antiarrhythmic medications can consider radiofrequency ablation prepregnancy so as to avoid both the arrhythmia and the medications when pregnant. Cardioversion has been used with success for acute tachyarrhythmias with hemodynamic deterioration during pregnancy. Implantable cardioverter-defibrillators have been used successfully during pregnancy with no adverse fetal effects.

Most congenital heart diseases do not require anticoagulant medications. Pregnancy is associated with a relative hypercoagulable state, with 20% reductions in the prothrombin time and in the activated partial thromboplastin time. Although these reductions protect against bleeding at delivery, thromboembolic disease can occur, leading to pulmonary embolic disease or arterial stroke if right to left shunting is present. These phenomena are not major consequences of pregnancy among most women with congenital heart disease but can lead to embolic disease due to suboptimal anticoagulation in women whose underlying cardiac disease requires anticoagulation (such as artificial heart valve).

Maternal cyanosis also predicts increased maternal and fetal risk. Postpartum cardiac complications occur among 90% of women with cyanotic congenital heart disease (CHD) versus 19% with acyanotic CHD. If oxygen saturation maintains above 90%, the risk decreases. Use of oxygen in cyanotic CHD has not been shown to benefit either mother or fetus. Maternal cyanosis also is complicated by high hematocrit and hyperviscosity, sometimes requiring phlebotomy.

Maternal functional cardiac classification is a major determinant of risk. Women whose cardiac disease is associated with severe limitation or inability to carry out ordinary physical activity

(Classes III or IV) are at significant risk for cardiac complications. A scoring system gives one point for each of the following four findings if present: functional class III or IV; previous heart failure, transient ischemic attack, stroke or arrhythmia; left heart obstruction (mitral valve area <2cm^2, aortic valve area <1.5 cm^2, or peak left ventricular outflow gradient >30 mmHg); and left ventricular systolic ejection fraction <40%. Zero points were associated with a 4% risk for maternal primary cardiac complications, such as pulmonary edema, arrhythmia requiring treatment, stroke, cardiac arrest, or death. A 1-point score raises the risk to 26%, and a >1 point score was associated with a 62% risk. Neonatal complications tripled compared to matched controls without heart disease.

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Content Specifications:

Know the effects of maternal cardiac disease and its treatment on the fetus

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A 34-weeks'-gestation male infant was born in a taxi and transferred to a neonatal intensive care unit. His Apgar scores were unknown, but he cried at birth and was breathing spontaneously and in no distress on admission 1 hour after birth. His mother is an 18-year-old primigravida who did not obtain prenatal care before this delivery. She reported no illnesses during her pregnancy. The infant's blood was cultured on admission, and he was started on antibiotics, which were discontinued when the blood culture was reported to be sterile at 48 hours. He had a benign course and was tolerating increasing enteral nutrition until the sixth day, when he began looking ill, developed temperature instability, irritability, and feeding intolerance. Physical examination revealed a lethargic infant with tachypnea, hepatomegaly, and two small vesicles on an erythematous base on the posterior scalp. His eyes appeared normal. Laboratory investigation showed neutropenia and thrombocytopenia as well as elevated liver enzymes and prolonged prothrombin time and partial thromboplastin time. The direct bilirubin was reported as 1.4 mg/dL (23.94 mmol/L) with a total of 8.8 mg/dL (150.48mmol/L) Cerebrospinal fluid (CSF) was normal. The infant was recultured for bacteria and viruses, and the CSF was sent for herpes simplex DNA. The infant was restarted on intravenous antibiotics and an antiviral agent. CSF was negative for herpes simplex DNA, but throat swab and vesicle fluid grew herpes simplex virus. No bacteria were cultured.

Of the following, the RECOMMENDED course of treatment for this infant is

1	intravenous acyclovir for 7 days to 10 days
2	intravenous acyclovir for 14 days
3	intravenous acyclovir for 21 days
4	intravenous acyclovir for 21 days plus 2 years of oral acyclovir
5	intravenous vidarabine for 21 days

You selected 2 , the correct answer is 3 .

Neonatal herpes simplex virus infection manifests itself in three syndromes: mucocutaneous (skin, eye, mouth), encephalitic, and disseminated. The first form is associated with the best outcomes but can progress to blindness. The latter two have high incidences of poor neurologic outcomes and mortality. The onset can be from birth to age 4 weeks, although the disseminated form occurs the earliest (age 4 days to 10 days). In most cases, maternal history is unrevealing.

Acyclovir is the drug of choice for the treatment of herpes simplex infection in the newborn. The length of intravenous treatment recommended by the AAP Committee on Infectious Diseases varies with the type of presentation. The current recommendation is to give intravenous acyclovir in a dose of 60 mg/kg per day divided into 3 doses over 14 days for the mucocutaneous variety and 21 days for the more severe forms. Because the infant in the vignette has disseminated disease, 21 days of treatment is recommended. Courses shorter than 14 days are not recommended for neonatal conditions, and the 14-day course is only appropriate for the mucocutaneous variety of neonatal infection.

The addition of long-term oral acyclovir to the initial intravenous therapy is the subject of an intriguing report from Duke University. The outcomes for the 16 infants in this report appear to be considerably better than those in previous reports. However, this is a report of an

uncontrolled experience with a small number of subjects, which leaves considerable doubt not only about the efficacy of the regimen but also about its safety. Larger, controlled studies are under way. The results of these will provide better grounds for guidelines.

There is some information that the outcome expected for vidarabine is not statistically different from that of acyclovir. However, the pediatric and neonatal experience with acyclovir is much more extensive than with vidarabine, making acyclovir the drug of choice.

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Content Specifications:

Understand the causes and differential diagnoses of infections of the skin and mucous membranes

Understand the clinical manifestations of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster

Understand the diagnostic criteria of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster

Understand the treatment of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster

Understand the complications of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster

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A 960-g, 29-weeks'-gestation male infant was born by cesarean section to a 25-year-old mother who developed eclampsia. She was treated with betamethasone, intravenous labetalol, and magnesium sulfate before a cesarean delivery. The infant's Apgar scores were 5 and 7 at 1 and 5 minutes, respectively, and he was ventilated and given surfactant for respiratory distress. He weaned from the ventilator at age 4 days and was taking full enteral feedings by age 2 weeks.

Three days later, he had a distended abdomen, guaiac positive stools, and portal venous air on abdominal radiograph. Feedings were stopped, intravenous alimentation restarted, and treatment begun with cefotaxime, ampicillin, and metronidazole. His condition deteriorated, with evidence of metabolic acidosis, thrombocytopenia, and fixed dilated bowel loops. A laparotomy revealed a walled-off perforation and 15 cm of gangrenous ileum; this was resected, and an ileostomy was created. Three weeks later, he was back to full enteral feedings and doing well. When he reached 2,400 g, he was returned to the operating room for bowel reanastomosis. The operation took longer than expected. Three hours after he returned from surgery, he vomited 10 mL of red blood. The nasogastric tube was found to be obstructed and was replaced. Copious blood (about 40 mL) was suctioned from his stomach.

Of the following, the MOST likely reason for this bleeding is

1	bleeding from ileal anastomosis
2	disseminated intravascular coagulopathy
☒ 3	esophageal varices
4	hemorrhagic gastritis
5	necrotizing enterocolitis

You selected 3, the correct answer is 4.

In this vignette, hemorrhagic gastritis, although rare, is the most likely cause of severe upper gastrointestinal (GI) bleeding. Reports of life-threatening upper GI bleeding in newborns have related the episodes to stress, surgical procedures, prematurity, and drugs, such as corticosteroids and nonsteroidal anti-inflammatory agents. A bleeding gastric or duodenal ulcer or a gastric duplication could have produced copious bleeding as well. Similar hemorrhages have been reported in apparently healthy term newborns.

In this vignette, the volume of blood documented to have been lost is 50 mL, about 25% of the infant's blood volume (assuming a blood volume of approximately 85 mL/kg of body weight). With such acute blood loss, signs of hemodynamic compensation occur, including tachycardia and shunting of blood to vital organs, such as the brain, heart, and adrenals. Hypotension usually becomes evident when more than 25% to 30% of blood volume is lost. Immediate and ongoing replacement of the lost blood (mL for mL) might save the infant's life. If hemorrhage is too rapid or not noticed in time, or if the losses are not adequately and promptly replaced, shock may ensue, along with other consequences, such as multiple organ failures and disseminated intravascular coagulopathy (DIC).

The hemorrhage in the infant in this vignette is not likely to be coming from the newly created anastomosis, because bleeding that originates from the ileum is unlikely to reach the stomach.

It also is unlikely that the initial hemorrhage in this apparently healthy infant would have been due to DIC in the absence of another inciting factor, and that the upper GI tract would have been the only site of bleeding.

Esophageal varices are also rare in newborns. There is no indication of liver disease or hepatosplenomegaly in the infant in this vignette.

Necrotizing enterocolitis (NEC) does reoccur in infants when the original episode leaves an area of partial obstruction. However, this infant had a laparotomy the day of the hemorrhage, and there was no mention of such an obstruction or other diseased bowel. In addition, although GI bleeding often is seen with NEC, usually, it is lower GI bleeding and not this massive.

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Content Specifications:

Understand the differential diagnosis of hemorrhagic disorders of the gastrointestinal (GI) tract of newborns, including the various coagulation disorders that cause GI hemorrhage

Understand the clinical manifestations of hemorrhagic disorders of the GI tract of newborns, including the various coagulation disorders that cause GI hemorrhage

Understand the approach to therapy of hemorrhagic disorders of the GI tract of newborns, including the various coagulation disorders that cause GI hemorrhage

Understand the clinical manifestations of NEC

Know the complications of medical and surgical treatments of NEC

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You are called to review an ultrasound examination of a twin gestation. No amnionic separation between the twins is present, and there is a single umbilical cord. The perinatologist suspects that these are conjoined twins. You are asked to meet with the family.

Of the following, the MOST common type of conjoined twins is:

1. craniopagus

2. ischiopagus

3. omphalopagus

4. pygopagus

5. thoracopagus

You selected **5**, the correct answer is **5**.

Conjoined twins, which occur in approximately 1 in 50,000 to 1 in100,000 live births, are the result of incomplete division of a monozygotic embryo at the time of cleavage of the embryonic disk (13 days to 15 days after conception). It is estimated that conjoined twins occur in approximately 1% of monozygotic twins. Conjoined twins always have monoamniotic placentation. The umbilical cords of conjoined twins often are fused and may contain 2 to 7 umbilical vessels.

Conjoined twins are more common among females than males. There is no evidence of temporal or seasonal clustering of conjoined twins, and there is no maternal age effect on the frequency of conjoined twins. Many conjoined twins have additional birth defects, such as neural tube defects and orofacial clefts, which are not obviously linked to the conjoining.

Conjoined twins are classified based on the site of attachment into five types: thoracopagus (75% of conjoined twins), pygopagus (20%), ischiopagus (5%), craniopagus (<1%) and omphalopagus (<1%). Prenatal diagnosis usually is made by an ultrasound that reveals conjoined fetuses in a single sac. Approximately 40% of conjoined twins are stillborn. Premature delivery complicates many conjoined-twin pregnancies. The extent of fusion of shared organs determines the success of surgical separation. Thoracopagus is the most common form of conjoined twins. The twins are fused at the thorax and upper abdomen with a single site of umbilical cord insertion. The typical posture for thoracopagus twins is with heads hyperextended and backs relatively straight. Cardiovascular evaluation by echocardiogram and cardiac catheterization is necessary to establish the existence of two separate hearts before planning surgical separation of the twins.

Craniopagus conjoined twins that survive pregnancy and the first few days after birth usually share little brain tissue; however, such twins usually have a shared blood supply to their brains. Successful separation of craniopagus twins requires staged operations with gradual rerouting of the shared blood supply.

Ischiopagus conjoined twins are joined at the pelvis and may share portions of their abdominal wall, liver, bowel, ureters, bladder, and genitalia. This rare form of conjoined twins may have two (bipus), three (tripus), or four (tetrapus) lower extremities. Ischiopagus conjoined twins may also have spinal cord fusion, which presents an additional challenge to separation.

Most omphalopagus conjoined twins have a joined gastrointestinal tract, biliary tree, liver, and bladder. In rare cases of omphalopagus, the joined attachments are limited to the intestine and bladder.

Pygopagus conjoined twins are joined at the buttocks and sacrum and have union of the gastrointestinal and genitourinary tracts. Occasionally, pygopagus conjoined twins also have fusion of the terminal spinal cord. Live-birth pygopagus twins are more commonly female (86%), whereas stillborns are commonly male (80%). Pygopagus twins can have a single fused or two nonfused rectums. Most reported living male pygopagus twins have had nonfused rectums that can be managed successfully with a posterior sagittal anorectoplasty. In contrast, pygopagus twins with a fused rectum require more extensive operative reconstruction.

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Content Specifications:

Know the types of and effects on the mother of multiple-gestation pregnancy

Know the morphologic development of the placenta

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A 4,300-g newborn has evidence of hypoxic-ischemic encephalopathy after a difficult delivery. Seizures begin 18 hours after birth but are well controlled by phenobarbital after intravenous loading doses totaling 140 mg. The next morning, you find a serum phenobarbital concentration of 32 mg/L and immediately give an intravenous dose of 25 mg. One hour after the dose, the serum phenobarbital concentration is 40 mg/L, and it is 29 mg/L at 36 hours after the dose.

Of the following, the daily dose of phenobarbital that is MOST likely to yield a steady state serum phenobarbital concentration of 30 mg/L is

1 10 mg

2 15 mg

3 20 mg

4 ❌ 25 mg

5 30 mg

You selected **4**, the correct answer is **3**.

The question can be answered by extracting two numbers: the volume of distribution (Vd) and the elimination time constant (k).

Vd is the apparent volume of body fluid into which a drug is diluted; it is expressed as liters (of fluid) per kg (of body weight). It can be greater than unity if the drug is sequestered, such as in a fat or bone depot, and makes it seem as if the drug is dissolved in a volume of blood much larger than actually exists. When a drug is administered, Vd can be estimated by dividing the dose per kg by the increase in the drug concentration.

$$Vd = \frac{dose\ per\ kg}{(increase\ in\ concentration)}$$

From the vignette,

$$Vd = \frac{25\ mg\ /\ 4.3\ kg}{(40\text{-}32)\ mg/L}$$

$$= 0.727\ L/kg$$

In one-compartment first-order kinetics, as exhibited by phenobarbital, the rate of elimination at a given instant is proportional to the drug's concentration:

$$\frac{dC}{dt} = -kC$$

in which C is the drug concentration and k is the elimination time constant. Rearranging and integrating gives:

$$C_t = C_0 e^{-kt}$$

In which C_t is the drug concentration at time t, C_0 is the starting concentration, and e is the base of the natural logarithms. Taking the logarithm of both sides and solving for k gives:

$$k = \frac{\ln(C_0/C_t)}{t}$$

or, from the vignette:

$$k = \frac{\ln(40/29)}{36 \text{ hrs}} = 0.0089 \text{ /hr}$$

The drug half-life, using a similar derivation, is then:

$t\frac{1}{2} = \ln(2)/k = 0.693/0.0089 = 77.6$ hrs

At steady-state, the amount of drug given to a patient is matched by the amount eliminated:

Dose/hour = kCVd = (0.0089 /hr)(30 mg/L)(0.727 L/kg) = 0.195 mg/kg/hr, or a total daily dose of approximately 20 mg. Thus, in the infant in this vignette, the daily dose of phenobarbital that is most likely to yield a steady state serum phenobarbital concentration of 30 mg/L is 20 mg.

This method can be used to derive the daily dose to approximate a desired drug concentration, or to find the constant infusion rate of a drug administered by drip, such as fentanyl or dopamine. Although there will be some ups and downs in the drug concentration if given by daily bolus, the long half-life relative to the dosing interval helps smooth the curve around the steady-state average.

The example given is typical for phenobarbital in a neonate, which can have a half-life of 43 hours to 199 hours. Phenobarbital is believed to exert its action by enhancing the response of the $GABA_A$ receptor, which induces synaptic inhibition. This drug also promotes its own elimination over time via the cytochrome P450 system and also induces uridine diphosphate glucuronosyl transferase, enhancing elimination of bilirubin and other drugs. Because of these factors, the "steady-state" dose will change over time.

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<u>Content Specifications</u>:

Understand basic pharmacokinetics and basic pharmacokinetic definitions, including the basic definitions of linear (single compartment) and nonlinear (multiple-compartment) pharmacokinetics

Understand the definitions of drug dose, serum concentrations, and volume of distribution, and know how these values are related mathematically

Understand the definitions of drug half-life, elimination rate constant and clearance, and know how these values are related mathematically
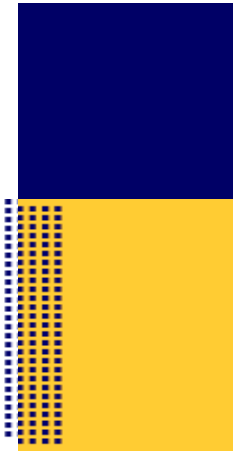
Understand the application of pharmacokinetic principles in administration of drugs by continuous infusion

Know how to calculate a drug dose to achieve a specific serum concentration

Know how to use serum drug concentrations to adjust the dosing regimen of a drug eliminated by first-order kinetics

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You attend the delivery of a 37-week-gestation female infant who is being born by repeat cesarean birth. Antenatal testing shows lung maturity. The infant's mother is healthy. The family history is positive for hypertension but no perinatal problems or children with medical conditions. Pregnancy has been uncomplicated and labor uneventful. Fetal monitoring showed a normal pattern before the mother was taken to the operating room. In the operating room, fetal monitoring is resumed, and no fetal heart rate is present. The cesarean section is performed emergently. The infant is born lifeless and is not responsive to resuscitation.

Of the following, the MOST accurate statement about stillbirths is:

1 Number of stillbirths each year is greatest at term gestation.

2 ☒ Rate of stillbirths in developed countries has been constant during the last 20 years.

3 Rate of stillbirths is similar for mothers of all ages.

4 Stillbirth indicates fetal death early in gestation.

5 Stillbirths outnumber neonatal deaths each year in the United States.

You selected 2, the correct answer is 5.

Stillbirth is one of the most common and least studied adverse outcomes of pregnancy. In developing countries, as many as 10% of pregnancies (nearly 4 million) end in stillbirth. In the United States, like other developed countries, nearly 1% (7 in 1,000) of all births is complicated by stillbirth. This number of deaths is greater than that due to neonatal death and sudden infant death syndrome combined. Little attention has been given to better understanding of stillbirth, its causes, prevention, and impact on family.

Fetal death is defined by the World Health Organization as the death of the conceptus before complete expulsion or extraction from its mother, irrespective of duration of pregnancy. The fetus whose death occurs in utero does not breathe after delivery or show other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles. These physiologic variables should be distinguished from transient cardiac contractions, fleeting respiratory efforts or gasps, and excludes termination of pregnancy. Stillbirth is a late fetal death that occurs from natural causes during the "late" stages of pregnancy. "Late" most often is defined as beyond 20 weeks' gestation, although different authors and health systems worldwide have used gestational ages of 22 to 28 weeks as the threshold for definition of stillbirth.

Variability in definitions of stillbirth, some of which include weight in grams, complicates comparisons of stillbirth among different healthcare systems. Synonyms commonly used for stillbirth include fetal demise and intrauterine fetal death. Stillbirths also are classified as antenatal or intrapartum. Miscarriage, or spontaneous abortion, usually refers to pregnancy loss from natural causes before 20 weeks' gestation.

The risk of stillbirth is associated with a number of factors, including gestational age. Confusion about stillbirth rates exists because various denominators have been used to calculate the rates. In recent years, the consensus is that the most appropriate denominator is the total number of undelivered pregnancies at a specific week of gestation, rather than the total number of births within a specific week of gestation. Using this denominator, it is clear that the absolute number of stillbirths is greatest at earlier gestations, but the risk of stillbirth is greatest at the highest gestational ages when there are fewer fetuses at risk. The stillbirth rate trends slowly upward from 0.4 per 1,000 pregnancies at 29 weeks' gestation to 0.6 per 1,000 pregnancies at 39

weeks' gestation. It then rapidly climbs to 1.8 per 1,000 pregnancies at 41 weeks' gestation.

There are numerous maternal risk factors for stillbirth other than gestational age. These factors include previous stillbirth, smoking, advanced maternal age, maternal obesity, low socioeconomic status, African-American race, postdates, low levels of education, maternal infection, maternal hypertension, placental abruption, abnormal placentation, maternal injury, oligohydramnios, maternal medical illnesses (such as diabetes, lupus, thyroid disorders, and cholestasis in pregnancy) and some medications and exposures (such as prescription pain medications during the first trimester, fertility drugs, cocaine, and pesticides) .

Fetal risk factors include: intrauterine growth restriction; multiple pregnancies; cord prolapse; congenital anomalies; monochorionic twin conceptuses; abnormal presentation; fetal infection, such as cytomegalovirus, parvovirus and *Ureaplasma urealyticum;* fetal hemoglobinopathies; antenatal brain injury; metabolic disorders, such as glycogen storage disease, aminoacidurias, peroxidase deficiencies; fetal disruptions; and chromosomal disorders.

Intrapartum factors, especially cord accidents and fetal-maternal hemorrhage, also increase stillbirth risk. Stillbirths can be explained in about 50% to 70% of cases using standardized diagnostic protocols that include autopsy and placental examination. Unfortunately, this leaves 30% to 50% of stillbirths unexplained.

The rate of stillbirths has decreased during the past several decades in developing and developed countries. In the United States, the rate fell from 14 to 6.7 per 1,000 births between 1970 and 1998. Much of this decline occurred in term and near-term births due to improvements in medical care, especially reduction in Rh isoimmune disease, fetal death associated with maternal diabetes, and asphyxia. Today, most stillbirths at term occur in infants with congenital anomalies.

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Content Specification:

Define perinatal, neonatal, postneonatal, and infant mortality

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A newborn female at term has excess nuchal skin and a shield-like chest. You suspect Turner syndrome. The mother, a registered nurse, asks you what cardiac problems to expect.

Of the following, the MOST common cardiac abnormality in Turner syndrome is:

1. aortic dissection

2. bicuspid aortic valve

3. coarctation of the aorta

4. partial anomalous pulmonary venous drainage

5. ventricular septal defect

You selected 5 , the correct answer is 2 .

Turner syndrome is a heterogeneous collection of disorders related to the X chromosome. The syndrome represents approximately 3% of conceptuses but only about 1 in 2,500 female births. Half of all patients have a single X chromosome, with approximately 80% missing the paternally derived X chromosome. Mosaics with a normal cell line make up 15%, and the rest have structural isochromosomes of the X chromosome. Recurrence risk is no higher than for the general population.

Congenital heart abnormalities are seen in up to 50% of patients with Turner syndrome, with monosomy-X patients having the higher rate. Reproductive, renal, and thyroid problems can occur.

Bicuspid aortic valve incidence in the general population is approximately 2%, making it second only to mitral valve prolapse. It is present in 30% to 50% of patients with Turner syndrome. Physical findings, when present, include an early systolic ejection click heard best at the apex, with a soft murmur at the upper right sternal border. Bicuspid aortic valves hold the risks in later life of valvular fibrosis, calcification, stenosis, regurgitation and infective endocarditis.

Coarctation of the aorta occurs in 7% to10% of patients with Turner syndrome. A webbed neck at birth increases the risk for finding coarctation. Symptoms seen when the ductus closes include shock from myocardial dysfunction, abdominal and lower limb hypoperfusion, and respiratory failure from pulmonary edema. Heart sounds may be normal unless the frequently seen bicuspid aortic valve or ventricular septal defect (VSD) also is present.

Valvular aortic stenosis affects 3% of patients with Turner syndrome. Patent ductus and patent foramen ovale lessen the severity at birth. Congestive heart failure can develop within two weeks of birth, but most patients present with a murmur within the first four months after birth.

Partial anomalous pulmonary venous return is seen in 2% of patients with Turner syndrome. In the general population, it is found in 0.6% of autopsy series and in 15% of cases of atrial septal defect. The partial flow back to the right side of the heart increases pulmonary overcirculation and increases the long-term risk for pulmonary artery hypertension and congestive heart failure.

VSD in isolation occurs in 1 in 244 patients with Turner syndrome and in 1 in 280 live births of the general population.

Other cardiovascular abnormalities in Turner syndrome include hypertension, lipid

abnormalities, and aortic dilatation and dissection.

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Content specifications:

Recognize the physical characteristics and chromosomal pattern of sex chromosome aneuploidy

Understand the pathophysiology, including genetics, of a neonate with a left-sided cardiac obstructive lesion

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Public health personnel report a recent upsurge in syphilis in your community. Healthcare colleagues ask you about the risks of transmission to infants, the signs of disease in newborns, and the impact of the disease on perinatal health.

Of the following, the MOST accurate statement regarding maternal-fetal transmission of *Treponema pallidum* is:

1 Fetal risk is greatest early in pregnancy.

2 Infants with disease will be symptomatic at birth.

3 Most women with syphilis will have unaffected newborns.

4 Risk of fetal infection is most affected by maternal stage of syphilis.

☒ 5 Transmission most often occurs by contact with genital tract lesions during birth.

You selected 5, the correct answer is 4.

