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11 November 08

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January: Question 1

A growth-restricted male infant was born by vaginal delivery at 35 weeks' gestation. His initial physical examination revealed jaundice without hepatosplenomegaly, a distended abdomen, edema, and otherwise normal skin findings. Results of laboratory tests revealed that he had a metabolic acidosis, hypoglycemia, cholestasis, unconjugated hyperbilirubinemia, hypoalbuminemia, markedly elevated prothrombin and thrombin times, and elevated ferritin and alpha-fetoprotein levels. Abdominal ultrasonography showed ascites, a small liver, and patent vessels.

Additional testing over the next few days revealed a normal complete blood count; negative blood cultures; normal ammonia, lactate, and uric acid concentrations; normal state newborn screening result; normal urine organic and plasma amino acid levels; negative viral panel; and normal mass spectroscopy of urinary bile acids. T2-weighted views on magnetic resonance imaging showed that the infant's liver, pancreas, and thyroid gland appeared darker than the spleen. Despite aggressive therapy targeted to his disorder, the infant died at age 7 days.

Two years later the couple's second pregnancy was complicated by oligohydramnios, intrauterine growth restriction, and fetal hydrops. The infection screening, fetal chromosomal analysis, and fetal echocardiogram were normal. This second male child was born at 34 weeks' gestation and died of hepatic failure at age 2 days.

The family is distraught and expresses a willingness to resort to any measure to have a healthy child.

Of the following, the MOST likely approach to prevent this disorder from occurring in a future pregnancy is:

1	conception with donor egg
2	conception with donor sperm
3	planned preterm delivery
4	serial blood transfusions during pregnancy
5	weekly intravenous immunoglobulin administration during pregnancy

You selected 5, the correct answer is 5.

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The infant in this vignette has abnormal synthetic liver function, evident by cholestasis, hypoalbuminemia, hypofibrinogenemia, and coagulopathy. The potential causes of fetal liver disease are listed in the Table.

Table

Table. Potential Causes of Neonatal Liver Failure*
Hematologic • Congenital leukemia • Hemophagocytic lymphohistiocytosis • Hepatic neuroblastoma • Myelodysplasia
Infectious • Cytomegalovirus • Enterovirus • Hepatitis A, B, and C virus • Herpes simplex virus • Human herpes virus 6 • Parvovirus B19 • Rubella • Syphilis • Toxoplasmosis
Metabolic • α_1-antitrypsin deficiency • 5 beta-reductase deficiency • Galactosemia • Glycogen storage disease • Hereditary fructose intolerance • Neonatal hemochromatosis • Niemann-Pick disease type C • Tyrosinemia • Zellweger syndrome
Vascular • Ischemia • Hemangiomatosis
Other • Mitochondrial cytopathy • Neonatal lupus erythematosus

*** Adapted from Murray and associates (2001) and Whitington and associates (2005).**

Most of the metabolic and infectious causes were eliminated by the infant's test results. Neonatal hemochromatosis (NH) is this infant's most likely diagnosis because of the following:

- **fetal onset of liver dysfunction**
- **elevated ferritin and alpha-fetoprotein (AFP) concentrations**
- **magnetic resonance imaging (MRI) findings showing a dark liver, pancreas, and thyroid gland**
- **recurrence in future pregnancies**

Neonatal hemochromatosis is the most common cause of liver failure in neonates. This disease is associated with iron overload. It is unclear whether iron overload causes the hepatic injury or if liver disease from various causes leads to impaired protein synthetic function with reduced iron-binding capacity followed by iron overload. Regardless of the pathogenesis, NH has an unusual inheritance pattern that cannot be explained by mendelian genetics. Atypical inheritance features include the following:

- **Sporadic occurrence with unaffected offspring before delivering the first infant with this disease**
- **A high recurrence rate (up to 80%, independent of sex) with future affected pregnancies leading to either a fetal loss or an ill infant**
- **Documented cases of women giving birth to affected infants with different male parentage**
- **Lack of affected infants with the same father and different female parentage**

Although mitochondrial inheritance may be suggested by the last two inheritance features noted above, the high recurrence rate makes this unlikely. Based on this inheritance pattern, conception with donor egg or donor sperm would not have avoided this fatal diagnosis because NH has neither a mitochondrial nor an X-linked mode of transmission.

Neonatal hemochromatosis begins in utero, with severe cases resulting in hydrops and fetal death, and milder cases associated with oligohydramnios, growth restriction, and/or premature birth. Iron deposition in the liver, pancreas, thyroid, heart, adrenal glands, and kidneys leads to multiorgan failure within a few days after birth. The liver is the organ most severely affected but functional deficits of other organs may be apparent. The spleen, lymph nodes, and bone marrow are spared. Infants typically present with hypoglycemia, marked coagulopathy, hypoalbuminemia, and edema. Jaundice is apparent within the first few days after birth. Serum aminotransferase concentrations are disproportionately low for the degree of hepatic injury, perhaps because of extensive hepatic necrosis. Affected infants are frequently misdiagnosed with overwhelming sepsis or a coagulation disorder. Some infants with NH may be incorrectly diagnosed with tyrosinemia because their hepatic metabolic dysfunction leads to elevated tyrosine levels.

Neonatal hemochromatosis is usually a diagnosis of exclusion and can be supported with further diagnostic testing showing elevated ferritin (>800 ng/mL [1797 pmol/L]) and AFP concentrations (>84,000 ng/mL [>188,748 pmol/L] in term infants and >200,000 ng/mL [449,400 pmol/L] in infants 32-37 weeks' gestation). While these tests are sensitive for detecting NH, these blood tests are not specific for NH and thus have a low positive predictive value for the diagnosis. When measured, the iron-binding capacity (transferrin) is low, consistent with impaired synthetic ability of the liver, and the iron saturation percentage is typically high. Although ultrasound imaging is nonspecific, MRI shows abnormal iron distribution in multiple organs in approximately 90% of proven cases. The diagnosis of NH can be suggested by histologic findings of the liver showing severe liver destruction with hepatic siderosis; however, extraheptic siderosis is required to confirm the diagnosis. Because patients with NH usually have a severe coagulopathy, salivary gland biopsy is preferred over liver biopsy because it offers a safer and more specific method of diagnosis. Sometimes the diagnosis of NH is based on autopsy results.

Neonatal hemochromatosis has been nearly universally fatal. Potential therapies are limited because many neonates die before a diagnosis is made. Only a few patients benefit from treatment with deferoxamine (an iron chelator) and antioxidants (such as *N*-acetylcysteine, prostaglandin E1, selenium, and/or tocopherol polyethyelene glycol succinate [vitamin E]). Some infants have survived after liver transplantation. However, if patients survive to have this option, mortality remains high (more than 70%).

In 2004, Peter Whitington reported a more effective therapeutic option than either liver transplantation or iron chelation/antioxidant cocktails. He hypothesized that NH may be an immune-mediated disorder and suggested that alloimmune antibodies against a fetal antigen, similar to Rh disease, would explain the unusual inheritance pattern. In this model, fetal liver injury leads to the accumulation of iron, rather than iron overloading causing the liver damage. To test this alloimmune-mediated hypothesis, Dr Whitington treated pregnant women with previous pregnancies affected by NH with weekly intravenous immunoglobulin (IVIG) from 18 weeks' gestation until delivery. Since this original report, more than 30 infants have been exposed to intrauterine IVIG. None of the infants has had intrauterine growth restriction, fetal liver disease, oligohydramnios, or hydrops. While 24 infants had biochemical evidence of NH (elevated serum ferritin and AFP levels), only six had clinical evidence of liver disease, most of whom responded to antioxidants. None of the infants required liver transplantation. This gestational regimen changed NH from a lethal to a nonlethal disease.

The mechanism of action of IVIG to prevent NH remains elusive. Perhaps IVIG reduces the maternal immune response to a fetal antigen by flooding the placental immunoglobulin transport mechanism with nonreactive antibodies. IVIG might blunt the maternal immune response to fetal antigens. Alternatively, IVIG might promote nonspecific antibody binding, which minimizes the binding of reactive alloantibodies to target antigens. These phenomena could be occurring simultaneously. Other proposed mechanisms include the following: neutralization of bacterial toxins and antigens; competitive inhibition of complement activation; downregulation of B- and T-cell function; modulation of soluble products; and/or an apoptosis blockade.

For first-born infants with NH who have not received the benefit of maternal IVIG administration, potential but unproven treatment options include IVIG administration to the newborn and/or an exchange transfusion with IgG-augmented blood (Whitington PF, personal communication, October 2005). These possible therapies require further investigation before use.

Do you want to add anything to your Learning Plan?
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American Board of Pediatrics Content Specification(s):

Recognize specific patterns of mendelian inheritance

Identify the etiology, clinical manifestations, and approach to diagnosis and therapy of neonatal ascites

Recognize the etiology and clinical manifestations of neonatal hypoglycemia

Know the etiology and differential diagnosis of metabolic and familial causes of cholestasis in the neonate

Know the various laboratory and radiographic techniques to diagnose the metabolic and familial causes of cholestasis in the neonate

Know the approach to treatment of neonates with metabolic and familial causes of cholestasis in the neonate

Know the etiologies and pathophysiologies of acquired defects in hemostasis

Know the clinical and laboratory manifestations of acquired defects in hemostasis, including disseminated intravascular coagulation and hemorrhagic disease of the newborn

January: Question 2

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A male infant was delivered at 39 weeks' gestation by a 27-year-old primigravida after an uneventful pregnancy. His Apgar scores were 9 and 9 at 1 and 5 minutes, respectively. The infant stayed in the regular nursery for 5 additional days because of poor feeding.

At 5 months of age, the infant is referred to your clinic because of a heart murmur and trouble gaining weight, associated with colic and reflux symptoms. The infant weighs 5.8 kg (5th percentile) and has an occipitofrontal circumference of 41.5 cm (10th percentile). He is receiving thickened feedings and omeprazole treatment. The infant has facial features dissimilar to those of his parents (Figure).

Figure

Cardiovascular examination shows a pulse rate of 120 beats per minute; respiratory rate of 36 breaths per minute; and blood pressures of 85/55 and 82/50 mm Hg in the right and left arms, respectively. A loud, harsh systolic crescendo-decrescendo murmur is heard best at the base of the heart with radiation to the neck and apex. No ejection click is present. A second soft blowing systolic murmur heard best in the axilla radiates to the back. No diastolic murmur is heard. Oxygen saturation in room air is 98%. The primary echocardiographic finding is shown in the video (NOTE: If you have a problem playing the file, you may need to update your QuickTime software. Go to http://www.apple.com/quicktime/download/, and click on "Free Download.").

Of the following, the laboratory test MOST likely to aid in the diagnosis of this infant's syndrome is:

1	fluorescence in situ hybridization (FISH) probe for 7q11 deletion

2	FISH probe for 20p12 deletion
3	FISH probe for 22q11 deletion
4	routine chromosome analysis
5	sequencing of the *PTPN11* gene

You selected 1, the correct answer is 1.

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The infant in this vignette has echocardiographic evidence of supravalvular aortic stenosis and clinical features of Williams syndrome. Such infants should undergo fluorescence in situ hybridization (FISH) study to detect a microdeletion at the 7q11 region.

Specific congenital heart defects are often associated with genetic syndromes (Table). The combination of minor or major anomalies with cardiac malformations often can suggest underlying conditions for which specific confirmatory tests exist.

Table

Table. Some Genetic Syndromes Associated With Specific Cardiac Malformations*

Cardiac Malformation	Most Specific Associated Genetic Syndrome	Test	Other Conditions That Can Have Same Cardiac Malformation
Atrial septal defect	Holt-Oram	Research only (*TBX5* gene mutations)	Turner syndrome; trisomy 21
	Kabuki	None	Noonan syndrome
Atrioventricular canal	Trisomy 21 (Down)	Routine chromosome study	Situs ambiguous 22q11 deletion
Coarctation of the aorta	Turner	Routine chromosome study	Kabuki syndrome
Conotruncal defects; interrupted aortic arch; truncus arteriosus; tetralogy of Fallot; perimembranous ventricular septal defect	22q11 deletion (DiGeorge/velocardiofacial syndromes)	Fluorescence in situ hybridization (FISH) to detect microdeletion of the 22q11 region	
	Dextrocardia and situs inversus (Kartagener)	Ciliary biopsy	
	Situs ambiguous	Research	
Hypoplastic left heart	Turner	Routine chromosome study	
	Jacobsen (11q-)	Routine chromosome study	
Peripheral pulmonary artery stenosis	Alagille	FISH (clinical) to detect microdeletion of the 20p12 region	Williams syndrome, Turner syndrome
		JAG1 gene mutation analysis (research)	
	Noonan	Sequence *PTPN11* gene	
Supravalvular aortic stenosis	Williams	FISH with 7q11 region probe	
Ventricular septal defect	Trisomy 21	Routine chromosome study	Kabuki syndrome, Holt-Oram syndrome
	22q11 deletion	FISH with 22q11 region probe	Trisomy 13; trisomy 18

*** Adapted from Beck and Hudgins (2003).**

Aortic stenosis occurs in 1 in 3,000 newborn infants, and may be subvalvular, valvar, or supravalvular. In the supravalvular form of this condition, as demonstrated in the echocardiogram from the infant in this vignette, a fibromembranous narrowing (arrows in video) is seen above the aortic valve. The aortic obstruction can lead to left ventricular hypertophy or aortic insufficiency.

Fluorescence in situ hybridization involves the use of a unique DNA sequence to "probe" for the complementary sequence in patients' chromosomes. The gene-specific DNA probe is labeled with a fluorochrome tag that can be visualized with a fluorescence microscope. During FISH, double-stranded DNA, as present in metaphase chromosomes or interphase nuclei on a cytogenetic slide, is denatured into a single-strand of DNA. The DNA bound to the slide is then renatured in the presence of excess copies of a single-stranded fluorochrome-labeled DNA base pair probe. The probe anneals or "hybridizes" to the site of the complementary DNA sequence on the chromosome. The probe signal can then be imaged on the chromosome or nucleus using a fluorescent microscope. The advantages of a FISH probe include the ability to rapidly analyze a large number of cells with high sensitivity and specificity and to analyze uncultured nondividing cells. However, FISH probes require knowledge of the loci involved in a disorder and the appropriate probes that will detect the aberration. This technique is generally used either to complement classic chromosome methods or as a substitute for the identification of chromosomes that are in metaphase or interphase, and should not be used as a screening tool.

Microdeletions such as seen in Williams syndrome were previously unknown because the chromosomal deletions and rearrangements were usually not visible on routine chromosome preparations. These syndromes are usually characterized by specific minor anomalies and major malformations. At times it is difficult to examine newborns for these minor anomalies because of the presence of edema, dressings, and extraneous instrumentation. FISH has facilitated the diagnosis of these syndromes in the absence of all of the usual diagnostic findings.

Williams syndrome occurs in about 1 in 20,000 births. It is a multisystem disorder that includes a characteristic facies described as "elfin," cardiovascular defects, and specific neurobehavioral traits. Neonates with Williams syndrome can have mild microcephaly and facial features that include medial eyebrow flare, a depressed nasal bridge, periorbital fullness, blue stellate irises, short palpebral fissures, short anteverted nares, a long philtrum, and a large mouth with a prominent lower lip. The cardiovascular disease results from an elastin arteriopathy that may affect any artery. The most common cardiac defect is supravalvular aortic stenosis occurring in 35% to 73% of cases. Other defects may include peripheral pulmonary stenosis, pulmonic valvular stenosis, atrial septal defect, and ventricular septal defect. The infant in the vignette had both supravalvular stenosis and peripheral pulmonary stenosis. Early onset of hypertension, likely caused by renal artery stenosis, is evident in 40% of patients with Williams syndrome by the age of 34 years. Neurobehavioral characteristics of patients with Williams syndrome include mild to moderate retardation but an overfriendly and outgoing personality often can mask mental deficiency.

Connective tissue abnormalities are common in infants with Williams syndrome who are usually hypotonic and have hyperextensible joints. Motor milestones are delayed, but infants usually begin walking by age 24 months. Many patients with Williams syndrome have feeding difficulties, including recurrent vomiting, gastroesophogeal reflux, colic, and diarrhea, which may hinder weight gain during the first year after birth. Approximately 10% of neonates with Williams syndrome have hypercalcemia, the cause of which is unknown.

Williams syndrome is one of the contiguous gene syndromes in which haploinsufficiency of multiple genes at the 7q11.23 locus contributes to the phenotypic features. At least 19 genes, apart from *ELN*, are included in the commonly deleted region. Hemizygosity at the elastin locus (*ELN*) on chromosome 7 occurs in 95% of patients with Williams syndrome. The *ELN* gene deletion results in the loss of elastin function and is likely responsible for the cardiovascular aspects of the disorder. Recent evidence suggests that elastin not only functions as a structural protein, but also acts as a signaling molecule and regulates the proliferation of smooth muscle

cells. The reduced deposition of elastin in arterial walls of patients with Williams syndrome and supravalvular aortic stenosis leads to increased proliferation of vascular smooth muscle cells and narrowing of the vessel lumen. The *LIMK1* gene, which lies telomeric to the *ELN* gene, has been implicated in the cognitive deficit of this syndrome because it is deleted in all patients with Williams syndrome.

In addition to its association with Williams syndrome, peripheral pulmonic stenosis can be seen in patients having Alagille syndrome, Noonan syndrome, or Turner syndrome. Alagille syndrome is an autosomal dominant disease with clinical variability, characterized by a paucity of intrahepatic bile ducts resulting in cholestatic jaundice. Infants with Alagille syndrome also have characteristic facial features including a broad forehead and a pointed triangular chin. Additional findings include vertebral anomalies (butterfly vertebrae); posterior embryotoxon; and retarded mental, physical, and sexual development. A mutation in the *JAG1* gene, located at chromosome 20p12, has been identified in approximately 70% of patients with Alagille syndrome. FISH testing to detect a 20p12 microdeletion is available, but is positive in only 7% of patients with Alagille syndrome. Supravalvular aortic stenosis has not been reported in patients with Alagille syndrome.

Velocardiofacial syndrome has an extremely variable phenotype. Physical characteristics may include a cleft palate, a prominent nose with a squared nasal root, minor auricular anomalies, narrow palpebral fissures with "hooded eyelids," a long face, retruded mandible with chin deficiency, long slender fingers, and conotruncal cardiac defects. The most common cardiac defects include interrupted aortic arch, perimembranous ventricular septal defect, truncus arteriosus, and tetralogy of Fallot. The thymus and or parathyroid glands may be hypoplastic or absent resulting in specific T-cell immunodeficiency and/or hypocalcemia. Neurobehavioral characteristics include learning disabilities and mild mental retardation. A microdeletion in the 22q11 region is responsible for velocardiofacial syndrome. A deletion in this region is also seen in patients with DiGeorge syndrome.

Noonan syndrome is an autosomal dominant disorder occurring in 1 in 2,500 newborns. Noonan syndrome should be considered in infants with a normal 46,XY or 46,XX karyotype who demonstrate a "Turner syndrome–like" phenotype, characterized by specific facial features that may include epicanthal folds, ptosis of the eyelids, low nasal bridge, downward slanting palpebral fissures, and low-set and/or abnormal auricles. The neck is short and often webbed and the posterior hairline is low. Infants with this condition have a broad shield-shaped chest. Congenital heart disease associated with Noonan syndrome most commonly involves pulmonic stenosis with valve dysplasia and hypertrophic cardiomyopathy. Additional cardiac defects may include septal defects, patent ductus arteriosus, and peripheral pulmonary stenosis.

Approximately 50% of patients with Noonan syndrome have a mutation in *PTPN11*, a gene that encodes for a nonreceptor-type protein tyrosine phosphatase SHP2. Mutations of *PTPN11* in animals cause abnormal semilunar valve development. The *PTPN11* gene is also involved in signaling pathways leading to cardiomyocyte hypertrophy.

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American Board of Pediatrics Content Specification(s):

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

Be aware of the maternal factors, incidence, and clinical manifestations of Down syndrome

Recognize the karyotype and clinical manifestations associated with the microdeletion syndromes

Recognize the karyotype and clinical manifestations associated with the contiguous gene disorders

Recognize the clinical features of the Noonan syndrome

Recognize the clinical features of the Williams syndrome

Understand the indications and limitations of molecular cytogenetic studies (eg, FISH), specifically in the diagnosis of aneuploidy and microdeletion syndromes

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January: Question 3

A 24-hour-old term infant is being evaluated for discharge. He was delivered by a 34-year-old primigravida woman at 38 weeks' gestation. Maternal prenatal tests were significant for a positive vaginal group B *Streptococcus* (GBS) culture at 35 weeks' gestation. Intravenous penicillin was administered to the mother 5 hours before delivery. The baby has been clinically well since birth. He is rooming in with the mother, is feeding well, and has voided and passed meconium. You are discussing the Centers for Disease Control and Prevention guidelines for the prevention of perinatal group B streptococcal disease with the house staff.

Of the following, intrapartum chemoprophylaxis for perinatal GBS disease is MOST likely to be unnecessary in a pregnant woman with:

1	negative GBS vaginal/rectal culture, labor at 38 weeks, history of GBS bacteriuria
2	negative GBS vaginal/rectal culture, labor at 30 weeks, history of previous infant with invasive GBS disease
3	positive GBS vaginal/rectal culture, elective cesarean section before rupture of membranes, and onset of labor at 38 weeks
4	positive GBS vaginal/rectal culture, labor at 38 weeks, rupture of membranes for 4 hours
5	unknown GBS vaginal/rectal culture, labor at 30 weeks, rupture of membranes for 4 hours

You selected 3, the correct answer is 3.

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Group B *Streptococcus* (GBS) emerged as a leading infectious cause of neonatal morbidity and mortality in the United States in the 1970s. Initial case series reported case-fatality rates as high as 50%. In the early 1980s, clinical trials demonstrated that administration of antibiotics during labor to women at risk of transmitting GBS to their newborns could prevent invasive disease in the first week after birth (ie, early-onset disease). These trials were the basis for the Centers for Disease Control and Prevention (CDC) recommendations for intrapartum antibiotic prophylaxis to prevent perinatal GBS disease.

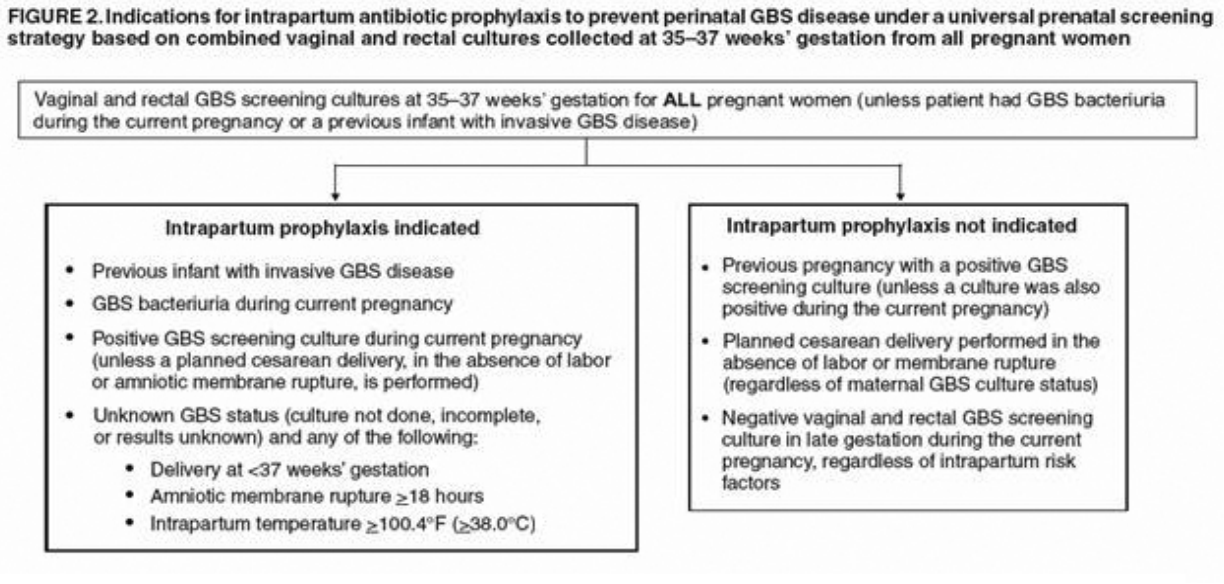
Original CDC guidelines issued in 1996 recommended the use of either a screening- or risk factor–based approach for prevention of perinatal GBS disease. The latter approach involved identification of candidates for intrapartum chemoprophylaxis according to the presence of intrapartum risk factors: delivering before 37 weeks' gestation, having an intrapartum temperature of 38.0°C (100.4°F) or higher, or rupture of membranes for more than 18 hours. These factors were associated with a six to seven-fold increase in the risk for early-onset disease.

CONTENT SPECIFICATIONS ADDRESSED ABP American Board of Pediatrics

In 2002, the CDC revised its recommendations based on evidence that the screening-based strategy was superior to a risk-factor–based strategy for the prevention of early-onset GBS disease in neonates. The screening-based method recommends screening of all pregnant women for vaginal and rectal GBS colonization between 35 and 37 weeks' gestation. Colonized women are then offered intrapartum antibiotics at the time of labor. Under both strategies, women with GBS bacteriuria

during their current pregnancy, or who previously gave birth to an infant with early-onset GBS disease are candidates for intrapartum antibiotic prophylaxis (Figure).

Figure: Indications for intrapartum antibiotic prophylaxis to prevent perinatal group B Streptococcus (GBS) disease.



Colonization with GBS in a previous pregnancy is not considered an indication for intrapartum prophylaxis in subsequent pregnancies; rather, women require evaluation for prenatal colonization with each pregnancy. Because colonization is transient, the predictive value of culture-based screening is too low to be clinically useful when performed more than 5 weeks before delivery; thus, many women with GBS colonization during one pregnancy will no longer be colonized during subsequent pregnancies.

The presence of GBS bacteriuria in a pregnant woman is a marker for heavy genital tract colonization. Therefore, women with any magnitude of GBS bacteriuria during pregnancy should receive intrapartum chemoprophylaxis. Vaginal and rectal screening at 35 to 37 weeks is not necessary for these women. Women with GBS urinary tract infections during pregnancy should receive appropriate treatment at the time of diagnosis as well as intrapartum GBS prophylaxis.

Intrapartum antibiotic prophylaxis to prevent perinatal GBS disease is not recommended as a routine practice for women undergoing planned cesarean deliveries in the absence of labor or amniotic membrane rupture, regardless of the GBS colonization status of the mother because the risk for disease is extremely low. Patients expected to undergo planned cesarean deliveries should nonetheless still undergo routine vaginal and rectal screening for GBS at 35 to 37 weeks' gestation because onset of labor or rupture of membranes may occur before the cesarean delivery is performed.

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References:

Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease: revised guidelines from CDC. *MMWR Recomm Rep.* 2002;51(RR-11):1-22

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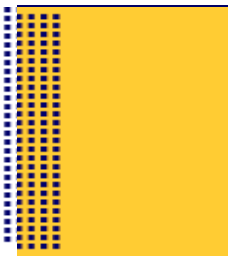
American Board of Pediatrics Content Specification(s):

Understand the epidemiology and prevention of group B streptococcal infection



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January: Question 4

For the infant younger than 12 months of age, differences in nutritional composition make bovine (cow) milk a poor substitute for human milk. Commercially available formulas designed to mimic the composition of human milk provide a better alternative when human milk is unavailable.

Of the following, the constituent found in HIGHER concentrations in whole bovine milk than in mature human milk is:

1	carbohydrate
2	fat
3	folic acid
4	protein
5	vitamin E

You selected 4, the correct answer is 4.

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Multiple differences exist between the nutritional composition of cow's milk (CM) and human milk (HM) (Table). Most of these differences put CM at a disadvantage and make it an undesirable substitute for HM in the neonate.

Table

Table. Composition of Cow's Milk and Human Milk

Component	Whole Cow's Milk	Mature Human Milk
Protein, g/100 mL	3.3	0.9
Whey:casein ratio, %	18:82	60:40
Fat, g/100 mL	3.4	3.9
Carbohydrate, g/100 mL	4.8	6.7
Major minerals, mg/100 mL		
Sodium	50	12-25
Potassium	156	40-55
Chloride	102	42
Calcium	123	20-25
Phosphorus	96	12-14
Magnesium	12	3.5
Trace minerals, µg/L		
Iron	460	300
Zinc	3500	1,200
Copper	100	250
Water-soluble vitamins		
Ascorbic acid, mg/L	17	40
Folate acid, µg/L	50	85
Pyridoxine, µg/L	470	93
Vitamin B_{12}, µg/L	4	1
Riboflavin, µg/L	1750	350
Thiamin, µg/L	300	210
Niacin, mg/L	0.8	1.5
Biotin, µg/L	35	4
Fat-soluble vitamins		
Vitamin A, IU/L	1,000	2,230
Vitamin D, IU/L	24	22
Vitamin E, IU/L	0.9	2.3
Vitamin K, µg/L	4.9	2.1

The protein concentration of whole CM is nearly four times that of mature HM (3.3 g/100 mL versus 0.9 g/100 mL). Qualitative differences in protein composition exist as well. For both HM and CM, protein constituents can be classified as either casein or whey. Caseins are proteins with low solubility in acid media. Whey proteins promote more rapid gastric emptying, and remain in solution after acid precipitation, facilitating their digestion. Mature HM is predominantly whey, with a whey-to-casein ratio of 60:40. Conversely, the fraction of whey in whole CM is relatively small (whey-to-casein ratio of 18:82).

In addition, HM and CM differ in the types of protein contained in the whey fraction. In HM, the major whey protein is a-lactalbumin, while the major whey protein in CM is ß-lactoglobulin. Additional whey proteins found in high quantities in HM and involved in host defense include lactoferrin, lysozyme, and secretory immunoglobulin A. These proteins are present only in trace quantities in CM.

The carbohydrate concentration of whole CM is less than that of mature HM (4.8 g/100 mL versus 6.7 g/100 mL). Both CM and HM contain lactose, which promotes softer stool, more nonpathogenic bacterial fecal flora, and improved absorption of minerals attributed to the presence of small quantities of unabsorbed lactose. Oligosaccharides, present in HM, play a role in host defense, because their structure mimics specific bacterial antigen ligands and prevents bacterial attachment to host mucosa.

The lipid concentration of whole CM is also less than that of mature HM (3.4 g/100 mL versus 3.9 g/100 mL). In HM, the lipid system provides 50% of the calories of the milk, and is structured to promote fat digestion and absorption. Lipids in HM are organized as fat globules and are higher in long-chain fatty acids than CM (98% versus 92%). Linoleic and linolenic acid (essential fatty acids) are found in limited amounts in CM. Likewise, arachidonic and docosahexaenoic acids (derivatives of linoleic and linolenic acids) are found in HM but not CM. These very-long-chain polyunsaturated fatty acids are important constituents of brain phospholipid membranes and have been linked to improved neurodevelopmental outcome. In addition, HM contains bile salt–stimulated lipase that facilitates fat digestion, resulting in less fat in the stool.