The incidence of syphilis in the United States declined progressively until the early 2000s, with some rise thereafter, mostly due to disease among homosexual males. The incidence among women decreased. National surveillance data for congenital syphilis (CS) show a progressive decrease in rate from 14.2 cases per 100,000 live births in 2000 to 11.2 cases per 100,000 live births in 2002. All nonwhite racial and ethnic populations shared in this decrease, while the rate among nonHispanic white infants remained constant. Geographically, the rate increased by 0.9% in the northeast United States, while it decreased by 12.5% to 29.5% in other areas of the country.

Among CS cases evaluated in 2002, 73.8% were associated with lack of or inadequate maternal treatment, 14% with treatment followed by an inadequate serologic response and inadequate infant evaluation, and 8.6% with an inadequate maternal serologic response to treatment with clinical or laboratory evidence of CS in the infant.

Fetal risk is most affected by the stage of disease in the mother. Primary syphilis manifests as a painless papule at the inoculation site, which ulcerates to produce a chancre. Although the chancre heals within three to six weeks, widespread dissemination occurs. Secondary syphilis manifests in about 25% of untreated patients in a wide variety of symptoms: a systemic papular rash involving trunk, extremities, palms and soles; lymphadenopathy; alopecia; and nonspecific neurologic manifestations. Similar to primary syphilis, these manifestations resolve, even in untreated individuals. Latent syphilis refers to asymptomatic infected individuals whose infection can be detected by serologic testing. Early latent syphilis-one year or less in duration-continues to be infectious, whereas transmission is not as probable (venereal or vertical) in late latent syphilis. The risk of CS based on maternal stage of syphilis is shown in the following Table.

Maternal stage	Primary	Secondary	Early latent	Late latent
Risk for CS	50%	50%	40%	10%

Although contact with an infectious lesion in the genital tract is a possible route of infection for the newborn, this mode of spread is unusual.

Treatment of maternal syphilis is an important factor influencing the rate of CS. Untreated mothers have a 70% to 100% likelihood of their infants becoming infected. Infection after

adequate maternal treatment occurs only 1% to 2% of the time. Factors associated with treatment failure include high Venereal Disease Research Laboratory (VDRL) titer (a nontreponemal test) at diagnosis and at the time of treatment or high titer at delivery, delivery at <36 weeks' gestation, early stage of maternal disease, or short interval between treatment and delivery. Because of the dramatic impact of maternal treatment, screening for syphilis is integral to prenatal care.

Treponema pallidum (TP), the spirochete responsible for syphilis, can gain access to the developing fetus early in gestation (it has been detected as early as 9 weeks' gestation), but its effects generally are not seen until after the fifth month, because TP exerts its pathophysiologic effect through host immune and inflammatory responses to infection. Fetal effect depends on fetal stage at time of infection and duration of untreated infection.

TP affects the placenta and readily crosses the placenta to affect the fetus. Histopathologic hallmarks include obliterative endarteritis (caused by binding of TP to endothelial cells, mediated by host fibronectin molecules bound to the surface of the spirochetes) and plasma-cell-rich mononuclear infiltrates (reflecting a delayed-type hypersensitivity to TP). Placental and fetal pathologic changes from transplacental infection are similar to those in acquired (venereal) disease. Placental abnormalities include a proliferative villitis and focal mononuclear cell proliferation, endo- and peri-vascular proliferation (with vascular obliteration), or necrotizing funisitis (deep inflammation of the cord matrix, phlebitis and thrombosis). Enlargement or thickening of the placenta often occurs. The more serious findings are clinically associated with stillbirths and with infants symptomatic at birth. Because fetal effects require fetal inflammatory and immune responses generally not seen until after the fifth month of pregnancy, this delayed fetal effect underscores the public health importance of early prenatal care and syphilis screening.

Most infants with CS are asymptomatic at birth. Clinical CS appears by the third to eighth week after birth among two out of three affected infants, with most becoming symptomatic by age 3 months. Emerging symptoms vary from the nonspecific (fever, irritability, failure to thrive) to the triad of "snuffles," palmar and plantar bullae, and splenomegaly. Snuffles, or syphilitic rhinitis, is highly contagious and precedes the cutaneous rashes by one to two weeks. Untreated, progressive chondritis, necrosis and perforation of the nasal septum lead to the saddle-nose of late CS. The vesicobullous lesions of the palms and soles are likewise highly infectious.

Other skin manifestations include oval, red, maculopapular lesions that evolve into copper-brown lesions with desquamation. Also seen are annular, petechial or purpuric lesions. Infants symptomatic at birth may be severely ill, with hypoglycemia, lactic acidosis, encephalopathy, disseminated intravascular coagulopathy, and shock. Hepatosplenomegaly is common, and hepatic involvement may worsen with penicillin therapy. One in six infants with CS presents with nonimmune hydrops. On radiographic examination, bony lesions, proportional to severity of illness, are present among 20% to 90% of CS-affected infants. The lower rate is seen among asymptomatic infants. Central nervous system involvement occurs in 60% of cases and may not be clinically evident.

CS diagnosis can be confirmed by finding the spirochete or its DNA in tissue or body fluids. Serologic testing of the infant's (not cord) blood showing a fourfold increase over the mother's values in VDRL or Rapid Plasma Reagin titer is consistent with CS, but significant risks for false-positive and false-negative findings make the DNA tests preferable if locally available.

CS treatment is with penicillin by one of two regimens: intravenous crystalline penicillin G at 50,000 U/kg per dose every 12 hours for 7 days and then every 8 hours for 3 more days, for a total of 10 days; or, intramuscular procaine penicillin G at 50,000 U/kg per dose given once-daily for 10 days. Symptomatic infants should be treated. If maternal treatment was inadequate (dose less than recommended dosage for maternal stage of disease or treatment started fewer than 30 days before delivery) or follow-up is not assured, treatment of infants at risk is recommended. Treatment should be monitored and VDRL titers followed.

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Content Specifications:

Understand the epidemiology of perinatal infections with *Treponema pallidum*

Understand the pathogenesis of perinatal infections with *Treponema pallidum*

Understand the prevention of perinatal infections with *Treponema pallidum*

Understand the clinical manifestations and diagnostic criteria of perinatal infections with *Treponema pallidum*

Understand the treatment of the perinatal infections with *Treponema pallidum*

Understand the complications of perinatal infections with *Treponema pallidum*

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You are reviewing with medical students the case of a term infant who developed overwhelming group B streptococcal (GBS) sepsis. In the course of your discussion, you examine the structure of the immunoglobulin (Ig) molecule as it applies to host defense.

Of the following, the MOST important function of the variable region of Ig is to bind Ig to:

1. antigens

2. macrophages

3. mast cells

4. neutrophils ❌

5. the first component of complement

You selected 4, the correct answer is 1.

Immunoglobulin (Ig) molecules are glycoproteins present in interstitial fluids, serum and lymph and on the surface of B cells. An Ig molecule is composed of four polypeptide chains assembled into a Y-shape (Figure). The four chains include two identical light chains and two identical heavy chains linked by disulphide bonds. The N-terminal end of an Ig molecule is called the variable or fragment antigen binding (Fab) region. The fixed or C-terminal portion is called the Fc region because this fragment of the molecule tends to crystallize in solution. The class (isotype) and subclass of Ig are determined by the heavy chain type. The five classes of Ig are IgG, IgA, IgM, IgD, and IgE. These classes differ in size, charge, carbohydrate and amino acid composition.

IgG is the major Ig in serum (75% of the total Ig pool). IgG is a monomeric four-chain molecule with four subclasses. IgG is the only Ig that crosses the placenta, providing passive immunity to the newborn. Transplacental passage of IgG from mother to fetus is facilitated by a specific IgG transport protein in the placenta. The half-life of maternally derived IgG in neonatal serum is 3 weeks to 4 weeks.

IgA is the second most abundant Ig in serum (15% of the total Ig pool).The structure of most IgA is a dimer of the four-chain structure joined by a J chain. IgA also has an additional polypeptide chain called the secretory component that provides resistance against degradation by proteolytic enzymes. IgA is the predominant Ig in colostrum, breast milk, saliva, and tracheobronchial and genitourinary secretions.

IgM (9% of the total Ig pool) is a pentamer of the four-chain structure joined by a J chain. The first antibodies produced in a humoral response are always IgM. IgM is a large molecule that does not cross the placenta. The blood of a term newborn has an IgM concentration that is approximately 10% of an adult serum concentration. An increase in newborn serum IgM concentration provides evidence of a congenital infection.

IgD (<1% of the total Ig pool) is comparable to IgG in size and structure but contains large amounts of carbohydrate distributed in multiple oligosaccharide units. IgD is a major component of the surface membrane of B cells and plays an important role as an antigen receptor in naïve B cells.

IgE (<1% of total Ig pool) is a single monomeric four-chain structure that is larger than IgG due to additional amino acid residues. IgE is found on the surface membrane of basophils and mast cells. IgE has an important role in mast cell activation and allergic reactions of immediate hypersensitivity.

Igs are bifunctional molecules that bind antigens and subsequently mediate effector functions. The primary function of the variable or Fab region of Ig is to bind antigens, such as microorganisms or toxins. Coating a microorganism with a molecule, such as Ig, that allows destruction by phagocytes is known as opsonization. The binding of an antigen to the Fab region of Ig involves the formation of multiple noncovalent bonds between the antigen and the amino acids of the binding site. The strength of the bond between antigen and antibody is called antibody affinity. Antigen-Ig reactions are highly specific. An antibody to group B streptococcus (GBS) will bind to GBS and confer immunity, but it will not combine with *Escherichia coli.*

The Fc region of Ig is the primary effector domain of the molecule. After antigen binding to the Fab, the Fc region is altered, triggering diverse host responses via cellular receptors and complement. Fc receptors are expressed on most myeloid cells, including basophils, mast cells, monocytes, macrophages, eosinophils, neutrophils, dendritic cells, and NK cells.

The Fc regions of IgG, IgM, IgA, and IgE can bind to cell surface receptors on macrophages, and the Fc regions of IgG1, IgG3, and IgA bind to receptors on neutrophils. When an opsonized microorganism binds to Fc receptors on the surface of a phagocytic cell, the cell membrane extends around the microbe and encloses it in a phagosome. Lysosomes fuse with the phagosome, releasing lysosomal enzymes to destroy the microbe.

Mast cells have surface receptors for the Fc portion of IgE. Mast cells, important in host defense at epithelial borders, are located in the dermis and in submucosal tissues of the gastrointestinal and respiratory tracts. Stimulation of Fc receptors on mast cells by antigen-IgE complexes triggers the release of histamine and eicosanoids that cause a local increase in blood flow and vascular permeability.

The classic complement pathway is activated when Ig-antigen complexes cleave C1 to C1q, C1r, and C1s. C1q is the fragment that binds to the Fc region of IgM or IgG to trigger the classic complement cascade.

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Content Specifications:

Know the normal immunoglobulin pattern in the newborn infant

Know the development and function of monocytes and macrophages

Know the function of immunoglobulins

Understand the role of neutrophils

Understand the role of eicosanoids (prostaglandins, leukotrienes) in inflammation

Education Module Learner

Typical structure of Ig molecule
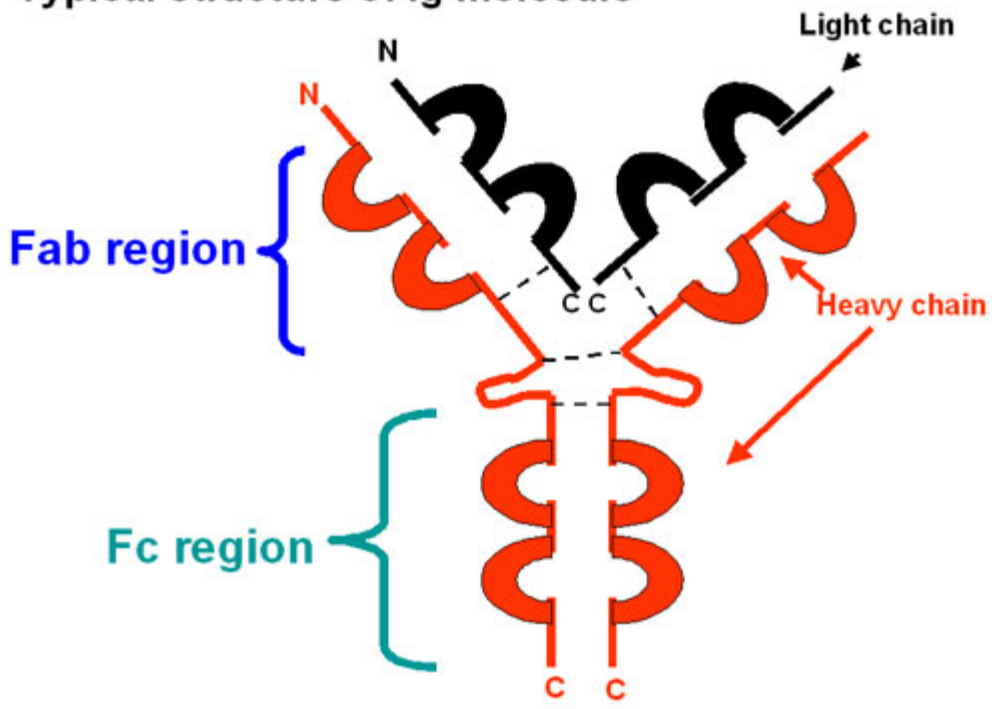
Light chain

N

N

Fab region

C C

Heavy chain

Fc region

C C

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A term infant presents 10 days after birth with noisy breathing, rhinorrhea, and difficulty with feeding. His birth history is significant for a forceps-assisted vaginal delivery with Apgar scores of 7 and 9 at 1 and 5 minutes, respectively. His mother's rapid plasma reagin was nonreactive, and her cervical swab for *Chlamydia* was negative. Physical examination of the infant reveals an afebrile patient with clear conjunctiva, watery nasal discharge and mild hypertelorism. Fluid obtained from the nares tests positive for Beta-2 transferrin.

Of the following, the MOST appropriate next step would be to:

1 attempt to pass a 6 French catheter through each naris

2 obtain head computed tomography and magnetic resonance imaging

3 start a trial of a topical vasoconstrictor to each naris

4 start a trial of dexamethasone ophthalmic drops to each naris

5 ✗ test the nasal discharge for the presence of glucose

You selected **5**, the correct answer is **2**.

Neonates are nasal breathers up to several months of age. As a result, anomalies or processes that cause nasal obstruction can present with significant respiratory distress, particularly if bilateral. Symptoms may be evident at birth with obstruction of airflow, minimal rhinorrhea, or a mucopurulent discharge secondary to mucostasis. Such symptoms may indicate a life-threatening disease or a transient, self-limiting process. In fact, some septal deformity may be evident on physical examination of up to 70% of newborns. Most infants with symptoms of pathologic significance present with stertor and grunting respirations, exacerbated by oral feeding. Maintenance of an adequate airway should precede any diagnostic evaluation.

Nasal obstruction may occur due to increased nasal secretions as a response of the nasal mucosa to a variety of stimuli, including infection. Anatomic blockage of the nasopharynx may cause obstruction with or without a nasal discharge.

The infant in the vignette presents with a mild nasal obstruction, exacerbated by feeding. The presence in the nasal fluid of Beta-2 transferrin, a protein produced by neuraminidase activity in the brain and uniquely found in cerebrospinal fluid (CSF), suggests a CSF leak, and the most appropriate next step would be to evaluate for the presence of an intranasal encephalocele by imaging with computed tomography (CT) to delineate a bony defect and magnetic resonance imaging (MRI) to depict the contents of a herniated mass.

An encephalocele is a rare congenital anomaly of the central nervous system in which intracranial contents, containing meninges, CSF, and neural tissue, protrude through a defect in the skull. The incidence of encephaloceles ranges from 1 in 3,000 live births in Southeast Asia, to 1 in 10,000 live births in North America.

Basal encephaloceles, comprising 5% of all encephaloceles, result from a defect in the floor of the anterior fossa and appear in the nasal cavity, nasopharynx, or posterior aspect of the orbit (Figure 1). Associated findings include hypertelorism, cleft lip and palate, and optic and cerebral anomalies. Though the lesion may present in later childhood with recurrent meningitis, in infancy, symptoms typically relate to obstruction of the nasopharyngeal airspace and may be complicated by spontaneous or trauma-induced CSF rhinorrhea.

Glucose is present in CSF, but its finding in nasal secretions is nonspecific as lesser amounts may be found in the nasal secretions from infectious rhinitis or lacrimal secretions. More

specific for CSF is the presence of Beta-2 transferrin. Intranasal examination often reveals a bluish compressible mass, differentiated from a nasal polyp by its pulsating and transilluminating nature, and midline position.

Passage of a catheter through the nasopharynx could cause neural tissue injury or increase the risk for meningitis, and it would not be indicated in the presence of CSF rhinorrhea. The timing of repair of a basal encephalocele varies, with respiratory distress, CSF leak, and risk of meningitis warranting early surgery. The long-term prognosis varies with the location of the lesion and the presence of associated anomalies.

Other nasal anatomic abnormalities causing nasal obstruction in the neonate include choanal atresia, piriform aperture stenosis, congenital cysts, and traumatic nasal septal deformities. Bilateral choanal atresia presents with immediate respiratory distress, while unilateral lesions often present with mucoid rhinorrhea. Traumatic septal deformities may occur in utero as a result of fetal head presentation, or during vaginal delivery, with or without forceps. Diagnosis is suspected with failure to pass a 6 French catheter through the nasopharynx. Choanal stenosis, or narrowing to less than 6mm, also may present with obstruction and difficulty in passing a catheter. Axial CT is the study of choice to delineate the atresia.

Infectious causes of neonatal rhinitis include *Chlamydia trachomatis* and congential syphilis. Although inclusion conjunctivitis is the commonest manifestation of perinatally acquired *Chlamydia* from colonized mothers, the organism's predilection for columnar epithelium can cause widespread infection of the respiratory tract. While nasopharyngeal infection can occur in the absence of overt conjunctivitis, chlamydial rhinitis should be suspected in the newborn older than 1 week who develops a mucopurulent nasal discharge preceded by conjunctivitis. Current erythromycin ophthalmic prophylaxis at birth does not eliminate nasopharyngeal carriage of *Chlamydia,* and oral erythromycin for 14 days remains the treatment of choice for nasopharyngeal eradication.

Congenital syphilis results from intrauterine transmission of the spirochete, occurring in up to 70% of untreated infected mothers. Symptoms usually appear in the first week after birth, and in as many as 50%, include a thin watery nasal discharge that becomes mucopurulent and sometimes bloody. Without treatment, ulceration of the nasal cartilage with ensuing chondritis and necrosis occurs, leading to the characteristic saddle-nose deformity. Marked nasal obstruction may result from the rhinorrhea, leading to the noisy breathing or "snuffles." Additional findings include a flattened nasal dorsum, frontal bossing, anemia, hepatosplenomegaly and a rash involving the palms and soles, usually appearing one to two weeks after the rhinitis. Diagnostic tests include serologic titers, CSF analysis, and long bone radiography. Penicillin remains the treatment of choice.

Neonatal rhinitis, characterized by mucoid rhinorrhea and nasal mucosal edema in the afebrile newborn, may result in stertor, poor feeding, sleep disturbance, and respiratory distress. Symptoms typically develop around 3 to 6 weeks after birth and resolve by age 6 months. Diagnosis is made by exclusion of infection or anatomic obstruction and a prompt response to nasal dexamethasone, usually within the first week of treatment. Gentle bulb suctioning and nasal saline drops provide some benefit, while prolonged use of topical vasoconstrictors can lead to rhinitis medicamentosa.

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<u>Content specifications</u>:

Know the etiology, differential diagnosis and management of nasal discharge in a newborn infant

Understand the clinical and radiographic findings of myelomeningocele and encephalocele

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Figure

Intranasal basal encephalocele

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A 31-weeks'-gestation female infant is admitted for prematurity. Her birthweight is 1730 g, and she is appropriately grown. She is clinically well after delivery and is placed in an incubator for thermoregulation. After reviewing her mother's prenatal evaluations, you note that her mother's hepatitis B status is unknown.

Of the following, the MOST accurate statement about the management of hepatitis B in this infant is that hepatitis B immune globulin (HBIG) should be:

1 deferred, and hepatitis B vaccine given immediately at half the term infant's dose.

2 deferred pending maternal testing if results are obtainable within 12 hours after birth.

3 given in combination with hepatitis B vaccine immediately.

☒ 4 given upon receipt of positive maternal hepatitis B antibody status within seven days.

5 given immediately.

You selected **4**, the correct answer is **2**.

Hepatitis B virus (HBV) is a DNA virus that circulates in the bloodstream and preferentially localizes in hepatic parenchymal cells. The frequency of HBV infection and patterns of transmission vary markedly throughout the world.

Endemicity is highest in China, Southeast Asia, eastern Europe, central Asian republics of the former Soviet Union, the Middle East, Africa, the Amazon basin, and the Pacific Islands. In these areas, most infections occur in infants or children younger than age 5 years; 70% to 80% of adults have been infected, and 8% to 15% have chronic HBV infection.

Endemicity is low in the United States, Canada, western Europe, Australia, and southern South America. Most infections in these regions occur in adolescents and adults. Only 5% to 8% of adults have been infected, and only 0.2% to 0.9% have chronic infection.

Transmission to infants is usually through contact with infected blood or body fluids and rarely from an infected placenta or from contaminated fomites. HBV is not transmitted by the fecal-oral route or through breast milk. Perinatal transmission is most likely (70% to 90%) for infants born to mothers who are positive for both HBsAg and Hepatitis E (HBeAg) antigens; the risk is 5% to 20% for infants born to HBeAg-negative mothers.

Although the risk is relatively low in the United States, HBV infection remains an important preventable cause for chronic liver failure and hepatocellular carcinoma during adult life. Hence, HBV prevention programs were developed.

These programs include:

- comprehensive immunization of infants, children, adolescents, and adults at high risk for HBV infection (such as high-risk ethnic groups; anyone with sexually transmitted disease; household contacts and sexual partners of people with chronic HBV; occupational risk groups, such as health care workers exposed to blood or people institutionalized for developmental disabilities; people undergoing hemodialysis; adoptees from countries with high HBV endemicity; inmates; clotting factor recipients; and international travelers)
- routine immunization of infants
- routine immunization of adolescents not previously immunized
- prevention of perinatal transmission through routine screening of all pregnant women

- **appropriate treatment of children born to HBsAg-positive women**

Immunoprophylaxis for HBV infections can be achieved with Hepatitis B immune globulin (HBIG) and Hepatitis B vaccine. HBIG provides short-term protection (3 to 6 months). It is prepared from hyperimmunized donors with high plasma anti-HBs and negative for antibodies to human immunodeficiency virus and hepatitis C virus.

HBIG is indicated only in specific postexposure circumstances. One such circumstance includes low birthweight infants born to mothers with unknown HBsAg status. HBsAg testing should be performed immediately in these mothers. HBIG may be given to preterm infants weighing ≥2000 g within seven days after birth if the mother is found HBsAg-positive. However, infants weighing less than 2000 g, like the infant in the vignette, should receive HBIG within 12 hours if the mother is either HBsAg-positive or if results of HBsAg testing are not available within 12 hours of birth.

Hepatitis B vaccine is recommended for all infants, with the first dose to be given soon after birth and before hospital discharge. Alternatively, the vaccine may be given by age 2 months but only in infants whose mothers are HBsAg-negative. In low birthweight infants whose mother's HBsAg status is unknown, like the infant in the vignette, Hepatitis B vaccine should be given within 12 hours of birth. Because vaccine immunogenicity in infants weighing less than 2000 grams at birth is relatively low, HBIG also should be given if maternal HBsAg status is not available within 12 hours of birth. In these low birthweight infants, the initial vaccine dose should not be counted toward the three doses of hepatitis B vaccine required to complete the immunization series. Furthermore, infants born to HBsAg-positive women should be tested for HBsAg and anti-HBs after completion of the immunization series and after loss of antibodies received from HBIG administered during infancy (chronological age 9 months to 15 months).

Hepatitis B vaccine is produced using recombinant DNA technology and has proven safe and highly effective (90% to 95% efficacy). It may be given with other vaccines, does not contain thimerosal, is rarely complicated by fever, anaphylaxis, or other disorders (sudden infant death syndrome; diabetes mellitus; demyelinating disease, including multiple sclerosis) and provides long-term protection. Hepatitis B vaccine dosing is the same in preterm and term neonates.

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Content Specification:

Plan the management of an infant whose mother's serum contains hepatitis B surface antigen

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A 36-hour-old male newborn, whose estimated gestational age at birth is 38 weeks and whose growth measurements are: birthweight 1,800 g (<5th percentile for gestational age), crown-heel length 46 cm (10th percentile), and head circumference 34 cm (50th percentile), has blood glucose of 24 mg/dL (1.3 mmol/L). The infant is receiving a continuous infusion of 15% glucose through an umbilical venous catheter at a rate of 9 mL per hour and no enteral feeds. He has no clinical evidence of respiratory distress, cardiac dysfunction, thermal imbalance, central nervous system manifestations, or sepsis.

Of the following, the MOST likely cause of hypoglycemia in this infant is:

1. excessive utilization of glucose

☒ 2. hyperinsulinism

3. impaired gluconeogenesis

4. inadequate intake of glucose

5. insensitivity to glucagon

You selected 2, the correct answer is 3.

The infant in this vignette is small for gestational age (SGA) whose cranial growth is relatively spared, consistent with asymmetric intrauterine growth restriction. Hypoglycemia, defined as blood glucose less than 30 mg/dL (1.7 mmol/L) is common in SGA infants. Hypoglycemia represents an imbalance between glucose influx into circulation and glucose efflux from circulation. The glucose influx into circulation is determined largely by exogenous intake of glucose, endogenous release of glucose from glycogen principally in the liver (glycogenolysis), and endogenous synthesis of glucose from nonglucose precursors (gluconeogenesis). The glucose efflux from circulation is determined largely by glucose utilization in the peripheral tissues, principally mediated by insulin.

Among the options in the vignette, the most common cause of hypoglycemia in SGA infants is impaired gluconeogenesis. Inadequate stores of glycogen also contribute to hypoglycemia. The gluconeogenesis pathway involves both mitochondrial and cytosolic enzymes (Figure 1). The formation of glucose or glycogen from pyruvate involves entry of pyruvate into the mitochondria and its conversion by pyruvate carboxylase (PC) to oxaloacetate. The oxaloacetate is converted to malate directly as well as indirectly through alpha-ketoglutamic acid, a product of deamination of glutamine. The malate exits the mitochondria and is reconverted to oxaloacetate in the cytosolic compartment. The oxaloacetate is converted to phosphoenolpyruvate by phosphoenolpyruvate carboxykinase (PEPCK). The phosphoenolpyruvate then is converted via a number of reversible steps into fructose 1, 6-bisphosphate, which is a precursor for fructose-6-phosphate, a reaction catalyzed by fructose 1, 6-bisphosphatase (F1, 6-Bpase). Glucose-6-phosphate, derived from fructose-6-phosphate, is the immediate precursor for glucose, a reaction mediated by glucose-6-phosphatase (G 6-Pase), and is the common intermediate for both glycogenolysis and gluconeogenesis. In addition to glutamine, the other key gluconeogenic precursors include alanine, lactate, and glycerol. Impaired gluconeogenesis as a consequence of lower activity of the key gluconeogenesis enzymes - PC; PEPCK; F1, 6-; and G6-Pase - offers the best explanation for hypoglycemia in SGA infants.

Hypoglycemia from excessive utilization of glucose in the peripheral tissues may occur with the increased work of breathing associated with respiratory disease, a shift in energy metabolism from aerobic to anaerobic pathways associated with circulatory disease, increased caloric

expenditure for thermoregulation, and increased glucose consumption by the brain. The latter may be associated with seizures, intoxication, meningitis, encephalitis, hypoxic-ischemic injury, trauma, and intracranial hemorrhage. The absence of such abnormalities in the infant in this vignette makes it unlikely that excessive utilization of glucose was the principal contributor to hypoglycemia.

Hypoglycemia secondary to hyperinsulinism is seen typically in the infant of a diabetic mother, the neonate with hemolytic disease, and the neonate with nesidioblastosis or islet cell adenomatosis. Other common causes of hyperinsulinemic hypoglycemia include genetic syndromes such as Beckwith-Wiedemann syndrome, maternal conditions such as beta-sympathomimetic treatment and ethanol consumption, and neonatal interventions, including placement of a high umbilical arterial catheter and exchange transfusion. Although hyperinsulinism can occur in sporadic cases, the pattern of secretion of insulin in SGA infants is usually similar to that seen in infants appropriately grown for their gestational age.

A full-term healthy human newborn subjected to fasting for 3 to 4 hours after birth produces glucose at a rate of 4 to 6 mg/kg per minute. This endogenous glucose production is sustained by the contributions of both glycogenolysis and gluconeogenesis. The oxygen consumption rate of the brain in such a newborn has been determined to be approximately 104 umol/100g brain tissue per minute. If the average weight of the brain is estimated to be 360 g, approximately 3.7 mg/kg per minute of glucose production would be required to meet the metabolic needs of the brain. In contrast, in SGA infants the glycogen stores may be depleted and gluconeogenesis is impaired. The brain size in relation to body size is greater, thereby increasing the oxygen demand. Thus, in the absence of an adequate exogenous intake, the endogenous production of glucose may not be sufficient to avert hypoglycemia. An intake of glucose to sustain a glucose infusion rate of 6 to 8 mg/kg per minute may be warranted.

Although the infant in this vignette is not receiving enteral feeds, he is receiving a constant glucose infusion through the umbilical venous catheter at a rate that can be calculated to be 12.5 mg/kg per minute. Persistence of hypoglycemia despite this high glucose intake warrants further diagnostic evaluation and other therapeutic options.

Glucagon is a peptide hormone released by the alpha cells of the pancreatic islets. Its major target tissue is the liver, and its principal action is stimulation of glycogenolysis with resultant release of glucose into circulation. Glucagon acts in concert with insulin to maintain euglycemia. Studies of glucagon in SGA infants have revealed no abnormalities of glucagon structure, secretion, or function. The lack of effect of glucagon in raising blood glucose in SGA infants may be explained by the lack of glycogen stores in the liver.

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Content Specifications:

Know the amino acid substrates for gluconeogenesis

Know the normal range of endogenous glucose production in term and preterm infants
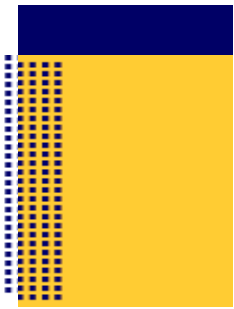
Recognize the etiology and clinical manifestations of neonatal hypoglycemia

Recognize the laboratory features of neonatal hypoglycemia

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A term female infant presents with abdominal distension, bilious emesis and failure of meconium passage 24 hours after birth. Pregnancy was complicated by drug abuse and preterm labor that was treated with magnesium sulfate. There was no history of maternal chorioamnionitis. Physical examination reveals an active and alert infant with abdominal distension and absent bowel sounds. There is no abdominal tenderness or erythema of the abdominal wall. The anus is patent. Complete blood count and serum chemistries are within normal limits. An abdominal radiograph is obtained (Figure 1).

Of the following, the MOST likely cause of this infant's symptoms is:

1	duodenal atresia
2	gastroesophageal reflux disease
3	Hirschsprung disease
☒ **4**	necrotizing enterocolitis
5	sepsis

You selected 4, the correct answer is 3.

Vomiting, failure to pass meconium, and abdominal distension are cardinal signs of intestinal obstruction. Therefore, the infant in this vignette has some form of intestinal obstruction.

A variety of lesions cause intestinal obstruction in the neonatal period. These lesions can be separated into high anatomic obstructions, low anatomic obstructions, and functional obstructions. High anatomic obstructions are caused by lesions that interrupt bowel continuity proximal to the midportion of the jejunum. The high lesions include: pyloric atresia; duodenal obstruction from atresia, stenosis, web, annular pancreas, or preduodenal portal vein; malrotation with or without midgut volvulus; and proximal jejunal atresia or stenosis. Low anatomic obstructions are distal to the midportion of the jejunum. The low lesions include ileal atresia or stenosis, meconium ileus, Hirschsprung disease, imperforate anus, small left colon syndrome, meconium plug syndrome, intussusception, and anorectal malformation. Functional obstructions may be caused by sepsis, electrolyte imbalance, necrotizing enterocolitis (NEC), and hypothyroidism.

Vomiting is one of the earliest and most consistent signs of intestinal obstruction in neonates. The onset, character, and severity of the vomiting depend on the cause of obstruction. Bilious vomiting is characteristic of obstruction distal to the ampulla of Vater and should be considered a symptom of malrotation until proven otherwise. With proximal lesions, bilious vomiting has a sudden presentation and may be forceful; however, it also may be a clinical symptom present in low obstructive lesions. Bilious vomiting is usually a late manifestation of imperforate anus. Nonbilious vomiting also may be encountered in the neonate with obstruction due to any type of lesion.

Failure to pass meconium is another sign of intestinal obstruction. Meconium normally is passed within 24 hours of birth in 95% of term infants, and within 48 hours in the remainder. Failure to pass meconium within the first 24 hours after birth is a classic finding for meconium ileus, meconium plug, anorectal malformations, and Hirschsprung disease. Failure to pass meconium also occurs in jejuno-ileal atresia, colonic atresia or stenosis, and intussusception. Neonates with proximal intestinal obstructions may pass meconium within the first 24 to 48 hours, but they will fail to have subsequent stools. With more proximal lesions, sufficient cells can be shed from the intestine distal to the point of obstruction to account for the meconium.

Some infants with anorectal anomalies will pass meconium through abnormal anatomic structures, such as small perineal openings or fistulae, or, in males with high anorectal lesions, through the urethra. Neonates with incomplete obstruction may pass meconium.

Abdominal distention is a common sign of neonatal intestinal obstruction and is a characteristic and frequent finding of low obstructive lesions. The degree of distention caused by low obstructive lesions tends to be progressive and severe. In neonates with high obstructive lesions, abdominal distention is variably present. When present, the distention tends to be confined to the epigastrium. The remainder of the abdomen may have a scaphoid appearance due to the lack of air passing the point of obstruction into the distal areas of bowel. Frequent vomiting relieves gastric distention; therefore, abdominal distention is an unreliable finding in intestinal obstruction due to high lesions. Abdominal wall tenderness, erythema, edema, and induration all suggest perforation and peritonitis.

After a thorough history and physical examination, all neonates with suspected intestinal obstruction should have plain abdominal radiographs, including an anteroposterior view and a left-side-down decubitus or cross-table lateral view.

Abdominal radiographs are the single most helpful test for defining the cause and level of intestinal obstruction. Normally, air can be demonstrated radiographically in the jejunum by 15 to 60 minutes, in the ileum by 2 to 3 hours, and in the colon by 3 hours after birth. Absence of rectal gas at 24 hours is abnormal.

Plain radiographs of neonates with high intestinal obstruction reveal dilated bowel loops proximal to the site of obstruction, with absence of distal gas beyond the obstruction. Some high obstructive lesions may be associated with characteristic plain radiographic findings, such as distended stomach with absence of distal gas in pyloric atresia, and "double-bubble" sign in duodenal atresia. Malrotation may present with a number of radiographic findings - a "gasless" abdomen in the setting of volvulus, "double-bubble" sign when there is complete obstruction of the duodenum, and a nonspecific bowel gas pattern. Although a history, a physical examination, and a plain radiograph usually are sufficient to diagnose most high intestinal obstructions, a contrast study may be needed for diagnosing malrotation.

The characteristic findings on plain radiographs for a low intestinal obstruction are multiple dilated bowel loops, often with air-fluid levels. Although plain radiographs may suggest a particular type of low intestinal obstruction ("soap bubble" pattern in meconium ileus, calcifications or free air in meconium peritonitis), they are rarely diagnostic. The abdominal radiograph findings presented in this vignette are consistent with low intestinal obstruction, such as in Hirschsprung disease. These findings are multiple dilated bowel loops over the upper and middle parts of the abdomen, with only a minimal amount of air overlying the pelvis in the rectal region. There is no evidence of pneumoperitoneum, pneumatosis, portal venous gas, or calcifications. All neonates with suspected low intestinal obstruction require a contrast enema.

Functional obstruction may be present in infants with NEC, sepsis, and congenital hypothyroidism. Plain radiographs of neonates with NEC will have edema of the bowel wall, generalized bowel distension, pneumatosis intestinalis, and, often, portal venous gas. In the setting of intestinal perforation, pneumoperitoneum or intraperitoneal fluid may be present. Prematurity is the most important risk factor for development of NEC; however, 10 % of those affected are term infants. The age of onset for NEC is inversely related to birthweight and gestational age. Preterm neonates born at or before 30 weeks' gestational age are diagnosed at a mean age of 20 days, whereas those born at term are diagnosed by age 7 days. Clinical history, physical examination, laboratory data, and plain abdominal radiographs are usually sufficient to diagnose functional intestinal obstruction.

Infantile gastroesophageal reflux manifests more often with regurgitation (especially after a feed) without abdominal distension or failure to pass meconium. Regurgitation is the effortless movement of stomach contents into the esophagus and mouth. It is not associated with distress, and infants with regurgitation often are hungry immediately after an episode. Regurgitation should be differentiated from vomiting, which denotes an active reflex process. In most typical cases of gastroesophageal reflux, a thorough history and physical examination suffice to reach the diagnosis.

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Content Specifications:

Understand the significance of vomiting and abdominal distention in the neonate

Realize the differential diagnosis of delayed passage of meconium

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SUPINE

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A veterinarian in your community has been diagnosed with listeriosis. Your obstetrical colleagues ask for your help in responding to recent concerns among their patients regarding perinatal infection with *Listeria monocytogenes*.

Of the following, the MOST accurate statement regarding infection with *Listeria monocytogenes* is:

1. Consumption of aged hard cheese has been associated with human outbreaks.

2. Human illness is infrequent in industrialized countries due to individual refrigerators.

☒ 3. Maternal infection during gestation rarely results in stillbirth.

4. Pregnant women are at lower risk of illness due to increased cell-mediated immunity.

5. Processed meats commonly are contaminated with *Listeria monocytogenes.*

You selected 3, the correct answer is 5.

Listeria monocytogenes **is an important cause of food-borne illness, and, since 2001, listeriosis has been a nationally notifiable disease in the United States.** *Listeria* **is a short, aerobic, Gram-positive, motile rod (bacillus) and may be confused with cocci and diphtheroids.** *Listeria* **species infect mammals, fish, and birds. Of the seven species,** *L. monocytogenes*, **serotype 4b, causes most outbreaks of human disease. Fecal-oral transmission is the probable means of spread. Animal-to-human transmission has been documented in veterinarians and farm workers, but most cases of listeriosis are food-borne.**

Listeriosis is reported more frequently in developed countries. In the United States, more outbreaks have been reported since the widespread use of individual refrigerators during the 1960s. *Listeria* **survives in soil, water, and sewage, and, because it tolerates low temperatures, can replicate in contaminated refrigerated foods, including cole slaw, deli and other prepared meats, pâté and ready-to-eat foods. In fact, up to 70% of hot dogs are reported to be contaminated with** *Listeria*. **Additional incriminated foods include unpasteurized milk, soft cheeses, raw vegetables, fish, and poultry. Hard cheeses, processed cheeses, and cottage cheese have not been associated with outbreaks. The incubation period for listeriosis is estimated at three weeks.**

Although a rare cause of food borne illness, *Listeria* **contributes to nearly 30% of deaths due to food-borne disease, and the case-fatality rate for systemic infection is 20% to 30%. In the United States, an estimated 2,500 persons each year become seriously ill with listeriosis, resulting in 500 deaths.**

Systemic illness due to *Listeria* **is most common among pregnant women (27% of all cases), their newborn infants, the elderly, and immunocompromised persons.** *L. monocytogenes* **activates T-cell-mediated immunity, which declines by the third trimester of pregnancy, placing the pregnant woman and her fetus at higher risk for infection.**

Infection during early gestation has been observed, and perinatal listeriosis results in stillbirth or neonatal death in 22% of cases. In most cases, the mother has a flu-like prodrome, a phase of bacteremia, followed within a week by amnionitis and preterm delivery. Early antibiotic treatment of infected mothers may prevent fetal or perinatal disease and its consequences.

Early onset neonatal disease results from transplacentally acquired bacteria, ascending infection from a colonized vagina, or from exposure during delivery. Neonatal listeriosis is associated with

sepsis, pneumonia, and meningitis and is fatal in as many as 50% of cases.

Dietary recommendations for preventing food-borne listeriosis include thorough cooking of raw food from animal sources, washing raw vegetables, avoidance of unpasteurized dairy products, and regular cleaning and disinfection of the insides of refrigerators.

Pregnant women specifically should be advised to avoid soft cheeses (feta, Brie, Camembert, blue-veined, and Mexican queso fresco), cook leftover foods or ready-to-eat foods (hot dogs) until steaming hot, and avoid cold deli meats or prepared salads (cole slaw).

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American Academy of Pediatrics. Listeria monocytogenes infections. In: Pickering LK, ed. *Red Book: 2003 Report of the Committee on Infectious Diseases.* 26th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2003:405-407

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Content Specification:

Understand the epidemiology and prevention of *Listeria monocytogenes*

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You are reviewing a complete blood count with differential obtained from an infant with sepsis. The immature to total neutrophil ratio is >0.4. You discuss the process of neutrophil differentiation and maturation with medical students.

Of the following, the MOST accurate sequence of neutrophil differentiation is:

1 metamyelocyte -> myeloblast -> promyelocyte -> myelocyte

❌ **2** myeloblast -> metamyelocyte -> promyelocyte -> myelocyte

3 myeloblast -> promyelocyte -> myelocyte -> metamyelocyte

4 promyelocyte -> metamyelocyte -> myeloblast -> myelocyte

5 promyelocyte -> myeloblast -> myelocyte -> metamyelocyte

You selected **2**, the correct answer is **3**.

Neutrophils are of central importance as a first line of host defense. Each human has approximately 1 billion neutrophils per kilogram of body weight. Neutrophils differentiate and mature in the bone marrow, are released into the bloodstream where they circulate or adhere to the vascular endothelium, then migrate into peripheral tissues where they interact with pathogens.

The total body neutrophil collection can be divided into five pools: the bone marrow neutrophil precursor (mitotic) pool, bone marrow storage (postmitotic) pool, blood circulation pool, marginated vascular pool, and peripheral tissue pool (Figure 1). Neutrophil homeostasis is maintained by release of mature neutrophils from the bone marrow storage pool into the circulation to replace senescent neutrophils removed by the tissue macrophages. Under normal conditions, neutrophil turnover is rapid, with approximately 10 million neutrophils released from the bone marrow every hour. During periods of stress, such as sepsis, neutrophil consumption is increased, and the processes of neutrophil differentiation, maturation, release, and demargination are accelerated.

Neutrophil differentiation and maturation in the bone marrow takes approximately nine days. Pluripotent stem cells give rise to progenitor cells (Figure 2). A single progenitor cell can be stimulated by growth factors into colonies of 100,000 cells, called a colony forming unit (CFU). The CFUs are named by the progeny they produce. A granulocyte-macrophage CFU (CFU- GM) differentiates into granulocytes (neutrophils, eosinophils, basophils) or monocyte/macrophages. Stimulation of a CFU-GM with granulocyte colony stimulating factor (G-CSF) results in the first morphologically identifiable neutrophil precursor, known as a myeloblast (Figure 3). Myeloblasts have fine, evenly distributed chromatin, several nucleoli, and a nongranular basophilic cytoplasm. Myeloblasts differentiate into promyelocytes. Promyelocytes have primary granules that contain myeloperoxidase, proteases and hydrolases. Promyelocytes differentiate into smaller, rounder myelocytes. Myelocytes have secondary granules that contain collagenase and lysozyme. Myelocytes develop into metamyelocytes. The protein synthesis seen in earlier stages of differentiation stops; the nucleus becomes indented, and its chromatin becomes coarse and clumped; and the cytoplasm stains pink, like that of a mature neutrophil. Metamyelocytes develop into bands, then into mature, segmented neutrophils. Metamyelocytes, bands, and mature neutrophils constitute the postmitotic, bone marrow neutrophil storage pool.

The release of neutrophils from the bone marrow storage pool into the circulation can be stimulated by factors such as tumor necrosis factor, interleukin-1, complement, corticosteroids, and epinephrine. In an infection, these factors stimulate the release of immature neutrophils

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(metamyelocytes and bands) from the postmitotic bone marrow storage pool. Increased ratios of immature to total neutrophil >0.2 have been used as a marker for neonatal infection. The bone marrow neutrophil storage pool is diminished in newborns in comparison to adults. Depletion of neutrophil stores is associated with risk of death in neonatal sepsis.

References:

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Content Specifications:

Recognize the causes and consequences of alterations in number and distribution of neutrophils

Understand the origin, maturational process, and regulation of leukopoiesis during development

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Fig. 1 Neutrophil pools

Fig. 2 Hematopoiesis

Pluripotent Stem Cell → Progenitor cell

Progenitor cell →
- Granulocyte, Macrophage Colony Forming Unit → Granulocytes Monocytes
- Erythroid Burst Forming Unit → Red Blood Cells
- Megakaryocyte Colony Forming Unit → Platelets

Differentiation (Mitotic) **Maturation (Post-mitotic)**

Myeloblast Promyelocyte Myelocyte Metamyelocyte Band Mature
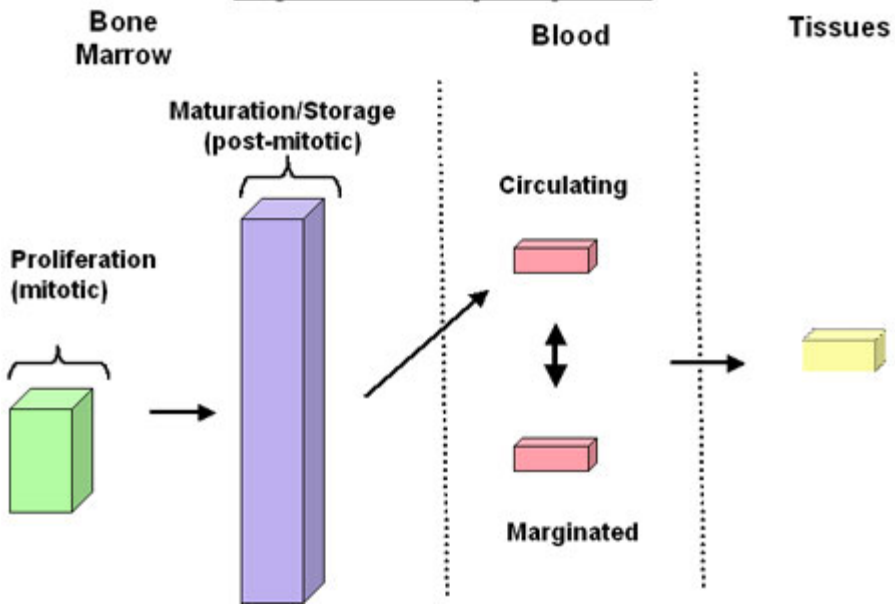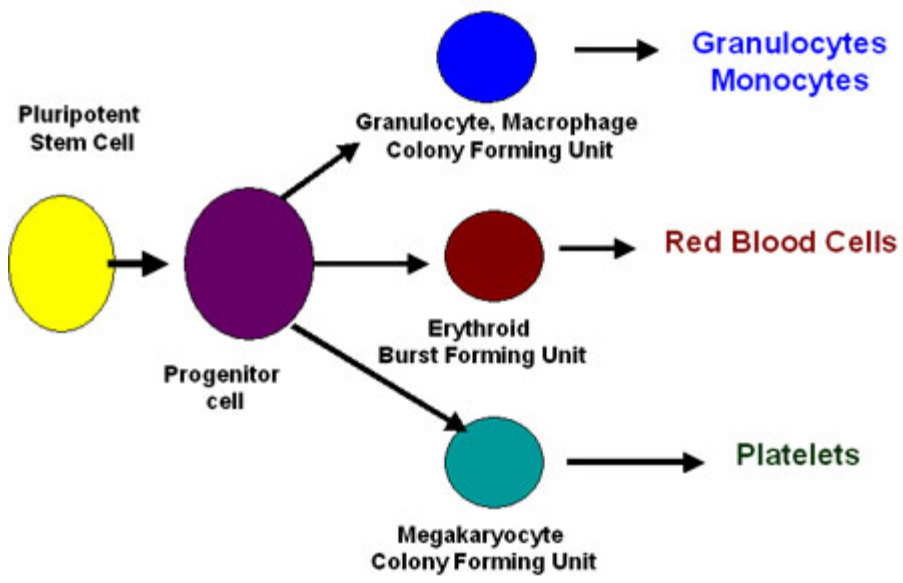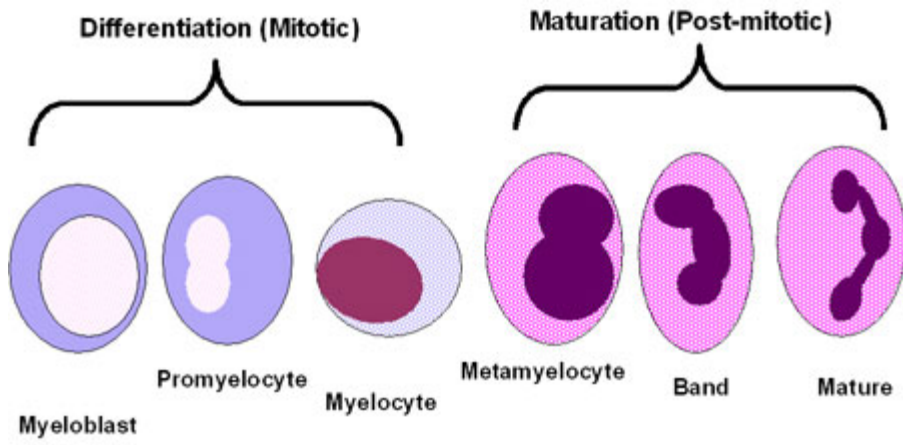
Fig. 3 Stages of Neutrophil Differentiation
and Maturation in Bone Marrow

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A woman is screened for glucose intolerance during pregnancy at 30-weeks' gestation. Her blood glucose measures 144 mg/dL (8 mmol/L) one hour after a 50-g oral glucose challenge. After an overnight fast, her blood glucose is 108 mg/dL (6 mmol/L). Two hours after a 75-g oral glucose load, it is 180 mg/dL (10 mmol/L). These results are consistent with glucose intolerance of pregnancy. Her physician recommends dietary advice, blood glucose monitoring, and potential insulin treatment.