Human milk and CM also differ with respect to the concentrations of vitamins and major and trace minerals. In general, concentrations of each are higher in CM. Notable exceptions (higher concentrations in HM than in CM) include folic acid, vitamin E, vitamin A, ascorbic acid, niacin, and copper. Substantially higher concentrations of sodium, potassium, and chloride in CM than in HM, coupled with the higher protein concentration, raise the renal solute load in infants consuming CM by as much as twofold, predisposing the infant to dehydration. Although the bioavailability of iron in HM is better, CM and HM are both poor sources of iron, and iron supplementation is recommended to prevent iron-deficiency anemia.

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American Board of Pediatrics Content Specification(s):

Understand the differences in the nutritional composition of human milk and cow milk

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January: Question 5

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11 November 08

12 December 08

A 14-day-old female infant, whose birthweight was 985 g and estimated gestational age at birth was 27 weeks, undergoes cranial ultrasonographic examination. Prior clinical course in this infant included mechanical ventilation for hyaline membrane disease, vasopressor treatment for systemic hypotension, and antibiotic treatment for suspected sepsis. Currently the infant is breathing spontaneously in room air, receiving enteral feeds by orogastric route, and maintaining stable vital signs in an incubator. The infant has no dysmorphic features or apparent congenital anomalies. The cranial ultrasonograph reveals cystic changes within the brain (Figure 1 and Figure 2).

Figure 1

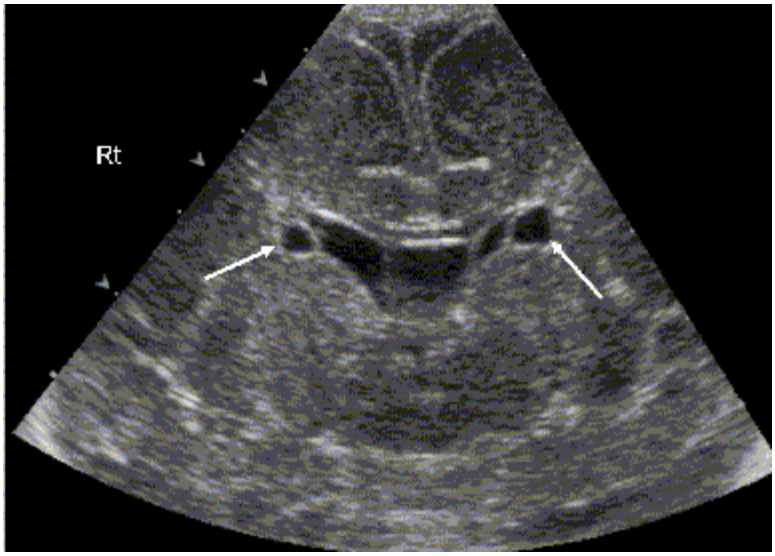
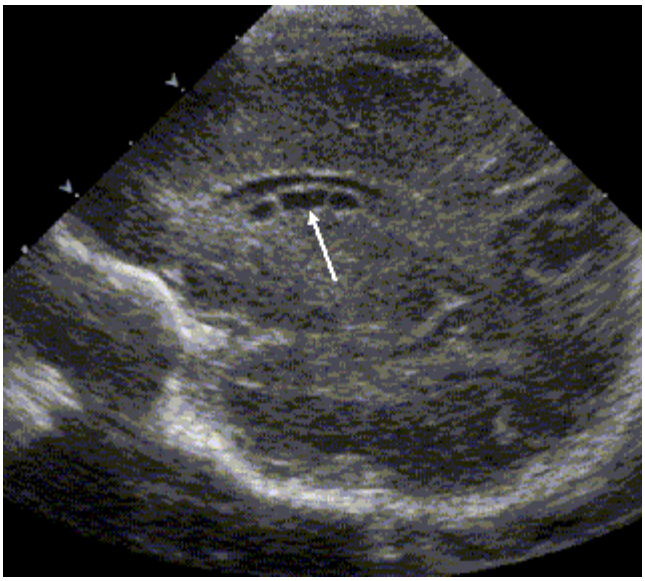


Figure 2



Of the following, the cranial ultrasonographic features of the cysts indicated by the arrows in this infant are MOST consistent with the diagnosis of:

1	cavum septum pellucidum
2	choroid plexus cyst
3	connatal cyst
4	cystic periventricular leukomalacia
5	Dandy-Walker malformation

You selected 3, the correct answer is 3.

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The differential diagnosis of intracranial cysts, detected with ultrasonography or other imaging modalities, includes a broad spectrum of conditions:

- **normal variants (eg, cavum septum pellucidum)**
- **developmental cysts (eg, Dandy-Walker malformation)**
- **cysts from perinatal injury (eg, periventricular leukomalacia)**
- **vascular cystlike structures (eg, vein of Galen malformation)**
- **hemorrhagic cysts (eg, periventricular-intraventricular hemorrhage)**
- **infectious cysts (eg, brain abscess)**

The intracranial cysts may be classified depending on their anatomic location as:

- **posterior fossa cysts (eg, Dandy-Walker malformation)**
- **supratentorial cysts in periventricular location (eg, connatal cyst)**
- **supratentorial cysts in non-periventricular location (eg, choroid plexus cyst)**

The anatomic location as well as the size and the shape of the cyst can help one arrive at a specific diagnosis of the intracranial cyst.

The cranial ultrasonographic features of the cysts in the infant in this vignette are most consistent with the diagnosis of connatal brain cysts. Connatal cysts, also called *frontal horn cysts*, are located at or just below the superolateral angles of the frontal horns of the lateral ventricles, mostly anterior to the foramina of Monro (Figures 1 and 2).

The connatal cysts are believed to be normal variants caused by close approximation of the walls of the frontal horns of the lateral ventricles proximal to their external angles. These cysts have a rounded configuration and vary in size in millimeters. The reported incidence of connatal cysts is 0.7% among preterm low-birthweight infants. These cysts are benign in clinical presentation and resolve spontaneously with maturation.

The septum pellucidum consists of two thin leaves of white matter surrounded by gray matter with a potential intervening space. The leaves are separated during fetal life, but fuse from back to front as the fetus approaches term or in the first few weeks after birth. The septum pellucidum forms the medial walls of the lateral ventricles and extends from the corpus callosum to the columns of the fornix. The cavum septum pellucidum results when the two leaves of the septum pellucidum have not yet fused, leaving behind a fluid-filled space between the lateral ventricles and below the corpus callosum (Figure 3 and Figure 4). It has a squarish configuration and varies in size in millimeters. It is a normal variant, more common in preterm neonates, benign in clinical presentation, and resolves spontaneously with maturation.

Figure 3: Cavum septum pellucidum (coronal view)

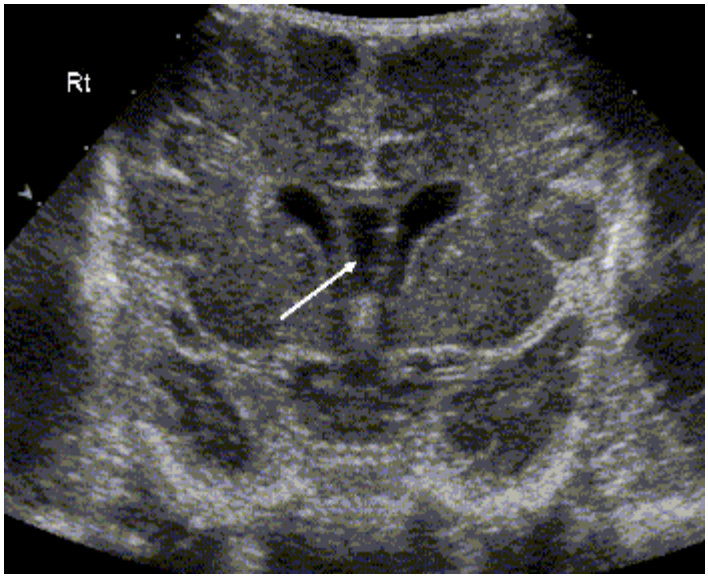
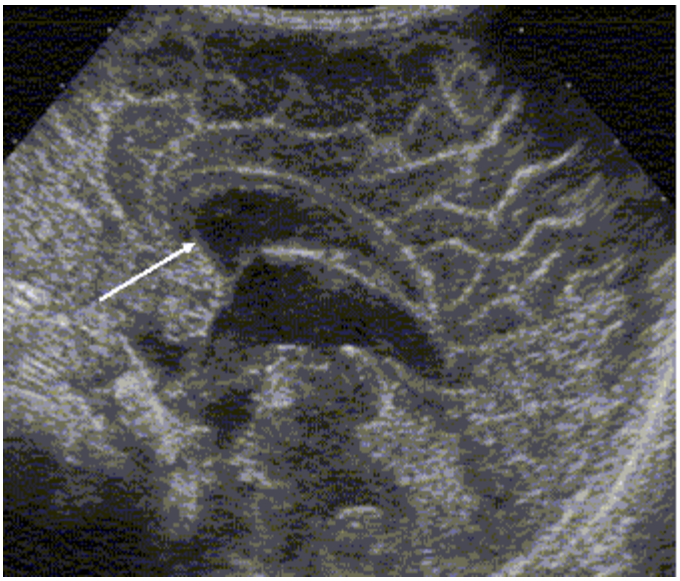
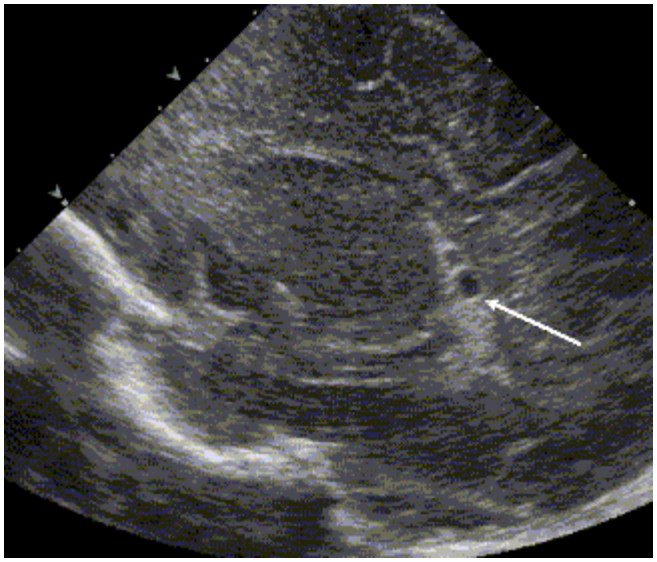


Figure 4: Cavum septum pellucidum (sagittal view)



Choroid plexus cysts are located in the body of the choroid plexus (Figure 5) or may protrude into the ventricular cavity. These cysts are spherical in configuration, single or multiple, unilateral or bilateral, and vary in size in millimeters. Isolated choroid plexus cysts are observed in fetuses in approximately 1% of all pregnancies. These cysts are believed to be a normal variant, benign in clinical presentation, and resolve spontaneously by 26 to 28 weeks of gestation. Choroid plexus cysts are more common in pregnancies complicated by fetal aneuploidy, particularly trisomy 18. The cysts in such conditions are usually larger (>1 cm diameter), bilateral, multiple, and often associated with neurodevelopmental abnormalities.

Figure 5: Choroid plexus cyst (sagittal view)



Periventricular leukomalacia (PVL) refers to white matter necrosis in a periventricular distribution. PVL is believed to result from ischemia reperfusion injury of the white matter, with free radicals being the final pathway to destruction of oligodendrocyte progenitors and impaired myelination. The major causative factors include hypotension, hypocarbia, and infection. The major risk factors include prematurity, respiratory distress, and perinatal asphyxia. The cysts in PVL are located superiorly to the frontal horns of the lateral ventricles and often extend to the parieto-occipital region (Figure 6 and Figure 7). The cysts are irregular in outline, multiseptate, often bilateral, and surrounded by an echogenic background. Ex vacuo dilatation of the ventricles often is present and represents severe white matter loss. The infants with cystic PVL are at significant risk for neurodevelopmental sequelae.

Figure 6: Cystic periventricular leukomalacia (coronal view)

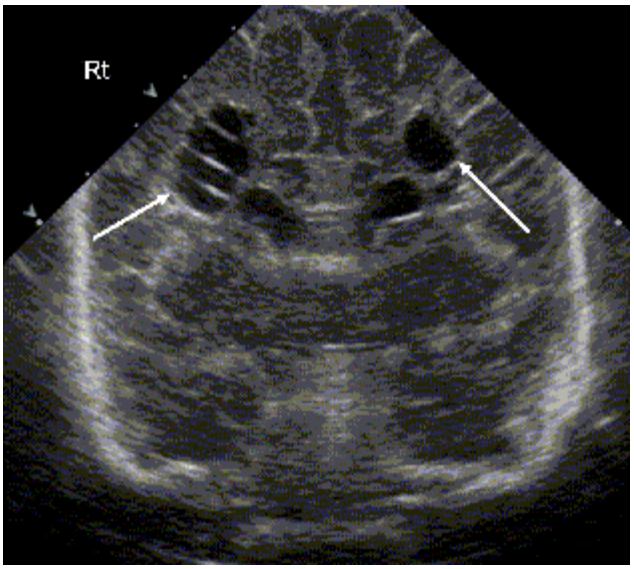
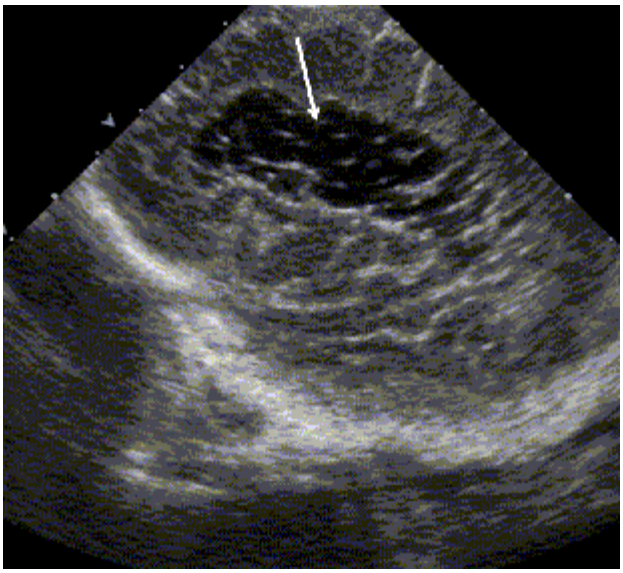
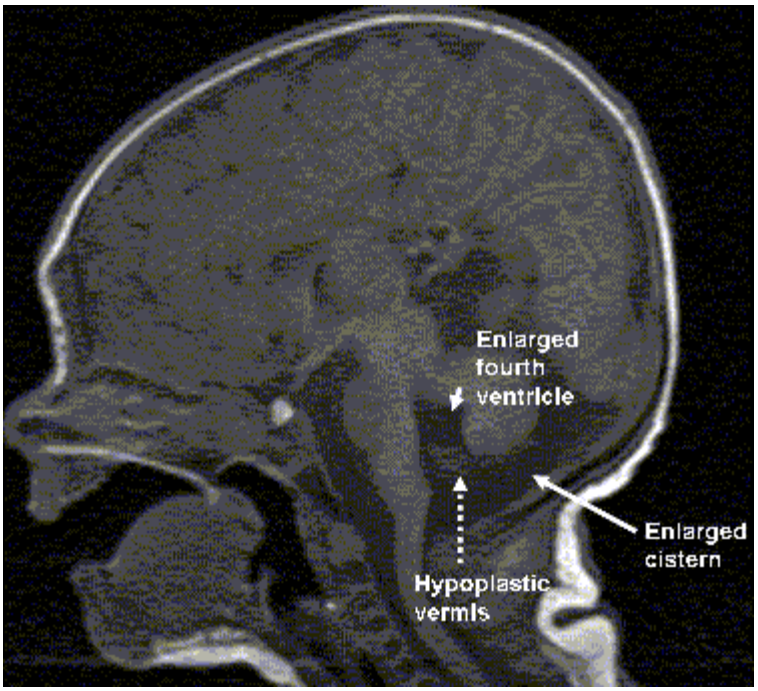


Figure 7: Cystic periventricular leukomalacia (sagittal view)



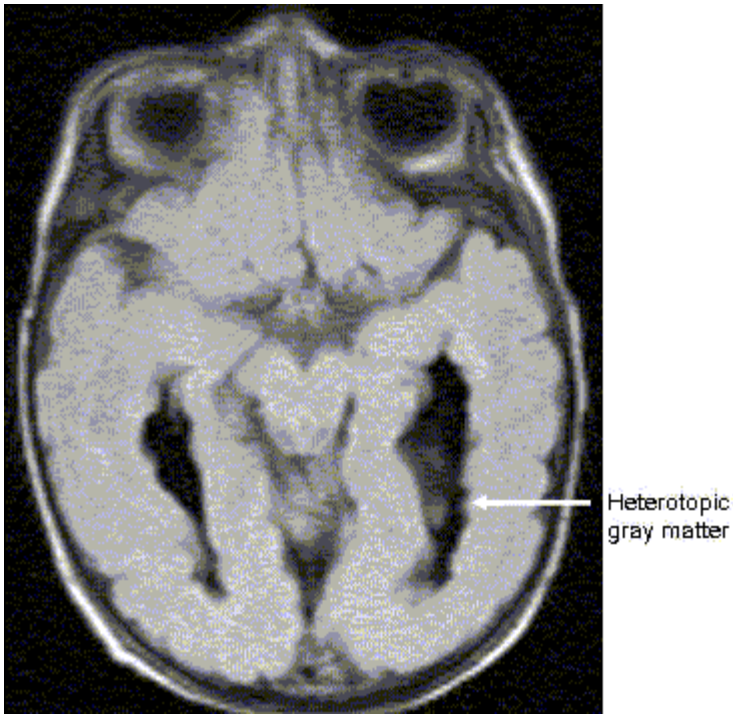
Dandy-Walker malformation is a developmental disorder characterized by complete or partial agenesis of cerebellar vermis, cystic dilatation of fourth ventricle, and enlargement of posterior fossa with elevation of tentorium (Figure 8).

Figure 8: Dandy-Walker malformation (sagittal view)



Dandy-Walker malformation accounts for approximately 5% to 10% of cases of congenital hydrocephalus, which may not become apparent until later during infancy. Associated abnormalities of the central nervous system occur in approximately 70% of cases and include agenesis of corpus callosum and defects in neuronal migration such as heterotopia (Figure 9). The neurological outcome depends on the severity both of the malformation and of the associated anomalies.

Figure 9: Dandy-Walker malformation (heterotopia)



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American Board of Pediatrics Content Specification(s):

Understand the clinical features of intraparenchymal cysts/periventricular leukomalacia, and intraparenchymal echodensities

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11 November 08

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January: Question 6

A 1,200-g infant is delivered at 29 weeks' gestation. His initial neonatal course is complicated by mild respiratory distress syndrome and apnea of prematurity. On the 16th postnatal day, emesis and a bloody stool are noted. Pneumatosis is evident on abdominal radiographs, consistent with the diagnosis of necrotizing enterocolitis. That evening, pneumoperitoneum is diagnosed, and emergent laparotomy is performed. Operative findings include necrosis and perforation of the distal ileum. A proximal ileostomy is created after resection of approximately 80% of the ileum. The ileocecal valve is spared. On postoperative day 10, enteral nutrition is resumed.

Of the following, this infant is MOST likely to experience impaired absorption of:

1	bile acids
2	calcium
3	folate
4	iron
5	lactose

You selected 1, the correct answer is 1.

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Bowel resection impairs digestion by reducing the intestinal surface area for absorption, and decreasing intestinal transit time. Short-bowel syndrome (SBS) occurs when a shortening of functional bowel results in inadequate enteral nutrition because of malabsorption of fluid, salts, and nutrients. In the neonate, the common causes of SBS include the loss of bowel resulting from small bowel atresia, volvulus, or necrotizing enterocolitis, and the presence of dysfunctional bowel owing to gastroschisis or total colonic aganglionosis (long-segment Hirschprung disease).

Following resection, impaired absorption of fluid, salts, and nutrients will be a function of the segment of bowel lost, as well as the digestive and absorptive capacity of the residual bowel (Table).

Table

Table. Intestinal Absorptive Function and Response to Resection*

Site	Absorptive Function	Potential Response to Resection
Duodenum	Iron, folate, calcium, selenium, monosaccharides, lactose, amino acids, fatty acids, vitamins A and B_1	• Decreased digestion of fat and fat-soluble vitamins • Anemia • Osteopenia
Jejunum	Glucose, galactose, amino acids, fatty acids, folic acid, biotin, zinc, potassium, vitamins C, D, E, K, $B_{1,2,3,6}$, iodine, calcium, magnesium, phosphorus *Proximal*: vitamins A and B_1, iron, folate, lactose *Distal*: disaccharides, dipeptides	• Nutritional deficiencies of the major substrates • Steatorrhea • Cholestasis • Mineral deficiencies • Bacterial overgrowth • Lactic acidosis
Ileum	Bile acids, bile salts, sodium, chloride, fat-soluble vitamins, vitamins C, $B_{1,2,3,6}$, zinc, iodine, calcium, magnesium, phosphorus *Proximal*: Disaccharides, potassium *Distal*: Vitamin B_{12}, intrinsic factor, cholesterol	• Vitamin (particularly B_{12}), mineral and zinc deficiency • Watery diarrhea • Steatorrheic diarrhea • Cholelithiasis
Ileocecal valve	Increases intestinal transit time (enhances digestion and absorption), barrier to reflux of colonic bacteria	• Diarrhea • Bacterial overgrowth • Lactic acidosis
Right and transverse colon	Water, sodium	• Fluid and electrolyte losses • Watery diarrhea

*** Adapted from Thureen and Hay (2005).**

The duodenum and jejunum are primary sites of amino acid, carbohydrate, and fat digestion and absorption. In addition, the absorption of most minerals and vitamins, with the exception of vitamin B_{12}, occurs here. Loss of this proximal bowel may result in deficiencies of iron, folate, and calcium, and lead to anemia and osteopenia. Jejunal resection, in particular, may result in significant vitamin and mineral deficiencies, particularly zinc, and nutritional deficiencies of the major substrates. Lactose intolerance resulting from impaired absorption of lactose as well as steatorrhea, cholestasis, and bacterial overgrowth and lactic acidosis from undigested disaccharides may also occur.

The ileum is also a site for disaccharide and fat digestion and absorption of fat and water-soluble vitamins. However, unique to the ileum is its primary role in the absorption of vitamin B_{12}, bile salts, and bile acids. Ileal resection, as in this vignette, will necessarily lead to impaired absorption of bile acids and bile salts, with the potential for fat malabsorption and cholelithiasis. Watery diarrhea from bile-induced colonic irritation, and steatorrhea may also occur. Long-term vitamin B_{12} deficiency may manifest as megaloblastic anemia and demyelinization of the spinal cord. Because calcium is absorbed throughout the small bowel, overall impairment of calcium absorption because of the loss of ileum, will be minimal in the presence of functioning proximal small bowel. The absorption of folate, iron, and lactose occurs in the proximal small bowel, and is not primarily affected by isolated ileal resection.

The ileocecal valve delays intestinal transit time, and serves as a barrier to prevent reflux of colonic bacteria into the small bowel. Loss of the valve allows small bowel bacterial overgrowth, which further impairs absorption of bile salts and vitamin B_{12}, and contributes to lactic acidosis. In addition, decreases in intestinal transit time compromises digestion and absorption of all nutrients.

The colon functions primarily to absorb water and electrolytes. Resection of the right and transverse colon leads to watery diarrhea, with the potential for significant fluid and electrolyte losses.

The occurrence of SBS is less a function of the amount of bowel resected, and more a function of the

capacity of the remaining bowel, as well as the capacity for intestinal adaptation. For example, provided the distal ileum and ileocecal valve remain intact, up to 90% of the small bowel may be lost without significant impairment in nutrition. The following factors influence the digestive and absorptive capacity of the small bowel after resection.

- **Length of remaining small bowel**
- **Site of remaining small bowel (jejunum or ileum)**
- **Presence of ileocecal valve**
- **Presence of colon**
- **Degree of intestinal adaptation over time**

Among infants with SBS, improved survival has been associated with residual small bowel length (SBL) greater than 38 cm, intact ileocecal valve, and intact colon. Higher mortality has been demonstrated with SBL less than 15 cm.

Intestinal adaptation, involving anatomical and physiological changes, affects the severity and duration of nutrient intolerance after bowel loss. A gradual increase in the absorptive surface area results from mucosal hyperplasia and increases in both intestinal length and diameter. The ileum, in particular, demonstrates significant adaptive capabilities after jejunal resection (70%-100% structural and functional increase). However, after ileal loss the jejunal capacity for adaptation is poor (20%-30% increase). Intraluminal nutrients (particularly long-chain fats), pancreatic and biliary digestive enzymes, and hormones such as enteroglucagon provide the stimulus for intestinal adaptation. Therefore, early reinstitution of even small enteral feeds is beneficial.

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American Board of Pediatrics Content Specification(s):

Realize the consequences of resection of the distal ileum and cecum

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January: Question 7

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11 November 08

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A 21-day-old male infant born at 24 weeks' gestation, with an endotracheal tube and a central venous catheter, has a small red papule on his anterior chest wall. The papule is surrounded by a rim of erythema. In the ensuing 6 hours, the papule increases in size and the area that surrounds it becomes more erythematous; in addition the infant now has a pustule on the back of his hand and in the right temporal region where peripheral intravenous catheters had been inserted. His activity level is less than before and he is no longer moving his right leg. When you examine his leg it is externally rotated; when rotated internally he appears to grimace. His axillary temperature is 38ºC, his heart rate is 165 beats per minute, and his blood pressure is 60/35 mm Hg, with a mean of 45 mm Hg. The cloudy fluid taken from the pustule on the dorsal surface of his hand is found to have gram-positive cocci in clusters. His white blood cell count is 24,000 cells/µL (24×10^9/L) (differential: 4 metamyelocytes, 14 bands, and 64 segmented neutrophils). The platelet count is 92×10^3/µL (92×10^9/L), down from 250×10^3/µL (250×10^9/L) 3 days earlier.

Of the following, the clinical feature MOST consistent with infection due to an invasive *Staphylococcus aureus* rather than due to coagulase negative staphylococci is:

1	gestational age less than 25 weeks
2	more than two foci of infection
3	normal blood pressure
4	presence of a central venous catheter
5	thrombocytopenia

You selected 2, the correct answer is 2.

***Staphylococcus* has become one of the prominent causes of serious late-onset infections in neonates. For most of the 20th century, *Staphylococcus aureus* was the predominant causal organism. However, in recent years, coagulase-negative staphylococci (CONS) have emerged as important pathogens in neonatal intensive care units, especially in very-low-birthweight (VLBW) neonates (<1,500 g). In a recent series on late-onset sepsis from the National Institutes of Child Health and Human Development (NICHD) network, 48% of episodes were caused by CONS and 8% by *S aureus*. Most VLBW neonates are colonized with CONS within the first week after birth. *S aureus* colonization is equally rapid in 50% to 70% of infants in the nursery. Invasive staphylococcal disease is preceded by colonization. VLBW neonates are at particular risk for developing invasive staphylococcal disease not only because of their immature host defense mechanisms, but also because of a number of therapeutic interventions such as use of intravascular catheters, endotracheal tubes, and oral gastric tubes; prolonged total parenteral nutrition; and corticosteroid use.**

***S aureus* has many surface proteins, including the microbial surface**

component–recognizing adhesive matrix molecule receptor that allows it to bind to tissues and foreign bodies coated with collagen, fibronectin, or fibrinogen, thus allowing a low inoculum of the organism to adhere to biomedical products. Although bacteremia without a focus is the most common presentation for both CONS and *S aureus* in neonates, abscess formation and dissemination to multiple sites is more likely to occur in neonates with *S aureus* bacteremia than in those with CONS bacteremia, as seen in the infant in the vignette. Manifestations of infection after *S aureus* bacteremia can include skin abscess formation at former catheter sites, thrombophlebitis, muscle or visceral abscesses, osteomyelitis and/or arthritis, meningitis, and pneumonia. The rapidity with which *S aureus* can cause focal pyogenic complications in a number of organ systems is helpful clinically in determining the origin of a bloodstream infection, even before culture results are available. The neonate in this vignette had multiple sites (three skin and one bone/joint) of *S aureus* infection. *S aureus* can cause osteomyelitis of the metaphysis of the proximal femur. The position of the metaphyses of the hip in relation to the joint capsule permits direct extension into the joint capsule.

Virulence of CONS is partially related to its ability to produce slime, an extracellular glycocalyx capsule, and/or a polysaccharide adhesin that are thought to increase its adherence to biomaterials. The biofilm reduces the accessibility of host defenses and antibiotics to the organisms. Antibiotic resistance is also an important virulence factor in CONS because most hospital-acquired strains are resistant to multiple agents including oxacillin, cephalosporins, and clindamycin. In addition to bloodstream infections, CONS can cause pneumonia, meningitis, ventriculoperitoneal shunt infections, right-sided endocarditis, and skin and soft-tissue infections. CONS has been grown in cultures from the gastrointestinal tract of infants with necrotizing enterocolitis. CONS infections are generally more indolent than infections caused by *S aureus*, which can be fulminant and are more likely to cause focal complications (primarily bones and joints) with subsequent morbidity. In the NICHD Neonatal Research Network, the death rate was higher among neonates with *S aureus* bacteremia than among those with CONS bacteremia.

Signs and symptoms of CONS or *S aureus* sepsis are usually nonspecific. Temperature may be elevated, normal, or depressed; respiratory signs such as tachypnea or apnea are common; and lethargy and feeding difficulties may be subtle or insidious. Most clinical indicators that prompt evaluation for *S aureus* or CONS are similar; however, it is more likely that hypoxemia is associated with CONS and hypotension with *S aureus*.

Prematurity is an important risk factor for bacteremia but cannot be used as a clinical feature to accurately predict whether a neonate has a CONS or *S aureus* infection. Although invasive CONS or *S aureus* are more common among small premature neonates, a large case series of neonates with CONS or *S aureus* found that those with CONS were more likely to have a lower birthweight and gestational age.

The presence of a central venous catheter for parenteral nutrition is associated with an increased risk of neonatal bacteremia. Rates of bloodstream infections increase with increasing duration of catheterization. CONS is the most common cause of catheter-related bloodstream infections among VLBW neonates. In a large retrospective study of neonates with CONS or *S aureus* infections, CONS was more likely to be associated with a history of central venous catheter or peripheral arterial catheter placement.

Thrombocytopenia (<150,000×10^9/L) is the most common hemostatic abnormality among newborns in the neonatal intensive care unit. Both viral and bacterial infections can cause thrombocytopenia in neonates. Multiple mechanisms are responsible for thrombocytopenia during bacterial sepsis, including consumption secondary to disseminated intravascular coagulation, endothelial damage, platelet aggregation secondary to binding of bacterial products to platelet membranes, immune-mediated thrombocytopenia, and decreased production from marrow infection. Thrombocytopenia is common among neonates who are acutely ill from either CONS or *S aureus* bloodstream infections. A large case series comparing neonates with CONS and *S aureus* infections found the hematologic indices to be similar. Neonates with persistent CONS bacteremia are more likely to have thrombocytopenia than those with nonpersistent

CONS bacteremia.

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American Board of Pediatrics Content Specification(s):

Understand the epidemiology and pathogenesis of neonatal infection with *Staphylococcus aureus* and *Staphylococcus epidermidis*

Understand the clinical manifestations and diagnostic criteria of neonatal infection with *Staphylococcus aureus* and *Staphylococcus epidermidis*

Understand the complications of neonatal infection with *Staphylococcus aureus* and *Staphylococcus epidermidis*

Understand the etiologies and pathophysiologies of neonatal thrombocytopenia and thrombocytosis

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January: Question 8

Over a 10-month period at your hospital, the numbers of newborns with minor congenital anomalies for each month, rearranged into ascending order were as follows: 1, 1, 1, 2, 3, 4, 9, 10, 10, 15. You are asked to compute the descriptive statistics of this list of numbers for presentation to the staff.

Of the following, the calculated value 5 BEST represents the list's:

1	accuracy
2	median
3	precision
4	standard deviation of the sample
5	standard error of the mean

You selected 4, the correct answer is 4.

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The descriptive, or summary, statistics for a list of measurements (the sample) include the mean, the median, the standard deviation, and the standard error of the mean. All are based on the standardized normal distribution. The normal curve is defined by the equation:

$$Y = (2\pi)^{-2}\, e^{(-X^2)/2}$$

where the standard deviation and the total area under the curve are both unity. Using the mathematical conventions of this system, the list of numbers in the vignette yield a median of 3.5, a mean of 5.6, a standard deviation of the sample of 5, and a standard error of the mean of 1.6. The terms "accuracy" and "precision" are not quantifiable values in this system, but are useful qualitative concepts.

The median of a list of numbers is the number in the middle: that is, the count of elements of the list that are above the median are the same as those below the median. In the vignette, there are 5 list elements above 3.5, and 5 elements below, so 3.5 qualifies as the median.

The mean is the arithmetic average of a list of numbers. The numbers are summed, and the total is divided by the count of the elements. In the vignette:

56/10 = 5.6

The standard deviation of the sample can most easily be calculated by using:

$$\text{Variance} = \frac{\Sigma(X_i^2) - [(\Sigma X_i)^2]/N}{N-1}$$

$$\text{Standard Deviation} = (\text{Variance})^{1/2}$$

where X_i represents each element in a list, and N is the count of the elements in the list. Inserting the numbers from the vignette gives:

$$\text{Variance} = \frac{538 - [56^2]/10}{9} = 24.9$$

$$\text{Standard Deviation} = (24.9)^{1/2} = 5$$

The standard error of the mean (SEM) gives an estimate of how close we think the calculated mean of the sample is to the true mean of the whole population. It can be calculated using:

$$\text{SEM} = \frac{(\text{Standard Deviation})}{N^{1/2}}$$

In the vignette,

$$\text{SEM} = \frac{5}{10^{1/2}} = 1.6$$

Precision is the quality of a series of measurements that gives the greatest refinement and mutual agreement in those measurements. The smaller the SEM of a sample, the more likely it is that the computed mean of a sample will be near the true mean of the population, and the more precise is the estimate of the population mean. The precision can be increased by increasing N, the count of the elements in a sample, or the number of measurements.

The accuracy of a measurement is its closeness to the true value. A series of measurements with a small N can have a large SEM and be imprecise, but have a sample mean that is very close to the true population mean and so be very accurate.

Minor anomalies are unusual morphologic features that in themselves result in no significant medical problems, but may be useful in alerting clinicians to major problems. Some examples are given in the Table. If a morphologic feature is seen in more than 4% of newborns, it is considered a normal variant. Using a list of about 40 minor anomalies, one study found an incidence of 14% among newborns. Another study using a list of 114 minor anomalies found an incidence of 40%.

Table

Table. Some Minor Anomalies in Newborns

Anomaly	Incidence, %
Epicanthal folds	0.4
Preauricular skin tags	0.2
Single palmar crease, bilateral	2
Syndactyly, toes 2-3	0.2

A child with three or more minor anomalies in the first study had a 90% risk of having one or more major anomalies. Other studies have found three or more minor anomalies associated with a major anomaly only 20% to 26% of the time.

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References:

Jones KL. *Smith's Recognizable Patterns of Human Malformation.* 6th ed. Philadelphia, Pa: Elsevier Saunders; 2006:817-834

Leppig KA, Werler MM, Cann CI, Cook CA, Holmes LB. Predictive value of minor anomalies: association with major malformations. *J Pediatr.* 1987;110:531-537

Marden PM, Smith DW, McDonald MJ. Congenital anomalies in the newborn infant, including minor variations. *J Pediatr.* 1964;64:357-371

Swinscow TD, Campbell MJ. *Statistics at Square One*. London, England: BMJ Books; 2002:12-38

Zar JH. *Biostatistical Analysis.* 4th ed. Upper Saddle River, NJ: Prentice Hall; 1999:34-83

American Board of Pediatrics Content Specification(s):

Know the frequency of minor congenital anomalies

Understand the concept of normal distribution and calculate the standard deviation, the standard error of the mean, and the median, and realize the importance of the *P* value

Define precision and accuracy, know what affects them, and how to enhance them

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January: Question 9

A 41-week-gestation boy is born to a healthy 28-year-old mother via cesarean section because of breech presentation. His birthweight is 2,850 g (15th to 25th percentile), length 50 cm (50th to 75th percentile), and head circumference 36 cm (>90th percentile). The pregnancy was uncomplicated, with normal amniotic fluid volume noted on ultrasonography. On physical examination he has hypotonia, areas of hypopigmentation, silvery hair, and bilateral cryptorchidism. In addition, he has poor eye movement, depressed facial expression, bilateral mild ptosis, and a high arched palate.

Of the following, the genetic mechanism underlying this child's condition MOST likely results from:

1	aneuploidy
2	chromosomal mosaicism
3	expansion of trinucleotide repeats
4	new mutation
5	uniparental disomy

You selected 5, the correct answer is 5.

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The infant described in this vignette has findings consistent with Prader-Willi syndrome (PWS; Table).

Table

Table. Diagnostic Criteria for Prader-Willi Syndrome*

Diagnostic Criteria	% Affected
Major	
Neonatal hypotonia	88
Feeding problems in infancy	79
Characteristic facial features	88
Hypogonadism	51
Minor	
Decreased fetal activity	62
Hypopigmentation	73
Eye abnormalities	68

***Adapted from Holm and colleagues (1993).**

PWS is attributed to genomic imprinting, that is, the expression of the gene depends on the sex of the parent donating the gene. PWS arises when the paternal copy of 15Q11.2-13 is deleted

(70% of cases). Maternal uniparental disomy of the 15 chromosome, resulting from nondysjunction (28% of cases), will also result in PWS. Rare cases involve mutations of the imprinting center. Loss of the maternal copy of 15q11.2-13 results in Angelman syndrome.

Aneuploidy refers to a change in the number of chromosomes; it is the most frequently observed type of cytogenetic abnormality. The two most commonly observed forms of aneuploidy are monosomy and trisomy. Monosomy is the lack of one of a pair of chromosomes, as seen in Turner syndrome. Trisomy is defined as having three chromosomes of a particular type, as seen in Down syndrome (trisomy 21), Edwards syndrome (trisomy 18) and Patau syndrome (trisomy 13).

Chromosomal mosaicism refers to a condition in which an individual has two or more cell populations that differ in the genetic makeup. This situation can affect any type of cell, including blood cells, gametes, and skin. This may lead to a phenotypically normal parent transmitting a mutation to offspring who may express the mutation.

Some regions in the genome have a repeated sequence of DNA, usually of three bases, that can expand from 20 to 30 repeats to more than 100 or even 1,000 repeats. The mechanism leading to an increase in number of repeats is not clear, nor is it clear how the increase leads to disease. Myotonic dystrophy, Huntington disease, and fragile X syndrome are disorders caused by expansion of triplicate repeat sequences.

New mutations may result in different inheritance patterns. Achondroplasia is an example of an autosomal dominant disease in which more than 80% of cases are caused by new mutations. Despite dominant inheritance, a patient with achondroplasia may not have a family history of the disorder and the recurrence risk for siblings is low, but may transmit the disease to future offspring.

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References:

Gunay-Aygun M, Schwartz S, Heeger S, O'Riordan MA, Cassidy SB. The Changing purpose of Prader-Willi syndrome: clinical diagnostic criteria and proposed revised criteria. *Pediatrics.* 2001;108:e92

Holm VA, Cassidy SB, Butler MG, et al. Prader-Willi syndrome: consensus diagnostic criteria. *Pediatrics.* 1993;91:398-402

Preece MA, Moore GE. Genomic imprinting, uniparental disomy and foetal growth. *Trends Endocrinol Metab.* 2000;11:270

Lodish H, Scott MP, Matsudaira P, et al. *Molecular Cell Biology*. 5th ed. New York, NY: WH Freeman and Co; 2003.

Scheimann A. Prader-Willi Syndrome. emedicine.com Web site. Accessed July 26, 2007, at www.emedicine.com/ped/topic1880.htm

American Board of Pediatrics Content Specification(s):

Understand how mosaicism modifies clinical presentation

Recognize the physical characteristics and chromosomal pattern of sex chromosome aneuploidy

Know fetal and placental manifestations of triploidy

Understand the etiology, molecular phenotype, and clinical manifestations of disorders associated with genetic imprinting, such as Prader-Willi syndrome

Recognize the DNA findings, clinical manifestations, and inheritance of expanding genes, such as myotonic dystrophy

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January: Question 10

Your neonatal unit recently received attention from the media because of a story about a local "miracle" baby. You have been asked to appear on a local television program to discuss the impact and current status of neonatal intensive care.

Of the following, the statement MOST consistent with the impact of neonatal intensive care is that:

1	additional neonatologists will reduce neonatal mortality
2	increased number of neonatal intensive care beds will reduce infant mortality
3	most very-low-birthweight infants are being delivered at the highest level facilities
4	recent improvements in infant survival reflect decreases in postneonatal mortality more so than neonatal mortality
5	volume of patients per year is inversely related to mortality at all levels of care

You selected 5, the correct answer is 5.

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The number of physicians devoting their practice to care of newborns only has increased substantially since the introduction of the term "neonatology" by Shaffer in 1960. In 1975, there was one physician board-certified in neonatal-perinatal medicine (NPM) per 10,000 deliveries in the United States. For each neonatologist at that time, there were approximately 1,200 premature infants, 800 low-birthweight infants, and 150 very-low-birthweight infants per year. Few hospitals had intensive care units.

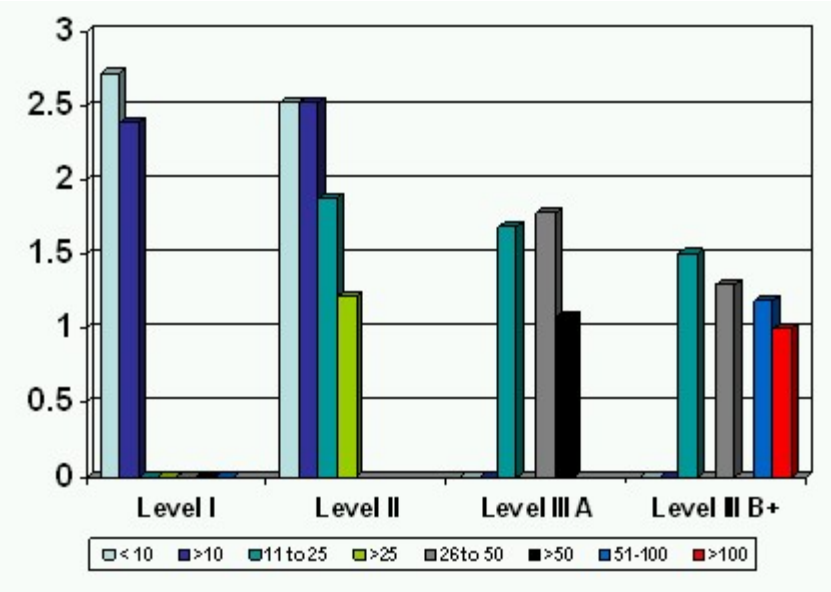
In 1976, the March of Dimes published *Toward Improving the Outcome of Pregnancy*, an important and influential document composed by representatives from the American Academy of Pediatrics, American College of Obstetricians and Gynecologists, American Medical Association, and the March of Dimes. In this document, regionalization of perinatal and neonatal care was recommended to ensure that high-risk mothers and sick newborns would be delivered at, or referred to, facilities using the most experienced staff and most advanced technologies.

By 1986, the number of certified neonatologists had quadrupled; as of the most recent neonatal-perinatal sub-board examination (2005), nearly 4,000 individuals have become certified. Presently, assuming that 70% of the practice effort of neonatologists (academic and private) involves clinical care, there are about 1,400 deliveries per clinical full-time equivalent, or about 7 clinical neonatologists per 10,000 live births in the United States.

The relationships between resources available (both physical and professional) and volume of patients have been analyzed to assess the impact of regionalized care. Current data suggest that

at all levels of neonatal intensive care, increased volume is accompanied by a reduction in odds ratio for mortality for the most vulnerable infants, those weighing less than 1,500 g at birth (Figure 1).

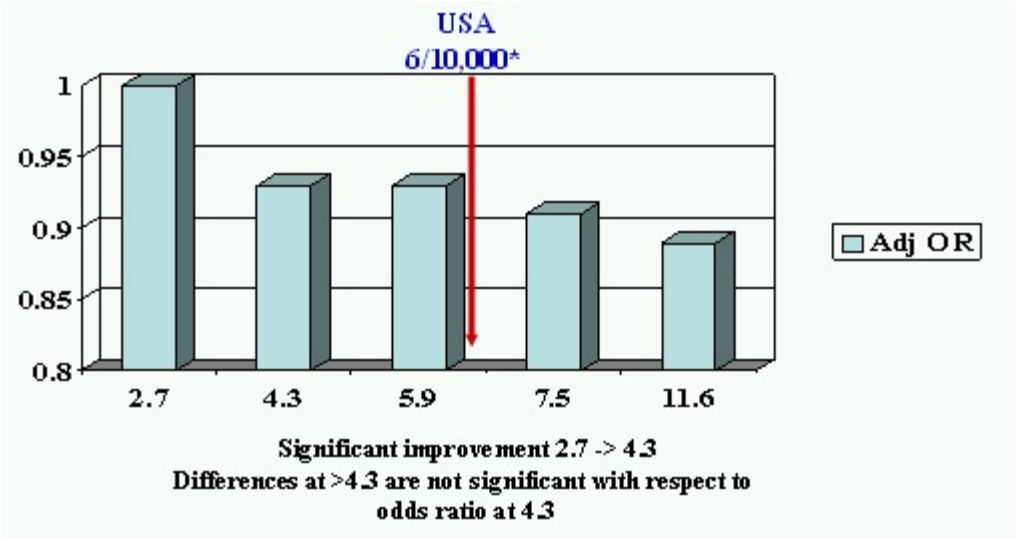
Figure 1: Odds ratio for mortality by level of neonatal intensive care and number of patients less than 1,500 g at birth (modified from Phibbs [2007])



Both level of care and patient volume influence survival. Compared with the reference group (level IIIB+, >100 very-low-birthweight infants per year—in red), both lower volume and lower levels of care were associated with higher risk for mortality. At all levels of care, increased volume is associated with a lower risk for mortality. In California, like many other states, fewer than 25% of very-low-birthweight infants were delivered at high volume/high level hospitals, in spite of the fact that 92% of such infants were delivered in urban areas with access to such hospitals. About one-fifth of the deaths among infants with birthweight less than 1,500 g may have been prevented if these infants were delivered at one of the sites with optimal outcomes. For less-populated urban and rural areas, creative strategies are needed to provide the benefits of training and experience found in high volume/high level hospitals while preserving timely access to care.

Neonatologists were once relatively scarce and the number of births “ascribed” to each was large. Increase in the number of neonatologists over time was associated with a reduction in neonatal mortality risk (Figure 2).

Figure 2: Odds ratio for mortality versus number of clinical neonatologists per 10,000 live births (adapted from Goodman [2002])

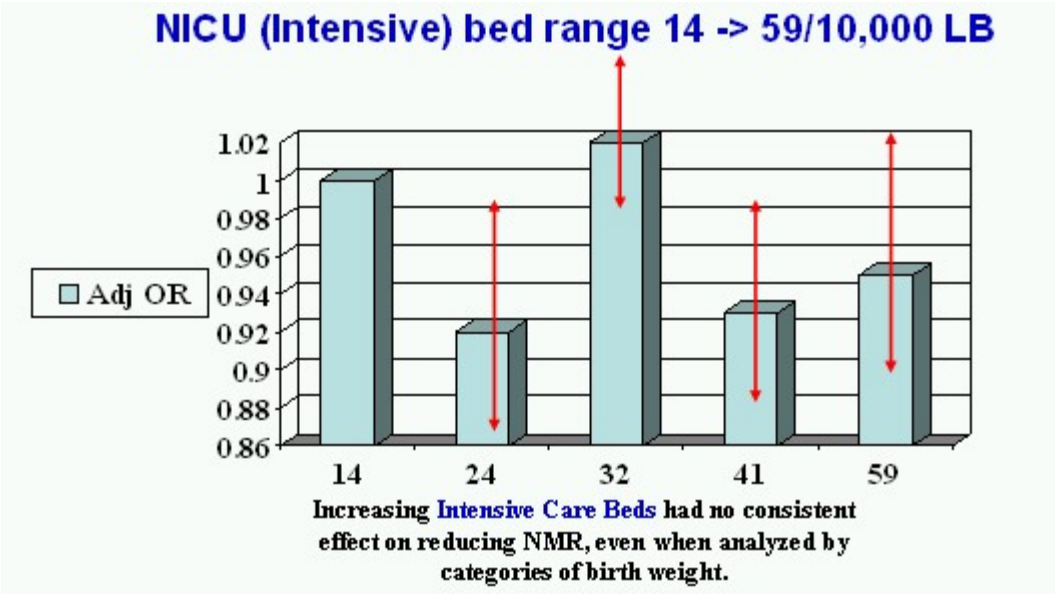


***Estimated 2700 Clinical FTE/4.5 million LB**

The mortality risk when going from 2.7 to 4.3 neonatologists per 10,000 live births is significantly lower. Additional increases in the number of neonatalogists, however, showed no statistically significant change. Note, at present there are about 7 clinical neonatologists per 10,000 live births in the United States. This evidence suggests that a further reduction in infant mortality is unlikely to result from an increased supply of neonatologists.

Following the successes of regionalized care, improved perinatal outcomes, and increasing numbers of both neonatologists and perinatologists, the number of beds allocated to neonatal intensive care has grown substantially. As the number of intensive care unit beds has increased, neonatal mortality rates have not seen a statistically significant or consistent change, even when the data are analyzed by birthweight categories (Figure 3).

Figure 3: Odds ratio for mortality versus neonatal intensive care beds per 10,000 births (adapted from Goodman 2002)



The evidence does not suggest that an improvement in neonatal mortality is likely with the addition of more neonatal intensive care unit beds.

Infant mortality has steadily decreased during the past 100 years. Infant mortality was approximately 120 in 1,000 live births a century ago. In the first half of the 20th century, infant mortality dramatically improved (Table).

Table

Table. Infant Mortality Rate per 1,000 Live Births in the United States Since 1900			
Year	**IMR**	**NMR**	**PNMR**
1900	120	…	…
1933	58.1	34	24.1
1940	47	28.8	18.3
1950	29.2	20.5	8.7
1960	26	18.7	7.3
1970	20	15.1	4.9
1980	12.6	8.5	4.1
1990	9.2	5.8	3.4
2000	6.9	4.6	2.3

IMR = infant mortality rate; NMR =neonatal mortality rate ; PNMR = postneontal mortality rate.

Before 1960, or the "preneonatology" period, infant mortality had decreased to 26 per 1,000 live births. The dramatic reduction in mortality rate was ascribed to improvements in the care and prevention of infectious diseases in infants beyond the neonatal period. Although neonatal mortality rates declined before 1960 as well, relatively larger reductions in neonatal mortality were noted after the introduction of neonatal intensive care.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:

Committee on Fetus and Newborn. Levels of neonatal care. *Pediatrics.* 2004;114(5):1341-1347

Goodman DC, Fisher ES, Little GA, Stukel TA, Chang CG, Schoendorf KS. The relation between the availability of neonatal intensive care and neonatal mortality. *N Engl J Med.* 2002;346:1538-1544

Phibbs CS, Baker LC, Caughey AB, Danielsen B, Schmitt SK, Phibbs RH. Level and volume of neonatal intensive care and mortality in very-low-birth-weight infants. *N Engl J Med.* 2007;356:2165-2175

American Board of Pediatrics Content Specification(s):

Understand issues in the organization of perinatal care (eg, regionalization, transport quality-control, practice guidelines)

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February: Question 1

A 6-month-old male infant born at 27 weeks' gestation is being discharged home. It is January. He has bronchopulmonary dysplasia requiring supplemental oxygen and diuretics, a small ventricular septal defect, and feeding incoordination. Gavage feeding of a high-caloric formula is being continued. A 19-year-old sibling who smokes cigarettes will be caring for the infant while his parents work. You have counseled the family members, including the sibling, about common infections and their prevention, immunizations, and the risks of exposure to tobacco smoke and environmental pollutants.

Of the following, the risk factor MOST associated with hospitalization for respiratory syncytial virus (RSV)–associated bronchiolitis in the infant in this vignette is:

1	bronchopulmonary dysplasia
2	formula feeding
3	teenage sibling
4	tobacco-smoke exposure
5	ventricular septal defect

You selected 1, the correct answer is 1.

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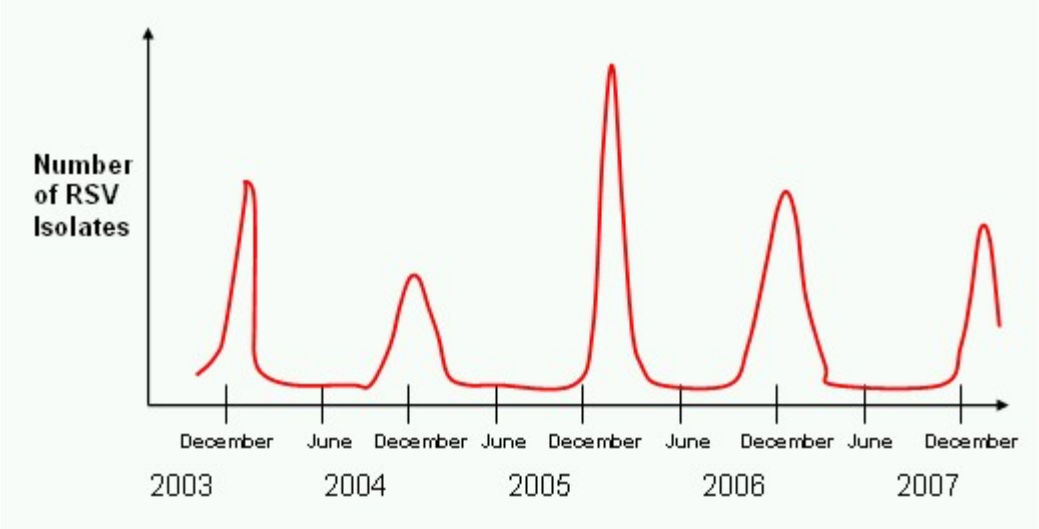
Bronchiolitis is a common lower respiratory tract infection that affects nearly all infants by the time they are 2 years old. In the United States, 20% of infants younger than 1 year old are seen in a clinic or emergency department, or are hospitalized (3%) for bronchiolitis. More than 120,000 hospitalizations and 450 deaths annually are attributed to bronchiolitis. Although two-thirds of the infants who die of bronchiolitis are born at term, high-risk populations include infants born prematurely or who have chronic lung disease, significant congenital heart disease, neurologic disorders, or immunodeficiency. Bronchiolitis has been associated with recurrent wheezing in early childhood. About 40% of infants hospitalized for bronchiolitis during their first year after birth have recurrent wheezing compared with 20% of infants without bronchiolitis. It is not clear whether the association between bronchiolitis and later wheezing is causal or a marker for genetic predisposition and limited respiratory reserve.

Respiratory syncytial virus accounts for two-thirds of bronchiolitis cases. Human metapneumovirus accounts for 3% to 12% of cases, and may occur together with RSV. Influenza, parainfluenza, rhinoviruses, and adenoviruses account for most of the remaining cases.

CONTENT SPECIFICATIONS ADDRESSED ABP American Board of Pediatrics

Respiratory syncytial virus is responsible for annual epidemics of infant and childhood respiratory disorders throughout the world. In the central United States, the RSV season typically begins in November, peaks between December and February, and ends in April (Figure). Regional and annual variations in the timing of the RSV season frequently exist.

Figure: Annual epidemics of respiratory syncytial isolates in the United States: variable onset (October-December) and peak number of infections (January-March)



Palivizumab, a humanized monoclonal antibody directed against the highly conserved F glycoprotein found on the surface of RSV, has become an important prophylactic measure to prevent severe RSV in high-risk infants. The presence of bronchopulmonary dysplasia, as in the infant in the vignette, prematurity, and congenital heart disease are the most significant high-risk factors for severe RSV infection. Palivizumab was found in large randomized trials of high-risk infants to reduce the severity of RSV infection. Severity of RSV disease in these trials was defined by rates of admission to a hospital or an intensive care unit, respiratory severity scores, length of hospitalization, and duration of supplemental oxygen use, all of which were reduced with palivizumab.

High-risk populations who are candidates for palivizumab prophylaxis during the RSV season are listed in the Table.

Table

Table. Criteria for Palivizumab Prophylaxis During Respiratory Syncytial Virus (RSV) Season

Age	Gestational Age	Requirements
<24 mo		Bronchopulmonary dysplasia during the 6 months before the next RSV season. Definition of Bronchopulmonary Dysplasia: Supplemental oxygen, bronchodilator, diuretic, or corticosteroid
<12 mo	<28 wk	
<6 mo	29-32 wk	
<6 mo	33-35 wk	2 of the following risk factors: • Child care attendance • School-age siblings • Exposure to environmental air pollution • Congenital abnormalities of the airways • Severe neuromuscular disease
<24 mo		Hemodynamically significant congenital heart disease (not present in the infant in the vignette) defined as those infants with: • Congestive heart failure and receiving medications for control • Moderate to severe pulmonary hypertension • Cyanotic heart disease • Surgical procedures requiring cardiopulmonary bypass (redosing is recommended)

For infants younger than 6 months old who are born at 33 to 35 weeks' gestation, two risk factors are required because none of these factors alone increases the risk of hospitalization substantially. Notice that exposure to tobacco smoke is not included as a risk factor. The arguments to omit recurring exposure to tobacco smoke stem from inconsistent associations in epidemiologic studies and the belief that exposure can be controlled by the family less expensively than giving monthly intramuscular injections of palivizumab. Carroll and colleagues recently described a significant association of maternal smoking and bronchiolitis in a large population-based retrospective cohort study of term infants. These findings provide more convincing evidence for the risk of passive tobacco smoke exposure to infants, even those born at term without predisposing risk factors.

Palivizumab prophylaxis has not been studied in immunocompromised children or those with cystic fibrosis, but strong theoretical support exists. Prophylaxis, therefore, should be individualized. Prophylaxis of hospitalized patients, especially those at high risk, to control hospital-acquired RSV has not been proven effective. Strict handwashing procedures, contact isolation, and supportive treatment should be emphasized if an infant acquires RSV while hospitalized. Palivizumab is not an effective treatment for acute infections.

Term and preterm infants born at 33 to 35 weeks' gestation without risk factors account for most cases of RSV during infancy and early childhood. Palivizumab has not proven cost effective in these populations and an effective vaccine has not been available. Parents and caregivers may prevent RSV infections by careful handwashing and limiting exposure to infected children and people, especially in crowded locations such as child care centers. Breast milk feeding is encouraged because immune function (RSV-specific antibody and lactoferrin) may be enhanced. The risk of severe RSV disease during the first 5 months after birth is significantly increased in infants fed formula rather than breast milk.

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References:

American Academy of Pediatrics. Respiratory syncytial virus. In: Pickering LK, Baker CJ, Long SS, McMillan JA, eds. *Red Book: 2006 Report of the Committee on Infectious Diseases.* 27th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2006:560-566

Black CP. Systematic review of the biology and medical management of respiratory syncytial virus infection. *Respir Care.* 2003;43(3):209-233

Carbonell-Estrany X, Figueras-Aloy J, Law BJ; Infeccion Respiratoria Infantil por Virus Respiratorio Sincitial Study Group; Pediatric Investigators Collaborative Network on Infections in Canada Study Group. Identifying risk factors for severe respiratory syncytial virus among infants born after 33 through 35 completed weeks of gestation. *Pediatric Infect Dis J*. 2004;23:S193-S201

Carroll KN, Gebretsadik T, Griffin MR, et al. Maternal asthma and maternal smoking are associated with increased risk of bronchiolitis during infancy. *Pediatrics.* 2007;119(6):1104-1112

Holman RC, Shay DK, Curns AT, Lingappa JR, Anderson LF. Risk factors for bronchiolitis-associated deaths among infants in the United States. *Pediatr Infect Dis J.* 2003;22(6):483-489

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Smyth RL, Openshaw PJM. Bronchiolitis. *Lancet.* 2006;368:312-322

The Impact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics.* 1998;102:531-537

Welliver RC. Review of epidemiology and clinical risk factors for severe respiratory syncytial virus (RSV) infection. *J Pediatr.* 2003;143:S112-S117

American Board of Pediatrics Content Specification(s):

Understand the epidemiology, pathogenesis, and prevention of neonatal infections with respiratory syncytial virus

Understand the treatment of neonatal infections with respiratory syncytial virus

Understand the complications of neonatal infections with respiratory syncytial virus

PREVIOUS NEXT

February: Question 2

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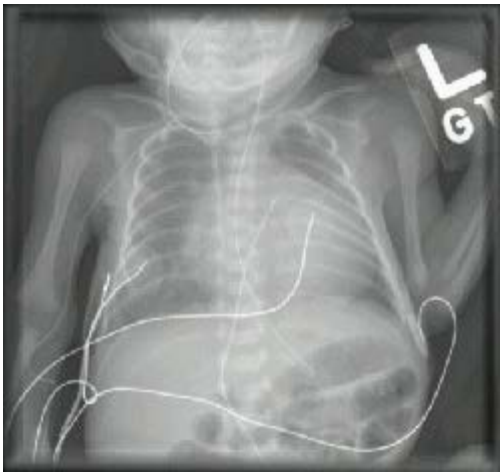
You are providing care to a 12-day-old infant with an estimated gestational age of 30 weeks who has intrauterine growth restriction. He was born by emergency cesarean section for fetal distress. He has been receiving total parenteral nutrition through an umbilical venous catheter and tolerating trophic feeds; his glucose infusion rate is 5 mg/kg per minute and his blood glucose concentration has been normal. You opt to place a peripherally inserted central catheter (PICC) line in anticipation of prolonged parenteral nutrition. A radiograph was obtained to evaluate the PICC line position after insertion (Figure).