Of the following, the neonatal outcome MOST improved by screening for and treating gestational diabetes is:

1. admission for neonatal intensive care

2. hypoglycemia requiring intravenous glucose

3. jaundice requiring phototherapy

4. macrosomia

5. respiratory distress needing oxygen for >4 hours

You selected **5**, the correct answer is **4**.

Gestational diabetes (carbohydrate intolerance) first recognized during pregnancy affects 1.4% to 14% of pregnancies. Glucose regulation during pregnancy becomes more challenging to the mother as pregnancy progresses. Because the fetus continuously and increasingly draws glucose across the placenta, interprandial hypoglycemia becomes more pronounced in later pregnancy.

Maternal blood glucose decreases to 55 to 65 mg/dL (3.1 to 3.6 mmol/L) after overnight fasting. Concentrations of estrogens, progesterone, and chorionic somatomammotropin (all diabetogenic hormones) rise linearly in the second and third trimesters, resulting in maternal tissue resistance to insulin, which requires a doubling of pancreatic insulin output to maintain euglycemia. If maternal insulin production is inadequate, maternal (and then fetal) hyperglycemia occurs.

Fetal hyperinsulinemia results in excessive storage of nutrients and fetal macrosomia. Insulin also stimulates catabolism of excess glucose, consuming oxygen stores. Hypoxia then can result in release of adrenal catecholamines, which can precipitate a cascade of hypertension, cardiac hypertrophy, erythropoietin release, and elevated hematocrit.

Perinatal complications associated with gestational diabetes include macrosomia, shoulder dystocia, birth injuries (especially nerve palsies and fractures), cesarean delivery, and hypoglycemia of the newborn. Perinatal mortality is not affected by gestational diabetes. Gestational diabetes is a risk factor for subsequent diabetes mellitus in the mother, and infants may have impaired glucose tolerance, obesity, and impaired intellect.

Screening for gestational diabetes remains controversial. The U.S. Preventative Services Task Force finds insufficient evidence to recommend either in favor of or against routine screening. In contrast, the American College of Obstetricians and Gynecologists recommends screening and treatment, albeit based on "limited or inconsistent scientific evidence." The American Diabetes Association recommends that screening be limited to women with risk factors, suggesting that screening women older than age 25 years with normal weight, no history of abnormal glucose tolerance, no family history of diabetes among first-degree relatives, no history of poor obstetric outcome, and no ethnic or racial basis for risk is not cost-effective. In

spite of these diverse recommendations, universal screening is included in the prenatal care of many pregnant women.

In a recent randomized controlled study (Crowther and associates) of gestational diabetes morbidities, screening for and treatment of the mother's condition affected fetal size, with reductions noted in incidence of large-for-gestational-age infants, ie, infants >90th percentile for gestational age (Relative risk [RR] 0.62; 95% confidence interval [CI] 0.47 to 0.81) and in incidence of macrosomia, ie, >4 kg birthweight (RR 0.47; 95% CI 0.34 to 0.64). Treatment of gestational diabetes showed no effect on perinatal mortality. When compared to infants of mothers with similar blood-sugar concentrations who received normal obstetrical care, infants born to mothers screened and treated for gestational diabetes showed a reduced risk for the combination of mortality with the morbidities of shoulder dystocia, bone fracture, and/or nerve palsy (RR 0.32; 95% CI 0.14 to 0.75). Mothers in the screened group were more likely to undergo induction of labor, but no more likely to be delivered by cesarean section. This study and the accompanying editorial (Greene and Solomon) support the evaluation for and treatment of gestational diabetes.

Many questions still remain, however, regarding precise diagnostic criteria and the exact relationship between gestational diabetes and perinatal outcomes. Among infants delivered to mothers screened and treated for gestational diabetes, admission for neonatal intensive care increased rather than decreased. Infants of the treated mothers showed no reductions in hypoglycemia requiring intravenous glucose, jaundice requiring phototherapy, or respiratory distress requiring oxygen beyond four hours after birth compared to infants of mothers whose glucose screening concentrations were similar but who were given standard obstetric care.

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<u>Content Specifications:</u>

Know the rationale and methods for screening for glucose intolerance in pregnancy

Understand the implications of fetal macrosomia

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NeoReviewsPlus

November 05

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A 7-day-old term African-American female infant presents with abnormal movements for the last two days. The abnormal movements consist of shaking of the head and left arm with twitching of the left eye, which then go on to involve the whole body. These episodes last a total of 10 to 35 seconds and occur four to six times a day. There is no loss of consciousness, cessation of breathing, or change in color or tone. There is no history of trauma. She is being fed regular infant formula with iron. There is no history of altered intake, elimination, temperature instability, respiratory distress or lethargy. Perinatal history is unremarkable. Physical examination reveals an awake, alert, active, afebrile infant without respiratory distress, and an unremarkable systemic examination. Complete blood count, head ultrasonography, and electroencephalography showed no abnormalities.

The laboratory data reveals:

Work-up

Sodium	142 mEq/L (142 mmol/L)	iPTH	18 pg/mL (1.9 pmol/L)
Potassium	5.9 mEq/L (5.9 mmol/L)	1,25 (OH)2 Vitamin D	112 pg/mL (268.8 nmol/L)
Chloride	107 mEq/L (107 mmol/L)	Maternal s calcium	9.6 mg/dL (2.4 mmol/L)
Bicarbonate	23 mEq/L (23 mmol/L)	Glucose	74 mg/dL (4.1 mmol/L)
BUN	5 mg/dL (1.8 mmol/L)		
Creatinine	0.4 mg/dL (35.4 mmol/L)		
Calcium	6.1mg/dL (1.5 mmol./L)		
Magnesium	1.8 mg/dL (0.7 mmol/L)		
Phosphorus	10.5 mg/dL (3.4 mmol/L)		
Albumin	3.4 g/dL (34 g/L)		

Of the following, the MOST likely cause of seizures in this infant is:

1	early neonatal hypocalcemia
2	late neonatal hypocalcemia
3	maternal parathyroid adenoma
4	primary hypoparathyroidism
☒ 5	vitamin D deficiency

You selected 5, the correct answer is 2.

Hypocalcemia is one of the most common causes of neonatal seizures. Hypocalcemia in term infants is defined as an ionized calcium (Ca) concentration of <4.4 mg/dL (1.10 mmol/L). If an ionized Ca measurement is not available, the traditional definition - total serum Ca <8 mg/dL (4

mmol/L) - can be used. In clinical practice, the diagnosis of hypocalcemia is based on the determination of ionized or total Ca. Serum magnesium (Mg) also should be measured, because hypomagnesemia may coexist and cause identical signs. Measurement of Ca-regulating enzymes is not recommended routinely unless hypocalcemia is prolonged, refractory, or recurrent.

The clinical and laboratory findings in the vignette are most consistent with late hypocalcemia.

Late hypocalcemia in neonates, much less common than early hypocalcemia, is due to intake of milk with a high content of phosphate. The onset of symptoms occurs most commonly during the first 5 to 10 days after birth, although clinical manifestations occasionally have appeared as late as 6 weeks after birth. Late neonatal hypocalcemia frequently was observed in infants fed cow's milk because of the high phosphate (P) content (956 mg/L). With the introduction of adapted infant formulas, late hypocalcemia, although not abolished, has become uncommon. Even with current formulas, however, formula-fed infants have lower serum ionized Ca and higher P in the first week of life, compared to breastfed infants. These differences do not correlate with different Ca:P ratios in formulas but rather with their absolute P amount: breast milk has about 140 mg/L of phosphorus, and current standard formula has at least twice as much phosphorus (280 mg/L). Although the higher P content of formulas, compared with human milk, may represent a risk factor for hypocalcemia, other factors must play a role, given the clinical rarity of this condition.

Late neonatal hypocalcemia most often occurs in otherwise healthy, full-term neonates. The intake of a high-phosphorus food in a relatively large volume, combined with decreased renal phosphorus excretion, leads to elevated serum phosphorus. The decreased renal phosphorus excretion is due to the physiologically low glomerular filtration rate of the newborn and the relatively high tubular reabsorption of phosphorus. The elevated serum phosphorus depresses serum calcium through deposition of calcium phosphorus in bone and possibly in other tissues. The normal physiologic response is an increased output of parathyroid hormone (PTH), which stimulates calcium release from bone and urine phosphorus excretion. This restores the normal serum levels of calcium and phosphorus.

Infants with late neonatal hypocalcemia may have normal or elevated PTH, but the PTH response is relatively inadequate because the serum calcium is low. In affected children, the immature parathyroid gland may not be able to respond appropriately. Alternatively, some of these infants may have an appropriate PTH response to hypocalcemia, but have end-organ resistance to PTH. This "transient pseudohypoparathyroidism" resolves itself.

Early neonatal hypocalcemia occurs during the first 72 hours after birth, usually before the infant achieves a significant oral intake of milk. Serum calcium reaches a nadir at approximately 24 hours. There are many mechanisms that account for early neonatal hypocalcemia. At birth, there is an interruption of the transplacental delivery of calcium, an active process that maintains a higher calcium level in the fetus than in the mother. In addition, newborns may have a relative hypoparathyroidism, attributed to the increased serum calcium of the fetus, which causes suppression of the parathyroid gland. Newborns also may have a relative refractoriness of the target cells to PTH. Other predisposing factors for early neonatal hypocalcemia are prematurity, maternal diabetes, perinatal asphyxia, and maternal anticonvulsants.

Hypocalcemia may occur in infants of mothers with hypercalcemia, which is commonly due to hyperparathyroidism from a parathyroid adenoma. The constant in utero suppression of the parathyroid gland can lead to neonatal hypoparathyroidism that is prolonged, sometimes lasting for months. The infants usually develop tetany during the first three weeks after birth, but it may occur later if the infant is breastfed. Often, the mother is asymptomatic, and the diagnosis depends on the length of time before maternal serum calcium is determined. Normal maternal calcium, as seen in this vignette, rules out maternal hyperparathyroidism.

There are many causes of primary hypoparathyroidism, including X-linked, autosomal recessive or dominant trait, association with ring chromosomes, or as part of the DiGeorge syndrome. In these conditions, along with hypocalcemia, hypoparathyroidism leads to hyperphosphatemia due to decreased renal excretion of phosphorus. PTH levels are either low or undetectable, although inappropriately normal levels in the setting of hypocalcemia may occur in children with some residual PTH production. Because PTH and hypophosphatemia are the normal stimuli for

the renal 1a-hydroxylase, 1,25-dihydroxyvitamin D levels are low. Normal 1,25-dihydroxyvitamin D and PTH levels in this vignette rule out primary hypoparathyroidism.

In vitamin D deficiency, hypocalcemia is primarily the result of poor intestinal calcium absorption. PTH levels increase as a response to the inadequate calcium, and this initially prevents the development of frank hypocalcemia by causing release of calcium from bone, decreasing urinary losses of calcium, and upregulating the activity of the 1a-hydroxylase that converts 25-hydroxyvitamin D into the active form of vitamin D, 1,25-dihydroxyvitamin D. When these compensatory mechanisms are inadequate, hypocalcemia develops. Most children with inadequate vitamin D receive medical attention for rickets before developing hypocalcemia. Children with vitamin D deficiency have elevated serum PTH, and, because of increased osteoclast activity, elevated serum alkaline phosphatase. Serum phosphorus is usually low due to decreased intestinal absorption and increased urinary excretion secondary to the effect of PTH. Vitamin D deficiency may be secondary to poor intake combined with inadequate exposure to ultraviolet light from the sun. In the United States, this condition is most common in African-American children who are breastfed but do not receive vitamin D supplementation.

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<u>Content Specifications:</u>

Understand the etiology and clinical manifestations of neonatal hypocalcemia

Understand the laboratory features and approach to therapy of neonatal hypocalcemia

| ◄ PREVIOUS | NEXT ► |

NeoReviewsPlus

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You are asked to meet with a family regarding impending delivery of a very low birthweight (VLBW) infant, estimated fetal weight 550 g, at 23 weeks' gestation. Based on literature review and data from your own perinatal center, you present a survival rate of 20% to 50% if delivery were to occur now, and a survival rate of 50% to 70% if the mother were to remain pregnant to 25 weeks' gestation. During the discussion regarding management of the pregnancy and of the infant at delivery and beyond, the family inquires about the functional status of infants who survive after being delivered at such a low gestational age.

Of the following, the prognostic statement MOST consistent with current data is that former VLBW infants:

1 are similar to normal-birthweight infants in educational needs if no neurosensory impairment is detected at 18 months.

2 experience similar rates of health problems in adolescence as normal birthweight controls.

3 have progressively lower rates of long-term disability as more aggressive neonatal care is provided.

4 ☒ rarely graduate high school.

5 show similar levels of self-esteem and health-related quality of life as former normal birthweight infants at adolescence.

You selected **4**, the correct answer is **5**.

As critical as survival data are to decision-making, recent discussions underscore the importance of understanding the long-term consequences of care decisions made for very low birthweight (VLBW) infants at the borderline of viability. Popular media publicize the successes, such as the high school graduation of the "smallest survivor of the neonatal intensive care unit," while some former tiny infants and their families quietly endure a life of profound disability.

Discussions with families place the neonatologist in a difficult position: not wanting to be unduly morbid, so as to preserve some hope, while honestly presenting a balanced and unbiased summary of what is known about the potential consequences of the current situation. This difficult position is confounded by the realities of biologic variability-not all infants of 23 weeks' gestation are developmentally equal-and lack of data regarding long-term outcome, not to mention the many individual variables added by maternal medical factors, genetics, and the like.

Nevertheless, neonatologists must accept their role in the counseling and decision-making process for high-risk and/or VLBW infants. After these discussions, "It is both legitimate and anticipated that parents, once informed of the risks of marked prematurity, are the ones to make the decision of whether to use aggressive interventions or to provide 'comfort care' for their child" (Paris 2005).

Although more aggressive perinatal and neonatal care is showing survival rate improvement, VLBW infants have considerable neurodevelopmental morbidity, and there is no evidence that the morbidity risk is decreasing. Hintz and associates compared 18-month-old infants delivered at =25 weeks' gestation with birthweights of 500 g to 1000 g in two consecutive time periods in the 1990s. Results are shown in Table 1.

It is notable that infants in the earlier time period were more likely to have Apgar scores of <5 at 5 minutes, patent ductus arteriosus, and severe intraventricular hemorrhage, whereas infants in

the later time period were more likely to have had antenatal steroids, cesarean delivery, surfactant treatment, and diagnosis of bronchopulmonary dysplasia and/or severe retinopathy of prematurity. Authors of this study (Hintz and associates) and of an accompanying editorial (Tyson & Saigal) share concerns that "early childhood neurodevelopmental outcomes among infants <25 weeks EGA are not improving in the postsurfactant era, despite more aggressive perinatal and neonatal treatment." These data should argue against statements meant to de-emphasize morbidity risks by suggesting that current infants getting more modern care experience fewer or less severe morbidities, until follow-up data support such claims. Conflicting data on the impact of inhaled nitric oxide on outcomes of premature infants underscore the need for comprehensive follow-up when innovations are introduced (Mestan 2005) (Van Meurs 2005) (Martin & Walsh 2005).

Although parents of former VLBW infants report their now-adolescent children are less competent than normal birthweight controls in sports, agility, or self-esteem, the patients themselves report their own health-related quality of life and self-esteem as similar to the controls.

Among VLBW survivors, adolescence brought a reduction in acute health problems, a decrease in utilization of medical resources, and some catch-up growth. Nevertheless, adolescents who had been VLBW as infants were more likely to have experienced seizures within the last two years (7% vs 1%, P = 0.03) and were more likely to have three or more current health problems reported by parents (35% vs 7%, P<0.0001) than controls of normal birthweight.

VLBW survivors may be expected to have a lower high school graduation rate than normal birth weight controls, but a significant percentage of VLBW infants do graduate. Results are shown in Table 2.

VLBW infants showed poorer cognitive and behavioral outcomes and a twofold increase in attention deficit hyperactivity disorder compared to normal birthweight controls. On the other hand, the former VLBW infants demonstrated less risk-taking, ethanol use, and substance abuse. Males had less contact with law enforcement, and females had fewer pregnancies.

Many follow-up programs extend only into early childhood, and such programs have identified significant morbidities. A study of English and Irish infants (Marlow 2005) born =25 weeks' gestation and evaluated at age 30 months showed considerable likelihood of disability, much of it severe. Results are shown in Table 3.

If the child's disabilities were severe at the 30-month evaluation, there was an 86% chance of severe or moderate disability at age 6 years. Due to the age at evaluation, these findings focused primarily on the major causes of impairment, such as cerebral palsy, blindness, deafness, or significant developmental delay. Hack and associates (2005) reported findings at age 8 years among 219 former VLBW infants born 1992 to 1995 as compared to normal birthweight controls from the same (largely disadvantaged) population. A total of 16% of the study population had neurosensory impairment (NSI). The findings of the total group, those without NSI, and the normal birthweight group were compared. Results are shown in Table 4.

The children lacking NSI showed significant differences from the normal birthweight group. The need for specialized equipment for walking and needs for help with feeding, dressing or toileting were limited to those children with NSI. The nonNSI cohort, nevertheless, showed considerably more needs than the similarly disadvantaged controls. Some 36% was on prescribed medications (versus 19% of controls). Experiences of the groups are summarized in Table 5.

Hospitalizations were mostly for respiratory problems or for CP in the NSI group. The greater needs in all these areas are significantly greater for the nonNSI group compared to controls. These data suggest that follow-up examination at age 18 months is not sufficient to understand the needs of VLBW infants, and that the absence of NSI will not avoid very significant added needs during the school years.

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Content Specifications:

Know the incidence of cerebral palsy in high-risk infants, such as those with extreme prematurity, hypoxic-ischemic encephalopathy, and symptomatic congenital infection

Recognize the disorders associated with cerebral palsy, including cognitive and communication disorders, seizures, sensory impairments, orthopedic deformities, emotional, and behavioral disorders

Know the incidence and range of severity of mental retardation in high risk groups, including infants with extreme prematurity, hypoxic-ischemic encephalopathy, or congenital infection, or intrauterine growth restriction

Know the functional impairments of children and adults with different levels of mental retardation, including borderline intelligence, and mild, moderate, severe, or profound mental retardation

Know the type and frequency of school-related and behavior problems in preterm infants

Understand the prenatal, perinatal, and neonatal risk factors associated with school and behavior problems

Know the various streams of development, such as language, gross motor, fine motor, problem solving, adaptive, social, and emotional

Know the significance of delay in development in one or more streams of development

Recognize the clinical features of infants who require a complete developmental assessment

Know the relationship of neurodevelopmental examination results to developmental outcome

Understand how neurodevelopmental disabilities affect function

Recognize the prenatal risk factors associated with developmental disabilities

Identify perinatal risk factors, including hypoxic-ischemic encephalopathy or prematurity, which affect subsequent developmental outcome

PREVIOUS   NEXT

Table 1

Birth epoch	MDI <70	CP risk	PDI <70	NDI risk	NSI	Unimpaired
1/93-6/96	40%	21%	32%	55%	28%	21%
7/96-12/99	47%	23%	31%	58%	22%	21%
OR**	0.63 *	0.80	0.85	0.72		

*significant
**Odds ratio by logistic regression analysis
Adapted from Hintz et al (2005)

CP = cerebral palsy; MDI = mental development index; PDI = psychomotor development index; NSI = one or more of CP, deafness, blindness; NDI (neurodevelopmental impairment) = one or more of CP, MDI<70, PDI<70, deafness or blindness; Unimpaired = no CP, MDI >85, PDI >85, neither blind nor deaf

Close

Table 2

US-born 1977-79	Mean IQ	HS grad rate	NSI	Subnormal height
VLBW survivors	87	74%	10%	10%
NBW controls	92	83%	<1%	5%

Adapted from Mandy 2005

Table 3

Age at evaluation	Severe disability	Moderate disability	Mild disability	Any disability
30 mos	23%			50%
6 yrs	22%	24%	34%	

Adapted from Marlow 2005

Table 4

Group	CP	Blind	Deaf	Asthma	IQ<70	Limited academic skills	Poor motor skills	Poor adaptive functioning
All VLBW	14%	0.5%	2%	21%	15%	18%	27%	44%
No NSI	0	0	0	22%	7%	12%	15%	40%
NBW	0	0	0	9%	2%	4%	6%	13%

Adapted from Hack (2005)

Close

Table 5

Group	PT or OT	PostNICU hospitalization	Separate or special class	Special school arrangement	Has IEP
All VLBW	31%	23%	27%	48%	39%
No NSI	19%	17%	20%	41%	29%
NBW	3%	6%	6%	12%	9%

Adapted from Hack (2005)

PT = Physical therapy; OT= Occupational therapy. IEP = Individualized Educational Plan

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A 41-week-gestation male infant is born by emergent cesarean section for fetal distress. His mother is 33 years old, she conceived using artificial reproductive technology, and she has received regular prenatal care. Fetal growth has been normal, and family history is unremarkable.

During labor, profuse vaginal bleeding is noted and associated with sustained fetal bradycardia. The infant is born with no spontaneous respirations, a heart rate of 50 beats/min, and hypotonia.

Resuscitation includes positive pressure ventilation, oxygen, endotracheal tube insertion, and intravenous epinephrine, volume expansion with saline and packed red blood cells, dopamine, and sodium bicarbonate. Spontaneous respirations are noted 9 minutes after birth. Initial arterial blood gas has a pH 7.01 and base excess -18 mEq/L. Apgar scores are 1, 1, 3, and 7 at 1, 5, 10, and 15 minutes after birth, respectively.

Neurological examination 4 hours later reveals the infant to be lethargic, hypotonic, moving little and difficult to arouse; Moro, grasp, and suck/swallow reflexes are weak or incomplete. Rowing and bicycling movements are associated with tonic horizontal deviation of the eyes and sustained eye opening. Tongue-thrusting movements are also present. Phenobarbital is given, and whole-body cooling to 33.5° Centigrade is initiated. You are talking with the infant's parents about possible outcomes.

Of the following, the MOST likely probability for death or moderate/severe disability for this infant is:

☒ **1**	5%
2	25%
3	45%
4	65%
5	85%

You selected **1**, the correct answer is **3**.

Hypoxic ischemic encephalopathy (HIE) occurs in 1 to 8 infants per 1,000 live births. It occurs when cerebral blood flow is unable to supply enough oxygen and nutrients to maintain oxidative metabolism.

Neonatal encephalopathy has many causes, including HIE. Most cases (69%) are associated only with antepartum risk factors (such as family history of seizures or neurological disease, infertility treatment, fetal growth restriction, maternal thyroid disease, preeclampsia, bleeding during pregnancy, congenital anomalies, and prenatal/perinatal infection). Approximately 25% of cases have both antepartum risk factors and evidence of intrapartum hypoxia. Approximately 4% of cases of neonatal encephalopathy are associated with intrapartum hypoxia due to complications, such as abruptio placenta and cord prolapse. About 2% of cases have no recognized risk factors.

The pathophysiology for HIE is complex and multifactorial. Reduction in cerebral blood flow and oxygen delivery initiates a cascade of deleterious biochemical and physiologic responses. Oxidative phosphorylation is impaired, and energy production dependent on anaerobic metabolism is overwhelmed, resulting in depletion of high-energy phosphate reserves, such as adenosine triphosphate. Lactic acidosis and impaired cell functions result.

Ion pump failure results in intracellular accumulation of sodium, calcium, and water (cytotoxic edema); membrane depolarization with release of excitatory neurotransmitters, such as glutamate; and intracellular fatty acid accumulation. Fatty acids react with oxygen free radicals (lipid peroxidation) produced during synthesis of prostaglandins, xanthine, and uric acid. In selective neurons, intracellular calcium also catalyzes production of nitric oxide, which acts as a free radical that damages cellular protein, nucleic acids, and lipids. Cell death due to necrosis or apoptosis may result if protective mechanisms are insufficient.

Patterns of injury after an ischemic insult depend on the severity of the insult, genetic predisposition, and gestational age at the time of the insult, due to selective vulnerability of neuronal subsets to injury during different developmental stages. Acute, severe insults usually involve the highly metabolically active neurons of the thalamus, caudate nucleus, globus pallidus, and putamen; multifocal and parasaggital necrosis in brain locations not as severely injured invariably coexists in severe HIE. Preterm infants most often present with perventricular white matter injury (eg, periventricular leukomalacia) after hypoxia-ischemia due to selective vulnerability of developing oligodendroglia and subplate neurons.

The brain injury with HIE is not static, but evolves over time. After the initial brain insult and resuscitation in the delivery room or recovery in utero, a second or delayed phase of brain injury may occur. This phase is thought to involve mitochondrial dysfunction secondary to subclinical but ongoing reactions associated with the primary insult, such as calcium influx, excitatory neurotoxicity, oxygen free radicals or nitric oxide production. Mitochondria may release apoptotic triggering proteins, such as cytochrome *c,* into the cytoplasm that activate cascades of proteolytic enzymes, such as caspases or cysteine proteases. Nuclear, protein, and lipid fragmentation ensues. This cellular injury may be exacerbated by inflammatory cells or mediators produced during perinatal infection.