Figure



The child subsequently has a precipitous drop in heart rate, develops cyanosis, and appears ashen. Peripheral artery pulses are absent. You immediately place an endotracheal tube (tip palpated in suprasternal notch) and begin conventional ventilation with 100% oxygen (equal breath sounds), but the heart rate drops further. Heart tones are muffled and the voltage on the cardiac monitor is low.

Of the following, the NEXT stage of management of the infant in this vignette should be:

1	fluid bolus through the umbilical line
2	high-frequency ventilation
3	pericardiocentesis
4	repeat chest radiograph
5	thoracocentesis

You selected 3, the correct answer is 3.

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The radiograph demonstrates a peripherally inserted central catheter (PICC) line beginning in the right upper extremity. The umbilical venous catheter (UVC) is also in a position that warrants concern; it projects into the left side of the cardiac shadow. The cardiac silhouette is enlarged, consistent with pericardial effusion, an uncommon but life-threatening complication of catheter insertion. Tamponade from pericardial effusion has been reported in 1% to 3% of neonates with umbilical venous catheters, with mortality rates ranging from 30% to 50%. Pericardial effusion should be considered in any neonate experiencing an acute deterioration with a central venous catheter in place because it represents an emergency situation that can be fatal unless there is a high index of suspicion and rapid diagnosis and intervention.

Most complications of PICC and other central lines are related to suboptimal positioning, hence confirmation of position is important. The recommended position for the tip of a UVC is the junction of the inferior vena cava and right atrium.

The clinical presentation of a line-related pericardial effusion is variable and can present any time after start of infusion. Possible mechanisms of injury include lodging of the tip against the beating heart, direct puncture by catheter tip, or endothelial osmotic damage and subsequent transmural necrosis caused by the hyperosmolar infusates. Correct position of the UVC may not guarantee uneventful catheterization. The most important aspect of the treatment of cardiac tamponade related to central lines is early recognition.

If suspected, infusion through the line should be stopped. Radiography or echocardiography should be performed immediately, and an attempt should be made to aspirate fluid from the catheter. If the response to conventional resuscitative procedures is inadequate, as in the infant in this vignette, diagnostic and therapeutic pericardiocentesis should be considered. Waiting for imaging in this situation is inappropriate.

In the presence of muffled heart tones, cardiomegaly on radiography, and precipitous deterioration, hypovolemia is unlikely. The risk of direct infusion of fluid into the pericardial space, however, is real, making the administration of a fluid bolus inappropriate.

The child's relative respiratory stability before this event suggests an extrapulmonary problem—temporizing by using another form of assisted ventilation such as high-frequency ventilation would delay life-saving treatment.

Repeating chest radiography is unlikely to give additional information helpful to this crisis. The radiograph presented demonstrates an abnormality that requires immediate attention. Any further delay would be dangerous.

Pneumothorax may also result in acute deterioration, but in this vignette the infant was not receiving continuous distending airway pressure or ventilation before the event. His breath sounds were equal and the endotracheal tube position was high in the trachea. This combination makes pneumothorax less likely and thoracocentesis or chest tube placement would likely not be helpful.

Do you want to add anything to your Learning Plan?
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References:

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Nadroo AM, Lin J, Green RS, Magid MS, Holzman IR. Death as a complication of peripherally inserted central catheters in neonates. *J Pediatr.* 2001;138:599-601

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Onal EE, Saygili A, Koc E, Türkyilmaz C, Okumus N, Atalay Y. Cardiac tamponade in a newborn because of umbilical venous catheterization: is correct position safe? *Pediatr Anaesth.* 2004;14:953-956

Paster S, Middleton P. Roentgenographic evaluation of umbilical artery and vein catheters. *JAMA.* 1975;231:742-746

American Board of Pediatrics Content Specification(s):

Understand the indications for and management of intravascular fluid volume replacement

Understand the indications and contraindications of drugs used for neonatal resuscitation

Understand the pathophysiology of an infant with a condition affecting the systemic blood pressure, such as shock or hypertension

Recognize the clinical features of an infant with a condition affecting the systemic blood pressure, such as shock or hypertension

Recognize the laboratory and radiographic features of an infant with a condition affecting the systemic blood pressure, such as shock or hypertension

Formulate a differential diagnosis of an infant with a condition affecting the systemic blood pressure, such as shock or hypertension

Understand the total management plan and associated potential complications of such management for an infant with a condition affecting the systemic blood pressure, such as shock or hypertension

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February: Question 3

A woman in her 38th week of pregnancy is admitted for severe headache, diarrhea, arthralgia, myalgia, and abdominal pain. She has had a fever and rhinorrhea for 3 days. When seen in the emergency room, her temperature is 38.7°C. She has a stiff neck. A spinal tap reveals a white blood cell count of 200/μL (90% lymphocytes); protein and glucose concentrations are normal. The woman is not in labor and the fetal heart rate is normal. An obstetrician is considering delivery now and asks you how this perinatal infection might affect the infant.

Of the following, the statement that MOST accurately describes such a perinatal infection in neonates is that:

1	Myocarditis is most frequently associated with echovirus 11 infections
2	Myocarditis or cardiopulmonary failure is the major determinant of outcome
3	Neonates born to mothers with an active infection should receive a dose of intravenous immunoglobulin
4	Nosocomially acquired infections are more severe than vertically transmitted infections
5	Stillbirth is common after an infection during the third trimester

You selected 2, the correct answer is 2.

Do you want to add anything to your Learning Plan?
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The woman in the vignette most likely has an enteroviral infection. The four classic groups of enteroviruses are the polioviruses, echoviruses, coxsackieviruses, and enteroviruses. More recently, the enteroviruses have been reclassified into five species (polioviruses and enteroviruses A through D). At least 67 serotypes are recognized and, for the most part, are transmitted by the fecal-oral route. Enteroviral infections peak during the summer and fall in temperate climates, but can occur throughout the year in tropical communities.

Enteroviral infections during pregnancy are quite common. During seasonal outbreaks, approximately 3% of pregnant women excrete enteroviruses at term. Most women with enteroviral infections are either asymptomatic or have mild symptoms. Mothers with echoviruses or coxsackie B, enteroviral groups most commonly associated with significant illness in newborns, often complain of fever and abdominal pain near delivery. Viral symptoms are commonly present in other family members as well.

Most neonates with enteroviral infections have a mild nonspecific illness without sequelae. Fever generally resolves in an average of 3 days and other symptoms resolve in approximately 7 days. Although most mothers with enterovirus infections transmit the virus to their offspring, the outcome is strongly influenced by the presence or absence of passively acquired maternal antibodies specific for the infecting enterovirus serotype. The timing of maternal infection, development of maternal IgG antibody, and timing of the delivery of the infant are critical factors in determining the outcome of a neonatal enteroviral infection. If

the fetus described in the vignette is delivered at this time, there is a potential for severe neonatal infection.

A small percentage of neonates who develop enteroviral infections have a severe, fulminate, life-threatening illness after vertical transmission at the time of birth. In such cases, onset of illness usually occurs within the first 2 to 5 days after birth. Symptoms are similar to those of an overwhelming bacterial infection. Infants may have extreme lethargy, hypoperfusion, fever, and a macular or maculopapular rash. Fulminant cases are often complicated by hepatitis and myocarditis. Myocarditis is most frequently caused by group B coxsackievirus type 2 to 5. Approximately one third of neonates will present with a biphasic illness. Initial symptoms of lethargy, poor feeding, or mild respiratory distress are often followed 2 to 5 days later by an abrupt onset of respiratory distress, tachycardia, cyanosis, jaundice, and diarrhea. Examination frequently reveals temperature instability, arryhythmias, hepatomegaly, and hypoperfusion. Electrocardiography can show low-voltage QRS complexes and dysrhythmias. Echocardiographic studies often indicate poor left ventricular or biventricular function.

Neonates with coxsackievirus myocarditis often have meningoencephalitis, pneumonia, hepatitis, pancreatitis, or adrenalitis. Mortality in infants with myocarditis alone is generally between 30% and 50%, but can be higher when other organs are involved. Infants with cardiopulmonary failure and central nervous system (CNS) disease caused by enterovirus 71 are at increased risk for developmental delay compared with infants with only CNS disease.

Neonates lacking a type-specific serum antibody are at increased risk of developing a symptomatic enteroviral infection. Intravenous immunoglobulin (IVIG) contains neutralizing antibodies to common circulating serotypes of the enteroviruses. Intramuscular immunoglobulin or IVIG have been administered to a number of neonates with severe enteroviral infections, but no clear conclusions can be made from these uncontrolled trials. In one randomized trial of neonates with enteroviral disease, IVIG (750 mg/kg) was associated with a modest boost of antibody titers to viral isolates, subtle clinical benefits, and quicker cessation of viremia in patients who received a high titer of neutralizing antibody to their own viral isolates. However, the study population was too small for definitive conclusions. No trial has studied prophylactic administration of IVIG to infants of mothers who had an active enteroviral infection at the time of delivery.

Nosocomial postnatal infections with enteroviruses occur less frequently than vertically acquired infections. Infant-to-infant transmission can occur via the hands of caregivers, parents, and visitors. Of 16 nursery outbreaks reported in one study, neonates who acquired an infection from their mother had more severe disease, whereas infants who acquired infection by a nosocomial route had a milder course of illness. Disease may have been milder in secondary cases because of partial protection by transplacental antibodies or an older age at the time of the infection.

Perinatal enteroviral infections can occur before, during, or after birth. Congenital anomalies have not been reported after either polioviruses or echoviruses, but coxsackieviruses A9 and B2 to B4 have been particularly associated with urogenital and cardiovascular anomalies. One case of a fatal disseminated, midgestational enterovirus 71 infection has been reported; stillbirth can occur after a maternal enterovirus illness, but this outcome is rare. Most enterovirus-infected neonates are presumed to acquire the infection either during delivery by exposure to maternal blood or genital secretions, or after delivery by exposure to oropharyngeal secretions or stool of the mother.

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Baley JE, Toltzis P. Perinatal viral infections. In:Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal Perinatal Medicine: Diseases of the Fetus and Infant.* 8th ed. Philadelphia, Pa: Mosby Elsevier; 2006:840-876

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Rotbart HA. Antiviral therapy for enteroviral infections. *Pediatr Infect Dis J.* 1999;18:632-633

American Board of Pediatrics Content Specification(s):

Understand the epidemiology, pathogenesis, and prevention of perinatal infections with coxsackievirus, echovirus, enterovirus, and poliovirus

Understand the clinical manifestations, diagnostic criteria, and treatment of perinatal infections with coxsackievirus, echovirus, enterovirus, and poliovirus

Understand the complications of perinatal infections with coxsackievirus, echovirus, enterovirus, and poliovirus

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February: Question 4

A full-term male infant with a prenatal diagnosis of bilateral severe hydronephrosis is admitted to the neonatal intensive care unit. Renal and bladder ultrasonography confirms the prenatal diagnosis and reveals an enlarged bladder. The infant is diagnosed to have posterior urethral valves by voiding cystourethrogram. While the infant is awaiting a therapeutic cystoscopy, he develops bradycardia at 30 hours of age. Laboratory data reveal the following serum concentrations:

Laboratory Test	Patient Result
Sodium, mEq/L (mmol/L)	125 (125)
Potassium, mEq/L (mmol/L)	7.8 (7.8)
Chloride, mEq/L (mmol/L)	110 (110)
Total calcium, mg/dL (mmol/L)	6.4 (1.6)
Ionized calcium, mg/dL (mmol/L)	2.6 (0.6)

Of the following, the MOST likely electrocardiographic finding in this infant is:

1	biphasic T wave
2	deep Q wave
3	flattened P wave
4	prolonged QT interval
5	prominent U wave

You selected 3, the correct answer is 3.

Do you want to add anything to your Learning Plan?
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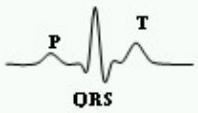
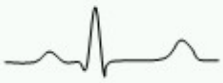
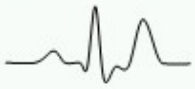
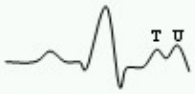
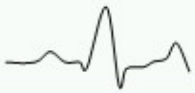
The infant in this vignette has acute renal failure complicated by hyperkalemia, hypocalcemia, and hyponatremia. Abnormal serum electrolyte concentrations can have profound effects on cardiac conduction and the corresponding electrocardiogram (EKG). Specifically, irregularities in extracellular calcium and potassium serum concentrations can alter myocyte membrane potential gradients and change the cardiac action potential. If the electrolyte abnormality is not treated, these changes can potentially precipitate life-threatening arrhythmias.

Infants with hyperkalemia may demonstrate a sequential progression of electrocardiographic changes (Table).

Table: Electrocardiographic (EKG) Findings in Infants With Electrolyte Abnormalities

Electrolyte Abnormality	EKG	Description of EKG
Hypercalcemia		Shortened QT interval
Hypocalcemia		Prolonged QT interval
Hyperkalemia	> 6.0 mEq/L (6.0 mmol/L) 	Tall peaked T wave Shortened QT interval Depressed ST segment
	>7.5 mEq/L (7.5 mmol/L) 	Prolonged PR interval Widened QRS complex Flattened P wave
	>9.0 mEq/L (9.0 mmol/L) 	Absent P wave Sinusoidal QRS wave
Hypokalemia	< 2.5 mEq/L (2.5 mmol/L) 	Slightly widened QRS complex Depressed ST Biphasic T wave due to visible U wave
	~1.0 mEq/L (1.0 mmol/L) 	Prominent U wave Flat T wave

These variations roughly correlate with potassium concentrations because of the corresponding cardiac sensitivity with greatest sensitivity in the atrial cells, followed by ventricular cells, his bundle cells, sinoatrial node, and interatrial tracts. Infants with mild hyperkalemia (>6.0 mEq/L [6.0 mmol/L]) exhibit tall peaked T waves, shortened QT intervals, and depressed ST-segments. As the potassium concentration increases (>7.5 mEq/L [7.5 mmol/L]), additional electrocardiographic changes include prolonged PR intervals, widened QRS durations, and flattened P waves. If treatment is initiated, these EKG findings can be reversed. However, without treatment, further elevations in the potassium concentration lead to the disappearance of P waves and further widening of QRS waves. Indeed, the QRS complexes may widen significantly and actually merge with the T waves, forming a sine wave; this latter electrocardiographic finding is primarily observed when the potassium concentration exceeds 9.0 mEq/L (9.0 mmol/L). The infant may then develop ventricular fibrillation or asystole.

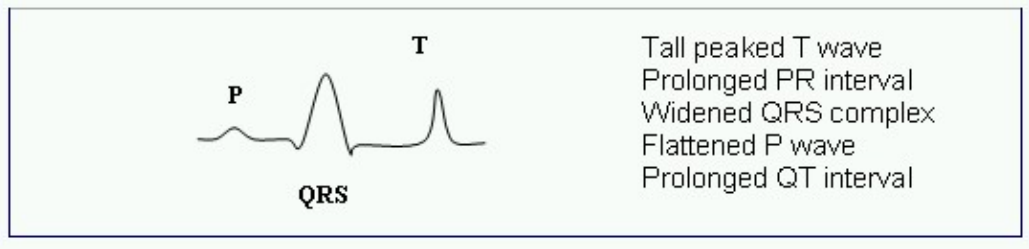
Infants with mild hypokalemia usually have normal EKGs. However, if moderate hypokalemia (concentrations <2.5 mEq/L [2.5 mmol/L]) develops, the EKG may show slightly widened QRS complexes, flattened T waves, and/or depressed ST segments. As the hypokalemia becomes more significant, U waves begin to increase in size and the appearance of the adjacent T and U waves is often described as a biphasic T wave. With extreme hypokalemia (concentrations ≤1.0 mEq/L [1.0 mmol/L]), the U waves may become large enough to fuse with the T waves. Severe hypokalemia predisposes infants to cardiac arrhythmias. Hypokalemia of any severity may increase the incidence of arrhythmias in infants treated with digitalis.

In contrast to abnormal potassium concentrations, abnormal calcium concentrations rarely cause arrhythmias. Hypocalcemia is defined as a total serum calcium concentration lower than 7 mg/dL (1.75 mmol/L). Ionized calcium concentrations typically range from 4.4 to 5.4 mg/dL(1.10-1.36 mmol/L) but values of 3 mg/dL (>0.75 mmol/L) are often adequate. A prolonged QT interval is the most common EKG

finding in patients with hypocalcemia (Table). In contrast, infants with hypercalcemia, defined by ionized calcium concentration that exceeds 5.4 mg/dL (1.35 mmol/L), with or without an elevated total calcium concentration greater than 10.8 mg/dL (2.7 mmol/L), may display shortened QT intervals.

The infant in this vignette with hyperkalemia and hypocalcemia may exhibit electrocardiographic findings similar to the EKG shown in the Figure.

Figure: Example of Possible Electrocardiogram in Infant in this Vignette



Because sodium concentrations have no impact on electrocardiographic findings, the infant's EKG will not reflect the abnormal sodium concentration. The presence of deep Q waves does not indicate any specific electrolyte abnormality. Rather, Q waves are attributed to myocardial injury, ventricular enlargement, or altered ventricular conduction.

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Martin CM, Furnas MD. Identifying drug-induced changes in electrocardiogram results of elderly individuals. *Consult Pharm*. 1997;12:1-8

Parham WA, Mehdirad AA, Biermann KM, Fredman CS. Hyperkalemia revisited. *Tex Heart Inst J.* 2006;33:40-47

Rodd C, Goodyer P. Hypercalcemia of the newborn: etiology, evaluation, and management. *Pediatr Nephrol.* 1999;13:542-547

Stefanaki E, Koropuli M, Stefanaki S, Tsilimigaki A. Atrioventricular block in preterm infants caused by hypocalcemia: a case report and review of the literature. *Eur J Obstet Gynecol Reprod Biol.* 2005;120:115-116

American Board of Pediatrics Content Specification(s):

Differentiate normal from abnormal electrocardiographic voltages, patterns, and rhythms in the fetus and newborn infant, including electrophysiologic characteristics

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February: Question 5

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A term newborn infant develops hypoglycemia unresponsive to feeding in the first hours after birth. The blood glucose concentration is 21 mg/dL (1 mmol/L) and 36 mg/dL (2 mmol/L) before and after feeding, respectively. Physical examination shows an infant with normal growth. The external genitalia consist of a small phallus and a rugated scrotumlike sac containing gonads. The gonads measure 1 cm in the long axis. The stretched phallus measures 1.9 cm in length and 0.7 cm in diameter. The rest of the physical examination findings are normal. The newborn's blood glucose concentration improves with an intravenous glucose infusion, but gradual weaning is unsuccessful during the next several days.

Of the following, the most likely diagnosis for the infant in the vignette is:

1	aromatase deficiency
2	chromosome abnormality (47,XXY)
3	congenital adrenal hyperplasia
4	isolated cortisol deficiency
5	pituitary insufficiency

You selected 5, the correct answer is 5.

The infant in the vignette almost certainly has pituitary insufficiency which affects both glucose homeostasis and genital development. The persistent requirement for higher than normal glucose intake to maintain normal blood glucose concentrations is because of a lack of pituitary hormone production (eg, growth hormone and adrenocorticotropic hormone [ACTH]) that would oppose the effects of insulin and increase glucose production. Growth hormone (somatotropin) and adrenal glucocorticoids (eg, cortisol) promote gluconeogenesis and help raise blood glucose concentrations. Growth hormone also suppresses the uptake of glucose by the liver. With pituitary insufficiency, growth hormone and ACTH are not secreted, resulting in hypoglycemia from unopposed insulin action.

The normal size of the stretched penis at birth is 2.5 to 5 cm with a diameter of 0.9 to 1.3 cm. The infant in this vignette has a micropenis (http://knowledge.emedicine.com/splash/shared/pub/cotw/0028answer.html). The testes in a newborn are normally 8 to 14 mm long. Penile development depends on the normal production of testosterone which is stimulated by pituitary-derived luteinizing hormone (LH). The production of adrenal androgens is stimulated by ACTH which is also deficient in this condition. An isolated deficiency of growth hormone, which occurs far less commonly than panhypopituitarism, could also present with hypoglycemia and micropenis. Isolated growth hormone deficiency was not an option offered in the vignette.

Aromatase (also known as cytochrome P450 aromatase) is a microsomal enzyme complex that converts androgenic steroids to estrogens.

Aromatase deficiency is a rare disease caused by a mutation of gene *CYP19* on chromosome 15 (15q21.2). It is an autosomal recessive disorder. Accumulation of androgens during pregnancy may cause virilization of a newborn female. Males are not affected. Females will have primary amenorrhea. Individuals of both sexes will be tall because the epiphyses remain open as a result of a lack of estrogen. Neonatal hypoglycemia is not described in this disorder.

The chromosome abnormality 47,XXY is also known as Klinefelter syndrome. Boys with Klinefelter syndrome inherit an extra X chromosome from either mother or father owing to nondisjunction during meiosis. Klinefelter syndrome occurs in 1 in 500 to 1 in 1,000 male births. The testes are small and firm. Other effects of Klinefelter syndrome are quite variable. Boys with Klinefelter syndrome are usually born with external genitals that look like those of other boys; however, micropenis at birth is described in some cases. Neonatal hypoglycemia is not a feature of Klinefelter syndrome.

Congenital adrenal hyperplasia (CAH) in girls presents with virilization including an enlarged clitoris that might be confused with a micropenis and rugated labia majora that can be confused with a bifid scrotal sac. However, finding gonads in these skin folds is highly unusual in girls with CAH. Boys with CAH have a normal appearance at birth, including that of their external genitalia. The prevalence of some degree of enzyme deficiency leading to variations in this condition is 1 in 60 individuals in the general population. Neonatal hypoglycemia can occur with CAH, but is not a common presentation.

Familial isolated glucocorticoid deficiency is a rare autosomal recessive disorder that presents as primary adrenal insufficiency, usually without mineralocorticoid deficiency, that can be lethal, if unsuspected. Indeed, in more than 50 published cases, 18 have been fatal. Affected children can present within the first 2 to 3 years of age with hyperpigmentation and recurrent hypoglycemia that can lead to convulsions or coma, chronic weakness, and failure to thrive. Typically they have deficient production of cortisol and adrenal androgens, in the presence of markedly elevated ACTH concentrations. Affected subjects achieve normal growth and development with steroid replacement and live an otherwise normal life. Testosterone production is not affected and micropenis is not described.

References:

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Radcliffe S. Long term outcome in children with sex chromosome abnormalities. *Arch Dis Child.* 1999;80:192-195

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Wilson TA. Congenital adrenal hyperplasia. emedicine.com Web site. Accessed April 10, 2007, at: http://www.emedicine.com/ped/topic48.htm

American Board of Pediatrics Content Specification(s):

Know the importance of the combination of micropenis and hypoglycemia

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February: Question 6

A male infant is born at 36 weeks' gestation to a mother with Graves disease. The newborn state screen shows that the infant has elevated thyroid-stimulating hormone and thyroxine concentrations. This corresponds with the excessive thyroid-stimulating hormone receptor-stimulating antibodies measured in the infant's mother.

Of the following, the MOST likely mechanism for transplacental transfer of these antibodies is:

1	active transport
2	facilitated diffusion
3	pinocytosis
4	placental break
5	simple diffusion

You selected 3, the correct answer is 3.

The infant in this vignette developed hyperthyroidism because of the intrauterine transplacental passage of the maternal thyroid-stimulating hormone receptor immunoglobulin (Ig) G antibodies. Pinocytosis is the process enabling IgG molecules to cross the placenta. During this process, trophoblasts on the maternal side of the placenta bind and engulf IgG molecules via specific neonatal Fc receptors, transport them across the cell, and release the antibodies on the fetal side. Because these Fc trophoblastic receptors bind specifically to IgG, this is the only major class of antibodies that can cross the placenta. Transplacental passage of IgG molecules increases with advancing gestational age, beginning early in the second trimester with most of the antibodies being transferred during the third trimester. Antibody transfer enables newborns to have a passive defense mechanism against some pathogens (a positive effect), or antibody transfer might cause transient manifestations of maternal antibody-mediated disease, such as Graves disease, myasthenia gravis, or autoimmune thrombocytopenia purpura (a negative effect).

Active transport is the carrier-mediated transfer of compounds against the concentration gradient that requires the expenditure of energy. Because the concentrations of amino acids, calcium, phosphate, magnesium, and water-soluble vitamins in fetal blood are greater than in maternal blood concentrations, these substances are transferred from the maternal to the fetal side of the placenta with this mechanism. Amino acids are actively transported into the syncytiotrophoblast via specific transporters and are then transferred by a passive leak down the concentration gradient to the fetal plasma. At least 10 sodium-dependent amino acid transporters have been identified in the placenta. Active transport mechanisms for amino acid placental transfer are intact by the late second trimester because fetal amino acid concentrations are higher than maternal concentrations by 18 to 21 weeks'

gestation.

Placental facilitated diffusion is the energy-independent movement of molecules across the microvillous or basal membranes of the syncytiotrophoblasts using transport proteins. This passive transfer is mediated by carrier proteins and occurs along the concentration gradient. Glucose is transported across the placenta by insulin-independent facilitated glucose transporters, also known as GLUT transporters. GLUT 1 is the most abundant subtype expressed in the human trophoblast.

Breaks in the placental membrane are caused by abnormalities within the placental structure and can cause maternal or fetal cells to cross the placenta. These breaks are atypical and are not involved in the normal transfer of compounds across the placenta.

Simple diffusion is the passive transfer of solutes. Oxygen, carbon dioxide, water, sodium, chloride, lipids, fat-soluble vitamins, and most maternal medications are transferred across the placenta with this mechanism. The direction of transplacental passage of these molecules depends on the: (1) concentration gradient; (2) surface area of the placental membrane; (3) placental blood flow; and (4) properties of the compounds, including lipid solubility, molecular weight, and protein-binding.

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Simister NE. Placental transport of immunoglobulin G. *Vaccine*. 2003;21(24):3365-3369

American Board of Pediatrics Content Specification(s):

Understand the placental transfer of immunoglobulins

Know the role of the placenta in the energy metabolism of the fetus, including transfer of glucose, electrolytes, and amino acids to the fetus

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February: Question 7

A term infant presents with low birthweight and microcephaly. Physical examination reveals short palpebral fissures, maxillary hypoplasia, short nose, and a smooth philtrum with a thin upper lip.

Of the following, the risk of a major anomaly in the presence of three or more minor anomalies is CLOSEST to:

1	1%
2	5%
3	10%
4	15%
5	20%

You selected 5, the correct answer is 5.

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The infant in the vignette exhibits a pattern of morphologic features consistent with a diagnosis of fetal alcohol syndrome. While major congenital anomalies are recognized in 2% to 3% of liveborn infants, up to 20% of infants exhibit minor anomalies or anatomic variants. The term *congenital* refers to the presence of the defect at birth, and does not imply causality. Defects imposing medical and social consequences for the infant, such as cleft palate and neural tube defects, are considered major anomalies, while structural alterations, such as epicanthal folds and a single palmar crease, that pose no significant health or social burden, are minor anomalies. However, the prevalence of a given feature can vary, based on race, ethnicity, and gender, blurring the distinction between a minor anomaly and a normal phenotypic variant. For example, while uncommon in the Caucasian population, natal teeth are considered a normal variant in the Native American population. As a result, physical differences occurring in 4% or more of a general population are considered normal phenotypic variants. In addition, minor anomalies may be familial, such as isolated ear tags and pits, which may exhibit an autosomal dominant pattern of inheritance. Therefore, family history should also be considered before assigning significance to the presence of a minor malformation.

Major anomalies, such as cleft lip, are easily identified; however, minor anomalies may be subtle and overlooked. Most minor anomalies (70%) affect the face or hands, which are areas of the body with great complexity and variability. Minor anomalies occur with increased frequency in infants born prematurely or with intrauterine growth restriction. Recognizing physical features as minor anomalies is important for the following reasons.

- **Minor anomalies may be markers for occult major malformations, such as sacral hair tufts associated with spinal dysraphism.**
- **Specific patterns of minor anomalies often define genetic syndromes, as with the typical constellation of features involving the face, hands, and feet of individuals with Down syndrome. However, in isolation, these same features carry less significance. For example, 45% of individuals with Down syndrome have single palmar creases, but this feature is found**

unilaterally in 4% and bilaterally in 1% of the general Caucasian population.

- Minor anomalies give consistent clues to the diagnosis of many multianomaly syndromes. For example, fetal alcohol syndrome is suggested by a pattern of minor morphologic features, including short palpebral fissures, maxillary hypoplasia, smooth philtrum with thin and smooth upper lip, altered palmar crease patterns, and small fifth fingernails.
- Finally, the risk of a major anomaly increases as the number of identified minor anomalies increases (Table). In fact, in the presence of three or more minor anomalies, the risk of a major anomaly reaches 20%. Therefore, the identification of multiple minor anomalies should prompt a search for coexistent major malformations.

Table

No. of Minor Anomalies	% of Newborns	Risk for Major Anomaly, %
0	79-84	1
1	15-20	3
2	0.8	10
≥3	0.5	20

References:

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American Board of Pediatrics Content Specification(s):

Know the frequencies of minor congenital anomalies

Know the frequencies of major congenital anomalies

PREVIOUS NEXT

February: Question 8

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11 November 08

12 December 08

You are asked to speak to students in a college epidemiology course about nutrition and the incidence of birth defects, with specific attention to folic acid supplementation.

Of the following, the MOST accurate statement about folic acid supplementation for the prevention of neural tube defects is that prevention is:

1	associated with a reduction of anencephaly rather than meningomyelocele
2	associated with elimination of recurrent neural tube defects
3	best achieved by providing folic acid tablets in prenatal clinics
4	effective only during the stage of neuronal proliferation
5	enhanced by food fortification of cereal products

You selected 5, the correct answer is 5.

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Daily folic acid tablet intake by all women capable of bearing children would be ideal to prevent neural tube defects, but is frequently not practical. Epidemiologic studies reveal that folic acid fortification of foodstuffs (such as cereal products) is more effective.

Neural tube defects are characterized by defects in the process of neurulation, the first step in the development of the central nervous system. During the first and second weeks of development, a rostrocaudal axis is defined in the embryo by the primitive streak and the adjacent notochord. The notochord is responsible for induction of the dorsal neural plate and the ventral neurenteric canal. During the third and fourth weeks of development, neural folds arise at the lateral margins of the neural plate. Growth of the neural folds results in a central neural groove (see http://www.med.umich.edu/lrc/coursepages/M1_/embryology/embryo/images/neural_crest_and_notocord.gif). The growing neural folds first meet at the level of the future medulla, followed by progressive closure of the neural groove to form the neural tube. The rostral (head) end of the neural tube—the anterior neuropore—closes at 24 days' development; the caudal (tail) end—the posterior neuropore—closes at 27 days. Closure of the anterior neuropore is followed by the stage of prosencephalization, during which the forebrain is formed, and neuronal proliferation, during which the regions of the nervous system are populated by neural and glial cells.

Failures in closure of the neural tube are termed *dysraphias*: anterior dysraphia results in anencephaly; posterior in myelomeningocele; and, total in craniorachischisis; total craniorachischisis is usually associated with early fetal death. Neural tube defects occur in 0.5 to 2 per 1,000 live births, with a wide variation reported among different populations. High incidences of anencephaly have been reported in Ireland, Scotland, Wales, New Zealand, Egypt, and the Arabian subcontinent. A low incidence of anencephaly has been found in Japan. Pathogenetic factors

for neural tube defects include both genetic and environmental influences, including drugs (valproic acid associated with spina bifida, but not with anencephaly), maternal diseases (diabetes), maternal environment (hyperthermia or ionizing radiation), maternal age (advanced), multiple syndromes, and maternal diet (folic acid deficiency).

Evidence showed that periconceptional folic acid supplementation could reduce the incidence of (but not eliminate) recurrent neural tube defects. Therefore it has been recommended that the diet of mothers with a history of having a child with a neural tube defect receive supplementation before conception and during their subsequent pregnancies. Because neurulation occurs during the first 28 days of embryonic-fetal development, effective supplementation must be established before that time; its initiation in prenatal clinics (after diagnosis of pregnancy) is unlikely to be effective. Following these recommendations, the recurrence rate dropped from 4.2% to 0.5% among women with one child with a neural tube defect; women who had more than one affected child had a recurrence rate drop from 9.6% to 2.3%. The effectiveness of folic acid in preventing neural tube defects is dose dependant: 20% reduction using 200 µg of folic acid per day, 36% reduction at 400 µg per day, and 82% reduction at 4 mg per day. Effectiveness of these regimens largely depends on supplementation during the first days after conception and would miss a significant number of pregnant women who discover their pregnancies later in gestation.

Epidemiologic studies suggested that neural tube defects in the entire population could be reduced by 60% if all women were to receive adequate folic acid. Folic acid supplementation is not known to affect the 40% of neural tube defects that are associated with aneuploidy, genetic syndromes, valproic acid toxicity, maternal diabetes, or hyperthermia. When folic acid supplementation was recommended as an intervention, its effectiveness was limited because of the need for its initiation before the period of fetal neurulation. In the United States, folic acid supplementation of flour, cornmeal, pasta, rice, and breakfast cereals was mandated as of January 1, 1998; Canada followed on November 11, 1998. It is estimated that fortification adds about 200 µg of folic acid per day—for that reason, even with a food fortification program in place, daily folic acid supplementation continues to be recommended for all women capable of becoming pregnant. Compared with the earlier time when only folic acid supplementation was the recommendation, food fortification has resulted in significant reduction in prevalence of neural tube defects (1.58 cases to 0.86 cases per 1,000 live births). Although all forms of neural tube defect were reduced, the decrease was greater for spina bifida (53%) than for anencephaly (38%) or encephalocele (31%). Among the Canadian provinces, the decrease in prevalence of neural tube defects after fortification was most dramatic in those regions with the highest prefortification incidences.

Dietary supplementation of folic acid for women capable of bearing children, combined with food fortification, is more effective than either strategy used alone for the prevention of neural tube defects.

Do you want to add anything to your Learning Plan?
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American Board of Pediatrics Content Specification(s):

Determine the nutrients and the relative amounts required for normal fetal growth

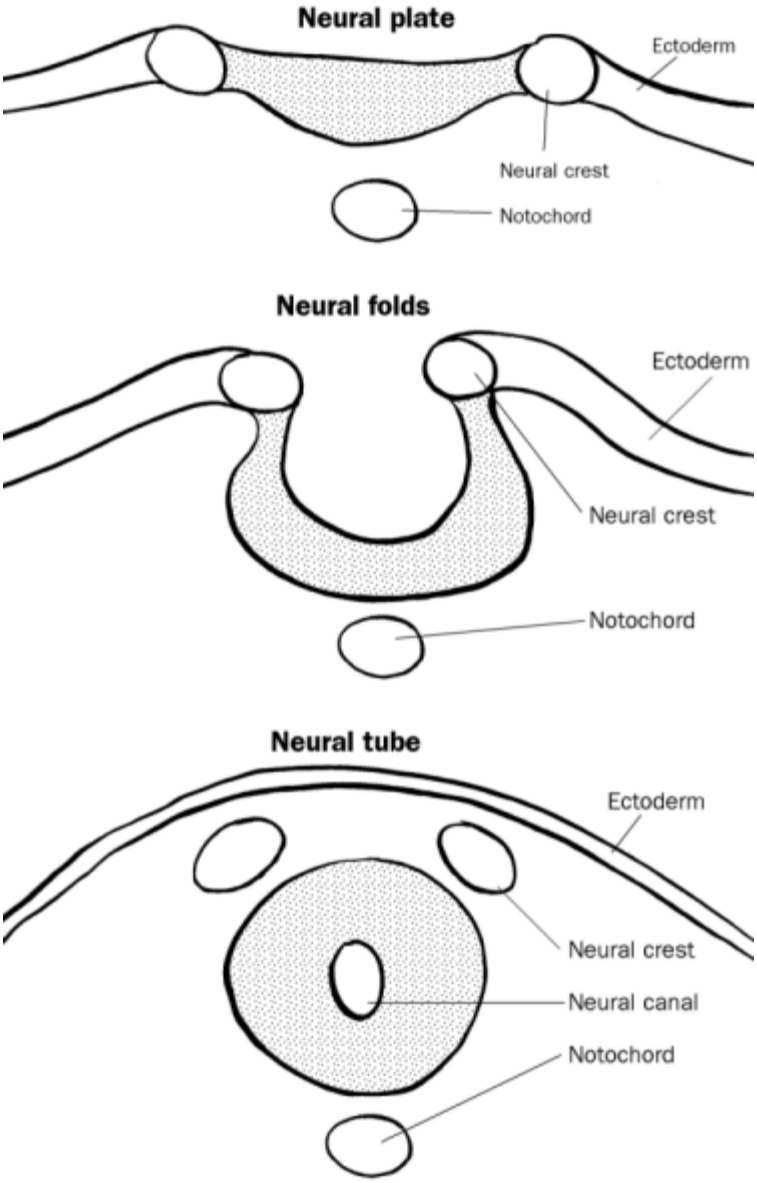
Recognize the clinical features, inheritance patterns, and complications of neural tube defects

Know the effects on the fetus of maternal hyperthermia

Understand the embryology, incidence, and differential diagnosis of myelomeningocele and encephalocele

Understand the prevention of myelomeningocele and encephalocele

PREVIOUS NEXT


Neural plate
Ectoderm
Neural crest
Notochord
Neural folds
Ectoderm
Neural crest
Notochord
Neural tube
Ectoderm
Neural crest
Neural canal
Notochord

February: Question 9

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11 November 08

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An infant, weighing 550 g at birth at 26 weeks' gestation, is soon to be discharged from your hospital. As you order a screening test for hearing, the mother, an insurance actuary, asks you what the probability is that her child will have a significant hearing loss.

Of the following, the factor associated with the HIGHEST risk for neonatal hearing impairment is:

1	aminoglycoside administration
2	Apgar score of 3 at 10 minutes
3	birthweight of 550 g
4	family history of hearing loss
5	" refer" result on initial hearing screen

You selected 4, the correct answer is 4.

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Retrospective analyses of the records of hearing-impaired children show significant associations with several neonatal risk factors (Table).

Table

Table. High-Risk Indicators for Hearing Loss in Neonates*

Indicators
Family history of SNHL, presumably congenital SNHL
In utero infection associated with SNHL (eg, toxoplasmosis, rubella, CMV infection, herpes, syphilis)
Ear and other craniofacial anomalies
Hyperbilirubinemia at levels that require exchange transfusion
Birthweight <1,500 g
Bacterial meningitis
Low Apgar scores (0-3 at 5 minutes, 0-6 at 10 minutes)
Respiratory distress (eg, due to meconium aspiration)
Mechanical ventilation >10 days
Ototoxic medication (eg, gentamicin) administered for >5 days or used in combination with loop diuretics
Physical features or other stigmata associated with a syndrome known to include SNHL (eg, Down syndrome, Waardenburg syndrome)

CMV = cytomegalovirus; SNHL = sensorineural hearing loss.
*** Adapted from Finitzo and colleagues (2000).**

The harder question to answer is: “Given the risk factor, what is the prospective probability of hearing impairment?” The factor associated with the highest risk for hearing impairment is a family history of hearing loss, conferring a 6.6 % chance of hearing impairment. Neonatal aminoglycoside administration is associated with a 1.5% risk, a “refer” result on initial hearing screen with a 2.5% to 5% risk, a birthweight of 400 to 1,000 g with a 2% risk, and an Apgar score of 0 to 3 at 10 minutes with a 3% risk.

Severe hearing loss (60 - 80 dB) or profound hearing loss (above 80 dB) affects 1 in 1,000 births. This is in contrast to the general population of the United States, where 9% have some degree of hearing loss.

A family history of hearing loss gives a 6.6% probability of hearing loss in the newborn. Half of all cases of neonatal hearing loss are genetic and half are acquired. Of those cases with genetic causes, 30% are syndromic and 70% are nonsyndromic. Of these nonsyndromic cases, 77% are autosomal recessive, 22% are autosomal dominant, and 1% are x-linked. More than 90% of the autosomal recessive cases have parents with normal hearing and no family history of hearing impairment. Familial hearing loss is usually sensorineural.

Syndromes associated with hearing loss include Down, Pierre Robin, CHARGE, Rubinstein-Taybi, Stickler, and Goldenhar. The hearing loss is more often conductive than sensorineural in origin. The group of neonates with hearing loss–associated syndromes has an overall incidence of hearing loss of 12%. Craniofacial anomalies alone are associated with a 5% risk.

Half of all cases of neonatal hearing loss are acquired, including associations with specific drugs, hypoxic-ischemic encephalopathy (HIE), persistent pulmonary hypertension of the newborn (PPHN), hyperbilirubinemia, and meningitis.

Aminoglycoside antibiotic exposure is associated with a 1% to 2% risk of neonatal hearing impairment. Premature birth or low birthweight (defined differently by various studies) is associated with a risk of hearing impairment of 2% to 6%. Because, in one study, 45% of patients in the neonatal intensive care unit received aminoglycosides, the existence of a separate risk from aminoglycosides is not clear.

Hypoxic-ischemic encephalopathy is associated with hearing loss in up to 10% of survivors. The specific definition of HIE varies from study to study, but, in general, the cases found by using the most stringent definitions are associated, counterintuitively, with the lowest chance of hearing impairment. Using an Apgar score of 0 to 3 at 10 minutes as a proxy for asphyxia and HIE, one large prospective national study found a 3% risk of hearing impairment. The usual pattern of hearing loss in HIE is sensorineural; however, conductive or central processing losses can also be seen. A frequent pattern found on hearing testing is bilateral, with the greatest loss seen in the higher frequencies.

In the past, PPHN was associated with a 20% to 53% risk of hearing loss, usually sensorineural. Hearing loss in PPHN was attributed to HIE, hyperventilation, hypocapnia, and furosemide use. One recent small study of PPHN, performed since the routine use of inhaled nitric oxide, did not find an increased risk of hearing loss.

Children with a bilirubin concentration of 25 mg/dL (428 mmol/L) or higher or the need for an exchange transfusion have a risk of permanent hearing loss of 4% to 12%. Although sensorineural hearing loss, especially at the high frequencies, is most often seen, vestibular and central auditory processing deficiencies can also occur. Hearing rescreening is recommended once the bilirubin concentration returns to normal.

Neonatal bacterial meningitis carries a 6% to 17% risk of hearing impairment, usually sensorineural. Cytomegalovirus (CMV) is the most common infectious cause of hearing loss; 0.5% to 2.5% of all newborns are infected (most asymptomatically). Up to 20% of these newborns infected with CMV may develop hearing loss, some not until the second year of life. Symptomatic neonates with CMV have a higher risk (61%) than asymptomatic neonates (7%).

For every neonate with true hearing loss, 20 to 40 normal-hearing children will have a “refer” on

initial hearing screening; “refer” confers a 2.5% to 5% risk of hearing loss. This low threshold for a “refer” allows great sensitivity to detect almost all neonates with hearing loss. Before hearing screening became universal, screening of only those children with risk factors (Table) would detect only half of all neonates with severe or profound hearing loss.

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References:

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Roizen NJ. Etiology of hearing loss in children: nongenetic causes. *Pediatr Clin N Am.* 1999;46:50-64

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Sgro M, Campbell D, Shah V. Incidence and causes of severe neonatal hyperbilirubinemia in Canada. *CMAJ.* 2006;175:587-590

American Board of Pediatrics Content Specification(s):

Know the incidence of hearing impairment in preterm infants

Know the incidence of hearing impairment in the general population

Know the incidence of hearing impairment in high risk infants, including those with hypoxic ischemic encephalopathy, persistent pulmonary hypertension, congenital infections

Know the type of hearing impairments associated with persistent pulmonary hypertension of the newborn

Know the type of hearing impairments associated with hypoxic-ischemic encephalopathy

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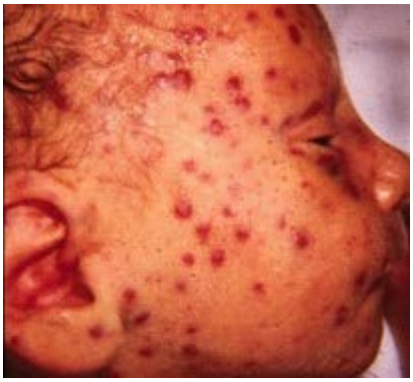
12 December 08

February: Question 10

A term infant presents with a rash (Figure). He is clinically stable without cardiopulmonary distress. The infant was born after an uncomplicated pregnancy and labor. The family history is negative for bleeding disorders.

Figure



Of the following, the histopathologic finding that is MOST likely to be present in these skin lesions is:

1	extramedullary hematopoiesis
2	Langerhans cell histiocytes
3	mononuclear infiltrate
4	neuroblastoma cells
5	venous malformations

You selected 1, the correct answer is 1.

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Blueberry muffin skin lesions in newborn infants, like those depicted in the infant in the vignette, are most often associated with extramedullary hematopoiesis. Histologically, the lesions consist of poorly circumscribed collections of nucleated and nonnucleated red blood cells, mostly confined to the dermis with extension into the subcutaneous tissue. Myeloid precursors may be present but are few in number.

Extramedullary hematopoiesis in skin lesions, or dermal erythropoiesis, is most commonly associated with infectious or hematologic disorders (Table).

Table

Table. Blueberry Muffin Skin Lesions: Differential Diagnosis*

Extramedullary hemato/erythropoiesis	Infections	Congenital infections: • Cytomegalovirus • Toxoplasmosis • Syphilis • Parvovirus • Coxsackie B2 • Rubella • Herpes simplex virus Sepsis
	Hematologic disorders	Twin-twin transfusion syndrome Fetomaternal hemorrhage Intrauterine intracranial hemorrhage Hemolytic disease Hereditary spherocytosis
	Glycogen storage diseases†	Gaucher disease type 2 (acute neuropathic form)
Neoplasia	Congenital leukemia	
	Solid tumor metastases	Neuroblastoma Rhabdomyosarcoma
	Histiocytoses (Langerhans cell histiocytoses)	
	Hemangiopericytomas/myofibromatosis	
Vascular	Hemangiomatosis	
	Multifocal lymphangioendotheliomatosis	
	Blue rubber bleb nevus syndrome	
	Glomangiomas (glomuvenous malformations)	

* Adapted from Holland and colleagues (2005).

† Personal communication, WA Engle, MD, August 15, 2007.

Intrauterine anemia appears to be a common factor for some of the causes of dermal erythropoiesis. The skin lesions are frequently mistaken to be "hemorrhagic-purpuric" in nature when, in fact, they consist of erythroid progenitors and cells. The lesions typically are 2 to 7 mm in diameter with the larger being circular and raised 1 to 2 mm above skin level. The larger lesions may be firm and vary from dark blue to dark magenta. Smaller lesions are frequently macular, ranging in color from dark red to pale grey–purple to copper brown. The skin lesions fade over 3 to 6 weeks. Of interest, dermal erythropoiesis occurs normally in the undifferentiated mesenchyme of the skin until about the fifth fetal month. Thereafter, erythropoiesis in the dermis disappears.

Langerhans cells are unique to the skin and serve as dendritic cells that take up and present antigens (such as bacteria) to macrophages and other effector cells for destruction and disposal. Histologically, lesions consist of a dense dermal infiltrate of large histiocytic cells that have eosinophilic cytoplasm, kidney-shaped nuclei, and, on electron microscopy, Birbeck granules (pentalaminar layers of cell membranes that look like a tennis racket).

Langerhans cell histiocytosis has replaced the terms *histiocytosis X*, *eosinophilic granuloma*, *Hand-Schuller-Christian disease*, *Letterer-Siwe disease*, and *congenital self-healing reticulohistiocytosis* (Hashimoto Pritzker variant). Although a rare disorder in infants, the diagnosis is considered when more common causes for blueberry muffin skin lesions are absent. Skin lesions may be generalized, multiple, and, in 25% of cases, solitary. The skin lesions appear as 2- to 10-mm yellow to brown papules or nodules. The nodules may be pseudovesicular, involve central ulceration, and resemble neonatal blistering disorders. Skin lesions resolve spontaneously during the first weeks after birth in the congenital self-healing

reticulohistiocytosis/Langerhans cell histiocytosis disorder that is frequently found in neonatal cases. Other lesions are erythematous and appear vascular, similar to lesions of hemangiomatosis and blue rubber bleb nevus syndrome. Langerhans cell histiocytosis also appears as eczematous or hemorrhagic scaling lesions. The prognosis with these disorders varies considerably from a self-limited disease to a life-threatening multisystem disorder.

Mononuclear infiltration of the skin characterizes infants with congenital monocytic leukemia. Congenital leukemia is the second most common malignancy during infancy (41 cases per million infants), second only to neuroblastoma (65 cases per million infants). Myelogenous leukemia is nine times more prevalent than lymphocytic leukemia. The lesion of leukemia cutis is characterized as a dense diffuse pleiomorphic mononuclear cell infiltrate below an intact but atrophic overlying epidermis. Myeloperoxidase is present in myelogenous leukemic cells and is responsible for a green color when skin lesions are compressed. Multiple 2- to 50-mm firm, erythematous, violaceous to blue papules or nodules typify leukemia cutis with early lesions being macular. Although the face and neck are commonly involved, lesions may be generalized. Survival with congenital leukemia is 20% to 30% with the presence of chromosomal abnormalities of tumor cells indicating a particularly poor prognosis. Spontaneous remissions have also been reported, but relapse within weeks to 10 years may occur in more than half the cases.

Neuroblastoma originates from neural crest cells of the adrenal medulla and sympathetic ganglia. Histologic examination of skin lesions demonstrates uniform small neuroblastoma cells with hyperchromatic round nuclei, frequent rosettes, and numerous mitoses. Necrosis, calcification, and fibrovascular septa are also found.

Skin metastases in neuroblastoma are found in about one third of neonatal cases; this is 10 times more frequent than at other ages at presentation. Neonatal cases, on the other hand, rarely have bone marrow involvement. The skin lesions are usually firm, skin-colored, or bluish nodules. When compressed, the nodules blanch for 30 to 60 minutes because of the presence of catecholamines. Periorbital ecchymoses ("raccoon eyes") and heterochromia irides from disruption of sympathetic innervations of the iris are unusual presentations that are indicative of neuroblastoma. The prognosis with neuroblastoma during infancy (5-year survival rate, 80%) is better than found at later presentations (5-year survival rate, 45%). The stage IV-S subgroup of neuroblastoma involves the liver, skin, and bone marrow; spontaneous remission is common and overall survival is greater than 90%.

Histologic examination may show venous malformations in the skin lesions of the blue rubber bleb nevus syndrome. Large irregular blood-filled vascular spaces that are lined by a thin layer of endothelial cells are found in the deep dermis and subcutis. This is a rare disorder in newborn infants but the abnormal vascular lesions often are present at the time of birth. The skin lesions have a variable morphologic appearance. The most characteristic lesion is a 1- to 50-mm dark blue-purple, soft, rubbery, easily compressible sac that wrinkles when compressed and refills when released (blue rubber nipple). Although lesions are generalized, the feet, other limbs, trunk, and face are most frequently involved. There may be hundreds of lesions in the skin. The gastrointestinal organs may be involved and bleeding may cause iron deficiency beginning in infancy. More severe bleeding may occur in the gastrointestinal and other involved organ systems (liver, spleen, thyroid, eyes, peritoneum, pleura, respiratory tract, muscle, bone, thymus, pancreas, retroperitoneum, genitourinary tract, parotid gland, and central nervous system). Chronic bleeding may require iron and blood replacement.

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Brough AJ, Jones D, Page RH, Mizukami I. Dermal erythropoiesis in neonatal infants: a manifestation of intra-uterine viral disease. *Pediatrics.* 1967;40(4):627-635

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American Board of Pediatrics Content Specification(s):

Identify the clinical and laboratory features of congenital leukemia

Recognize the cutaneous and laboratory manifestations of CMV

Recognize the cutaneous and laboratory manifestations of rubella

Recognize the cutaneous and laboratory manifestations of Langerhans cell histiocytosis

Know the etiology and cutaneous manifestations of nonpurpuric skin lesions

Recognize the clinical and laboratory features of neuroblastoma in the newborn

PREVIOUS NEXT

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11 November 08

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March: Question 1

You are called to examine a lethargic 16-hour-old appropriate-for-gestational-age male infant. He had Apgar scores of 1, 4, 6, 6, and 8 at 1, 5, 10, 15, and 20 minutes, respectively. The arterial cord gas revealed a pH of 6.86. On physical examination, he is found to be lethargic, but arouses to auditory stimuli. His tone is decreased and he has a prominent head lag, but his deep tendon reflexes are increased. The nurse reports that he is not interested in feeding. The infant has had a generalized tonic-clonic seizure that was controlled with phenobarbital.

Of the following, the MOST likely description of neurologic status, based on Sarnat and Sarnat criteria, in this infant, would be:

1	brain death
2	mild encephalopathy
3	moderate encephalopathy
✗ 4	no encephalopathy
5	severe encephalopathy

You selected 4, the correct answer is 3.

Do you want to add anything to your Learning Plan?
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Neurologic dysfunctions resulting from hypoxic-ischemic encephalopathy (HIE) include changes in tone, seizures, and an altered level of consciousness and reactivity. Careful neurologic examination and staging of the encephalopathy may help to determine the severity of insult and ultimate outcome.

CONTENT SPECIFICATIONS ADDRESSED ABP American Board of Pediatrics

Several scales have been developed to assess the severity of HIE. The Sarnat and Sarnat scale divides the stages of HIE into three levels using major clinical features (Table).

Table

Table. Clinical Staging and Outcome of Hypoxic-Ischemic Encephalopathy*			
Severity of Encephalopathy	**Mild (Stage I)**	**Moderate (Stage II)**	**Severe (Stage III)**
Level of consciousness	Alert (hyperalert)	Lethargic	Coma
Muscle tone	Normal	Hypotonic	Flaccid
Tendon reflexes	Increased	Increased	Depressed or absent
Pupils	Mydriasis	Miosis	Variable, often unequal, poor light reflex
Seizures	Absent	Common; focal or multifocal	Uncommon (excluding decerebration)
Electroencephalographic findings	Normal	Low voltage, periodic or paroxysmal	• Early: Periodic pattern with isopotential phases • Later: isopotential
Outcome	Normal	20%-40% abnormal	Death or 100% abnormal

* Adapted from Sarnat and Sarnat (1976) and Roland and Hill (1995).

The infant in this vignette demonstrates moderate encephalopathy (Sarnat stage II) with an altered level of consciousness (lethargy), hypotonia, seizures, and hyperreflexia. It is also common to find poor feeding, a decreased gag reflex, and constricted pupils in stage II.

With evidence of some degree of central nervous system activity, brain death would not be a consideration in the infant in this vignette.

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References:

Ashwal S. Brain death in the newborn: current perspectives. *Clin Perinatol.* 1997;24:859-882

Goh AY, Mok Q. Clinical course and determination of brainstem death in a children's hospital. *Acta Paediatr.* 2004;93:47-52

Roland EH, Hill A. Clinical aspects of perinatal hypoxic-ischemic brain injury. *Semin Pediatric Neurol.* 1995;2:57-71

Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. *Arch Neurol.* 1976;33:696-705

American Board of Pediatrics Content Specification(s):

Understand the clinical features and diagnosis of perinatal hypoxic ischemic encephalopathy

Understand the significance, limitations, and causes of low Apgar scores

Understand the interpretation of fetal scalp and umbilical cord blood gas and pH values

Recognize common neuromotor abnormalities during infancy

Recognize and know the significance of jitteriness in neonates

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March: Question 2

A 4-week-old infant born at 28-weeks' gestation has mild chronic lung disease following respiratory distress syndrome. His umbilical artery catheter was removed at 4 days of age. He has been receiving oral diuretic therapy and low flow nasal cannula oxygen. He has not emptied his stomach after his last three feedings, is irritable, and has had several episodes of opisthotonic posturing. His respiratory rate is 90 breaths per minute and his heart rate is 170 beats per minute. Right arm and left leg blood pressures are 115/85 and 120/88 mm Hg, respectively. Systolic blood pressure has been more than 100 mm Hg for the past 24 hours. Extremities are mottled. Brachial and femoral pulses are equal but weak. A gallop rhythm is heard at the apex. His liver edge is palpable 2 cm below the right costal margin. A chest radiograph shows cardiomegaly and increased interstitial markings. Echocardiography reveals left ventricular hypertrophy with poor myocardial contractility.

Of the following, the MOST appropriate immediate response to the hypertension in this neonate is to:

1	administer an intravenous dose of enalaprilate
2	administer an oral dose of captopril
3	administer an oral dose of furosemide
4	begin a continuous infusion of esmolol
5	begin a continuous infusion of nitroprusside

You selected 5, the correct answer is 5.

Hypertension occurs in approximately 2% of preterm and term neonates admitted to neonatal intensive care units. Determination of the true incidence is hampered by inconsistencies in definitions, variations in measurement techniques, and normal changes with gestational age and weight. Infants with blood pressures consistently greater than two standard deviations for age and gender are defined as having significant hypertension. The neonate in this vignette has a systolic blood pressure (115 mm Hg) well above the 95th percentile for age (Figures 1 and 2).

Figure 1: Systolic blood pressure by postmenstrual age (adapted from Zubrow and colleagues [1995])

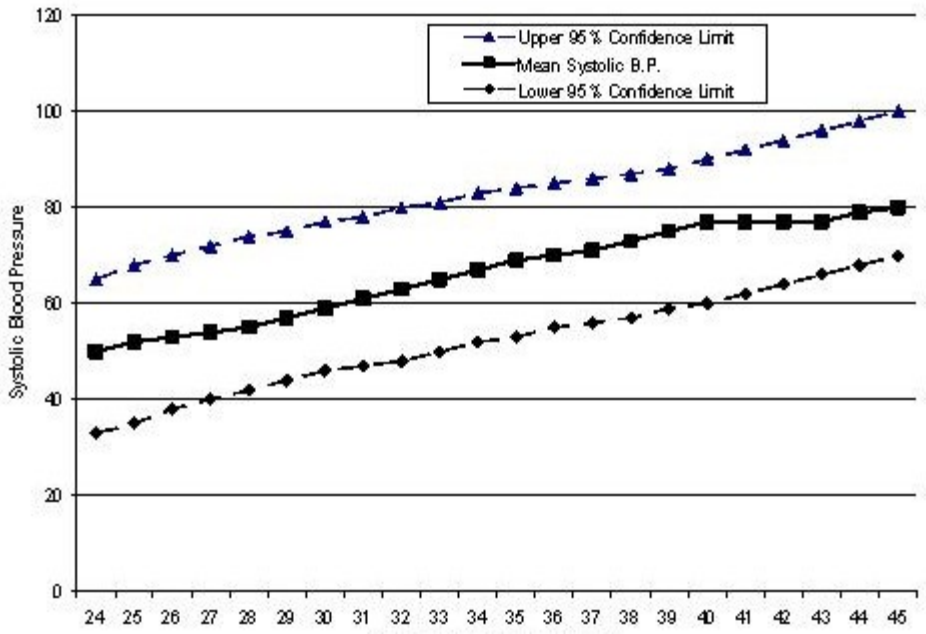
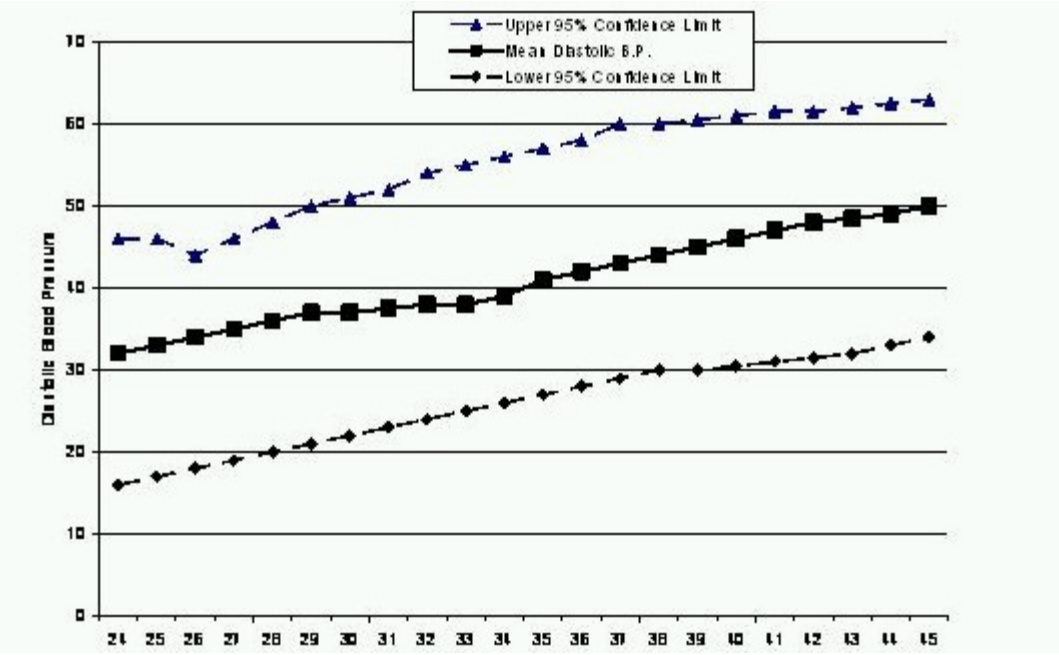


Figure 2: Diastolic blood pressure by postmenstrual age (adapted from Zubrow et al [1995])



Hypertension in the neonate may result from a wide variety of underlying causes (Table 1).