Prevention of the progression to the secondary phase of injury during HIE is being investigated, because severity of this secondary energy failure is correlated with adverse neurological outcome during early childhood. Prophylactic high-dose phenobarbital, oxygen radical inhibitors and scavengers, excitatory amino acid antagonists, nitric oxide synthesis inhibitors, and calcium channel blockade are several interventions being investigated, primarily in animal models. Studies on brain cooling to prevent or reduce the severity of the secondary energy failure, however, have been more promising than other interventions. Animal studies and small human trials have demonstrated improvement in neuropathological, cerebral energetic, electrophysiological and functional outcomes with brain cooling. These studies have advanced to randomized, multicenter clinical trials in human neonates with moderate to severe HIE.

Two randomized multicenter trials initiated cooling within 6 hours of birth for infants born at $\geq$36 weeks' gestation with moderate or severe HIE. Brain cooling was induced by either whole-body cooling or selective head cooling to achieve an estimated reduction in brain temperature of 2° to 5° Celsius. Whole-body cooling was induced using a cooling blanket system, and selective head cooling was achieved with a cooling cap system; selective head cooling also resulted in mild systemic hypothermia. Cooling was continued for 72 hours.

Moderate and severe HIE was defined in these studies using several parameters modeled after the Sarnat stages of HIE, as shown in [Table 1]:

- a hypoxic-ischemic event requiring resuscitation [history of an acute perinatal event (such as abruptio placenta, cord prolapse, severe fetal heart rate abnormality, uterine rupture) (Apgar $\leq$ 5 at 10 minutes)
- severe acidosis (cord or first blood gas within one hour of birth with pH <7 or base deficit >16 mmol/L)]
- moderate or severe HIE (determined by a certified examiner and based on the infant's level of consciousness, spontaneous activity, posture, tone, primitive reflexes and autonomic activity)
- amplitude-integrated electroencephalogram (aEEG) results (the head-cooling study)

The primary outcome of both studies included the combined frequency of mortality and moderate/severe (whole-body cooling) or severe (head-cooling) neurodevelopmental disability in survivors at age 18 months. The whole-body hypothermia study defined severe disability as any of the following: Bayley Mental Development Index (MDI) <70, Gross Motor Function (GMF)

level 3 to 5 (nonambulant, sits with support applied to lower back, or infants who have limited or no self-mobility), hearing impairment requiring aids, or blindness. The definition of moderate disability included Bayley MDI 70 to 85 and either GMF 2, hearing impairment with no amplification, or seizure disorder. The selective head-cooling study defined severe disability slightly differently, as GMF level 3 to 5, Bayley MDI <70, or bilateral cortical visual impairment.

The two large, multicenter brain-cooling studies randomized a total of 446 infants with moderate or severe HIE. The incidence of serious medical complications was similar between the groups. Infants who were cooled had lower heart rates, transiently elevated liver enzymes, scalp edema in the cooling-cap patients, and statistically insignificant trends for thrombocytopenia and difficulty with temperature control.

The combined outcomes of death or moderate/severe neurodevelopmental disability at age 18 months was reduced significantly in the whole-body cooling trial: 45% and 62% of infants in the hypothermia group and normothermia group, respectively, died or had moderate/severe neurodevelopmental disability [Risk Ratio, RR, (95% Confidence Interval [CI], 0.72 (0.55, 0.93)] (Table 2). Differences in secondary outcomes, none of which reached statistical significance, also are shown in Table 2.

Primary and secondary outcomes were not significantly different between the two groups in the selective head-cooling study (Table 3).

The results from these studies indicate a high risk for mortality and morbidity in survivors of moderate or severe HIE, despite modest improvement with whole-body hypothermia. Survival is anticipated in 60% to 70% of these infants (30% to 40% mortality), and most survivors escape severe neuromotor disabilities, which occur in 20% to 30%. The likelihood of survival with mild or no disabilities appears to be approximately 55% in babies with moderate/severe HIE who are treated with whole-body cooling. There appears to be a significant potential for some infants to survive with normal/mild abnormal mental and physical development, although this specific subpopulation is not addressed in either of the publications. This outcome is most likely for the infant in the vignette. Epilepsy after moderate/severe HIE affects approximately 15% of infants, visual impairment occurs in 6% to 10%, and significant hearing loss occurs in 4% to 8% of these infants. The selective head-cooling trial found that multiple disabilities affected 20% to 30% of infants with moderate or severe HIE.

The infant in the vignette has moderate HIE and has approximately a 45% risk of complications (death, disabling cerebral palsy, blindness, deafness, and epilepsy). The brain cooling studies appear to support the use of hypothermia initiated within 6 hours of birth in a select population of infants born at >36 weeks' gestation with moderate HIE. Additional studies are needed to further define the time limits when and if neurological rescue is possible in both moderate and severe HIE, as well as the optimal level and method of inducing hypothermia, and whether additional pharmacologic treatment might improve outcomes.

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Table 1: Sarnat Stages of Neonatal Encephalopathy

	Stage 1 Mild	Stage 2 Moderate	Stage 3 Severe
Level of consciousness	hyperalert	lethargic or obtunded	stuperous
Neuromuscular control			
Muscle tone	normal	mild hypotonia	flaccid
Posture	mild distal flexion	strong distal flexion	intermittent decerebration
Stretch Reflexes	overactive	overactive	decreased or absent
Segmental myoclonus	present	present	absent
Complex reflexes			
Suck	weak	weak or absent	absent
Moro	strong or low threshold	weak or imcomplete; high threshold	absent
Oculovestibular	normal	overactive	weak or absent
Tonic neck	slight	strong	absent
Autonomic function	generalized sympathetic	gneralized parasympathetic	Both systems depressed
Pupils	mydriasis	miosis	variable; oftern unequal; poor light reflex
Heart rate	tachycardia	bradycardia	variable
Bronchial and salivary secretions	sparse	profuse	variable
Gastrointestinal motility	normal or decreased	increased; diarrhea	variable
Seizures	none	common; focal or multifocal	uncomoon (excluding decerebration)
EEG Findings	normal (awake)	Early: low voltage, continuous delta and theta Later: periodic pattern (awake) Seizures: focal, 1-1½ Hz, spike and wave	Early: periodic pattern with isopotential phase Later: totally isopotential
Duration	<24 hours	2 to 14 days	hours to weeks

Table 2

Outcomes of Whole-body Cooling Multicenter, Randomized Trial

	Outcome	Hypothermia %	Normothermia %	RR (95%CI)
Primary	Death or moderate/severe disability	45	62	0.72 (0.55,0.93)
Secondary	Death	24	36	0.66 (0.43,1.01)
	Death or moderate/severe disability after moderate HIE			0.67 (0.38,1.03)
	Death or moderate/severe disability after severe HIE			0.82 (0.64,1.06)
	Disabling cerebral palsy	20	29	0.69 (0.38,1.28)
	Blindness	6	14	0.38 (0.12,1.19)
	Hearing aids	4	6	0.64 (0.15,2.75)

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Table 3

Outcomes of Selective Head-Cooling and Mild Systemic Hypothermia Trial

	Outcome	Hypothermia %	Normothermia %	OR (95%CI)	*P* value
Primary	Death or severe disability	55	66	0.61 (0.34, 1.09)	0.10
	Death	33	38	0.81 (0.47, 1.41)	0.48
	Severe neuromotor disability	19	31	0.54 (0.25, 1.17)	0.12
	Bayley MDI <70	30	39	0.66 (0.32, 1.36)	0.27
	Bilateral cortical visual impairment	10	17	0.5 (0.19, 1.39)	0.22
Secondary	Multiorgan dysfunction	84	81	1.24 (0.64, 2.40)	0.61
	Multiple disabilities	21	31	0.61 (0.29, 1.32)	0.24
	Bayley PDI <70	30	41	0.63 (0.30, 1.31)	0.26
	Bilateral sensorineural hearing loss	8	6	1.47 (0.37, 5.84)	0.72
	Epilepsy	15	16	0.92 (0.38, 2.24)	1.00
Bayley MDI	Median (range)	84.5 (49 to 116)	77.0 (49 to 121)		0.11
Bayley PDI	Median (range)	87.0 (49 to 127)	79.5 (49 to 125)		0.06

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A 1770-g female infant was born at 35 weeks' gestation to a 23-year-old mother. Atrioventricular canal was identified on prenatal ultrasound. Amniotic fluid karyotype was normal as well as a normal "triple screen." Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Physical examination was normal. Echocardiogram confirmed a complete endocardial cushion defect as well as a patent ductus arteriosus. Systemic and pulmonary arterial pressures were similar. Initial chest radiograph was normal. Enteric feedings were begun without difficulty, and the infant began to breastfeed and nipple feed fairly well by one week after birth.

By the second week, however, she developed subcostal retractions and tachypnea, and she began to tire during feedings. Chest radiograph demonstrated increased pulmonary vascular congestion and moderate cardiomegaly. Digoxin and daily diuretics were begun.

At the beginning of the third week, the infant developed feeding intolerance and vomited two feedings in a row. Physical examination showed no change in general appearance, skin temperature of 36.5° C, a heart rate of 102 beats/min and respiratory rate of 48 breaths/min. Examination of the chest revealed normal heart sounds, except for a relatively prominent P2 and a grade 2/6 holosystolic murmur heard best at the left sternal border. The precordium was not hyperactive; breath sounds were normal without rales, but there were mild to moderate supraclavicular and subcostal retractions. Abdominal examination found no organomegaly or distention, normal bowel sounds, and no tenderness.

Of the following, the single investigation MOST likely to explain the setback in feeding would be:

1. blood culture

2. digoxin concentration

3. esophageal pH analysis ❌

4. plain abdominal radiograph

5. serum electrolytes

You selected **3**, the correct answer is **2**.

Digoxin toxicity always should be considered when gastrointestinal symptoms and/or cardiac arrhythmia occur in a newborn treated with digoxin. Whenever digoxin is prescribed, health professionals and parents should be reminded of the narrow therapeutic index (ie, the drug dose that produces an undesired effect is close to the dose that causes the desired effects), as well as the dangers of overdosing this drug. Although heart rates as low as 95 beats/min can occur in healthy newborn infants, the usual heart rate varies between 110 and 180 beats/min in this population.

Early signs of digoxin toxicity in young infants include drowsiness, feeding intolerance, vomiting, and cardiac arrhythmia. The most common cardiac arrhythmia is sinus bradycardia and prolonged PR interval. Second and higher degrees of atrioventricular (AV) block are more serious toxicities, which can be life-threatening. The infant in this vignette may well be suffering from digoxin toxicity, and a serum digoxin concentration is needed.

Digoxin is the most commonly used cardiac glycoside for newborns. It improves inadequate circulation in patients with congestive heart failure and can slow the heart rate in some types of narrow QRS tachycardia. The main physiologic action of digoxin is to increase the force and velocity of ventricular contraction of a failing heart. It also has electrophysiological effects,

decreasing the conduction velocity through the AV node and prolonging its refractory period. The primary mechanism of action is an inhibition of Na^+, K^+-ATPase in the heart.

Measuring serum digoxin in premature infants has been problematic in that digoxin-like immunoreactive factors (DLIF) exaggerate the apparent digoxin concentration in this population. DLIF not only cross-react with digoxin in immunoassays but also inhibit Na^+, K^+-ATPase. The concentration of DLIF normally is below the detection limit of most digoxin assays but is increased in patients who have expanded extracellular volumes. Newly born term and premature infants, as well as patients with renal failure, essential hypertension, liver disease, pre-eclampsia, diabetes mellitus, and congestive heart failure fit into this category. Blood samples should be obtained 10 to 12 hours after the last loading or maintenance dose. The usual therapeutic range for newborns is 0.8 to 2 ng/mL (1 to 2.6 nmol/L). Serum levels >3.6 ng/mL (>4.6 nmol/L) are considered to be in the toxic range. Newer assays have substantially eliminated the cross-reactivity and have produced lower values in newborns. Consult laboratory staff to interpret the values reported.

Although sepsis might present with gastrointestinal symptoms and bradycardia, tachycardia and temperature instability are more common, and the infant's general appearance usually worsens. Sepsis should be considered in this vignette but is less likely to be the cause of the vomiting than digoxin toxicity, given the physical examination.

Gastroesophageal reflux (GER) could be considered in a premature infant with vomiting and feeding intolerance. Virtually 100% of otherwise normal premature infants have some GER. Therefore, a test for GER likely will be positive. In this vignette, however, there is no indication of airway problems, cyanosis during vomiting, or other chronic episodes that would create a suspicion of pathologic reflux or GER disease (GERD). The onset was described as more acute than is seen with GERD. GERD might be considered if other problems are ruled out, and symptoms become persistent or chronic.

A plain abdominal radiograph would help in the diagnosis of mechanical or functional obstruction that might underlie the vomiting described in the vignette. Acquired disorders such as necrotizing enterocolitis or midgut volvulus might be considered, although the lack of abdominal distention or tenderness on examination makes them less likely.

Serum electrolyte abnormalities are an important consideration for any infant receiving digoxin, especially when diuretics are being administered at the same time. Diuretics reduce the reabsorption of sodium from renal tubules, which might result in secondary potassium wasting. Low serum potassium can lead to tachycardia and can potentiate the toxicity of digoxin, leading to other arrhythmias. Low potassium also can cause adynamic ileus and vomiting. In the latter condition, abdominal distention and reduced or absent bowel sounds would be expected. These features were not found in the infant in the vignette, making electrolyte imbalance a more remote possibility than digoxin toxicity as a cause of the vomiting and bradycardia.

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Content Specification:

Recognize the therapeutic indications for and toxicity of digoxin in treating cardiovascular distress

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A 31-week-gestation African-American female infant is admitted from the delivery room for tachypnea and retractions. Physical examination is also remarkable for appropriate growth for gestational age and for widespread vesicles and pustules that involve the forehead, palms, and soles. No microcephaly, hepatosplenomegaly, or petechiae are present. The infant's mother had a cerclage placed at the 19th week of pregnancy for premature cervical dilation. During the last three weeks, she also was treated for syphilis and chlamydia.

Of the following, the disorder MOST likely to cause this infant's skin manifestations is:

1. congenital candidiasis

2. congenital syphilis

3. erythema toxicum

4. infantile acropustulosis

5. neonatal pustular melanosis

You selected 5, the correct answer is 1.

There are many causes for vesicles, pustules, and blisters of the skin in neonates. These vesiculopustular and blistering diseases may be infectious, transient, or uncommon congenital disorders (Table 1 and 2). These types of lesions on the palms and soles of infants at birth are relatively uncommon.

Congenital candidiasis is an uncommon condition acquired in utero or during delivery. Risk factors include cervical sutures (ie, cerclage), retained intrauterine device, prematurity, and maternal vaginal candidiasis. A generalized skin eruption may be present, in addition to systemic manifestations involving the blood, lung, meninges, and urinary tract. The skin lesions range from erythematous papules, diffuse erythema (especially in preterm infants), vesicopustules and bullae to a fine scaling rash. Most frequently, a fine erythematous papular rash presents and then evolves into a more pustular and scaly eruption. Any area of the skin may be involved including the palms and soles; this distribution differentiates the skin lesions from that of erythema toxicum and miliaria. Although congenital candidiasis is unusual, the rare presentation of infantile acropustulosis at birth makes congenital candidiasis more likely the cause for the skin lesions in the infant in the vignette. However, other diagnostic testing may be required to differentiate from intrauterine herpes simplex, pustular miliaria rubra, and neonatal pustular melanosis.

Congenital syphilis may present with blistering and ulcerations of the skin, although these skin lesions only occur in 3% of cases. Bullae, not vesicles or pustules as in the infant in the vignette, often are located on the palms, soles, knees, and abdomen. Furthermore, these bullae often are superimposed on dusky, hemorrhagic, or erythematous skin. Bullous lesions on the hands and feet at birth also may be due to congenital candidiasis, infantile acropustulosis and epidermolysis bullosa (Table 2). Additional testing may be required to make this differentiation.

Erythema toxicum is a common skin finding in neonates, with most cases involving term infants and presenting 24 to 48 hours after birth. Erythema toxicum may present with varying combinations of erythematous macules, wheals, papules, and pustules. Occasionally, vesicular lesions appear and subsequently become pustular. The face often is the first site where lesions are found; lesions also may be found on the trunk, buttocks, and proximal extremities. Erythema toxicum rarely appears at birth, in preterm infants, or on the palms and soles. It is

unlikely to cause the skin lesions in the infant in this vignette.

Infantile acropustulosis rarely is found at birth. The cause for this disorder is unknown. It presents as <u>pruritic</u> vesiculopustules on the hands and feet, usually during the first weeks and months after birth. Recurrent crops of lesions lasting 5 to 10 days characterize the disorder. The lesions evolve by flattening, developing scales, and leaving a hyperpigmented macule. Intense pruritus with irritability accompany the lesions. Infantile acropustulosis usually is not widespread and usually does not present at birth; it is unlikely to cause the skin disorder in the infant in the vignette.

Neonatal pustular melanosis is a relatively common skin disorder that presents at birth. Term infants usually are affected, and lesions are almost always present after birth. The skin lesions include pustules without underlying erythema, ruptured pustules with a surrounding collaret of scale, and hyperpigmented macules without scale. All of these lesions may be present at the same time. The lesions may be 1 mm to 10 mm in diameter, although most are 2 mm to 3 mm. Any site on the skin may be affected, including the palms and soles. Most common sites include the forehead, neck, back, and behind the ears. The infant in the vignette is preterm and does not have the mixture of lesions often found with neonatal pustular melanosis.

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<u>Content Specifications:</u>

Understand the etiology and differential diagnosis of bullous skin lesions

Understand the cutaneous and laboratory manifestations of congenital syphilis

Understand the cutaneous and laboratory manifestations of severe candidiasis

Know the etiology and cutaneous manifestations of nonpruritic skin lesions

Table 1

Vesiculopustular Diseases Presenting at Birth

	Disease	Skin morphology	Skin distribution	Clinical caveats
Infectious	Group B streptococcus	Vesicles, bullae, erosions, honey-crusted lesions	Any area	Pneumonia, bacteremia, meningitis
	Haemophilis influenzea	Vesicles, crusted areas	Any area	Bacteremia, meningitis
	Congenital candidiasis	Erythema, small papules and pustules	Any area; palms and soles often involved	Prematurity, foreign body in cervix
	Intrauterine herpes simplex	Vesicles, pustules, erosions, scars, areas of missing skin	Any area, often scalp	Low birthweight, microcephaly, chorioretinitis
	Neonatal varicella	Vesicles on erythematous base	Generalized	Maternal primary varicella 7 days before to 2 days after delivery
Transient skin lesions	Erythema toxicum neonatorum	Erythematous macules, papules, pustules, wheals	Any area except palms and soles	Term infants, unusual in preterm infants
	Neonatal pustular melanosis	Pustules without erythema; collarettes of scale; hyperpigmented macules	Any area; often on forehead, ears, back, fingers and toes	Term infants, more common in black infants
	Miliaria crystallina	Fragile vesicles without erythema	Forehead, upper trunk and arms	Occasional history of overwarming or fever
Uncommon causes	Infantile acropustulosis	Vesicles and pustules	Hands and feet, occasionally elsewhere	Pruritus, recurrent crops
	Eosinophilic pustular folliculitis	Pustules	Scalp and face; occasionally trunk or extremities	Pruritus, recurrent crops
	Congenital self-healing histiocytosis	Vesicles, crusts, papules, nodules, petechiae	Any area	Rarely mucosal or extracutaneous sites

	Incontinentia pigmenti	Vesicles, hyperkeratosis in linear arrays	Trunk, scalp or extremities	Extracutaneous involvement of eye, teeth, nervous system, development

Table 2

Blistering, Bullous and Erosive Disorders Presenting at Birth

	Disease	Skin morphology	Skin distribution	Clinical caveats
Infectious	Group B streptococcus	Vesicles, bullae, erosions, honey-crusted lesions	Any area	Pneumonia, bacteremia, meningitis
	Congenital syphilis	Bullae or erosions	Hands, feet and perioral	Lack of prenatal care, hepatosplenomegaly, bony lesions
	Intrauterine herpes simplex	Vesicles, pustules, widespread erosions, scars, areas of missing skin	Any area, especially scalp	Low birthweight, microcephaly, chorioretinitis
	Fetal varicella	Scarring, limb hypoplasia, erosions	Any area, especially extremities	Maternal varicella in first trimester
Transient lesions	Sucking blisters	Flaccid bullae or linear erosion, occasionally 2 symmetric lesions	Fingers, wrists, occasionally foot	
	Perinatal trauma/ iatrogenic injury	Erosions, ulcerations	Cause-specific	Perinatal history of monitoring, prolonged labor and/or vacuum or forceps delivery
Uncommon causes	Epidermolysis bullosa	Bullae and skin fragility	Focal or wide-spread, often on hands, feet, other sites of friction or trauma	Pain, irritability and difficulty feeding; extracutaneous findings in eye, respiratory tract, or gastrointestinal system
	Mastocytosis	Nodules with wheal or bullae, blisters	Focal or generalized	Hives, flushing, irritability, sudden pallor, diarrhea
	Maternal bullous disease	Tense or flaccid bullae	Generalized	Maternal history of blistering disease
	Intrauterine epidermal necrosis	Erosions and ulceration without vesicles or pustules	Generalized, mucus membranes spared	Prematurity, rapid mortality

	Congenital erosive and vesicular dermatosis	Erosions, vesicles, crusts, erythematous areas	Generalized, usually sparing face, palms and soles	Prematurity, occasionally collodion membrane, transparent skin, reticulated vascular pattern
	Restrictive dermopathy	Rigid, tense skin with erosions, linear ulcerations	Generalized	Joint contractures, micrognathia, natal teeth
	Aplasia cutis congenita	Bullae or erosions	Scalp or face	Extracutaneous manifestations of the nervous system, chromosomes, limb-reduction abnormalities
	Absent dermal ridges and congenital milia syndrome	Bullae	Fingers, soles	Absent dermal ridge patterns, multiple milia, autosomal dominant

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You are asked to evaluate a 20-hour-old, 5-kg male with poor perfusion and tachypnea. The mother, who has diabetes, reports that the infant feeds poorly. On examination, the heart rate is 188 beats per minute, respiratory rate is 75 breaths per minute, and capillary refill time is 3 to 4 seconds. An ejection murmur is heard at the right upper sternal border. Oxygen saturation in room air is 92% in the right and left arms. Echocardiography shows a left-ventricle wall thickness of 10 mm (Figure).

Of the following, the drug most likely to be useful in this child is:

☒ 1	dobutamine
2	dopamine
3	furosemide
4	milrinone
5	propranolol

You selected **1**, the correct answer is **5**.

The infant in the vignette has signs of hypertrophic cardiomyopathy (HCM), sometimes known as obstructive cardiomyopathy. It may be seen during the neonatal period in up to 30% of infants of diabetic mothers, although other possible associations include Noonan syndrome, Pompe disease, and the mitochondrial diseases. Signs may include tachypnea or cyanosis from pulmonary congestion, poor perfusion, or feeding difficulties. A double or triple apical impulse may be felt, caused by ventricular contraction, exaggerated atrial contraction, and early ventricular filling. A systolic ejection murmur signifies aortic outflow obstruction and becomes louder with a larger subaortic gradient.

Alternatively, infants of diabetic mothers may have congestive cardiomyopathy without hypertrophy. These infants often respond to correction of underlying polycythemia, hypoglycemia, hypocalcemia, or hypomagnesemia. The thickened myocardium seen in the echocardiogram of the infant in the vignette makes this diagnosis less likely.

Treatment of obstructive HCM usually includes a beta-blocker such as propranolol. By reducing sympathetic stimulation, propranolol reduces ventricular contractility and heart rate. This effect reduces the subaortic outflow gradient and the oxygen demands on the thickened myocardium, and reduces the chance of myocardial ischemia and damage. Propranolol binds to a G-protein, which then is prevented from helping in the production of adenylate cyclase and cyclic adenosine monophosphate (cAMP), resulting in decreased activity of protein kinase-A and lowered intracellular calcium levels. Its toxicity often is related to its nonselective blocking of beta-1 and beta-2 adrenergic receptors; it is relatively contraindicated in bronchospasm (beta-2) and severe congestive heart failure (beta-1).

Inotropic agents such as dobutamine, dopamine, and milrinone, may increase subaortic outflow gradients and myocardial oxygen demands. These agents usually are not recommended in obstructive HCM.

Dobutamine binds to a and ß adrenergic receptors and works through G-proteins to increase cAMP levels, resulting in higher intracellular calcium availability. It has inotropic and limited chronotropic activity and also will lower peripheral vascular resistance (PVR). Coronary blood flow and myocardial oxygen delivery improve. Toxicities include arrhythmias, tremor, and vomiting.

Dopamine also binds to a and ß adrenergic receptors, but with more peripheral a effect, raising PVR. This gives a higher blood pressure than dobutamine, although long-term outcome data are not available to suggest the initial use of one agent over the other. The two often are used together. Some practitioners advocate dobutamine initially for the congestive cardiomyopathy of perinatal asphyxia, to reduce afterload. Similarly, dopamine often is started in septic shock to help increase PVR and stabilize the peripheral vascular derangements. Dopamine binds to receptors in the kidney and selectively reduces renal vascular resistance in premature infants. Available data suggest that dopamine and dobutamine reduce mesenteric vascular resistance equally. Toxicities of dopamine include arrhythmias, tremor, and vomiting. Subdermal extravasation can cause blanching and necrosis and can be treated with local infiltration of phentolamine, an alpha-agonist. Dopamine also inhibits thyrotropin release, delaying valid thyroid screening results.