Table 1

Table 1. Common Causes of Hypertension in Neonates*
Causes
Renovascular†
Thromboembolism
Renal artery stenosis
Renal venous thrombosis
Compression of renal artery
Cardiac†
Coarctation of the aorta
Pulmonary†
Bronchopulmonary dysplasia
Renal Disease†
Congenital
Polycystic kidney disease
Multicystic-dysplastic kidney disease
Ureteropelvic junction obstruction
Acquired
Acute tubular necrosis
Hemolytic-uremic syndrome
Obstruction by tumor
Endocrine
Congenital adrenal hyperplasia
Pseudohypoaldosteronism type II
Medications/Intoxications
Maternal
Opioids (cocaine, heroin)
Infant
Dexamethasone
Theophylline
Caffeine
Pancuronium
Phenylephrine
Neoplasms
Wilms tumor
Mesoblastic nephroma
Neuroblastoma
Neurologic
Pain
Intracranial hypertension
Seizures
Miscellaneous
Closure of abdominal wall defect
Adrenal hemorrhage
Hypercalcemia
Extracorporeal membrane oxygenation
Birth asphyxia

* Adapted from Ettinger and Flynn (2002).
† These categories account for most of the cases.

Renovascular hypertension is the most frequent cause of hypertension among premature neonates, accounting for up to 89% of all cases. The most common cause of renovascular hypertension is secondary to umbilical artery catheterization. Hypertension following umbilical catheterization appears with equal frequency among neonates with high or low umbilical catheters. Thrombi have been demonstrated on 25% to 81% of umbilical catheters. An association between the presence of local thrombi and the development of hypertension has been established in at least one trial. Clot fragmentation from thrombi has been documented, suggesting that embolization to the kidneys could cause areas of renal infarction and result in hyperreninemia and hypertension.

The presentation of hypertension in neonates can be quite variable. Nonspecific symptoms

such as poor feeding, irritability, and lethargy are common. In neonates with severe hypertension, significant cardiopulmonary symptoms may develop, including tachypnea, impaired perfusion, congestive heart failure, and hepatosplenomegaly. Hypertensive encephalopathy, presenting with tremors, opisthotonic posturing, hemiparesis, seizures, and coma, may also occur.

A wide variety of oral and intravenous antihypertensive agents may be considered for neonatal hypertension (Table 2).

Table 2

Table 2. Antihypertensive Medications for Neonates*

Drug	Dose	Interval	Action
Intravenous			
Enalaprilate	10-20 µg/kg/dose	Q 8-24 h	Angiotensin-converting enzyme inhibitor
Esmolol	100-300 µg/kg/min	IV infusion	Beta blocker
Hydralazine	0.1-0.4 mg/kg/dose	Q 4-6 h	Vasodilator
Labetalol	0.25-3.0 mg/kg/h	IV infusion	Alpha and beta blockers
Sodium nitroprusside	0.5-8.0 µg/kg/min	IV infusion	Vasodilator
Nicardipine	1-3 mcg/kg/min	IV infusion	Calcium channel blocker
Oral			
Amlodipine	0.1-0.3 mg/kg/dose	Q 12-24 h	Calcium channel blocker
Captopril	0.01-0.5 mg/kg/dose	Q 6-12 h	Angiotensin-converting enzyme inhibitor
Chlorothiazide	5-15 mg/kg/dose	Q 12 h	Distal tubule diuretic
Furosemide	1-6 mg/kg/dose	Q 8-24 h	Loop diuretic
Labetalol	1 mg/kg/dose	Q 8-12	Alpha and beta blockers
Propranolol	0.5-1.0 mg/kg/dose	Q 6-12 h	Beta blocker

* Adapted from: Ettinger and Flynn (2002).

Treatment should be individualized according to the suspected underlying cause and acuteness of the infant's hypertension. As seen in the vignette, infants showing signs and symptoms of cardiopulmonary failure or hypertensive encephalopathy should be given a continuous infusion of an antihypertensive agent such as nitroprusside or nicardipine. These agents have a rapid onset and a very short half-life, allowing titration of the dose for the desired effect. Furthermore, continuously infused antihypertensive agents reduce the wide fluctuations in blood pressure associated with intermittently administered agents. Preterm neonates with immature periventricular circulation are at increased risk for cerebral ischemia and hemorrhage during rapid declines in blood pressure, so slow correction of severe hypertension is optimal. Blood pressure should be lowered by no more than 25% during the first 8 hours of treatment and then maintained at the 95th percentile for 24 to 48 hours.

Sodium nitroprusside, a direct-acting arteriolar and venous vasodilator, effectively lowers blood pressure during a hypertensive crisis in neonates. A rapid onset of action and short half-life (3-4 minutes in adults) allows dose titration of blood pressure within the desired range. Nitroprusside is metabolized to thiocyanate in the liver and kidney, presenting a risk of cyanide toxicity with prolonged treatment (>3 days) and/or high (>3 µg/kg per minute) doses. During treatment, continuous heart rate and intraarterial blood pressure monitoring is recommended. Red blood cell cyanide and serum thiocyanate concentrations also are monitored daily. The infusion is started at 0.25 to 0.5 µg/kg per minute and titrated until the desired response is obtained. The usual maintenance dose is less than 2 µg/kg per minute. Duration of treatment should be as short as possible. Nicardipine has also been reported to be an effective alternative for managing an acute hypertensive crisis in neonates.

Enalaprilate, an intravenous long-acting angiotensin-converting enzyme (ACE) inhibitor, blocks conversion of angiotensin I to the potent vasoconstrictor angiotensin II. It also prevents the breakdown of bradykinin, a potent vasodilator. Vascular resistance is reduced without reflex tachycardia. Enalaprilate can be used in neonates with moderate hypertension, but is generally contraindicated in renal failure because of unpredictable antihypertensive efficacy, prolonged duration of action (8-24 hours), and potential to cause oligouria in neonates with impaired renal function.

Captopril, another ACE inhibitor with a shorter half-life than enalaprilate, is an oral agent used to treat moderate to severe hypertension. Its beneficial effects are attributed to afterload reduction and inhibition of salt and water retention. Loss of renal perfusion and renal failure may occur if it is used in neonates with bilateral renovascular disease or with renal artery stenosis in a solitary kidney. Oral captopril would not be the preferred first-line antihypertensive treatment for the neonate in the vignette who has severe symptomatic hypertension and unknown renal function. In cases of suspected renovascular hypertension, captopril or other ACE inhibitors may be indicated once the acute hypertensive crisis has resolved.

Esmolol is an effective intravenous beta blocker with a rapid onset and short half-life. It has been used in a continuous infusion to treat postoperative hypertension in infants after cardiac surgery. Limited data on the use of this medication in neonates as well as its relative contraindication for use in neonates with chronic lung disease, especially at higher doses, make esmolol a poor candidate for first-line treatment of hypertension in the infant in the vignette.

Furosemide, a loop diuretic, can reduce preload in neonates with congestive heart failure. It is often used in conjunction with other antihypertensive agents to treat hypertension in neonates with congestive heart failure; however, it would not be an effective first-line antihypertensive agent for a neonate with severe hypertension, especially when given orally.

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Wiest DB, Garner SS, Uber WE, et al. Esmolol for the management of pediatric hypertension after cardiac operations. *J Thorac Cardiovasc Surg*. 1998;4:890-897

Zubrow AB, Hulman S, Kushner H, Falkner B. Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicenter study. *J Perinatol.* 1995;15:470-479

American Board of Pediatrics Content Specification(s):

Understand the pathophysiology of an infant with a condition affecting the systemic blood pressure, such as shock and hypertension

Recognize the laboratory and radiographic features of an infant with a condition affecting the systemic blood pressure, such as shock or hypertension

Understand the total management plan and associated potential complications of an infant with a condition affecting the systemic blood pressure, such as shock and hypertension

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March: Question 3

A neonatologist keeps a database of information about admissions to the neonatal intensive care unit. Among the variables recorded is the admission temperature. He is interested in summarizing the data to report to the obstetric staff and the transport team. He has almost 1,000 records, but the following are for the last 12 inborn infants admitted to his unit (for manageable calculation).

Infant	Temp (°C)
1	37.2
2	37.4
3	36.9
4	35.9
5	35.1
6	36.8
7	36.3
8	36.5
9	36.3
10	34.9
11	35.5
12	36.7

For this table, calculate the mean, median, standard deviation (SD), and standard error of the mean (SEM) for these admission temperatures.

Of the following, the SD and SEM calculated for the array of temperatures are closest to:

1	SD = 0.05; SEM = 0.20
2	SD = 0.20; SEM = 0.06
3	SD = 0.40; SEM = 0.12
4	SD = 0.80; SEM = 0.25
5	SD = 1.05; SEM = 0.25

You selected 4, the correct answer is 4.

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Of the statistics requested, the simplest estimate of the central tendency of an array of values is the *median*. To find the median, reorder the list of values with the highest on top, the next highest next, and so forth, down to the lowest. If the list contains an odd number of values, then the number in the middle becomes the value of the median. For an even number of

observations, the average of the two numbers in the middle would be the median. In this case, with 12 numbers, the two middle values are both 36.3°C.

The *mean* (m) is the sum of the numbers in an array divided by the number of values. The formula is: m = ?x / N where ?x represents the sum of all individual values (x) and N is the number of values. The difference between the median of a sample and its mean gives the observer a rough idea of the skewness of the distribution (an asymmetrical bell stretched out on one side or the other). The mean for this array is 36.2°C.

The *variance* (S_2) is a measure of the variation of values found in an array. The formula for variance is:

$$S_2 = \frac{\sum(X - m)^2}{N - 1}$$

In words, the variance is the sum of the squares of the differences between the mean and each value divided by one less than the number of values. For the array given in the vignette, the variance is 0.684. This statistic is used to calculate the standard deviation. The *standard deviation* (SD) is defined as the square root of the variance.

$$SD = \sqrt{\frac{\sum(X - m)^2}{N - 1}}$$

For the array of temperatures in the vignette, the SD is 0.83.

Histograms of many biologic measurements often produce a normal or bell-shaped curve. Values with the highest incidence in the sample or population correspond to the middle of the curve. The mean value is found here. The points at which the shoulders of the bell curve make a transition from convex to concave correspond to 1 SD from the mean. With small samples, the curve is not reliably bell-shaped and the SD is best estimated with a formula. In a normal distribution, 68% of the total population have measurements between -1 SD and +1 SD from the mean. About 95% of the population fit within 2 SDs from the mean.

The *Z score* is the distance in SDs that an individual value is from the mean. This is expressed as:

$$Z = \frac{X - m}{SD}$$

Z gives us an idea about whether an individual fits well within a certain population or has some reason not to. Individuals who fit within 2 SDs of the mean are generally not suspected to be significantly different from the general population. An individual whose measurement falls outside 2 SDs for the population arouses suspicion. That individual's measurement is higher

than the 97.5 percentile or lower than the 2.5 percentile. This suspicion is subjective, however, and based on general experience. It explains why a probability score (P) of less than .05 (5%) is often the criterion for "statistical significance" or launching a diagnostic evaluation. However, in some situations .05 is not used. For example, we define the small-for-gestational age infant as less than the 10th percentile instead of the usual 2.5th percentile because infants with birthweights below the 10th percentile have a sufficiently high incidence of morbidities (eg, hypoglycemia) to make screening this group worth the effort and expense.

The *standard error* is also known as the standard error of the mean (SEM) or the SD of

$$SEM = \frac{SD}{\sqrt{N}}$$

the sample estimate.

It is an estimate of the variability of mean values obtained when several small samples are taken from the same population. It gives us an idea of the range in which the actual population mean might exist. SEM is obtained by dividing the SD by the square root of the sample size. As you can see from the formula, the larger the sample size, the better the estimate of the true mean. For the array of temperatures in the vignette, the SEM is 0.24.

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Standard deviation and variance. HyperStat online Web site. Accessed July 17, 2007, at: http://davidmlane.com/hyperstat/A16252.html

Z-score. Accessed July 17, 2007, at: http://www.ltcconline.net/greenl/Courses/201/probdist/zScore.htm

American Board of Pediatrics Content Specification(s):

Understand the concept of normal distribution and calculate the standard deviation, the standard error of the mean, and the median, and realize the importance of the *P* value

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March: Question 4

A mother was undergoing repeat cesarean section at 38 weeks' gestation under general anesthesia. In the delivery room, the infant needed endotracheal intubation for assisted ventilation. The endotracheal tube was placed successfully with the tip in the suprasternal notch after three initial failed attempts at intubation. In the neonatal intensive care unit, the infant showed sustained spontaneous respirations by 15 minutes after birth, and underwent extubation. The next day, the infant was doing well and started to breastfeed. On auscultation of the chest, however, you noted mild biphasic stridor.

Of the following, the anatomical area of the respiratory tract MOST likely to produce the stridor is:

1	anterior nasal
2	choanal
3	laryngeal
4	subglottic
5	tracheal

You selected 4, the correct answer is 4.

Stridor occurs when a narrowed portion of the airway yields turbulence in the air flow. In general, biphasic stridor results from narrowing in the subglottic region and is usually not accompanied by voice abnormalities. Inspiratory stridor accompanies narrowing at the laryngeal or vocal cord level, whereas expiratory stridor suggests an intrathoracic condition.

Subglottic stenosis is defined as an airway diameter smaller than 4 mm in the term infant and smaller than 3 mm in the preterm infant. Subglottic stenosis may be acute and acquired, as suggested by the infant in this vignette, who underwent multiple attempts at intubation. The airway is surrounded by the cricoid cartilage. The cricoid is the only fixed ring of cartilage, and mucosal edema easily may cause transient obstruction at this level. Subglottic stenosis occurs in about 8% of infants who require prolonged intubation. Factors increasing the risk of subglottic stenosis include duration of intubation, endotracheal tube size and motion, and number of intubations. For severe subglottic stenosis, especially if associated with an inability to extubate, anterior cricoid split or tracheostomy may be required.

Subglottic stenosis may be congenital, caused by either membranous or cartilaginous tissue, resulting in bilateral or circumferential narrowing in the subglottic region. Stridor, present at birth, may worsen with time. Subglottic stenosis also may be the result of subglottic hemangioma, which, along with bilateral vocal cord paralysis, constitutes potentially life-threatening forms of congenital stridor. In such cases, stridor is not noted initially, but becomes evident and progressively increases over a

few months. One half of children with subglottic hemangioma have a raised, erythematous birthmark (cutaneous hemangioma) on the chest. The hemangiomata gradually enlarge through the first year and involute thereafter. Subglottic cysts have been reported after intubation. These cysts have a delayed onset of symptoms (1 to 2 months after extubation) and may cause progressive stridor. Diagnostic techniques for subglottic stenosis include microlaryngoscopy and/or bronchoscopy. Some cases require intervention, including laser excision, steroids, interferon-alpha 2a administration, or cricoid split, or tracheostomy.

Blockage of the airway at the anterior nasal level, which could occur from prolonged irritation of nasal mucosa with subsequent scarring, or at the choanal level, would not be expected to produce stridor. Neonates with nasal obstruction often present with cyanosis when quiet, which is relieved by crying, because infants are often obligate nose-breathers. Congenital nasal obstruction may occur because of nasal pyriform aperture stenosis or deviated septum, or it can be due to gliomas and encephaloceles. Choanal blockage may be relieved by using an oral airway pending anatomic confirmation with computed tomography and definitive treatment by an otolaryngologist

Inspiratory stridor reflects obstruction at the laryngeal level, at or above the level of the vocal cords. Laryngomalacia is the most common form of congenital stridor—representing 70% to 80% of cases. Characterized by an intermittent, whooping-type, late inspiratory stridor with little or no associated distress, laryngomalacia is generally benign and resolves in 90% of patients by 1½ years of age. However, some infants, like those with congenital subglottic stenosis, will become more symptomatic during the first months after birth. A few patients (<5%) require epiglottoplasty or tracheostomy.

Inspiratory stridor also may result from unilateral or bilateral vocal cord paralysis, the second most common cause of stridor. Bilateral vocal cord paralysis may be associated with a weak cry accompanied by retractions and/or cyanosis. The retractions increase with agitation, and feeding difficulty may result in failure to thrive. The condition may be life-threatening. Unilateral vocal cord paralysis usually is not associated with respiratory distress, but may result in hoarseness or a breathy voice in later life. Diagnosis is made by means of flexible upper airway endoscopy. Unilateral vocal cord paralysis seldom requires treatment. Bilateral vocal cord paralysis requires search for associated central nervous system disease. If the Arnold-Chiari anomaly is present, surgical decompression may result in resolution of the cord paralysis. In other cases, tracheostomy followed by vocal cord lateralization may be needed unless the condition resolves spontaneously.

Due to a failure of the posterior larynx and/or cricoid to fuse, laryngeal cleft may have associated stridor depending on the degree of associated subglottic narrowing and/or redundant supraglottic tissue. Recurrent respiratory symptoms or infection associated with aspiration, difficult swallowing, and choking suggest this rare condition. Microlaryngoscopy or bronchoscopy can be used to confirm the diagnosis; aspiration may be found on contrast swallow study. Repair is done surgically.

Expiratory stridor reflects intrathoracic airway turbulence, as would be found with tracheomalacia, its most common cause. Tracheomalacia may be present at birth. Most cases gradually improve and require no intervention, but some cases are associated with various vascular anomalies. Tracheal or bronchial webs may also create expiratory stridor. An aberrant innominate artery may compress the anterior trachea. Double aortic arch or other vascular rings may impinge on the trachea and the esophagus. Unilateral bronchomalacia or impingement on only one bronchus may produce expiratory stridor associated with unilateral air-trapping on chest radiography. The various causes of expiratory stridor can be diagnosed by means of techniques such as chest radiography, bronchoscopy, fluoroscopy, contrast esophography,

magnetic resonance imaging, and computed tomography. Treatment of tracheomalacia includes observation, mucolytics, continuous positive airway pressure, and tracheostomy. Webs and stenoses are ruptured, dilated, or resected. Treatment of impingements depends on the specific condition and its anatomic structure.

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American Board of Pediatrics Content Specification(s):

Know the complications of tracheal intubation, including subglottic stenosis

Know the various causes of stridor in the newborn

Identify the potential complications of airway management in the delivery room and know their management

Understand the factors that affect airway resistance and how resistance changes with various lung disorders

Know the factors that influence upper airway patency

Understand the clinical features of an infant with airway obstruction, such as vascular rings, choanal atresia, and tracheal abnormalities

Plan appropriate management for an infant with airway obstruction, such as vascular rings, choanal atresia, and tracheal abnormalities

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March: Question 5

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A 4,129-g male infant, born at 40 weeks' gestation, presents with a palpable left flank mass 48 hours after birth. Labor was complicated by meconium-stained fluid and fetal distress. Apgar scores were 3 and 7 at 1 and 5 minutes, respectively. Pregnancy was complicated by gestational diabetes. The infant's vital signs include a systolic blood pressure of 104 mm Hg and a diastolic blood pressure of 65 mm Hg. He is oliguric, with macroscopic hematuria. Abdominal ultrasonography demonstrates an enlarged left kidney, with loss of corticomedullary differentiation, and poor visualization of the left main renal vein.

Of the following, the finding MOST associated with this infant's diagnosis is:

1	an enlarged kidney with multiple cysts
2	decreased fractional excretion of sodium
3	increased protein C activity
4	reverse diastolic blood flow in the renal artery
5	thrombocytosis

You selected 4, the correct answer is 4.

The infant in the vignette has clinical and ultrasonographic findings consistent with renal vein thrombosis (RVT). Although rare, with an incidence of 2.4 per 1,000 neonatal intensive care admissions, thromboembolic events (TE) occur more often in neonates than in older children, and more often involve term or late preterm infants. Several factors increase the neonate's susceptibility to thrombosis, including an increased red blood cell mass and viscosity, small vascular caliber, and low levels of proteins that are important in coagulation regulation and fibrinolysis. Venous thrombosis (62% of TE) is more common than arterial thrombosis (34% of TE), and is associated with intravascular catheters in more than 80% of cases. Pathologic states characterized by reduced blood flow, increased blood viscosity, hyperosmolality, or hypercoagulability increase the neonate's risk for thrombosis. Examples include hypoxia, polycythemia, sepsis, shock, dehydration, and maternal type 1 or gestational diabetes.

Renal vein thrombosis is the most common non–catheter-related venous TE in newborns. Over 80% of RVT present in the first month and usually within 48 hours of delivery. Thrombus formation begins with sludging in the small-caliber intrarenal veins, with propagation of the clot to the main renal vein extending into the inferior vena cava (IVC) in approximately 50% of cases. Bilateral disease occurs in fewer than 25% of cases, and unilateral disease involves the left renal vein nearly twice as often as the right. Ipsilateral adrenal hemorrhage occurs in approximately 20% of cases, and more often in the presence of left RVT. Anatomical differences explain this propensity, because the left adrenal vein drains into the left renal vein, and not directly into the IVC, as with the right adrenal vein.

Underlying genetic prothrombotic conditions occur in as many as two-thirds of infants with RVT, and in the presence of acquired risk factors,

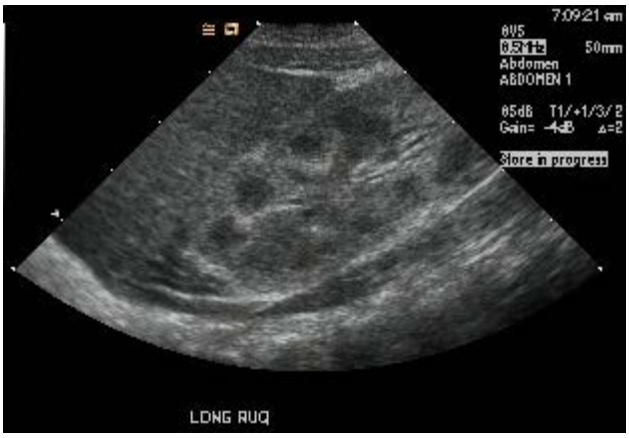
predispose the neonate to thrombosis. Factor V Leiden (1691G?A) mutation is present in nearly 40% of neonates with RVT, and is also an independent risk factor for RVT. Up to 5% of white individuals are heterozygotes for this mutation, increasing their risk of thrombosis five- to sevenfold, while homozygotes have an 80-fold increased risk. Prothrombin gene defects, elevated lipoprotein(a), lupus anticoagulant, anticardiolipin antibodies, and deficient activity of antithrombin III and proteins C and S also confer an increased risk of thrombosis.

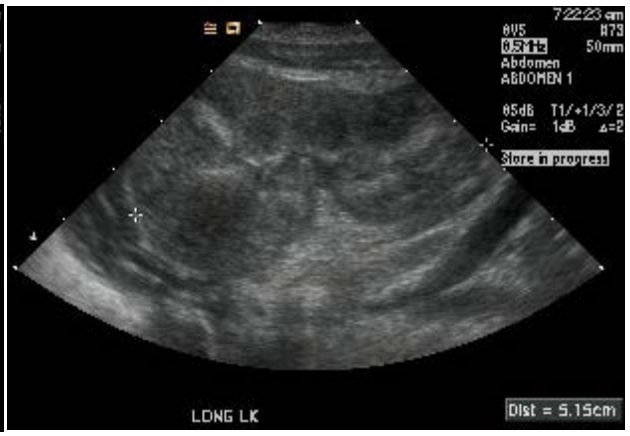
The clinical presentation of neonatal RVT varies, and includes a renal mass, microscopic or macroscopic hematuria, thrombocytopenia, hypertension, oliguria, anuria, proteinuria, and impaired renal function. The "classic triad" of a palpable flank mass, gross hematuria, and thrombocytopenia is present in fewer than 25% of cases. In addition, coagulation times may be prolonged, coagulation factors depleted, and fibrin degradation products increased. Although generally an inflammatory response, severe thrombocytosis increases the risk for thrombosis, but is not commonly associated with neonatal RVT. Thrombosis of the renal vein causes intrinsic renal disease leading to renal insufficiency or acute renal failure (more often with bilateral RVT). Therefore, the anticipated fractional excretion of sodium (FENa) would be elevated (>2.5%) in contrast to states of prerenal failure, in which the FENa is less than 2.5%.

Ultrasonography is the preferred method of study to confirm the diagnosis of RVT. The affected kidney is enlarged and echogenic, with loss of corticomedullary differentiation (Figures 1A and 1B).

Figure 1A: Normal right kidney

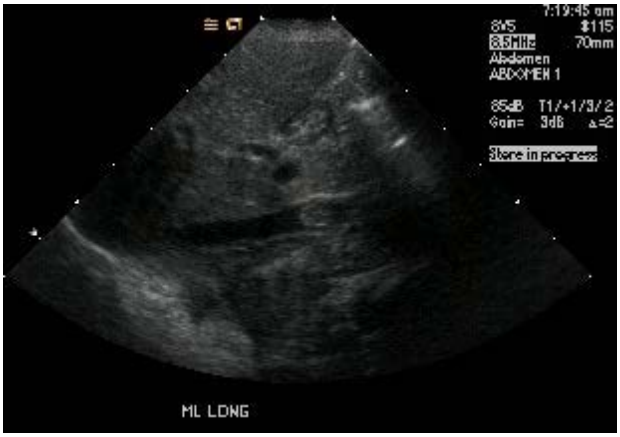
Figure 1B: Enlarged echodense left kidney, with loss of corticomedullary differentiation





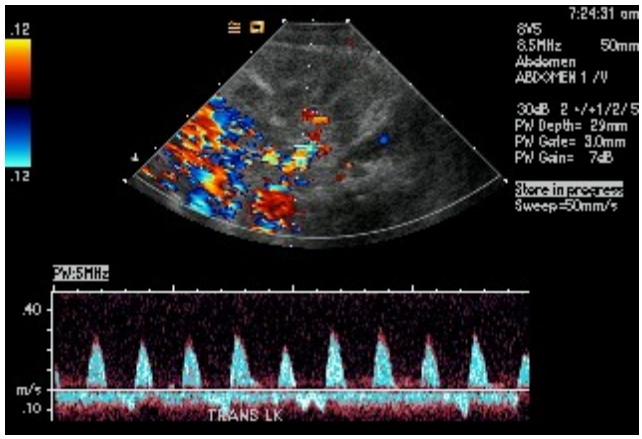
Echolucencies, or cysts, are not characteristic findings. Thrombus may or may not be visualized in the renal vein, but is more easily seen in the IVC (Figure 2).

Figure 2: Focal echogenic nodule in inferior vena cava consistent with thrombus



Color-flow Doppler analysis demonstrates a decrease in the amplitude, or absence of venous signal, abnormal flow patterns in renal venous branches, or evidence of venous collateral development. Reverse diastolic blood flow is seen in the ipsilateral renal artery, owing to the increased vascular engorgement of the affected kidney (Figure 3).

Figure 3: Doppler examination of left renal artery showing reverse diastolic blood flow



Mortality associated with RVT has been documented at 15%, with most deaths resulting from associated disease or renal failure. In the presence of unilateral RVT without uremia or IVC extension, management is supportive, with attention to fluids, electrolytes and underlying illness. The use of anticoagulants and thrombolytic agents is controversial, and carries the risk of bleeding. Heparin therapy should be considered in cases of unilateral RVT with IVC extension. The use of both heparin and thrombolytics may improve outcome in the presence of bilateral disease. Thrombectomy is rarely indicated.

Sequelae of RVT include glomerular disease (3%-100%), tubular dysfunction (9%-47%), renal scarring or atrophy (27%-100%), and hypertension (9%-100%). Bilateral disease carries an increased risk of chronic renal failure, and patients with this condition should receive lifelong renal follow-up.

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Schmidt B, Andrew M. Neonatal thrombosis: report of a prospective canadian and international registry. *Pediatrics.* 1995;96:939-943

American Board of Pediatrics Content Specification(s):

Know the etiology, clinical manifestations, laboratory features, and management of renal vein thrombosis

Understand the effects of various illness on renal function

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March: Question 6

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11 November 08

12 December 08

A 35-week-gestation female infant with symmetrical growth restriction is born via vaginal delivery to a 21-year-old woman with polyhydramnios. The infant has large bullous lesions over her hands, feet, and knees. Her nails are normal. She has areas of denuded skin on the abdominal and chest walls, several of which have atrophic bases with increased vascularity (Figure 1 and Figure 2).

Figure 1

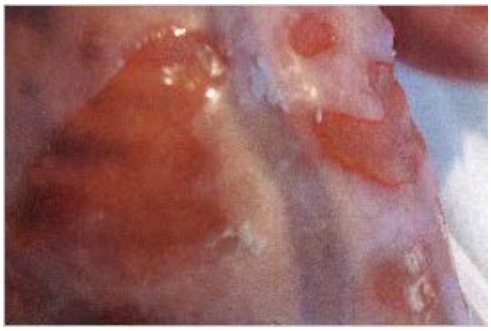
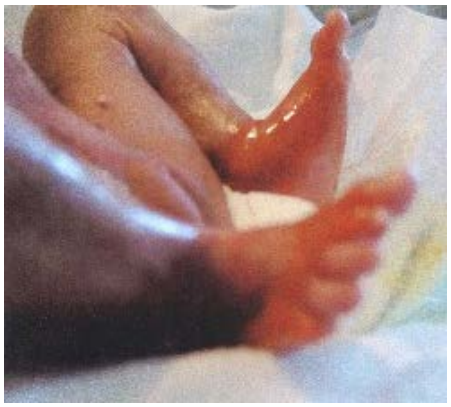


Figure 2



The mother denies skin rashes or infections during her pregnancy, and no one in the family has a history of skin disorders. Vital signs are normal. A complete blood count is normal.

Of the following, the statement that MOST accurately relates to the family of skin disorders affecting this neonate is that:

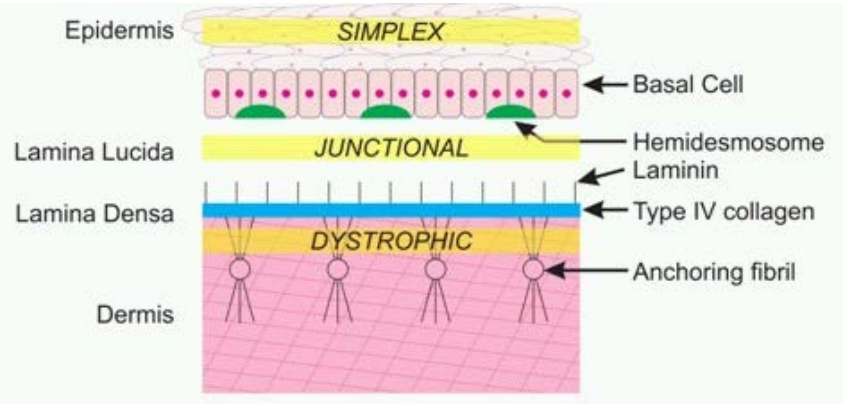
1	Clinical features will establish the subtype and prognosis
2	Growth restriction is common among neonates with the dominant subtype
3	Mortality is more common among dominant subtypes
4	Oral mucosal involvement is an ominous prognostic sign
5	Pyloric atresia may occur in the recessive subtype of this disorder

You selected 5, the correct answer is 5.

Epidermolysis bullosa (EB) encompasses a heterogeneous group of dermatoses characterized by blistering of the skin and often, extracutaneous manifestations. EB is classified into three general categories: intraepidermal or simplex subtypes comprising 92% of cases, junctional subtypes comprising 1% of cases, and subepidermal or dystrophic subtypes comprising 5% of cases. About 2% of cases remain unclassified. All forms present with blisters after minor trauma and heat. Because the milder simplex type often goes unreported and is the most common form of EB, the exact incidence is unknown. The occurrence estimate from the National Epidermolysis Bullosa Registry is around 50 cases per 1 million births.

Subtypes of EB result from various inherited defects of the proteins that maintain skin integrity. Molecular genetic studies among EB variants have demonstrated mutations in at least 10 distinct genes that encode for eight structural proteins of the cutaneous basement membrane. These structural proteins form a link from the basal epithelial cells across the basement membrane to the underlying dermis. When one of these proteins is altered by a mutation, as in EB, weakness in the structural chain will lead to mechanical fragility. Clinical phenotypes vary according to the region within the skin where the defective protein is expressed and at the depth at which blistering occurs (Figure 3).

Figure 3



Recently a revised classification system for inherited EB was developed which reflects the molecular basis of EB as well as clinical, epidemiologic, and laboratory data (Table 1).

Table 1

Table 1. Presentation and Diagnoses of Epidermolysis Bullosa (EB) Subtypes in the Neonatal Period*

Major EB Subtype/OMIM No.	Protein System Involved	Inheritance	Onset	Skin Findings	Other Complications	Prognosis
EBS/Weber-Cockayne 131800	Keratin 5 or 14	AD	Infancy or early childhood	Localized blisters on palms and soles	Blisters of oral cavity	Good
Köbner 131900	Keratin 5 or 14	AD	Birth	Generalized blisters with predilection of palms and soles, focal callosities of palms and soles	Blisters of oral cavity, superinfections	Good, some patients improve after puberty
Dowling-Meara 131760	Keratin 5 or 14	AD	Birth	Generalized herpetiform-grouped blisters, often confluent callosities of palms and soles	Blisters of oral cavity	Good, improvement with age
JEB/Herlitz 226700	Laminin 5 (α3/β3/γ2 chain)	AR	Birth	Generalized blisters, atrophic scarring, dystrophic or absent nails, exuberant granulation tissue	Growth retardation, overwhelming infections, massive blistering of oral cavity and other mucous membrane involvement	Death, mostly within first 2 years of life
Non-Herlitz 226650	Laminin 5 or type XVII collagen	AR	Birth	Generalized (some patients localized) blisters, alopecia, dystrophic or absent nails, granulation tissue	Growth retardation, caries, blistering of oral cavity and other mucous membrane involvement, less severe than Herlitz form	Good
JEB with pyloric atresia 226730	α6β4 Integrin	AR	Birth	Generalized blisters, dystrophic or absent nails, atrophic scarring	Polyhydramnios, congenital pyloric atresia, growth retardation, blistering of oral cavity and other mucous membranes	Often early death, some patients good prognosis
DEB/Dominant DEB 131750	Type VII collagen	AD	Birth	Blisters with predilection of acral sites, atrophic scarring, milia, dystrophic or absent nails	Rarely blisters of oral cavity	Good, improvement with age
Hallopeau-Siemens recessive DEB 226600	Type VII collagen	AR	Birth	Generalized blisters, atrophic scarring, milia, dystrophic or absent nails, alopecia	Growth retardation, gastrointestinal and ocular involvement, squamous cell carcinomas	Disability, reduced life expectancy

AD = autosomal dominant; AR = autosomal recessive; DEB = dystrophic epidermolysis bullosa; JEB = junctional epidermolysis bullosa; OMIM = Online Mendelian Inheritance in Man database.

*** Adapted from Bauer and colleagues (2002).**

Clinical features of EB may be quite variable in newborns. Extracutaneous involvement, due to the presence of structurally defective proteins in tissues other than the skin, occurs especially in patients with recessive forms of EB and adds to the variability in clinical expression. Special attention should be paid to determine if other organ systems are involved to establish the correct clinical diagnosis as well as to prevent potential complications. Sites of extracutaneous involvement most commonly seen in EB are the teeth, gastrointestinal tract, upper respiratory tract, genitourinary tract, eyes, and cardiovascular system (Table 1). Common gastrointestinal manifestations include dysphagia, esophageal stricture or stenosis, pyloric stenosis, and anal stricture. Neonates with a recessive subtype of junctional EB may present with polyhydramnios secondary to pyloric atresia.

Evaluation of a patient with suspected EB should include a mapping of the family pedigree and a skin biopsy. Light microscopy can help determine the level of the cleavage, but the results are often difficult to interpret. Electron microscopy, the gold standard for diagnosis, not only identifies the level of the skin cleavage, but also

the appearance of specific structures that form transmembrane attachment complexes. Immunofluorescent antigen mapping of three known basement membrane antigens may reveal type-specific patterns of binding in the microscopic clefts in EB skin. DNA mutation analysis helps to confirm the clinical and microscopically suspected diagnosis and is the basis for genetic counseling and first-trimester prenatal diagnosis.

Some subtypes of EB are severe and present with life-threatening diseases during the neonatal period. Others are mild and do not manifest symptoms until adolescence. Generally, recessive forms are more severe and at least one recessive subtype of dystrophic EB is associated with low birthweight. Growth restriction has not been reported in the dominant subtypes of the disorder.

Oral mucosal involvement is common among neonates with EB. Oral blistering occurs not only in severe forms of EB such as the recessive pyloric atresia-junctional EB that can be fatal in early infancy, but also in EB simplex, an autosomal dominant relatively mild form of EB. Although oral mucosal involvement does not infer a poor prognosis, it can present care management challenges; oral ulcers may render feeding painful and laborious.

There is no specific cure available for EB (Table 2).

Table 2

Table 2. Management of Epidermolysis Bullosa in the Neonatal Period*

Management Strategies
Minimize trauma to skin Handle gently When applying instruments or monitors, use wrapping or suturing instead of taping if possible.
Provide ideal (moist)wound-healing environment Open and drain tense vesicles larger than a dime with sterile needle or blade, leave roof intact. Perform gentle daily débridement of crust. Apply emollients *and* nonstick primary dressing. Protect wound and secure primary dressing with secondary dressing such as gauze wrap. Tape dressing to itself.
Prevent sepsis and bacterial superinfection of wounds Observe wounds for purulence. Monitor colonization with weekly surveillance cultures. Apply topical antibiotics combined with emollient on open erosions to control colonization. Cover gram-positive organisms with intravenous antibiotics if signs or symptoms of sepsis are present.
Maximize nutrition with minimal trauma Recommend breastfeeding if there is mild oral involvement and the infant can feed through pain. If not, have mother pump breast milk, and bottle feed with high flow nipple or drip feeds. Maximize calories.
Monitor for extracutaneous complications Eye: Request ophthalmology consultation for redness or photophobia. Gastrointestinal: If oral cavity is involved, watch for feeding intolerance. Genitourinary: Look for gross hematuria, meatal narrowing in boys. Polyhydramnios: Look for pyloric atresia. Respiratory: Monitor airway for hoarse cry or stridor as a sign of laryngeal involvement.
Provide psychosocial support Emphasize unpredictability of course even when subtype is known. Discuss usual short-term complications in general terms. Provide access to peer counseling through Internet sites and local chapters of national patient advocacy groups.

* Adapted from Frieden and Howard (2001).

Treatment is directed at preventing skin trauma to avoid formation of new blisters, early management of secondary bacterial infections, support of wound healing, and maintenance of good nutrition. The primary preventive measure in caring for neonates with EB is avoidance of blister formation. Even minimal friction can produce blisters. After blisters have formed, the goal is to promote wound healing by protecting involved skin with nonadherent or petrolatum-impregnated dressings. It is often recommended to drain blisters that are larger than the size of a dime to prevent them from expanding. The blister roof should be left intact. Oozing or bleeding areas should be patted and never rubbed. Artificial skin substitutes can be helpful when applied to areas of skin that will not heal. Analgesia is often needed during dressing changes. Prevention of secondary bacterial infections is vital because sepsis is a leading cause of death in neonates with EB. Topical antibiotics should be applied to open skin surfaces and varied every few months to avoid development of resistance. Prophylactic oral antibiotics are not recommended.

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American Board of Pediatrics Content Specification(s):

Recognize the cutaneous and laboratory manifestations of epidermolysis bullosa

Understand the inheritance patterns of epidermolysis bullosa

Know the treatment of epidermolysis bullosa

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11 November 08

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March: Question 7

You are called to the emergency room for a primagravida mother delivering precipitously at 30 weeks' gestation. You arrive before the obstetrician. The soon-to-be father tells you that the mother takes a medicine for some sort of a thyroid problem. As you prepare for the birth of the infant, you consider the potential fetal and neonatal complications that may accompany maternal thyroid disorders and treatments.

Of the following, the substance that BEST crosses the placenta is:

1	iodide ion
2	thyroid-stimulating hormone
3	thyrotropin-releasing hormone
4	thyroxine
5	triiodothyronine

You selected 1, the correct answer is 1.

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The thyroid hormones contribute relatively little to growth of the fetus compared with that of the child. Fetal growth is most dependent on insulin and insulinlike growth factors, while childhood growth is dependent on both thyroid and growth hormones. In general, the maternal and the fetal thyroid systems remain separate and largely independent. However, there is some interaction between maternal and fetal thyroid physiologic processes, with the fetus needing either a normal endogenous thyroid system, or a mother with a normal thyroid system for growth and development. If both maternal and fetal systems are deficient, as with an athyrotic infant born to an untreated hypothyroid mother, the child is at risk for developmental delays.

During fetal life, some substances involved in the normal thyroid system can cross the placenta. The mother is the sole source of fetal iodide ion, which passes freely across the placenta to the fetus. Thyrotropin-releasing hormone (TRH), made by the fetus or the mother, can cross the placenta to some degree. Thyroxine (T_4) and triiodothyronine (T_3) can cross the placenta in small amounts only. Thyroid-stimulating hormone (TSH) does not cross the placenta.

Iodide ion crosses the placenta with the aid of several membrane transport proteins, including pendrin, a protein also found in the thyroid gland. Iodide is essential for the production of T_3 and T_4. Although T_3 and T_4 concentrations in the first trimester fetus are almost undetectable, the absence of iodide ion at this time is associated with developmental deficiencies. The World Health Organization has stated that dietary iodine deficiency is the world's leading cause of preventable mental retardation. Iodine deficiency can sometimes manifest as fetal goiter, because of the overabundance of fetal TSH made in response to the abnormally low T_3 and T_4 concentrations. Interestingly, too much iodide ion can also cause fetal goiter, by inhibiting release of T_4 and T_3 from the thyroid gland, again causing an overabundance of TSH.

Thyroid-stimulating hormone also known as thyrotropin, is a 16-kD glycoprotein similar in structure to human chorionic gonadotropin. It is made in the anterior hypophysis in response to TRH or in response to low T_3 and T_4 concentrations. It does not cross the placenta. The concentration of TSH in the fetus may be as much as twofold higher than that in the mother.

Thyrotropin-releasing hormone is a tripeptide made in the hypothalamus and transported to the anterior pituitary via the hypophyseal portal venous system. Fetal TRH is made in the pancreas and in the placenta, as well as in the hypothalamus. A TRH-degrading enzyme in the maternal blood limits maternal serum TRH to nearly immeasurable concentrations, so very little ever reaches the placenta. Exogenously administered TRH can cross the placenta to some degree, and has been studied as an agent to enhance fetal lung maturation, with inconsistent results.

Thyroxine, also known as tetraiodothyronine, is found in species ranging from tunicates to frogs, where it is involved in the metamorphosis from tadpole to adult. In humans, T_4 elevates cellular metabolism by binding to proteins in the nuclei of certain cells to modulate transcription of certain genes. Its synthesis is based on two tyrosine residues, each with two iodine molecules. Only small amounts of T_4 are made in the fetus, and even smaller amounts are transmitted from the mother to the fetus. The fetal serum concentration of T_4 in midgestation is around 1% of the maternal serum concentration. These small amounts may have some significance for the fetus. Because of a relatively low concentration of thyroid-binding globulin in the fetus, more of the fetal T_4 is in the active free-T_4 state rather than the inactive, bound state.

Triiodothyronine is structurally similar to T_4, but missing an iodine in the outer ring. It is 6 to 10 times more potent than T_4, but is made by the thyroid gland at half the rate of T_4. Peripheral conversion in certain tissues of T_4 to T_3 is the largest source of T_3. The T_4-to-T_3 converting enzyme is present earliest and in highest concentration in the fetal brain, suggesting the importance of the thyroid system to fetal brain development. Only a small amount of maternal T_3 crosses the placenta.

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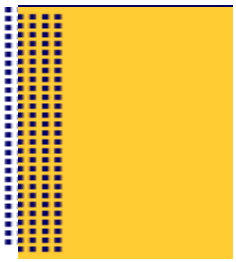
American Board of Pediatrics Content Specification(s):

Understand the relationship between fetal and maternal thyroid physiology

Know the physiological roles of the hormones and other proteins involved in the regulation of thyroid function



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March: Question 8

A 3-month-old female infant, postmenstrual age 38 weeks, has bronchopulmonary dysplasia. You are discussing handwashing, avoidance of crowds, and administration of palivizumab during the winter months with the parents and nurse practitioners. The infant's mother, a microbiologist, asks for details about the action of palivizumab.

Of the following, the component of the respiratory syncytial virus that is TARGETED by palivizumab is:

1	F protein
2	G protein
3	interferon
4	nonstructural protein 1
5	RANTES

You selected 1, the correct answer is 1.

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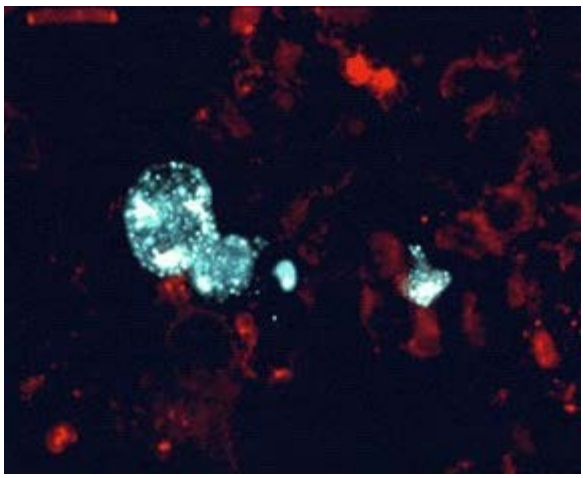
Respiratory syncytial virus (RSV) is a highly infectious paramyxovirus, closely related to parainfluenza, measles, and mumps viruses (Figure 1).

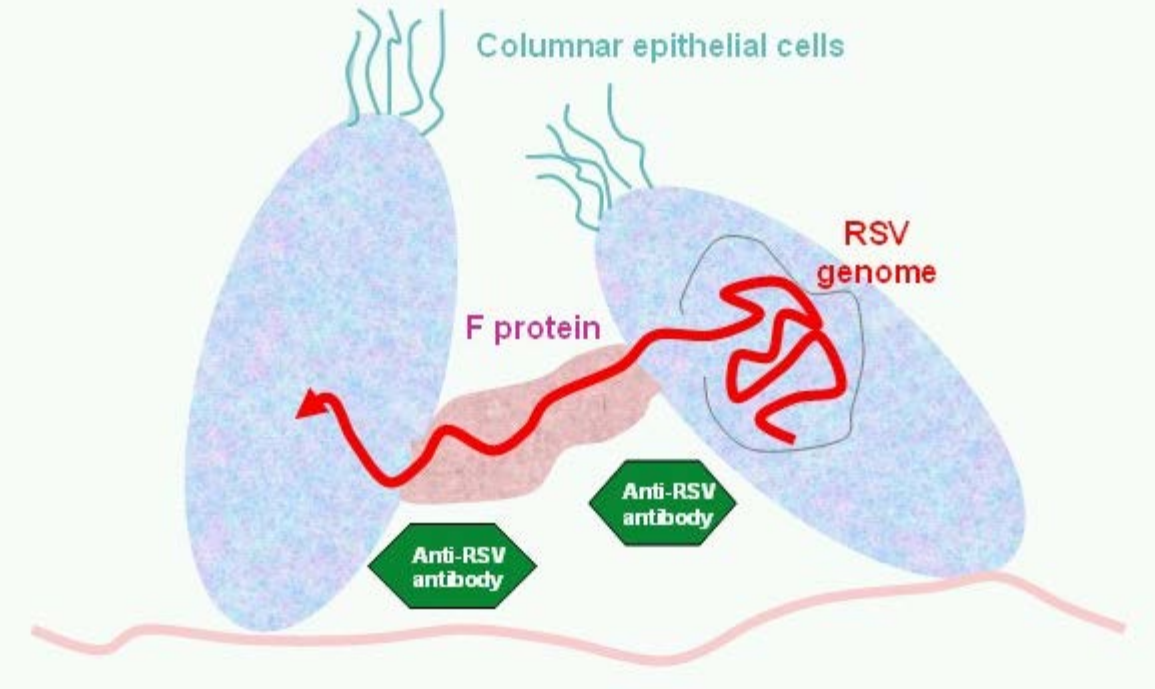
Figure 1: Respiratory syncytial virus on electron micrograph-variable shape and size (120-300 nm)



A single strand of RNA containing 10 genes comprises the genome. Two proteins, protein F and G, are found on the surface of the virus and are important for cell-cell transmission of virus and variability of viral strains, respectively.

The F protein on the surface of the virus is responsible for syncytia formation. The F protein causes fusion of infected nasal mucosal cells with uninfected cells, merging of the membranes of infected cells, and the characteristic appearance of large, multinucleate cells (Figure 2).

Figure 2: Protection by F protein of respiratory syncytial virus (RSV) genome passing between epithelial cells



The F protein provides a portal for movement of the viral genome into uninfected cells that protects the genome from contact with antibodies within mucosal secretions; this mechanism of immune protection is unique to RSV because most other viruses move from the nasopharynx into the bloodstream before causing disease. The F protein is highly conserved among RSV strains, and is the target of the humanized mouse monoclonal antibody palivizumab.

Two predominant strains of RSV are responsible for infections. Strain A is more virulent than strain B and tends to be more prevalent in the United States. Several serotypes of each strain have also been identified, mostly associated with variability of the G protein, a glycoprotein on the surface of the virus responsible for attachment to the host cell. Variability of the G protein accounts for a limited immune response, frequent reinfections, and difficulty in vaccine development.

The immune response to an RSV infection results in production of RSV-specific IgM, IgG, and IgA antibodies. Anti-RSV antibodies are important because the severity and frequency of reinfections decrease with subsequent infections, maternal antibodies are protective during the first 1 to 2 months after birth, and monoclonal antibody administration reduces the incidence of hospitalization for RSV disease. Anti-RSV antibodies, however, are insufficient protection against RSV because of antigenic variation in type A and type B RSV strains. Cell-mediated immunity, principally the release of antiviral proteins such as interferon-gamma and interleukin 4 and 5 by T-lymphocytes, is also important to defend against RSV disease. Infants younger than 6 months or who have deficient T-lymphocyte function are prone to have more severe morbidity with RSV and shed the virus longer than other patients.

The RSV attaches to ciliated epithelial cells that line the airways. The location of these ciliated cells in the airways explains the propensity for bronchiolar infection rather than within alveoli and alveolar saccules. Although most viruses induce a T-helper-1 response with production of high concentrations of the antiviral interferon-gamma, models of RSV infections in young

animals produce a T-helper-2 response. This is characterized by production of interleukin 4 and 5, not interferon, and is an immunologic response similar to asthma and atopy in older patients. RSV also upregulates Toll-like receptor 4 (TLR4) expression on bronchial epithelial cells; TLR4 receptor activation increases airway sensitivity to the inflammatory effects of bacterial endotoxins. Elevation of interleukin 8 and 10 concentrations during RSV infections is responsible for attracting polymorphonuclear leukocytes into the airways.

A chemokine called RANTES (*r*egulated on *a*ctivation, *n*ormal *T*-cell *e*xpressed and *s*ecreted) is produced by epithelial cells, fibroblasts, smooth muscle cells, and inflammatory cells that infiltrate the peribronchial tissues when RSV infects the lung. RANTES recruits monocytes, memory T cells, and eosinophils, and activates T cells that suppress RSV proliferation. Although beneficial in suppressing RSV infection, RANTES causes bronchoconstriction and wheezing. Specific genetic polymorphisms of RANTES may affect disease severity and propensity for wheezing during childhood. An additional response to RSV by infected cells is the synthesis of nonstructural proteins (NS1 and NS2) that confer resistance to the antiviral action of interferon. Vaccines targeting these nonstructural proteins are being investigated to augment RSV destruction by interferon.

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Carroll KN, Gebretsadik T, Griffin MR, et al. Maternal asthma and maternal smoking are associated with increased risk of bronchiolitis during infancy. *Pediatrics.* 2007;119(6):1104-1112

Holman RC, Shay DK, Curns AT, Lingappa JR, Anderson LF. Risk factors for bronchiolitis-associated deaths among infants in the United States. *Pediatr Infect Dis J.* 2003;22(6):483-489

Simoes EA. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. *J Pediatr.* 2003:143:S118-S126

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The Impact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics.* 1998;102:531-537

Welliver RC. Review of epidemiology and clinical risk factors for severe respiratory syncytial virus (RSV) infection. *J Pediatr.* 2003;143:S112-S117

American Board of Pediatrics Content Specification(s):

Know the role of immunoglobulin supplementation

Know the function of T lymphocytes

Know the changes in cytokines that occur with infection

Understand the epidemiology, pathogenesis, and prevention of neonatal infections with respiratory syncytial virus

Understand the clinical manifestations and diagnostic criteria of neonatal infections with respiratory syncytial virus

Understand the treatment of neonatal infections with respiratory syncytial virus

Understand the complications of neonatal infections with respiratory syncytial virus

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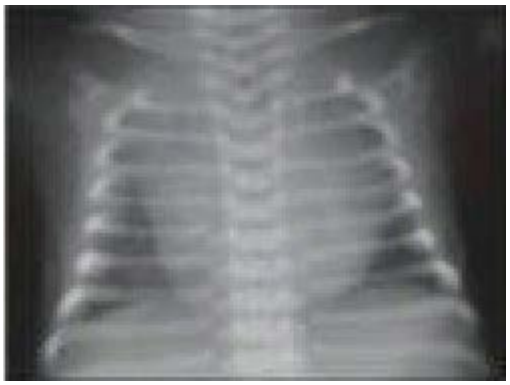
March: Question 9

You are asked to review a chest radiograph of an infant being seen by his pediatrician. The 4,193-g boy was delivered last evening by scheduled, repeat cesarean section at 39 weeks' gestation to a 29-year-old mother. He had received oxygen overnight, but now is in room air with a respiratory rate of 70 breaths per minute. The chest radiograph was just taken (Figure).

Figure



Of the following, the cardiac finding on the chest radiograph is MOST likely the result of:

1	alpha-iduronidase deficiency
2	carnitine deficiency
3	hyperinsulinism
4	lysosomal alpha-1,4-glucosidase deficiency
5	viral cardiomyopathy

You selected 3, the correct answer is 3.

Hyperinsulinism resulting from maternal hyperglycemia is the most likely underlying cause for this infant's pronounced cardiomegaly. Often mothers with gestational diabetes go undetected in spite of their insulin intolerance and hyperglycemia during pregnancy. Fetal insulin concentrations increase in response to the glucose transferred across the placenta, resulting in fetal macrosomia, hypertrophic cardiomyopathy, and organomegaly involving the liver and muscles.

Despite improving respiratory status, which was likely a result of delayed fluid mobilization from the lung secondary to cesarean delivery without preceding labor, and no apparent signs of deterioration, the infant should be carefully observed. Many of these infants will have a systolic outflow murmur associated with septal hypertrophy, and some will have significant cardiac

obstruction. An echocardiogram may be helpful.

L-Carnitine (ß-hydroxy-?-trimethylaminobutyric acid) is an essential component in the transport of long chain fatty acids into mitochondria, where they undergo ß-oxidation. Low concentrations of carnitine are common in premature infants receiving total parenteral nutrition without adequate carnitine supplementation. Because the normal heart receives approximately 60% of its total energy supply from fatty acid oxidation, this function of carnitine is thought to be of major importance. A number of case reports have shown that some patients with carnitine deficiency will exhibit cardiomyopathy. Adequate concentrations of carnitine are required for normal energy metabolism and contractile function of the heart. Although short-term moderate secondary carnitine deficiency, in and of itself, does not have a major effect on the cardiac contractile function, substrate oxidation may be altered. With longer durations of carnitine deficiency, alterations occur within the heart that may result in impaired contractile performance. These patients generally present with additional metabolic derangements including profound hypoglycemia. In this vignette, carnitine deficiency is unlikely to be the cause of cardiomegaly.

Some viruses including the coxsackie B virus may cause severe and often fatal infections in newborn infants. Infection may be transmitted transplacentally in late pregnancy, with the infant developing heart failure after delivery, because of severe myocarditis. More frequently, infection is transmitted during the birth process or postnatally via the mother or other virus-infected infants in the hospital. Some infected neonates may be asymptomatic, but others may develop illness at 3 to 7 days after exposure ranging from a mild febrile illness to a severe fulminant multisystem disease and death. Myocarditis, pneumonia, and meningoencephalitis may occur in addition to severe hepatitis that may be accompanied by profuse hemorrhage. Coxsackie B virus can be recovered from the myocardium, brain, spinal cord, and feces. In this vignette, the infant is well appearing without systemic illness; thus, the cardiomegaly is unlikely to be secondary to a viral infection.

Hurler disease is a mucopolysaccharidosis caused by a defect in alpha-iduronidase. Infants with this disease present later than seen in this vignette. Affected patients usually present closer to 1 year of age with cloudy corneas, hepatosplenomegaly, coarse facial features, hirsutism, stiff joints, kyphosis, and poor central nervous system function.

Pompe disease is an autosomal recessive disorder caused by mutations in the gene encoding lysosomal alpha-1,4-glucosidase. The classic infantile form of this disorder is characterized by cardiomyopathy and severe generalized muscular hypotonia. The median age at symptom onset is reported to be 2 months and at diagnosis 5 months. Presenting findings include cardiomegaly (92% of infants), respiratory distress (78%), muscle weakness (63%), feeding difficulties (57%), and failure to thrive (53%). Pompe disease would be unlikely to produce pronounced cardiomegaly within 5 days of birth.

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van den, Hout HM, Hop W, van Diggelen OP, et al. The natural course of infantile Pompe's

disease: 20 original cases compared with 133 cases from the literature. *Pediatrics.* 2003;112:332

Wappner RS, Hainline BE. Introduction to inborn errors of metabolism. In: McMillan JA, Feigin RD, DeAngelis C, Jones MD, eds. *Oski's Pediatrics: Principles and Practice.* 4th ed. Philadelphia, Pa: Lippincott, Williams & Wilkins; 2006:2145

Way GL, Wolfe RR, Eshaghpour E, et al. The natural history of hypertrophic cardiomyopathy in infants of diabetic mothers. *J Pediatr*. 1979;95:1020

American Board of Pediatrics Content Specification(s):

Understand the pathophysiology, including genetics, of an infant with a condition affecting myocardial performance, such as cardiomyopathy, myocarditis, tumor, and electrolyte imbalances

Recognize the clinical features in an infant with a condition affecting myocardial performance, such as cardiomyopathy, myocarditis, tumor, and electrolyte imbalances

Recognize the laboratory and radiographic features of an infant with a condition affecting myocardial performance, such as cardiomyopathy, myocarditis, tumor, and electrolyte imbalances

Formulate a differential diagnosis of an infant with a condition affecting myocardial performance, such as cardiomyopathy, myocarditis, tumor, and electrolyte imbalances

Know the normal range of endogenous glucose production in term and preterm infants

Understand the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of fatty acids

Understand the clinical manifestations, diagnostic criteria, and treatment of perinatal infections with coxsackievirus, echovirus, enterovirus, and poliovirus

Understand the etiology, clinical manifestations, laboratory features, treatment, and management of infants with lysosomal and peroxisomal, and mitochondrial disorders

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March: Question 10

A full-term male infant is born to a mother with chorioamnionitis. Because of severe respiratory distress and persistent cyanosis, the infant is intubated and placed on high ventilatory support. He appears mottled and is hypotensive. His blood pressure improves after he receives two normal saline boluses and a dopamine drip at a rate of 20 µg/kg per minute. A few hours later, he again becomes hypotensive and echocardiography is performed. The study reveals a structurally normal heart, normal right ventricular function, hyperdynamic left ventricular function, and a high cardiac index.

Of the following, the MOST effective medication to treat this infant's hypotension is:

1	digitalis
2	dobutamine
3	epinephrine
4	isoproterenol
5	milrinone

You selected 3, the correct answer is 3.

Infants with symptomatic hypotension may have cardiogenic, hypovolemic, or distributive shock. *Cardiogenic* shock occurs when inadequate tissue perfusion is attributable to cardiac dysfunction manifested by impaired contractility, ventricular emptying, and cardiac filling. *Hypovolemic* shock is a common type of shock in the neonate and occurs when an infant's blood volume is below a critical threshold; this leads to decreased ventricular filling and reduced stroke volume. Cardiac output will wane unless the heart rate and/or stroke volume increase. *Distributive* shock is the result of an inadequate relative intravascular volume because of severe vasodilation.

In this vignette, the infant's hypotension is most likely because of either hypovolemic shock with sepsis-induced capillary leakage and third spacing or distributive shock with sepsis-induced vasodilation. This infant's blood pressure would most likely improve with volume resuscitation and/or another vasoconstrictor, such as epinephrine. Increasing the infant's inotropic ability would have little additional benefit, because the infant's echocardiogram showed appropriate cardiac function. Medications that lower systemic vascular resistance might further exacerbate the infant's hypotension.

Cardiac pharmacologic agents are classified by their sympathetic receptor activity (Table).

Table

Table. Adrenergic Receptors*		
Receptor	**Action Site**	**Major Cardiac Effect**
Alpha-1	Arterial and venous smooth muscle Cardiac myocytes	Vascular smooth muscle contraction Positive inotropy
Alpha-2	Sympathetic nerves (pre- and postsynaptic) Central nervous system	Vascular smooth muscle relaxation
Beta-1	Cardiac myocytes Conduction cells (e.g., Purkinje fibers, sinoatrial and AV nodes)	Positive inotropy Positive chronotropy Conduction velocity induction
Beta-2	Peripheral vascular smooth muscle (both arterial and venous) Bronchial smooth muscle cells	Vascular smooth muscle relaxation

* Adapted from Brodsky and Martin (2003).

Epinephrine has a dose-dependent effect on both beta- and alpha-adrenergic receptors. Lower doses of epinephrine induce beta-receptor activity and lead to increased inotropic and chronotropic effects, which result in increased cardiac output with decreased systemic vascular resistance and variable effects on the mean arterial blood pressure. Higher doses bind alpha-adrenergic receptors, inducing vasoconstriction in addition to increasing cardiac output. The increased afterload is associated with enhanced diastolic pressure, creating an additional benefit of improving coronary artery perfusion.