Furosemide may be useful in congestive heart failure where volume overload needs to be relieved. In obstructive HCM, it may cause hypovolemia, poor ventricular filling, and a worsening of the subaortic gradient. Furosemide interferes at the chloride-binding site of the sodium-potassium-chloride cotransporter, inhibiting reabsorption of sodium and water in the ascending limb of the loop of Henle. Toxicities include hypokalemia, alkalosis, ototoxicity, nephrolithiasis, and renal failure.

Milrinone is another inotropic drug that increases cAMP levels. Instead of working through a cell-surface receptor, it works directly in the cell to inhibit the action of phosphodiesterase and so prevent the hydrolysis of cAMP. It has an inotropic effect on the heart and a dilating effect on veins and arterioles, effects that do not depend on neurotransmitter stores or receptors. It simultaneously can raise cardiac output and lower PVR, without increasing myocardial oxygen demand significantly. Toxicities include arrhythmias, tremor, thrombocytopenia, and vomiting. Milrinone is of benefit in right ventricular failure and in weaning cardiac surgery patients from cardiopulmonary bypass. Its role is being investigated in treating the early hypotension of the severely premature newborn.

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Content specifications:

Recognize the therapeutic indications for and toxicity of inotropic agents in treating cardiovascular distress

Recognize the clinical features in an infant with a condition affecting myocardial performance, such as cardiomyopathy, myocarditis, tumor, and electrolyte imbalances

Understand the mechanism of action of commonly used autonomic agonist and antagonist
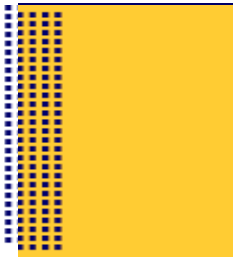
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NeoReviews Basic Self Assessment

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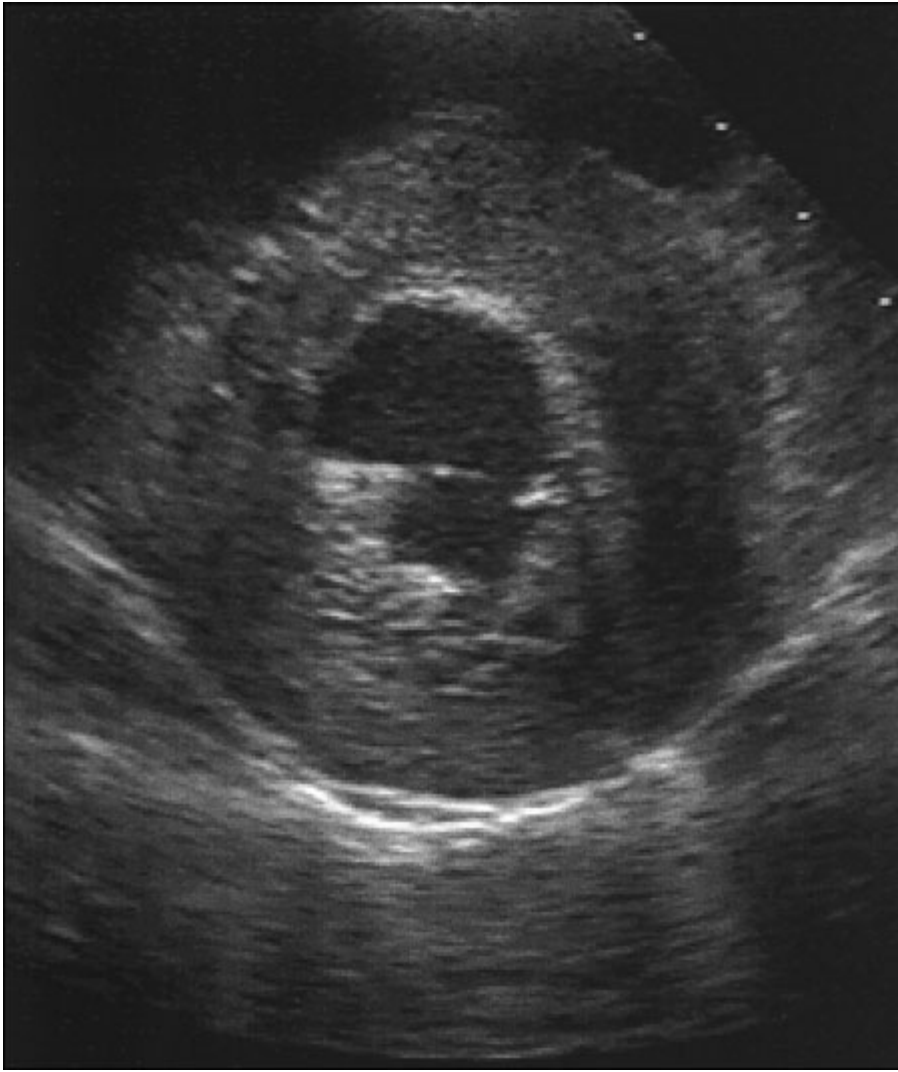A term male infant develops temperature instability, hypothermia, and hypoglycemia. On physical examination, he has pudgy cheeks and sagging jowls. His hair and eyebrows are sparse, brittle, and silver-colored. Microscopic examination of the hair shows pili torti. Family history is significant for a brother who had similar hair and eyebrows. The brother developed seizures at age 3 months and died at age 2 years after progressive neurologic deterioration.

Of the following, the trace element whose dysfunctional metabolism is MOST likely to account for the genetic disorder in this family is:

1 chromium

2 copper

3 manganese

❌ **4** selenium

5 zinc

You selected 4, the correct answer is 2.

An element is considered a trace element if it constitutes <0.01% of total body weight. Trace elements include chromium (Cr), cobalt, copper (Cu), fluoride, iodine, iron, manganese (Mn), molybdenum, nickel, selenium (Se), silicon, vanadium, and zinc (Zn). Trace elements play important roles in metabolism as essential components of metalloenzymes or as cofactors for enzymes. Trace element homeostasis is a tightly regulated process. Dietary deficiencies in trace elements are most severe during periods of rapid growth. Excess intake of trace elements can result in toxic accumulations. There are several rare genetic disorders that result in life-threatening accumulations or deficiencies of trace elements.

The family described in this vignette has Menkes disease (MD), also known as kinky hair disease. MD is a lethal, X-linked, recessive disorder of Cu metabolism. The incidence of MD in the United States is 1 in 300,000 live births. Internationally, MD is most common in Australia, where the incidence is 1 in 35,000 live births.

The clinical features of MD include silvery, sparse, brittle, steel-wool-like hair. Hair changes may not be present in the newborn period. Skin is hypopigmented, mottled, doughy, and lax. Seizures begin within the first few days or months after birth. Progressive neurologic deterioration occurs, marked by loss of developmental milestones, hypotonia, hypothermia, and lethargy. Most patients die by age 3 years. MD is characterized by a systemic Cu deficiency due to a defect in intestinal Cu transport. Cu is essential for brain metabolism, serving as a cofactor to amyloid precursor protein, dopamine-beta-hydroxylase, superoxide dismutase, and ceruloplasmin. Impaired Cu metabolism during early development leads to severe neurodegeneration. Parenteral administration of Cu can modify the course of the disease if started shortly after birth.

Cr serves as a cofactor for insulin. The biologically relevant form of Cr is the trivalent ion. Cr^{3+} is required for proper carbohydrate and lipid metabolism. There are no known genetic disorders of Cr^{3+} metabolism. Cr^{3+} deficiency may occur during prolonged parenteral nutrition or may be associated with protein calorie malnutrition. Cr^{3+} deficiency may result in impaired glucose metabolism.

Mn is a cofactor for enzymes such as Mn superoxide dismutase, arginase, pyruvate carboxylase, and glutamate-ammonia ligase. There are no known genetic disorders of Mn

metabolism. Although there are no documented abnormalities in humans deficient in Mn, animals deficient in Mn exhibit growth restriction, ataxia, and bone abnormalities. Of greater concern than Mn deficiency is Mn toxicity. Mn excess has been reported through dietary and occupational (as in welders) exposure. Mn toxicity causes confusion, muscle cramps, and poor coordination. Accumulation of Mn in brain tissue can result in a progressive disorder of the extrapyramidal system similar to Parkinson disease. Excessive Mn in children receiving long-term parenteral nutrition may contribute to cholestatic disease.

Se is an essential component of several proteins, including Se-dependent glutathione peroxidase, selenoprotein P, and deiodinase. Se is incorporated into these proteins as selenocysteine. Glutathione peroxidase is important in protecting lipids in polyunsaturated membranes from oxidative degradation. Impaired glutathione peroxidase antioxidant activity is important in oxidative diseases, such as bronchopulmonary dysplasia and retinopathy of prematurity. There are no known genetic disorders of Se metabolism. Inadequate concentrations of Se in the Chinese diet account for the development of Keshan disease, a form of juvenile cardiomyopathy that has a dual cause of Se deficiency and enteroviral infection. Toxicity from Se excess is minor. Excessive Se intake causes irritation of mucous membranes, irritability, pallor, and indigestion.

Zn is an integral cofactor for many enzymes involved in nucleic acid and protein metabolism. Zn is an important component of DNA and RNA polymerase, transcription factors (Zn-fingers), and enzymes involved in energy metabolism. Acrodermatitis enteropathica (AE) is an autosomal recessive disorder of Zn metabolism. AE is caused by the reduced uptake of dietary Zn by enterocytes, and the ensuing systemic Zn deficiency. Clinical features of AE are similar to those of severe dietary Zn deficiency and include alopecia, perioral and acral bullous lesions, diarrhea, and impaired growth. Symptoms usually begin two to three weeks after weaning from breast milk, because breast milk contains a Zn binding factor that augments Zn absorption. Formula-fed infants with AE become symptomatic one to two months after birth. The gene responsible for AE encodes a protein involved in dietary Zn uptake from the intestinal lumen. Supplemental oral Zn can overcome the deficiency in intestinal Zn absorption and improve the clinical features of AE.

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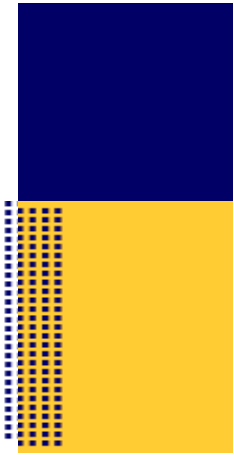
Content Specifications:

Understand the clinical manifestations and diagnosis of zinc deficiency

Understand the management and prevention of zinc deficiency

Understand the clinical manifestations and diagnosis of copper deficiency

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Understand the clinical manifestations and diagnosis of selenium deficiency

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Understand the clinical manifestations and diagnosis of manganese deficiency

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December 05

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You are asked to consult regarding potential sepsis in a term newborn. The infant delivered after 12 hours of labor, and membrane rupture occurred 5 hours before delivery. Maternal fever of 101.8° F (38.8° C) was noted during labor. Epidural analgesia was used. Maternal group B streptococcal colonization status is unknown. No uterine tenderness was described. Apgar scores were 8 and 9 at 1 and 5 minutes after birth, respectively. The infant's examination is within normal limits. A blood culture was done by the primary care physician, and empiric antibiotic treatment has been started. As you consider your recommendations, you review the general problem of suspected sepsis among term infants.

Of the following, the MOST accurate statement regarding suspected sepsis among term infants is:

1   Acute phase reactants are most helpful in determining the need for starting treatment among asymptomatic infants.

2   Documented sepsis usually is associated with neonatal symptoms.

3   Risk factors for sepsis strongly influence duration of antibiotic treatment among blood-culture negative infants.

4   Suspected sepsis has little impact on census in the neonatal intensive care unit.

5   Symptom onset with neonatal sepsis often is delayed beyond 24 hours after birth.

You selected 2 , the correct answer is 2 .

Suspected sepsis is a frequent consideration among newborns and results in evaluations for sepsis in 7% to 13% of live births. Of those evaluated, only 3% to 8% ultimately have documentation of sepsis by the gold standard-a positive blood culture. This results in an incidence of proven sepsis neonatorum of 2 in 1,000 live births. With this high index of suspicion and relative low occurrence, possible sepsis has a considerable impact on newborn care.

Sepsis evaluations generally are based on risk factors or neonatal symptoms. Clinical risk factors for neonatal sepsis include maternal fever (>100.4° F [38.5° C]), membrane rupture more than 18 hours before delivery, chorioamnionitis, sustained fetal tachycardia, or delivery at younger than 37 weeks' gestation. Maternal group B streptococcal colonization presents risk for sepsis. Neonatal symptoms often are nonspecific, such as apnea, tachypnea, lethargy, temperature instability, or feeding difficulties. Although many resources give guidance for evaluations and initial treatment, little evidence-based data support decisions regarding discontinuation or duration of antibiotic treatment among blood-culture-negative infants.

Approximately 85% of infants who ultimately have blood-culture-proven sepsis neonatorum present with symptoms, most commonly respiratory, less than 24 hours after birth. Another 5% of infants have symptoms by 48 hours after birth. A positive blood culture is uncommon among asymptomatic infants. The reliability of blood cultures to rule out sepsis relates most strongly to the volume and technique of blood collection. Careful skin antisepsis and avoidance of femoral sampling can reduce contamination, and obtaining a sample of >0.5 mL (preferably 1 mL or more) can reduce false-negative cultures. Blood cultures in proven sepsis are positive by 36 hours after birth in almost all cases. The likelihood that a negative culture at 36 hours will remain negative is 99.8%.

Acute phase reactants (C-reactive protein and elastase alpha$_1$-proteinase inhibitor) and immature to total neutrophil ratio are most useful for their negative predictive value (99.7%), especially when used serially. When used together, these tests have a sensitivity of only 23%,

but a specificity of 99.7%. Positive predictive value is 87.6%. For these reasons, acute phase reactants are not reliable enough to determine the need for initial treatment. When used together and serially, however, they can be most helpful in supporting decisions to stop antibiotic treatment.

Whether antibiotic treatment is begun because of maternal risk factors or neonatal symptoms, blood-culture-negative infants frequently are kept on antibiotics after culture results are reported. In a study by Spitzer and associates, the presence of and number of risk factors did not influence the mean duration of antibiotic treatment of blood-culture-negative infants. Antibiotics were stopped in 3 days or less about 70% of the time, whereas about 1 in 8 of these infants was treated for 7 days or more. A large percentage of infants received treatment for 4 to 6 days, longer than needed for blood culture results, yet shorter than recommended for sepsis treatment.

Suspected infection among term infants has a major impact on neonatal intensive care, resulting in more admissions than respiratory distress of premature infants. Length of stay is influenced by the duration of antibiotic treatment. Criteria for use of antibiotic treatment among blood-culture-negative infants are needed to address this impact on neonatal intensive care unit census and length of stay.

Most cases of documented neonatal sepsis are symptomatic, and it is unusual for those symptoms to have their onset beyond 24 hours of age.

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Content Specification:

Understand the causes and risk factors for sepsis

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A term male infant is admitted for possible congenital syphilis. He appears clinically well. His mother has had four pregnancies, the latest one year ago, and all have been complicated by recurrent syphilis. She also has a history of lupus, *Chlamydia,* gonorrhea, and cocaine use.

The mother's nontreponemal titer at her single prenatal visit at 28 weeks was positive, as was her treponemal test; she received penicillin. Postnatal testing revealed positive treponemal and nontreponemal tests in both mother and cord blood of the infant. The nontreponemal titer had increased fivefold compared to the testing at 28 weeks. The infant's nontreponemal titer was elevated but twofold less than his mother's titer. Urine samples from both mother and infant were positive for cocaine.

Of the following, the MOST appropriate indication for additional evaluation of this infant for congenital syphilis is:

1 elevation of infant's quantitative nontreponemal titer

2 positive cord blood nontreponemal test

3 positive maternal treponemal test

4 positive maternal nontreponemal test

5 rise in maternal quantitative nontreponemal titer

You selected **3**, the correct answer is **5**.

Congenital syphilis is caused by *Treponema pallidum,* a thin, motile, corkscrew-shaped spirochete that dies quickly outside its host. Transmission may occur at any time during gestation, usually from transplacental spread. Nearly all infants born to mothers with primary or secondary syphilis will be infected, although only half will be symptomatic.

Symptoms within the first 4 weeks after birth may include hepatosplenomegaly (91%), metaphyseal dystrophy (95%), anemia (64%), jaundice (49%), cerebrospinal fluid changes (44%), periostitis (37%), polymorphic maculopapular rash that involves palms and soles (31%), snuffles (12%), and joint swelling (3%). Nephrosis and myocarditis also may occur. Late (ie, many years after birth) manifestations of untreated congenital syphilis, irrespective of presence of early symptoms, may include interstitial keratitis, 8th-nerve deafness, Hutchinson teeth (notched central incisors), anterior bowing of shins, frontal bossing, mulberry molars, saddle nose, rhagades (evolution of oromucosal lesions), and Clutton joints (symmetric, painless swelling of the knees).

Antenatal maternal screening has significantly reduced the number of symptomatic congenitally infected infants in industrialized countries. However, syphilis remains a major cause for fetal death, hydrops, prematurity, and postnatal illness in developing countries. If pregnant women with secondary syphilis are untreated, 40% of the pregnancies end in spontaneous abortion, stillbirth, or perinatal death. Syphilis also is more common among people with human immunodeficiency viral infection.

Diagnosis of syphilis has been hampered because *T. pallidum* cannot be cultured readily or stained with simple laboratory supplies. Four categories of tests have been developed to establish the diagnosis of syphilis. These include direct microscopic examination of tissue lesions, nontreponemal tests for screening and quantitation of antibody concentration, confirmatory treponemal tests, and direct antigen detection tests used in research settings.

Serologic evaluation for syphilis includes both nontreponemal tests (Venereal Disease Research

Laboratory (VDRL); rapid plasma reagin (RPR); automated reagin (ART); and treponemal tests (fluorescent treponemal antibody absorption [FTA-ABS], *T pallidum* particle agglutination [TP-PA]).

Nontreponemal tests provide quantitative results that help monitor disease activity and response to therapy. Nontreponemal (reagin) tests measure immunoglobulin M and immunoglobulin G antibodies to the lipoidal material released from damaged host cells as well as to lipoprotein-like material and possibly by cardiolipin released from treponemes.

A sustained fourfold decrease in titer is expected with successful treatment. A fourfold increase in these titers indicates reinfection or relapse; it is the best indicator for additional evaluation of an infant whose mother previously had syphilis, as in the infant in this vignette.

The positive maternal nontreponemal and treponemal tests individually are not adequate to recommend additional testing of the infant in this vignette. Persistent positive tests after maternal syphilis may last up to one year for nontreponemal tests and many years for treponemal tests. Furthermore, positive results for nontreponemal tests may be transiently positive during pregnancy, during infections (such as hepatitis, infectious mononucleosis, varicella, measles, malaria), and after immunizations or technical error. Chronic false-positive results with nontreponemal tests occur in women with collagen vascular diseases like lupus erythematosus, narcotic addiction, leprosy, cancer, and advanced age. False-positive treponemal test results for syphilis occur in up to 1% of the general population; therefore, such tests are not useful for screening purposes. Lupus erythematosus, advanced age, Lyme disease, infectious mononucleosis, drug addiction, leprosy, and other treponemal diseases (such as yaws and pinta) also are associated with false-positive results. Nontreponemal tests for syphilis are useful in screening programs because they are inexpensive, automated, relatively simple, accurate, and reproducible. Maternal serum is the best indicator of infection, followed by neonatal serum; cord blood is least reactive, so it has the highest rate of false-negative results. In the vignette, the cord blood nontreponemal test was positive, suggesting congenital syphilis. However, additional testing is needed to establish the diagnosis.

A presumptive diagnosis of congenital syphilis can be made from physical, radiographic, serologic, and direct microscopic examinations of tissue lesions and placenta. All symptomatic infants should have additional tests such as quantitative nontreponemal and treponemal serology, VDRL on cerebral spinal fluid, complete blood cell count, platelet count, long-bone radiographs (unless the diagnosis has been established otherwise), microscopic dark-field or direct fluorescent antibody testing of tissue lesions, and placental evaluation.

Asymptomatic infants born to a mother with a presumptive diagnosis of syphilis based on screening serology should have similar screening nontreponemal and treponemal tests performed. If the maternal titer has increased more than fourfold or the infant titer is greater than the mother's titer, additional studies, such as those described above for symptomatic infants, should be performed. In the vignette, the maternal titer increased fivefold, but the infant was asymptomatic and had a nontreponemal titer lower than the maternal titer. Therefore, additional evaluation should be performed due to the rise in maternal titer.

Additional evaluation may be indicated in an asymptomatic infant whose mother has a positive nontreponemal and treponemal test if the mother has one or more of the following conditions:

1. Syphilis untreated, or inadequately treated, or treatment not documented

2. Syphilis during pregnancy treated with a nonpenicillin regimen, such as erythromycin

3. Syphilis during pregnancy treated with an appropriate penicillin regimen but without the expected fourfold decrease in nontreponemal antibody titer after therapy

4. Syphilis treated less than one month before delivery (because treatment failures occur, and the efficacy of treatment cannot be assumed)

5. Syphilis treated before pregnancy but with insufficient serologic follow-up to assess the response to treatment and infection status

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Content Specifications:

Know how to diagnose and manage fetal infection

Understand the epidemiology of perinatal infections with *Treponema pallidum*

Understand the clinical manifestations and diagnostic criteria of perinatal infections with *Treponema pallidum*

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A male African-American infant is born at 24 weeks' gestation to a 21-year-old primiparous mother by emergency cesarean section because of preterm labor and partial placental abruption. One dose of betamethasone was given about 6 hours before delivery. Birthweight was 840 g, length 35.5 cm, and head circumference 24.5 cm. There were no anomalies. Physical characteristics were consistent with obstetric dates. A brother has a history of frequent infections.

The infant had severe respiratory distress that was difficult to manage, with a total of 52 days of ventilation, and is being treated with continuous positive airway pressure and supplemental oxygen on postnatal day 60. His weight is 1680 g, and he has not gained much during the previous 10 days. He is being evaluated for routine immunizations. Cranial sonogram is normal.

Of the following, the MOST appropriate reason to delay immunizations in this infant is:

1 current weight less than 1750 g

2 failure to thrive

3 sibling with an unspecified immune disorder

4 still needing continuous positive airway pressure

5 still receiving supplemental oxygen

You selected **2**, the correct answer is **2**.

For infants age 2 months, the recommended active immunizations include hepatitis B, diphtheria, tetanus, and pertussis (DTaP), *Haemophilus influenzae* Type b, inactivated polio, and pneumococcus. An extremely low birthweight infant with a history of chronic lung disease, such as the infant in this vignette, also would be eligible to receive palivizumab, an intramuscular passive immunization against respiratory syncytial virus (RSV), during the part of the year when RSV infections are endemic.

The *Red Book,* published by the American Academy of Pediatrics (AAP), recommends that premature infants "should, *with few exceptions*, receive all routinely recommended childhood vaccines at the same chronological age as should full-term infants." The publication further recommends that dosages should not be reduced or divided for premature infants. It is considered reasonable to use needles that are shorter than those needles recommended for larger infants and to give the injections over two to three days to adjust for the reduced muscle mass of the premature infant.

The "few exceptions" alluded to in the statement represent the main focus of this question. The advice of the AAP Committee on Infectious Diseases (the *Red Book* authors) is that infants who are medically stable are eligible for vaccination at the usual chronological age. What is meant by "medically stable" is further described as a) not being treated for serious infection, b) not being treated for a metabolic disorder, c) recovering, d) growing, and e) cardiovascular, renal, and respiratory systems not unstable.

The one answer that fits the criteria for delaying routine immunization is "not gaining weight" or "failure to thrive." The current weight, however small, specifically is mentioned as not relevant to the decision. If the respiratory support were getting more intense or there were some other indication that the infant's respiratory status is unstable, there would be a reason to wait, but that is not the case in this vignette.

In days past, a suspicion of a congenital immune disorder in the family would have been a good

reason to delay some immunizations. Any live-virus vaccine, such as live polio vaccine, could cause severe or even fatal illness in an infant with an immune disorder. However, neither live polio vaccine nor any other live vaccine is recommended routinely at the two-month visit, making the suspicion of an immune disorder in the family irrelevant to the decision to provide the recommended vaccines.

References:

American Academy of Pediatrics. Immunization in special clinical circumstances: preterm and low birthweight infants. In: Pickering LK, ed. *Red Book: 2003 Report of the Committee on Infectious Diseases.* 26th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2003:66-68

Content Specification:

Know the immunizations recommended by the American Academy of Pediatrics and the appropriate schedules for immunizing preterm and full-term infants

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A female infant of 35 weeks' gestation is admitted to the neonatal intensive care unit for mild respiratory distress and temperature instability. Her mother is a 23-year-old woman with no medical illnesses, and this is her first pregnancy. Family history is remarkable for seizures in a cousin, neurofibromatosis in an uncle, and hypertension in both sets of grandparents.

The mother's menstrual cycles have been regular every 28 days until she became pregnant. A small amount of vaginal bleeding was noted 3 weeks after her last normal menstrual period. Prenatal care began at 9 weeks' gestation, dated from the first day of her last menstrual period. Sonography at that time was consistent with a gestational age of 9 weeks. Subsequent sonographs at 20 and 28 weeks' gestation were consistent with dates and normal fetal growth.

Fetal heart tones were heard at 13 weeks' gestation using Doppler technology. Fundal height estimation of gestational age had been consistently 2 weeks behind that, based on the first day of the last menstrual period. Physical examination after birth is remarkable for tachypnea, nasal flaring, and minimal subcostal retractions. The infant's temperature is 35.6° C on admission. Oxygen saturation by pulse oximetry is 96%. Her Ballard score is consistent with a gestational age of 33 weeks.

Of the following, the MOST accurate measure of gestational age is:

1	embryonic crown-rump length at 9 weeks' gestation
2 ☒	fetal heart tones using Doppler technology
3	fundal height measurements
4	gestational sac diameter measurement at 5 weeks' gestation
5	postnatal Ballard score

You selected 2, the correct answer is 1.

Gestational age assessment is a fundamental determination for physicians caring for pregnant women, children, and their families. Knowledge of gestational age is an indicator of neonatal maturity and associated morbidity and mortality. Clinical interventions and management strategies often can be anticipated when the gestational age is known. For example, an infant assessed to be 26 weeks' gestation at birth can be anticipated to have some respiratory distress and, perhaps, would benefit from surfactant replacement. Indeed, from a public health perspective, gestational age at birth and birthweight are indicators of the population's fetal and neonatal health.

Gestational age generally is based on the first day of the last normal menstrual period. This estimation is the gold standard when the menstrual cycle length is regular and occurs approximately every 28 days. If the duration of the menstrual period is shorter or longer than usual, as occurs in some women with variable durations of preovulatory and blastocyst implantation phases of the menstrual cycle, the last menstrual period may inaccurately reflect gestational age. Maternal recall error about the first day of the last normal menstrual period, implantation bleeding several weeks into the pregnancy (as seen in the mother in this vignette), and preconception amenorrhea after oral contraceptive use add to the variability in gestational age assessment. Because of this variability, more accurate methods of determining gestational age continue to be investigated.

In the absence of reliable menstrual dates, the most accurate assessment of gestational age is with sonographic measurement of the embryonic crown-rump length. When performed between

5 and 12 weeks' gestation, as in this vignette, dating is accurate to +3 days. In contrast, gestational sac diameter measurement performed sonographically at about 5 weeks' gestation is accurate to within 5 days.

Sonographic measurement of the triad of biparietal diameter, femur length, and cerebellar transverse diameter are accurate to within 10 days and 14 days at 15 to 22 weeks' gestation and >22 weeks' gestation, respectively.

Maternal physical measures of fundal height and Doppler detection of fetal heart tones are accurate to only ±2 to 3 weeks. Postnatal physical examination using the Ballard scale is accurate to ±2 weeks if the infant is born ≥28 weeks' gestation and ±3 weeks if the infant is born <28 weeks' gestation.

<u>References:</u>

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<u>Content Specification:</u>

Know the ultrasound findings and their limitations in determining gestational age

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A 3-day-old infant is blue and feeding poorly. The heart rate is 190 beats/min. The liver is 2 cm below the right costal margin. A chest radiograph suggests a large right-heart silhouette. You suspect a right-sided cardiac lesion. A prostaglandin drip is started.

Of the following, the condition MOST typically associated with a large right-heart silhouette on a chest radiograph is:

1. critical pulmonary stenosis

2. Ebstein anomaly

3. pulmonary atresia with intact ventricular septum

4. ☒ pulmonary atresia with ventricular septal defect

5. tricuspid atresia

You selected **4**, the correct answer is **2**.

Right-sided cardiac lesions have a variety of presentations. Obstruction to ventricular outflow results in increased right atrial pressure and shunting across the atrial septum, spilling deoxygenated blood into the left atrium and then into the systemic circulation, causing cyanosis. Right heart failure may cause an enlarged liver. Right atrial enlargement can affect heart conduction, causing supraventricular tachycardia. Of the given lesions, Ebstein anomaly is associated most typically with a large right heart on a chest radiograph.

Ebstein anomaly (Figure 1), first described in 1866, occurs in 1 in 25,000 live births and involves displacement of the tricuspid valve into the right ventricle. Maternal lithium exposure may be a risk factor. The marked right atrial enlargement is caused by a combination of tricuspid regurgitation and the abnormal contraction pattern of the atrialized portion of the right ventricle. The right atrial enlargement is associated with pulmonary hypoplasia, poor right ventricle output, supraventricular tachycardia, congestive heart failure, hypoxemia, and acidosis. Tachycardia, often seen, is associated with poor right ventricle filling but also may be caused by Wolff-Parkinson-White syndrome, found in up to 30% of patients with Ebstein anomaly. The most likely murmur is one of tricuspid insufficiency heard at the lower left sternal border. Pulmonary blood flow can be enhanced by using prostaglandin E1 to keep the ductus arteriosus patent. Respiratory alkalosis along with high inspired oxygen can lower pulmonary vascular resistance.

Critical pulmonary stenosis (Figure 2) was described by Morgagni in 1761. It results in right ventricular hypertrophy, right-to-left atrial shunting and hypoxemia, and pulmonary blood flow that are dependent on the patency of the ductus arteriosus. The ventricular wall hypertrophy narrows the lumen of the right ventricle. Right heart failure is prevented by atrial shunting, but at the cost of producing cyanosis. Low flow through the pulmonary valve gives only a soft heart murmur at the upper right sternal border. The right heart does not appear enlarged on chest radiography.

Pulmonary atresia with intact ventricular septum (Figure 3) occurs in approximately 1 in 12,000 live births. Blood exits the right atrium through the atrial septum. Pulmonary blood flow is dependent on patency of the ductus arteriosus. Right ventricular volume may be normal or reduced secondary to a hypertrophic right muscle mass. The coronary arteries can arise from the right ventricle, sometimes resulting in coronary insufficiency and myocardial infarction at birth. Isolated pulmonary atresia without tricuspid valve involvement does not exhibit a large right heart silhouette on chest radiography.

Pulmonary atresia with ventricular septal defect ([Figure 4](#)) occurs in approximately 1 in 14,000 live births. It can be associated with a microdeletion of region 22q11 or other chromosomal abnormalities. Pulmonary blood flow can come from the ductus arteriosus or aortopulmonary collateral arteries. Patients present with cyanosis and exhibit a single second heart sound. Right-sided heart failure and a large right heart on chest radiography rarely are seen until pulmonary vascular resistance decreases in the first four weeks after birth.

Tricuspid atresia ([Figure 5](#)) was described by Kreysig in 1817, and it occurs in approximately 1 in 20,000 live births. Incoming blood to the right atrium must exit via an atrial shunt, resulting in cyanosis. Pulmonary blood flow depends on a patent ductus arteriosus or a ventricular septal defect. More than 90% of cases have a ventricular septal defect, allowing filling of the right ventricle. In most of these cases, however, pulmonary stenosis often limits pulmonary blood flow unless the ductus arteriosus remains open. A closing ductus results in severe hypoxemia and acidosis. The right heart is not enlarged on chest radiography.

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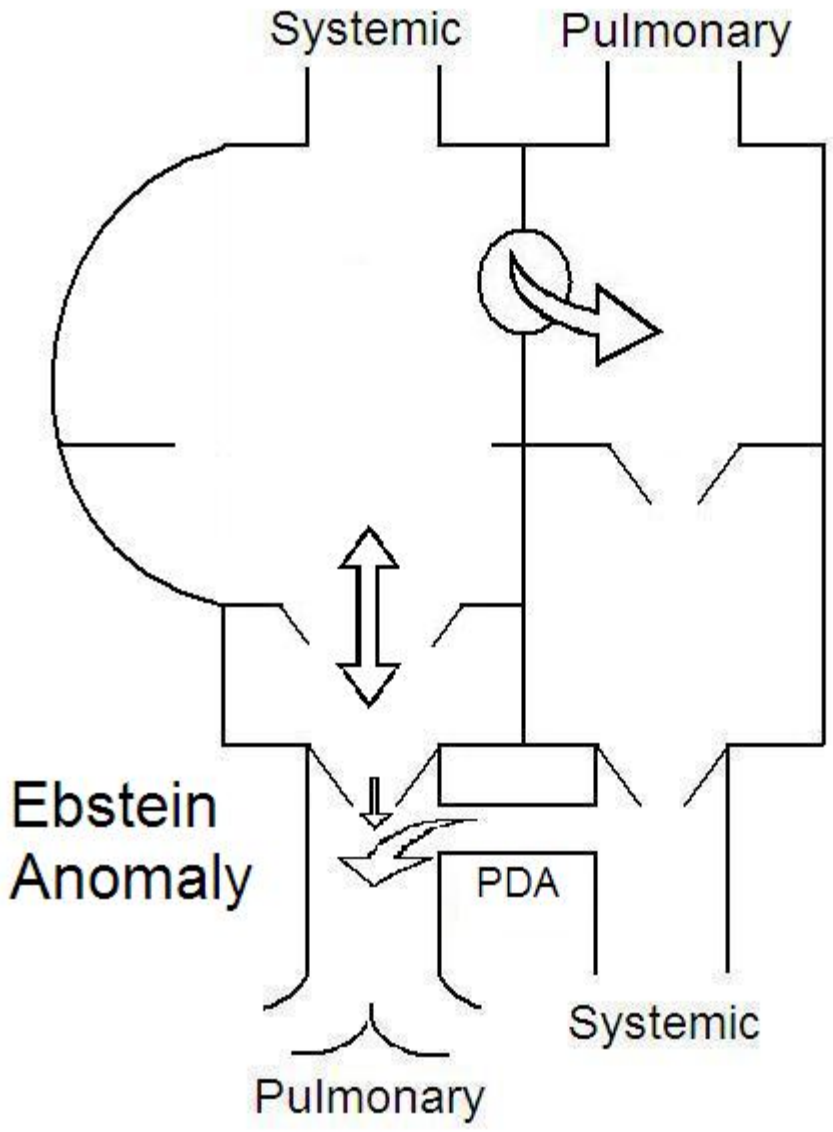
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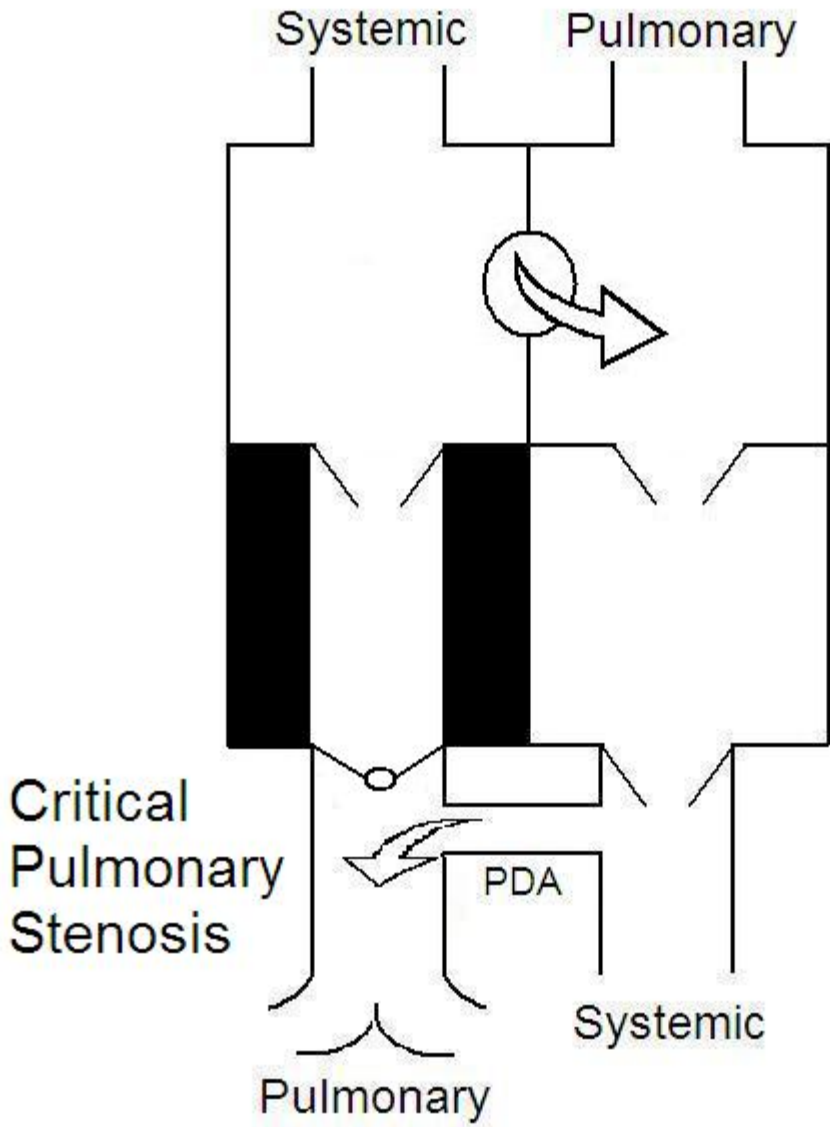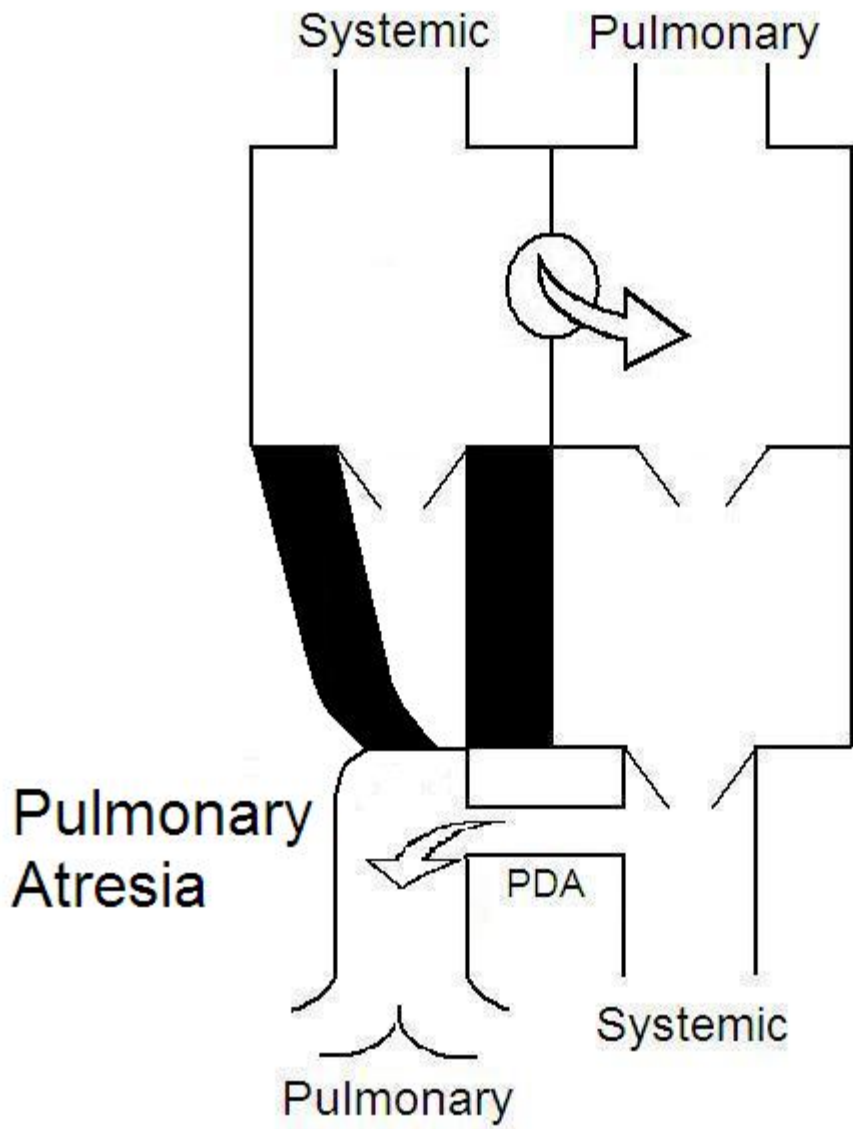
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Recognize the clinical features of a neonate with a right-sided cardiac lesion

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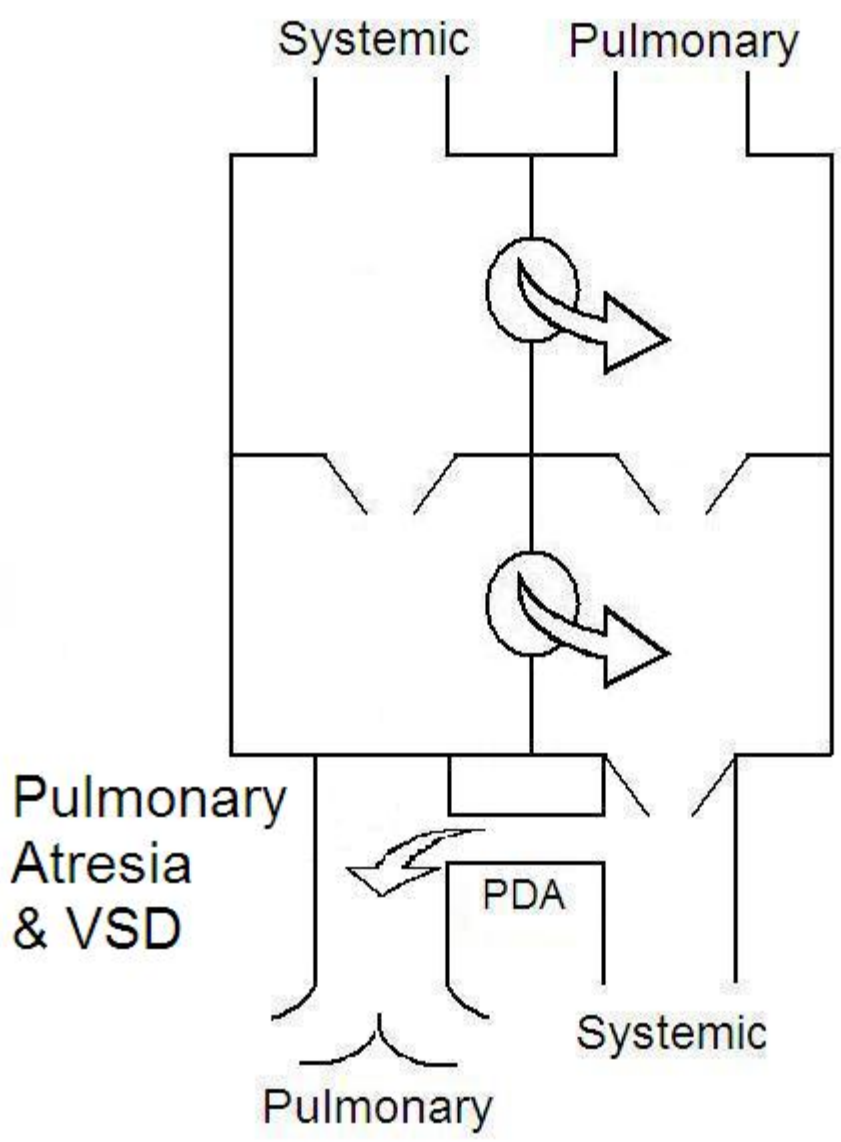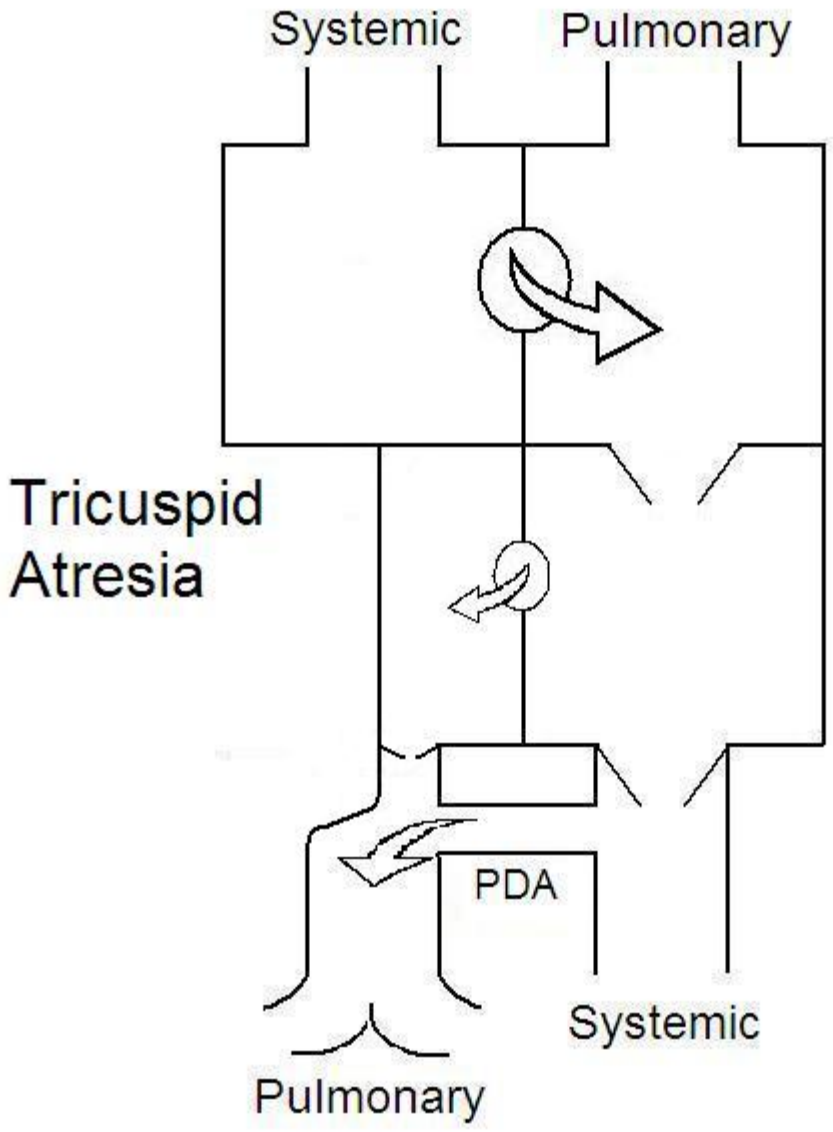
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Ebstein
Anomaly

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Systemic

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Critical
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Tricuspid Atresia

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A term male infant was born vaginally with the help of outlet forceps to a 29-year-old primiparous woman with no history of complications during pregnancy. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. After appearing stable for a time, the infant received an injection of vitamin K and routine eye prophylaxis, consisting of 0.5% erythromycin ointment. Physical examinations at birth and before discharge 36 hours after birth showed no abnormalities except for excessive tearing from both eyes. Further examination showed reactive round pupils, normal eye movement, pale conjunctivae, clear media, and normal red reflexes bilaterally, with some resistance to bright light.

Of the following, the MOST likely explanation for the ophthalmic findings in this infant is:

☒ **1**	conjunctivitis
2	corneal trauma
3	dacryocystitis
4	glaucoma
5	irritation from eye prophylaxis

You selected **1**, the correct answer is **4**.

Glaucoma is a condition associated with abnormally high intraocular pressure, which can damage the optic nerve and cause permanent blindness if not treated. In the normal eye, aqueous fluid constantly is produced by the ciliary body and drained through the trabecular meshwork at the junction of the iris and the cornea. The relative rates of formation and drainage of the aqueous humor determine the intraocular pressure.

Congenital glaucoma may occur because of a malformation of the eye's drainage system, or it may be secondary to another eye condition. Congenital glaucoma affects boys in 65% of cases, and 70% of cases involve both eyes.

The classic symptoms of congenital glaucoma are epiphora (tearing), photophobia, and blepharospasm (twitching of the eyelids). Two of these symptoms are found in the infant in this vignette. Before age 3, eye tissues stretch more easily. If the eye pressure is elevated, the eye becomes enlarged (buphthalmos), which can manifest as megacornea. A corneal diameter of 12 mm or more at birth, when the normal limit is 10.5 mm, suggests glaucoma.

Congenital glaucoma may be an isolated disease, or it may be associated with other conditions, such as aniridia, rubella syndrome, Lowe syndrome, Hallermann-Streiff syndrome, Axenfeld or Reiger syndrome, and Sturge-Weber syndrome. Suspicion of congenital glaucoma should trigger a consultation with an ophthalmologist. The definitive treatment is surgical, although medications might be prescribed to try to reduce intraocular pressure while surgery is being arranged.

Conjunctivitis can cause tearing and some photophobia, as described in the infant in this vignette. However, the conjunctivae are inflamed, not pale, and the discharge is often cellular, not watery. Matting of the eyelids often is seen.

Dacryocystitis usually manifests as a purulent exudate in the medial canthal area along with a swelling and induration of the lacrimal sac. Photophobia is not described with this condition. Dacryocystitis often involves only one eye.

The eye prophylaxis associated with the highest incidence of irritation is silver nitrate.

Erythromycin ointment is preferred in many institutions to prevent the chemical conjunctivitis caused by silver nitrate. It is, therefore, an unlikely cause of the symptoms in the infant in this vignette.

Finally, corneal abrasions can occur with a traumatic delivery. Outlet forceps procedures are designed to reduce birth trauma, but misapplication of forceps over the eye can be traumatic. The bilateral nature of the condition in the vignette as well as the lack of any description of skin abrasions makes trauma an unlikely cause.

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<u>Content Specifications:</u>

Recognize the signs of congenital glaucoma

Recognize the conditions associated with congenital glaucoma

`◄ PREVIOUS`   `NEXT ►`

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Kohelet and associates reviewed carefully collected coded records of more than 7,000 very low birthweight (VLBW) infants to discern factors related to clinical seizures in this population. They documented seizures in 5.6% of the population. Among the factors associated with seizures were 1) onset of prenatal care, 2) use of antenatal corticosteroids, 3) maternal hypertension, 4) mode of delivery, 5) intrauterine growth, 6) resuscitation at birth, 7) respiratory distress syndrome, 8) patent ductus arteriosus, 9) necrotizing enterocolitis, and 10) intraventricular hemorrhage. They reported several associations.

However, if one assumes that none of the factors really is associated with neonatal seizures (null hypothesis) and that the results occurred purely by chance, it still would be possible that one or more of the 10 factors would seem to have an association with neonatal seizures with the probability (P value) less than 0.05.

Of the following, the BEST estimate of the random chance for at least one of the 10 simultaneously investigated factors to come out with $P < 0.05$ is:

1	<1%
☒ 2	20%
3	40%
4	60%
5	80%

You selected **2**, the correct answer is **3**.

The solution to this problem represents a classic exercise in probability. The key to the question is the phrase "at least one." It implies that one positive result could have happened, as well as two, three, four, or 10, among the 10 factors investigated. At first glance, finding the exact probability is not an easy calculation.

It would help to review important principles in estimating probabilities. The probability (P) of an event is equal to the number of ways a particular event can occur divided by the total number of possible outcomes. A simple example would be to estimate the probability of getting at least one 4 by rolling a 6-sided die twice. In this case, the probability of rolling a 4 on each try would be 1/6 or about 16.7%. However, because we have to consider all cases in which at least one 4 is rolled, we would have to consider the number of ways this scenario could play out. In this case, six possibilities exist with each roll, and two rolls would give us 6 x 6 or 36 possible combinations or outcomes. By writing out the 36 possible outcomes of two throws of a die (Table), then counting those that contain a 4, we easily can find the probability of rolling at least one 4.

1st	1	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3
2nd	1	2	3	**4**	5	6	1	2	3	**4**	5	6	1	2	3	**4**	5	6

1st	4	4	4	4	4	4	5	5	5	5	5	5	6	6	6	6	6	6
2nd	1	2	3	**4**	5	6	1	2	3	**4**	5	6	1	2	3	**4**	5	6

By inspection, there are 11 pairs with at least one 4, so the estimate of probability of the event

would be 11 in 36 or 30.6%. This method is straightforward but would be cumbersome for problems of more complexity and certainly unwieldy for the question posed in this vignette.

The best alternative to solving the "at least one" question is to look at the obverse. If two outcomes are mutually exclusive (ie, obtaining "heads" with the toss of a coin eliminates the possibility of obtaining "tails" with that toss), then the sum of the probabilities of mutually exclusive outcomes would be 100%. In this case, the total of outcomes *without* a 4 in them plus the total *with* a 4 add up to all possible outcomes (100%). It is much simpler to find the probability of not getting a 4 and subtracting that from 100%. The probability of not getting a 4 is 5/6 (83.3%) for each roll. Because the two rolls are independent of each other, the combined probability is the product of the two individual probabilities. This comes out to $(5/6)^2$ or 69.4% for the two rolls. Subtracting this probability from the 100% yields the same 30.6% obtained through the direct counting method.

Now we can return to the problem in the vignette. The probability for each potentially predisposing factor to reach significance at *P* <0.05 is 5%. The probability of each factor NOT reaching significance is then 95%. For 10 factors, having no positive results would be $(95/100)^{10}$ or 60%. Therefore, the chance of having at least one factor come up positive, given complete randomness, would be the obverse, 40%.

Now that we see how common it would be to get a falsely positive result, we should be skeptical about "significant" associations reported at the *P* <0.05 level when multiple tests are done in the same analysis. This problem in interpretation has been addressed with the Bonferroni correction, which advises that the appropriate level of confidence to accept in simultaneous comparisons would be alpha (the probability of rejecting the null hypothesis in error) divided by n (the number of tests). In the study in the vignette, 0.05/10 or *P* <0.005 would be the appropriate alpha to require. As it happens, Kohelet and associates looked at 16 individual variables and found nine of them with univariate *P*-values less than the required 0.003. They chose their variables very wisely.

References:

Kohelet D, Shochat R, Lusky A, Reichman B. Risk factors for neonatal seizures in very low birthweight infants: population-based survey. *J Child Neurology.* 2004;19:123-128

The following Web sites, accessed June 2, 2005, contain the principles of probability needed to solve this problem:

http://www.mathgoodies.com/lessons/vol6/complement.html
http://www.mathgoodies.com/lessons/vol6/independent_events.html
http://mathworld.wolfram.com/BonferroniCorrection.html

Content Specifications:

Identify and evaluate the efficacy of study designs commonly used in clinical research

Understand the null hypothesis

Understand alpha (type I) and beta (type II) errors

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NeoReviewsPlus

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NeoReviews Basic Self Assessment

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Access My Learning Plan

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View course using IE 8

You are asked to evaluate a 6-day-old term female with neutropenia. The pregnancy was uncomplicated, including no history of pregnancy-induced hypertension. The infant's absolute neutrophil count is 850 cells/mL. Her physical examination is remarkable for short limbs, long trunk, and mild bowing of legs. Her hair and eyelashes are fine, sparse, and light-colored. Her skin is hypopigmented, and she has redundant skin folds around her neck. Her parents are Amish. A brother had short stature and recurrent thrush. He died at age 5 years from an overwhelming varicella infection.

Of the following, the MOST likely cause of neutropenia in this infant is:

1	cartilage-hair hypoplasia syndrome
☒ 2	dyskeratosis congenita
3	Kostmann syndrome
4	reticular dysgenesis
5	Shwachman-Diamond syndrome

You selected 2, the correct answer is 1.

The main role of neutrophils is phagocytosis and destruction of pathogens. Individuals with decreased numbers of neutrophils or abnormal neutrophil function have increased susceptibility to life-threatening infections.

The concentration of circulating neutrophils changes greatly after birth and varies depending on gestational age. There is a normal surge in absolute neutrophil count (ANC) after birth that peaks at 12 hours in term newborns and 18 hours in premature infants. Neutropenia in a term newborn is defined as an ANC <3000 cells/mL in the first 48 hours after birth and <1500 cells/mL thereafter. The ANC of a premature infant is lower than that of a term newborn. Neutropenia in a premature infant is defined as an ANC <500 cells/mL in the first hours after birth to an ANC <1000 cells/mL beyond 60 hours after birth.

Neutropenia may be caused by increased neutrophil consumption, decreased neutrophil production, or both. Increased neutrophil consumption by nonimmune mechanisms (such as sepsis) or immune mechanisms are the most common causes of neutropenia. Rare genetic disorders of decreased neutrophil production or abnormal neutrophil maturation have been described.

The infant and her brother described in this vignette have cartilage-hair hypoplasia syndrome (CHH). CHH is an autosomal recessive disorder characterized by neutropenia, T-cell immunodeficiencies, short-limbed dwarfism, redundant skin folds around the neck, and sparse, fine hair. In the United States, most patients with CHH are of Amish descent. Internationally, CHH is most common in Finland, where the reported incidence is 1 in 23,000 births. Moderate neutropenia and lymphopenia result in opportunistic infections with *Candida* species, *Pneumocystis carinii,* and cytomegalovirus. Because of T-cell immunodeficiencies, patients with CHH are particularly prone to life-threatening varicella infections. The cause of CHH has been identified as mutations in the ribonuclease mitochondrial RNA processing gene on 9p. Stem cell transplantation is the treatment of choice.

Dyskeratosis congenita (DKC) is an X-linked recessive disorder characterized by pancytopenia, nail dystrophy, abnormal skin pigmentation, and mucosal leukoplakia. Most patients with DKC are asymptomatic at birth. Irregular reticular hyperpigmentation surrounding areas of

hypopigmentation first appear on the upper torso between ages 5 and 15 years. The mean age at death is 24 years as a consequence of opportunistic infection, malignant transformation of the leukoplakia, or pancytopenia. DKC is caused by mutations in the DKC1 gene localized to Xq28. DKC1 encodes dyskerin, which is important in ribosome synthesis. Some patients with DKC have been cured by bone marrow transplantation.

Kostmann syndrome is an autosomal recessive disorder in which there is an arrest of neutrophil development in the bone marrow at the promyelocyte or myelocyte stage. Few mature neutrophils are found in the bone marrow, and the neutropenia is severe (ANC consistently <200 cells/mL). Monocytosis and eosinophilia are common. Life-threatening bacterial infections develop in the first months after birth. The mechanism of neutropenia in Kostmann syndrome may be a defect in signal transduction through the granulocyte-colony stimulating factor (G-CSF) receptor and mutations in the elastase gene involved in neutrophil maturation. Treatment with recombinant G-CSF may increase the number of circulating neutrophils, thereby reducing the number and severity of infections. Patients who do not respond to G-CSF may benefit from bone marrow transplantation.

Reticular dysgenesis (RD) is a rare syndrome of neutropenia, thymic dysplasia, and lymphoid hypoplasia. RD often is classified as a variant of severe combined immunodeficiency disorders. A defect of stem cells leads to absent production of all myeloid cells in RD. Red blood cell and platelet production are normal. Most patients with RD develop serious infections a few days after birth. Death from overwhelming infection occurs in early infancy. G-CSF is not effective. Stem cell transplantation is the treatment of choice.

Shwachman-Diamond syndrome (SDS) is an autosomal recessive disorder characterized by neutropenia, pancreatic insufficiency, and skeletal abnormalities. The incidence of SDS has been reported at 1 in 10,000 to 200,000 births. The ANC is usually <500 cells/mL, and neutrophil chemotaxis often is defective. Thrombocytopenia that results in epistaxis, melena, and easy bruising is present in approximately 25% of patients. Pancreatic insufficiency causes steatorrhea, diarrhea, and failure to thrive. Short stature and metaphyseal dysplasia are common. Height and weight are usually less than the 3rd percentile. Patients with SDS are at increased risk of developing leukemia. The neutropenia of SDS may respond to G-CSF. Allogenic stem cell transplantation also has been used successfully.

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Content Specifications:

Recognize the causes and consequences of alterations in number and distribution of neutrophils

Understand the origin, maturational process, and regulation of leukopoiesis during development

Understand the role of neutrophils

Recognize the etiology and pathophysiology of neonatal leukopenia

Understand the differential diagnosis of neonatal leukopenia

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A 2-day-old infant has sudden tachycardia, with a heart rate of 240 beats/min. She remains hemodynamically stable. A bag of ice and water applied to the face restore normal heart rate quickly and easily. The maneuver is repeated twice more over the next day, each time with a stable child and an easy conversion. Between episodes, an electrocardiogram shows a short PR-interval and a delta-wave leading each R-wave (Figure 1).

Of the following, the class of antiarrhythmic drug MOST likely to benefit this child is

1 class Ia - sodium channel blocker, fast recovery

2 class Ic - sodium channel blocker, slow recovery

3 class II - beta blocker

4 class III - potassium channel blocker

5 class IV - calcium channel blocker

You selected **3**, the correct answer is **3**.

Symptomatic but hemodynamically stable Wolff-Parkinson-White syndrome (WPW) in a neonate, as seen in this vignette, is best treated with esmolol or propranolol, class II (beta-blocker) antiarrhythmic drugs.

WPW occurs in 0.1% to 0.3% of the general population and has been associated with defects on several chromosomes. Most cases are sporadic and nonfamilial, although the occurrence in first-degree relatives is 3%. Pre-excitation of the ventricles via an accessory pathway manifests in the electrocardiogram as a delta wave leading the R-wave. The aberrant conduction via the accessory pathway can cause supraventricular tachycardia (SVT), as in the infant in this vignette.

Immediate treatment is with vagal maneuvers, as in the vignette, or with intravenous adenosine. Although digoxin frequently is used in neonatal SVT, its use is controversial in pre-excitation syndromes such as WPW, in which the impairment to atrioventricular (AV) node conduction may be greater than any effect on the accessory pathway and may lead to atrial fibrillation and ventricular tachydysrhythmia. Initial treatment with a beta-blocker has a better chance of slowing conduction via the accessory pathway.

The antiarrhythmic drugs are classified by their site of major action Class I drugs block the sodium channels responsible for the rapid upward depolarization of the cardiac action potential. Class II drugs provide beta blockade. Class III drugs block the channels (mainly potassium channels) that shorten the action potential; these drugs prolong the action potential. Class IV drugs block calcium channels.

Class	Major Site of Action	Example
Class I	Sodium channel	Procainamide, lidocaine, flecainide
Class II	Beta adrenergic	Esmolol, propranolol
Class III	Potassium channel	Amiodarone
Class IV	Calcium channel	Verapamil

Digoxin and adenosine are not classified by this scheme. No drug has a purely single action, and these drugs often are combined for their secondary effects.

It may help to remember this classification scheme by associating the classes with their main effects on the cardiac myocyte action potential [as illustrated in this drawing](#).

Class I drugs change the upstroke, classes II and III drugs work on the sustained depolarization phase, and class IV drugs affect depolarization.

Class I drugs (sodium-channel blockers) can be differentiated further by their rate of recovery from block into class Ia, Ib, and Ic for medium, fast, and slow recovery, respectively. Procainamide (class Ia) is useful in treating SVT and ventricular tachycardia. Toxicities can include vomiting, AV-block, or a lupus-like syndrome with fever, rash, and thrombocytopenia. Lidocaine (class Ib) is used for short-term treatment of ventricular arrhythmia and can cause convulsions or respiratory arrest. Flecainide (class Ic) is used to treat SVT and can cause bradycardia, ventricular tachycardia, and congestive heart failure.

Class II drugs, such as long-acting propranolol and short-acting esmolol, are helpful in the management of SVT, long QT syndrome, and some ventricular dysrhythmias. Toxic effects include hypotension, AV block, hypoglycemia, and bronchospasm. These adverse effects are less common in neonates than the adverse effects of other antiarrhythmics that might be used in WPW, such as procainamide or amiodarone. Their safety makes class II drugs the most appropriate choice for the infant in the vignette.

A class III drug, such as amiodarone, is useful in the treatment of SVT and ventricular tachycardia. Its adverse effects limit its use to dysrhythmias that are resistant to other drug regimens. These adverse effects include photosensitivity, corneal deposits, hyper- or hypothyroidism, weakness, peripheral neuropathy, and hepatitis.

A class IV drug, such as verapamil, is useful in some cases of SVT in some pediatric patients. It is contraindicated in children younger than age 1 year due to their greater sensitivity to its negative inotropic effects. Complete AV block also can be seen.

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Content Specification:

Plan appropriate management of a dysrhythmia in a newborn infant, including noninvasive and invasive management of electrophysiologic disturbances, and understand the potential adverse effects of approaches and drugs used
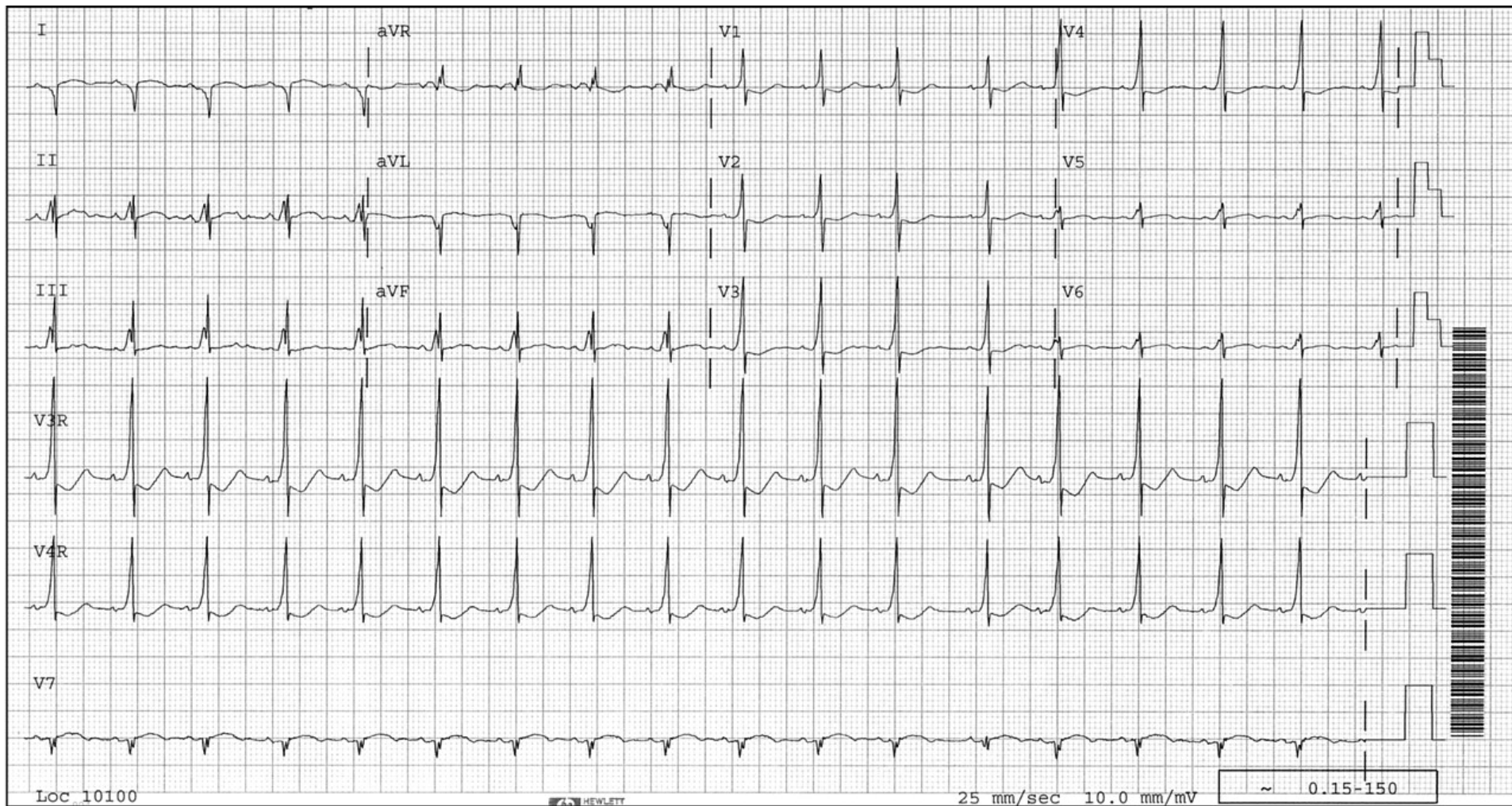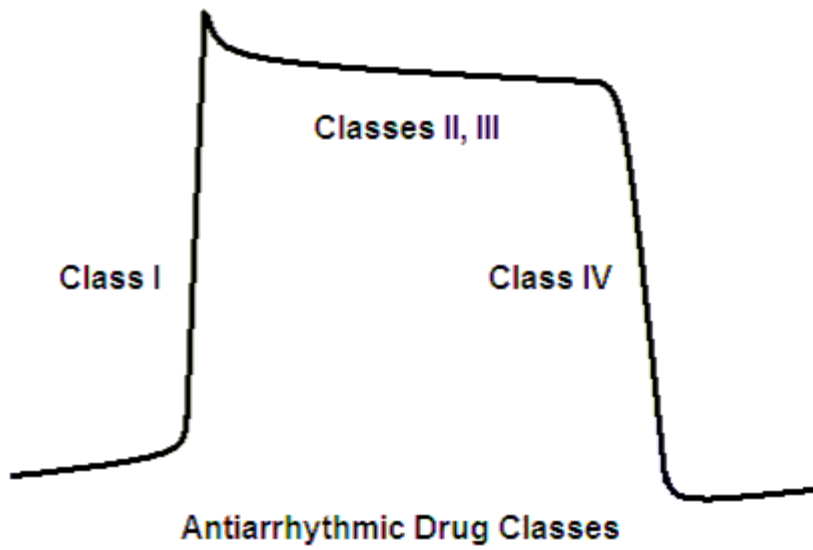
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Antiarrhythmic Drug Classes

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A 28-day-old female infant who weighs 1,300 g at an estimated postmenstrual age of 30 weeks is receiving full enteral feeds of her own mother's milk by orogastric gavage. The infant is breathing spontaneously in room air, maintaining normal body temperature in an incubator, and showing physical activity appropriate for her age. Her growth in the previous week is estimated at 15 g/kg per day, and her energy intake is calculated at 120 kcal/kg per day. She has no clinical evidence of renal or gastrointestinal dysfunction, and she is receiving no medications other than nutritional supplements. As a part of a research trial, she is enrolled in a study of energy balance.

Of the following, the energy cost in this infant is HIGHEST with:

1	diet-induced thermogenesis
2 ☒	physical activity
3	resting metabolism
4	thermoregulation
5	tissue synthesis

You selected 2, the correct answer is 3.

The energy balance is represented by the equation:

Energy intake = Energy storage + Energy expenditure + Energy excretion

Energy intake is determined by the nutritional intake from both enteral and parenteral routes. Energy storage represents the energy deposited during growth. Energy expenditure is a sum of the energy cost of resting metabolism, diet-induced thermogenesis, physical activity, thermoregulation, and tissue synthesis. Energy excretion represents the fecal and urinary loss of energy.

The unit of energy is a kilocalorie or a kilojoule. A calorie is defined as the amount of heat required at atmospheric pressure to raise the temperature of 1 g of water by 1 degree centigrade. A kilocalorie (kcal) represents 1,000 calories. A kilojoule (kjoule) is calculated by the equation: kjoule = kcal x 4.184.

Energy equilibrium is shown in the **Figure**.

The energy cost is highest with resting metabolism, estimated at approximately 60 kcal/kg per day for the growing preterm infant in this vignette. Resting metabolism represents cellular metabolic activity under basal conditions measured typically in the absence of thermal stress and activity and in a state of fasting. Whereas a 12-hour fast is standard in adults for determination of basal metabolic rate, fasting conditions in neonates are simulated by performing measurements just before an enteral feed provided at 3-hour intervals.

The energy cost of resting metabolism includes energy expended in cellular function as well as energy expended in evaporative water loss. The latter is estimated at 0.6 kcal/g of water lost by evaporation. The major factors that influence resting metabolism include postnatal age and body composition. Resting metabolism increases from approximately 40 kcal/kg per day during the first week after birth to approximately 60 kcal/kg per day in the ensuing weeks in growing preterm infants. A leaner body composition relatively devoid of fat, as in small for gestational age infants, is associated with a higher resting metabolism.

Diet-induced thermogenesis, also called specific dynamic action or thermic effect of food, represents the increase in metabolic rate that follows a feed. Two distinct thermic responses to food ingestion have been described. The first thermic response to food is the increase in energy expenditure observed directly after a feed and is called the obligatory component of diet-induced thermogenesis. It represents the energy cost of digesting, absorbing, and processing ingested nutrients. The second thermic response to food is the sustained increase in basal metabolism that accompanies chronic overfeeding and is called the facultative component of diet-induced thermogenesis. It is influenced largely by thyroid hormones and the sympathetic nervous system.

In preterm infants, the energy cost of diet-induced thermogenesis is estimated at 3 to 7 kcal/kg per day. The major factors that influence diet-induced thermogenesis include energy intake and diet composition. Diet-induced thermogenesis is greater with a higher energy intake and a protein-rich diet.

In marked contrast to its role in adults, physical activity is a minor contributor of energy expenditure in preterm infants. Preterm infants spend most of their time sleeping, estimated at 80% to 90% of a 24-hour period, compared with approximately 50% in term infants and 30% in adults. Preterm infants spend a greater proportion of their sleep in active - rapid eye movement (REM) - sleep, and the oxygen consumption is higher during REM sleep than during quiet (nonREM) sleep. However, the overall effect of both activity and sleep state on total energy expenditure in preterm infants is minimal.

Preterm infants can increase the metabolic rate during activity by up to 36% over the resting rate, as compared with 72% in term infants and 400% to 500% in adults. In preterm infants, the energy cost of physical activity is 3 to 7 kcal/kg per day.

In preterm infants managed in a thermoneutral environment, the energy cost of thermoregulation is minimal, estimated at no more than 5 kcal/kg per day. A thermoneutral environment is a range of ambient temperatures within which the metabolic rate of the infant is at its minimum, and no expenditure of energy is required either for heat generation or heat dissipation. The infant in this vignette has a stable body temperature and is unlikely to have a high energy cost of thermoregulation.

The energy cost of growth includes energy expended in the synthesis of new tissues as well as energy stored in these tissues. The energy cost of tissue synthesis is estimated at 0.4 to 1.7 kcal/g weight gain in preterm infants. Using an average value of 1 kcal/g weight gain, the energy cost of tissue synthesis in the infant in this vignette growing at a rate of 15 g/kg per day can be calculated at 15 kcal/kg per day. In addition to postnatal weight gain, the energy cost of tissue synthesis is influenced by the composition of the weight gain. For example, the cost of depositing absorbed dietary fat into adipose tissue is much lower than the cost of synthesizing new protein or glycogen. The stored energy can be estimated by subtracting from the energy intake the energy expended, as shown in its various components in this vignette, and the energy excreted. The latter is reflected in the fecal and urinary loss of energy, estimated at 10 to 30 kcal/kg per day in preterm infants. Much of this loss is accounted for by the incomplete absorption of nutrients, largely fat, provided by the enteral route. Loss of nitrogen-containing substances in the urine represents a minor fraction of the excreted energy.

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<u>Content Specifications:</u>

Understand the caloric cost of physical activity

Understand the caloric cost of maintaining body temperature

Understand how to ascertain and calculate the caloric requirements to ensure optimal growth of preterm infants

[PREVIOUS] [NEXT]