Digitalis, an extract of the foxglove plant, generates a positive inotropic effect by inhibiting the Na+/K+ ATPase pump in cardiac myocytes, indirectly increasing the intracellular calcium concentration. Digitalis has a negative chronotropic effect because it decreases atrioventricular nodal conduction velocity and enhances the refractory period, reducing the transmission of atrial impulses to the ventricles. Additional chronotropic suppression occurs because digitalis increases vagal tone.

Dobutamine is a synthetic catecholamine with potent direct beta-1 and some beta-2 adrenergic action. These adrenergic effects lead to a mild increase in chronotropism, enhanced inotropism with an increase in stroke volume, and peripheral vasodilation. This latter effect is probably secondary to production of the metabolite 3-*O*-methyldobutamine, which is a potent inhibitor of alpha-adrenoreceptors. Dobutamine is an effective medication for cardiogenic shock or myocardial dysfunction because it does not increase afterload. However, it may decrease coronary perfusion because of this decrease in systemic vascular resistance.

Despite having a similar name to dobutamine, the endogenous catecholamine dopamine acts differently than dobutamine. Dopamine has a dose-dependent action, leading to renal vasodilation by dopaminergic receptor activation; enhanced inotropy and chronotropy by stimulating beta-1 adrenergic receptors; and increased systemic vascular resistance by alpha-1 action at low, medium, and high doses, respectively. As a precursor of norepinephrine, dopamine leads to increased release of endogenous norepinephrine and thus, with prolonged use, it is less effective, correlating with lower norepinephrine stores.

Isoproterenol is a synthetic catecholamine with nonspecific beta-agonist activity and minimal alpha-adrenergic effects. It has a positive inotropic effect, leads to significant chronotropic action, and decreases systemic vascular resistance. Isoproterenol use is limited by its potent increase in heart rate, which precedes its inotropic effect, and also its potential decrease in coronary blood flow because of cardiac muscle vasodilation.

Milrinone is a non–receptor-mediated agent, acting by selective inhibition of phosphodiesterase type III, which results in cyclic adenosine monophosphate (cAMP) accumulation in the myocardium. cAMP increases the force of myocardial contraction as well as the rate and extent of myocardial relaxation. It is an excellent inotropic medication that can be used long term without the development of tolerance because its action is receptor-independent. cAMP-induced relaxation of the vascular smooth muscle cells also leads to vasodilation. Milrinone can reduce the afterload of both the left and right ventricles.

The actions of the aforementioned cardiotropic agents are based on data from older children and adult studies. It is possible that neonates have a different response to these medications because of variations in receptor number and myocyte function. Premature infants also may have unique

responses compared with full-term infants. In addition to needing age-based comparison studies, further research is warranted to determine whether treatment of systemic hypotension using any agent in premature infants is effective at increasing cerebral perfusion and/or decreasing cerebral injury.

Do you want to add anything to your Learning Plan?
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Brodsky D, Martin C. Cardiology. In: *Neonatology Review*. Philadelphia, Pa: Hanley & Belfus; 2003:85-121

Engle WD, LeFlore JL. Hypotension in the neonate. NeoReviews.org Web site. Accessed July 15, 2007, at: http://www.neoreviews.org/ (subscription required)

Gooneratne N, Manaker S. Use of vasopressors and inotropes. UpToDate Web site. Accessed July 11, 2007, at: http://www.uptodate.com (subscription required)

Sladen RN. Pharmacology of shock: an update. *Can J Anesth.* 2002;49:R1-R5

American Board of Pediatrics Content Specification(s):

Recognize the therapeutic indications for and toxicity of digoxin in treating cardiovascular disease

Recognize the therapeutic indications for and toxicity of inotropic agents in treating cardiovascular disease

Recognize the therapeutic indications for and toxicity of vascular afterload-reducing agents

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April: Question 1

A child is born at 28 weeks' gestation and is now 7 days old, receiving mother's milk by gavage and parenteral nutrition. A capillary blood sample has a pH of 7.28, PCO_2 of 35 mm Hg, and a bicarbonate concentration of 16 mmol/L. Urine pH is 7.5 with an otherwise normal urinalysis. You suspect renal tubular acidosis of prematurity.

Of the following, the portion of the nephron MOST responsible for renal tubular acidosis of prematurity is the:

1	ascending tubule of the loop of Henle
2	descending tubule of the loop of Henle
3	distal convoluted tubule
4	medullary collecting tubule
5	proximal convoluted tubule

You selected 5, the correct answer is 5.

Almost every part of the mammalian nephron is involved in acid-base balance. The ultrafiltrate from the glomerulus has a bicarbonate concentration equal to serum. Most (80%) of this bicarbonate is reabsorbed back into the blood at the proximal convoluted tubule. The distal convoluted tubule reclaims the remaining bicarbonate and acidifies the urine, using the production of ammonium and titration of phosphates and sulfates. Some of the protons are directly secreted into the urine in the proximal portion of the collecting tubule. A problem at any of these sites can affect acid-base balance, but the site most affected in the premature human is the proximal convoluted tubule.

Several factors interfere with the premature infant's ability to excrete the normal daily acid load of 1 to 2 mEq/kg. The largest factor, the nonreabsorption of bicarbonate by the proximal tubule, is caused by the lower serum bicarbonate concentration at which the proximal tubule stops reabsorbing bicarbonate back into the serum. This threshold concentration is 15 to 21 mEq/L in the premature neonate, instead of the normal 22 to 24 mEq/L in the older child and adult; the premature neonate wastes the bicarbonate in the urine before it can be retained to reach a normal serum bicarbonate level. Other factors include a low glomerular filtration rate, preventing adequate delivery of phosphates and other buffers to the distal tubule. The immature distal tubule cells have less surface area and fewer sites for organic acid transport, as well as lower available energy to devote to organic acid transport.

Neonates with renal tubular acidosis (RTA) of prematurity get better. Most premature infants can acidify their urine well by 6 weeks of age, but an adult level of control of acid-base status is not reached until 2 years.

Neonatal RTA can occur as any of a number of disorders unrelated to prematurity. These disorders are grouped into type 1 distal RTA, type 2 proximal RTA, and type 4 hyperkalemic RTA. A rare type 3 RTA has been described as a mixed proximal and distal disorder associated with osteopetrosis and abnormalities in carbonic anhydrase activity.

Primary type 2 proximal RTA may be sporadic or familial. It is rarely seen in isolation, but is more often seen in neonates as part of Fanconi syndrome: tubular wasting of electrolytes and nutrients. Fanconi syndrome can be seen alone or as part of cystinosis, tyrosinemia, Lowe syndrome, or galactosemia. Clinical signs of type 2 proximal RTA may include lethargy, vomiting, or failure to thrive. Laboratory findings include a serum normal-anion-gap acidosis and a urine pH less than 5.5; the intact distal tubule acidification mechanism allows a lower urine pH than with type 1 distal RTA.

Primary type 1 distal RTA is rare in neonates. It is most often seen as part of other disorders, such as sickle cell anemia, osteopetrosis, nephrocalcinosis, or amphotericin toxicity. Clinical signs may include lethargy, vomiting, and failure to thrive. Laboratory findings include a urine pH higher than 6.5 and a serum normal-anion-gap acidosis. Hypokalemia develops as a result of potassium excretion in place of the impaired proton excretion.

Type 4 hyperkalemic RTA is caused by deficiency of, or insensitivity to, aldosterone. Deficiency could be from Addison disease or congenital adrenal hyperplasia, and aldosterone insensitivity could be secondary to urinary obstruction, pyelonephritis, or a primary gene defect. The resulting hyperkalemia interferes with genesis of ammonium in the distal tubule, preventing adequate acid excretion. Symptoms may range from failure to thrive to fever, vomiting, and shock.

Treatment of RTA involves adding extra base to the diet, such as acetate in the intravenous fluids or citrate in the enteral fluids. Daily doses as large as 10 mEq/kg may be needed for some of the more severe proximal RTA cases, and are typically only 2 to 3 mEq/kg per day for cases of distal RTA. Type 4 (hyperkalemic) RTA may also require a mineralocorticoid and treatment of the hyperkalemia.

The tubules of the loop of Henle set up the osmolarity concentration gradient of the medulla, which is then used by the medullary collecting tubule to concentrate the urine. The tubules of the loop of Henle are not involved in acid-base balance.

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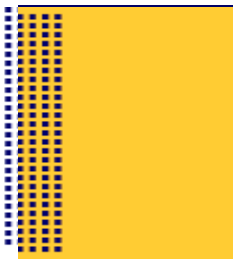
Kaplan BS. Glomerulonephropathies and disorders of tubular function In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn.* 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:1307-1313

Soriano JR. Renal tubular acidosis: the clinical entity. *J Am Soc Nephrol.* 2002;13:2160-2170

American Board of Pediatrics Content Specification(s):

Recognize the causes, diagnosis, and treatment of renal tubular acidosis in the neonate

Be able to differentiate between proximal, distal, and transient renal tubular acidosis



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April: Question 2

A 3-month-old female infant born at 25 weeks' gestation presents at the emergency department 4 days after being discharged home. She had an uneventful initial hospital course and went home without supplemental oxygen or medications other than vitamins with iron. She was feeding well and growing. Her immunizations were up to date and she received palivizumab on the day of discharge. She has not been able to eat for the last 12 hours. After removing the winter clothing and blanket, the infant is seen to be tachypneic, cyanotic, and wheezing. Rapid antigen analysis of nasal secretions is positive for respiratory syncytial virus and adenovirus.

Of the following, the anatomic site MOST affected by respiratory syncytial virus is the:

1	alveolus
2	bronchiole
3	bronchus
4	larynx
5	pleura

You selected 2, the correct answer is 2.

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Respiratory syncytial virus (RSV) was first recognized in infants and children more than 150 years ago and was termed *congestive catarrhal fever* because of the initial presentation as an upper respiratory disorder with productive cough and low-grade fever. Infection of the nasopharynx is the predominant form of infection in human subjects. The typical course lasts as long as 2 weeks. Infants with low lung function and anatomically small airways (such as those born prematurely, with bronchopulmonary dysplasia, younger than 6 months of age, and male) are at higher risk for RSV infections and are predisposed to have chronic wheezing or asthma.

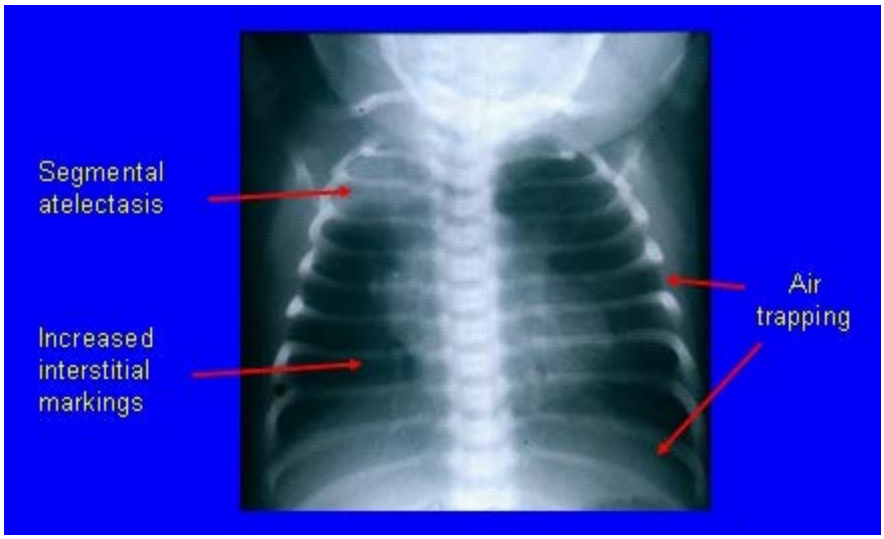
In 30% to 50% of infants, especially those who are younger than 6 months of age and still relatively immune deficient, a lower respiratory infection (such as bronchiolitis, or occasionally, pneumonia or bronchitis) follows the upper respiratory illness 2 to 3 days later. The larynx and pleura are not frequent sites for infection by RSV in infants.

Air trapping is associated with bronchiolar edema, inflammation, and secretions that compromise the small size of the airways of high-risk infants. Wheezing and other signs of respiratory distress may occur and, if severe, cause hypoxemia and hypercarbia. Apnea is a presenting sign in about 20% of infants, especially those born prematurely or admitted to an intensive care unit. Organ systems outside of the nasopharynx and lung are not directly infected by RSV. However, with severe RSV disease, multisystem organ failure may accompany hypoxemia, hypercarbia, and secondary infections.

Male and female infants are equally infected by RSV but male infants are hospitalized about twice as frequently. Hospitalization of male infants with RSV may be because their airways are shorter than those of female infants. Other risk factors for severe infections requiring hospitalization include prematurity, bronchopulmonary dysplasia, immunodeficiency, congenital heart disease, low socioeconomic status, air pollution, recurrent tobacco smoke exposure, and formula feeding. Another risk factor for severe infection with RSV is acquisition of infection during the third and fourth months after birth, a time when maternally acquired antibody wanes and infant T-cell function is deficient.

The destruction of ciliated epithelial cells results in production of copious secretions, impaired ciliary function, and symptoms specific to the upper airways (upper respiratory illness) or the lower airways (bronchiolitis). Proinflammatory cytokines (such as histamine and interleukin 1 and 6) are released by injured epithelial cells causing capillary leak, generation of secretions, and release of additional chemokines. Interstitial edema, inflammatory cell infiltration, surfactant dysfunction, and bronchoconstriction also result in additional airway narrowing and obstruction. Alveoli and alveolar saccules are not frequently involved with RSV infections of the lower respiratory tract. Chest radiographs may show focal infiltrates that represent atelectasis (due to airway obstruction and resorption of gas distal to the obstruction) more often than a true pneumonitis (Figure).

Figure: Chest radiograph of respiratory syncitial virus bronchiolitis



A diagnosis of RSV infection is frequently determined by clinical findings alone. If hospitalization is required, rapid antigen detection tests and viral cultures may be performed to help guide use of antibiotics and isolation strategy. Interestingly, infants presenting with lower respiratory viral illnesses may be coinfected with more than one virus. Rhinovirus and adenovirus have been identified with RSV. It is unclear whether human metapneumovirus, a virus that causes lower respiratory infections that peak later in the year than RSV but is also associated with recurrent wheezing in childhood, coinfects with RSV. Secondary bacterial infections occur in fewer than 10% of cases; antibiotic administration may be indicated if the patient has high fever or appears toxic. Dehydration may occur if feedings are interrupted because of respiratory distress.

Treatment of bronchiolitis, including that due to RSV, is supportive. Nasopharyngeal suctioning has proven beneficial. Oxygen supplementation, fluid and nutritional supplementation, mechanical ventilation, and extracorporeal membrane oxygenation, although not subjected to randomized trials, are supportive interventions that have been provided to infants with RSV infections. Severity of infection and admission to the hospital is reduced with seasonal administration of a humanized monoclonal antibody against the F protein of RSV, palivizumab. Other important interventions to prevent acquisition of RSV include thorough handwashing, limiting contact with others who have upper or lower respiratory illnesses, and feeding with breast milk.

A number of treatments for RSV infections have been studied with equivocal results. Examples of such treatments include bronchodilators, nebulized epinephrine, corticosteroids, ribavirin, surfactant, immunoglobulin, heliox, vitamin A, interferon, and erythropoietin. Novel antiviral agents targeting the RSV genome (NS1, P, N, or L genes) have shown promise in treating RSV in animal models.

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American Academy of Pediatrics. Respiratory syncytial virus. In: Pickering LK, Baker CJ, Long SS, McMillan JA, eds. *Red Book: 2006 Report of the Committee on Infectious Diseases.* 27th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2006:560-566

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Black CP. Systematic review of the biology and medical management of respiratory syncytial virus infection. *Respir Care.* 2003;43(3):209-233

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Understand the treatment of neonatal infections with respiratory syncytial virus

Understand the complications of neonatal infections with respiratory syncytial virus

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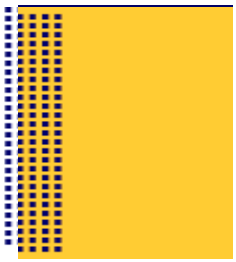

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April: Question 3

A term infant with suspected sepsis requires mechanical ventilation and vasopressor agents for severe respiratory failure and hypotension, respectively. An umbilical artery catheter is placed for continuous blood pressure monitoring and frequent blood sampling. After 7 days of treatment, a dampened umbilical artery waveform is noted and the catheter is removed. Subsequently, the infant develops hypertension, hematuria, and oliguria. Ultrasonography demonstrates a large renal artery thrombus. Anticoagulation with heparin is considered.

Of the following, the MOST accurate statement regarding heparin in the neonate is that:

1	heparin activity is dependent on the presence of antithrombin
2	heparin clearance is slower than in older children and adults
3	heparin-induced thrombocytopenia is dose-dependent
4	heparin requirement is lower than that of older children and adults
5	partial thromboplastin time is the most reliable marker for therapeutic effect

You selected 1, the correct answer is 1.

Although rare, with an incidence of 2.4 per 1,000 neonatal intensive care admissions, thromboembolic events (TEs) occur more often in neonates than in older children. Of all TEs, venous thrombosis occurs more commonly than arterial, 62% versus 34%. Several factors predispose the neonate to thrombosis, including an increased red blood cell mass and viscosity, small vascular caliber, and low concentrations of proteins that regulate coagulation and fibrinolysis. Pathologic states characterized by reduced blood flow, increased blood viscosity, hyperosmolality, or hypercoagulability increase the neonate's risk for thrombosis. Examples include hypoxia, polycythemia, sepsis, shock, dehydration, and maternal diabetes. Associated underlying genetic prothrombotic conditions are found in at least 20% of neonates with a TE. Factor V Leiden (1691G?A) mutation is most common, but prothrombin gene defects, elevated lipoprotein(a), and deficient activity of antithrombin III and proteins C and S also increase risk.

An indwelling vascular catheter is the greatest risk factor for either arterial (>90%) or venous (>80%) thrombosis. The infant in the vignette presents with a renal artery thrombosis, associated with the use of an umbilical artery catheter (UAC). Screening ultrasonography of neonates with a UAC demonstrates thrombi in up to 35% of patients, angiography demonstrates thrombi in up to 64%, and autopsy reveals thrombi in approximately 65% of cases. Most arterial TEs are asymptomatic or present with minor symptoms, such as dysfunction of the catheter, hematuria, hypertension, and intermittent underperfusion or color change of the lower extremities. However, significant arterial TEs, up to 3%, can result in limb compromise, necrotizing enterocolitis, renal hypertension, cerebral infarction, and other organ

failure. Mortality may be as high as 21% in the presence of a major arterial TE. The addition of heparin to umbilical catheter infusions prolongs patency and may reduce the incidence of thrombosis.

Management of major arterial thrombosis remains controversial and insufficiently studied in the neonate. Thrombus location, the presence of organ or limb impairment, and the risk of bleeding influence treatment. In the presence of minor thrombi, catheter removal and supportive management often result in rapid resolution of symptoms. The infant with a large or occlusive thrombus may benefit from anticoagulation and/or thrombolytic treatment. Surgical thrombectomy carries a high risk of mortality and is rarely the preferred treatment option. In many cases, surgical thrombectomy is not feasible.

Heparin acts as an anticoagulant by catalyzing the ability of antithrombin to inactivate certain coagulation enzymes, particularly thrombin. Therefore, heparin activity is dependent on the presence of antithrombin, and an increased anticoagulant effect may be achieved by supplying fresh frozen plasma or antithrombin concentrate.

Optimal heparin dosing is less predictable in neonates than in adults. As a result of a larger volume of distribution, the clearance of heparin is faster in term neonates, and the half-life is reduced by two thirds. Therefore, the heparin requirements of term neonates are higher than those of adults.

In the neonate, variable concentrations of coagulation factors and baseline prolongation of partial thromboplastin time (PTT) complicate the use of PTT to monitor heparin effect. Heparin activity level, reported by most laboratories as an anti–factor Xa concentration, is considered a more reliable marker of anticoagulant effect. For most TEs, therapeutic heparin activity corresponds to an anti–factor Xa concentration of 0.3 to 0.7 U/mL (corresponds to a PTT value of 60-85 seconds; 1.5 to 2.5 times the baseline normal). Although the duration of heparin treatment is usually 1 to 2 weeks, longer durations may be needed for resolution of some thrombi.

Adverse effects related to heparin treatment are hemorrhage and heparin-induced thrombocytopenia (HIT). The incidence of major bleeding is unknown in the neonate, but reported to be 1.9% in older children treated with heparin. Increased risk of intracranial hemorrhage and recent major surgery are contraindications to heparin treatment. Heparin anticoagulation is rapidly reversed with intravenous protamine administration. Heparin-induced thrombocytopenia is an immune-mediated complication characterized by persistent low platelet counts and thrombosis due to platelet activity. The incidence of HIT in the neonate may be as high as 40%. HIT is not dose-dependent and resolves with discontinuation of heparin. Long-term heparin treatment has been associated with osteoporosis in older children and adults.

Low-molecular-weight heparin (LMWH) preparations (eg, enoxaparin) have a more predictable pharmacokinetic profile than unfractionated heparin, require less frequent anti-Xa monitoring, and can be administered subcutaneously. As with unfractionated heparin, data on the usage of LMWH in neonates are limited, but its safety and efficacy in older children and adults have been demonstrated. Oral anticoagulants (eg, warfarin) function by reducing plasma concentrations of the vitamin K-dependent proteins. Because neonates are functionally vitamin K deficient, they are more sensitive to oral anticoagulants and have a higher risk of associated bleeding. Oral anticoagulants should be avoided in neonates.

Thrombolytic therapy may be indicated for the neonate with significant thrombotic complications, but the safety and efficacy data are minimal. Thrombolytic agents, such as tissue plasminogen activator, act by converting plasminogen to plasmin, which in turn cleaves fibrinogen and fibrin. Thrombolysis can be achieved by local or systemic administration of a thrombolytic agent. Although the correlation between hemostatic parameters and efficacy is poor, fibrinogenolysis can be monitored with fibrinogen concentration and fibrin degradation products. Generally, fibrinogen concentrations decrease by 20% to 50%, but should be maintained at about 100 mg/dL to minimize risk of bleeding. Baseline deficiencies in plasminogen and other thrombolytic factors may need to be corrected with fresh frozen plasma if fibrinogen levels remain high. Clinical improvement is usually seen within 6 to 12 hours of treatment. Major bleeding is the most significant risk of thrombolytic therapy, and occurs in 20% of pediatric patients. Bleeding should be treated with factor replacement using fresh frozen

plasma or cryoprecipitate.

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American Board of Pediatrics Content Specification(s):

Know the etiology, clinical manifestations, laboratory features, and management of renal artery thrombosis

Understand the mechanism of action, therapeutic indications for, and toxicity of anticoagulants used in the newborn period

Understand the mechanism of action, therapeutic indications for, and toxicity of thrombolytics used in the newborn period

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April: Question 4

A 26-year old primiparous woman presents with labor at 24 weeks' gestation. On speculum examination, a fully-effaced cervix is dilated 2 cm. No fluid is noted to come from the cervical os. To provide time for antenatal corticosteroid effect , tocolytic therapy is being discussed.

Of the following, the tocolytic agent that exerts its effect through blockade of myometrial contractile stimulants is:

1	beta-adrenergic receptor agonist
2	calcium channel blocker
3	magnesium sulfate
4	nitric oxide donor
5	prostaglandin synthesis inhibitor

You selected 5, the correct answer is 5.

Preterm labor (PTL) is defined as labor occurring after 20 weeks' but before 37 weeks' gestation. It is defined by the presence of regular uterine contractions at frequent intervals associated with cervical effacement (>80%) or dilatation (at least 2 cm). Generally, more than four contractions per hour are needed to cause cervical change. Preterm birth complicates 10% to 15% of all pregnancies. It is the commonest cause of neonatal morbidity and mortality, and causes 75% of neonatal deaths that are not associated with congenital anomalies. Therefore efforts to prevent or inhibit PTL are warranted.

Decisions about management of PTL are made based on estimated gestational age (less than 34 to 36 weeks' gestation), estimated weight of the fetus (<2,500 g), and presence of contraindications to tocolysis (Table 1).

Table 1

Table 1. Contraindications to Suppression of Preterm Labor*

Maternal Factors	Fetal Factors
Severe hypertensive disease • exacerbation of chronic hypertension • eclampsia • severe preeclampsia Pulmonary or cardiac disease • pulmonary edema • adult respiratory distress syndrome • valvular disease • tachyarrhythmias Advanced cervical dilatation (> 4 cm) Maternal hemorrhage • abruptio placentae • placenta previa • disseminated intravascular coagulation	Fetal death or lethal anomaly Fetal distress Intrauterine infection (chorioamnionitis) Therapy adversely affecting the fetus (eg, fetal distress because of attempted suppression of labor) Estimated fetal weight ≥ 2500 g Erythroblastosis fetalis Severe intrauterine growth restriction

* Adapted from Roman and Pernoll (2007).

A number of drugs and other interventions have been used to prevent or inhibit preterm labor; none has been very effective. Because of uncertainty about progression of labor despite tocolytic medications, the American College of Obstetricians and Gynecologists has recommended that tocolysis *may be considered* when uterine contractions are regular and the changes in cervical dilatation and effacement are appreciable.

Tocolytic agents in current use inhibit myometrial contractions but do not affect the primary stimulus for preterm labor. Tocolytics function through one of two mechanisms, alteration of intracellular metabolic pathways or blockade of myometrial contractile stimulants. Intracellular messaging is altered by B-adrenergic receptor agonists (ritodrine, terbutaline), nitric oxide donors (nitroglycerin), magnesium sulfate, and calcium-channel blockers (nifedipine). Agents that inhibit the synthesis or action of myometrial contractile stimulants include prostaglandin-synthesis inhibitors (indomethacin) and oxytocin antagonists (atosiban).

The decision to use a specific tocolytic agent should be carefully considered because of the side effects associated with each agent (Table 2).

Table 2

Table 2. Side Effects and Complications of Common Tocolytics

Tocolytic Agent	Mechanism of Action	Maternal Effects	Fetal/Neonatal Effects
Beta-mimetics (ritodrine, terbutaline)	Act directly on beta receptors (β_2) to relax the uterus	• Pulmonary edema • Hypotension • Tachycardia • Nausea/vomiting • Hyperglycemia • Hyperinsulinemia • Hypokalemia • Cardiac arrhythmias • Myocardial ischemia • Shortness of breath • Tremors • Nervousness	• Tachycardia • Hyperinsulinemia • Fetal hyperglycemia • Neonatal hypoglycemia • Hypocalcemia • Hypotension • Myocardial and septal hypertrophy • Myocardial ischemia • Ileus • Possible increased risk for intraventricular hemorrhage
Magnesium sulfate	Competitively blocks Ca2+ influx across the cell membrane; activates adenyl cyclase and cyclic adenosine monophosphate	• Flushing • Nausea/vomiting • Headache • Generalized muscle weakness • Shortness of breath • Diplopia • Pulmonary edema • Chest pain • Hypotension • Tetany • Respiratory depression	• Lethargy • Hypotonia • Respiratory depression • Demineralization with prolonged use
Indomethacin	Prostaglandin synthase inhibitor	• Gastrointestinal effects: Nausea/vomiting, heartburn, bleeding • Coagulation disturbances • Thrombocytopenia • Renal failure • Hepatitis • Elevated blood pressure in hypertensive patients	• Renal dysfunction • Oligohydramnios • Pulmonary hypertension with prolonged therapy (> 48 hours) • Postpartum patent ductus arteriosus • Premature constriction of ductus arteriosus in utero • Increased risk for necrotizing enterocolitis and intraventricular hemorrhage
Nifedipine	Inhibits calcium uptake into uterine smooth muscle cells via voltage-dependent channels, thereby reducing uterine contractility.	• Hypotension • Tachycardia • Headache • Flushing • Dizziness • Nausea/vomiting	• Sudden fetal death • Fetal distress • Tachycardia • Hypotension
Atosiban	Synthetic oxytocin analogue that competitively antagonizes oxytocin-induced contractions.	• Nausea • Allergic reaction • Headache	• bradycardia • Fetal tachycardia
Nitric oxide donors	Vasodilators that cause myometrial relaxation through production of cGMP	• Dizziness • Hypotension • Flushing	• Limited data available

The use of multiple tocolytic agents simultaneously may have an additive effect but also increases the risk of serious side effects.

Prostaglandin synthase (cyclooxygenase, COX) is responsible for converting arachidonic acid to prostaglandin H_2. Such prostaglandins are important for stimulating changes in myometrial gap junctions and intracellular calcium signaling that occur during labor. COX-1 is an isoform of prostaglandin

synthase constitutively expressed in the myometrium, decidua, and fetal membranes. COX-2 is an inducible isoform that increases in the decidua and myometrium during labor, both term and preterm. Indomethacin is a nonspecific COX inhibitor that reduces prostaglandin production, and is the most commonly used agent for inhibiting preterm labor. Newer COX-2 inhibitors, such as nimesulide, are under investigation. Maternal side effects associated with prostaglandin synthase inhibitors may include gastrointestinal bleeding, blood pressure elevation, and coagulation disturbances (Table 2). Fetal and neonatal side effects may include renal effects and reduction in amniotic fluid volume. With prolonged use, generally defined as longer than 48 hours, the ductus arteriosus may close and cause fetal and neonatal pulmonary hypertension, a risk pertinent to the case in the vignette.

B-adrenergic-receptor agonists increase the intracellular concentration of cyclic AMP, an activator of protein kinase. Protein kinase inhibits myosin light-chain kinase, thereby inhibiting myometrial contraction. A metaanalysis of several studies has demonstrated a reduction in preterm birth within 48 hours after treatment, but this effect is not detectable at 7 days. No effect on perinatal morbidity and mortality was found. Maternal side effects may be significant, especially pulmonary edema and arrhythmias (Table 2). Fetal and neonatal side effects may include tachycardia, fetal hyperglycemia, neonatal hypoglycemia, and myocardial ischemia.

Nitric oxide donors, such as nitroglycerin, have not been extensively used for prevention of preterm labor. Nitric oxide vasodilates smooth muscle cells within the uterus by activating guanylyl cyclase that induces cyclic GMP production. Myosin light-chain kinases are inactivated and muscle relaxation occurs. Small randomized trials and case studies involving acute uterine relaxation indicate that nitric oxide donors may be beneficial, although additional study is necessary. Maternal side effects include flushing, hypotension, and dizziness; information about fetal and neonatal side effects from maternal administration is limited (Table 2).

Magnesium sulfate decreases the intracellular concentration of calcium in myometrial cells, thereby inducing relaxation. Although widely used, efficacy in prolonging labor is yet to be clearly established. Maternal side effects may include diplopia, hypotension, muscle weakness, and pulmonary edema (Table 2). Fetal and neonatal side effects may include hypotonia and respiratory depression.

Calcium channel blockers directly inhibit the intracellular influx of calcium and release of calcium from the endoplasmic reticulum, both important for muscle contraction. Nifedipine is the agent most often used, however, no placebo-controlled trials have been reported. Therefore, evidence for safety and efficacy is limited. Maternal side effects associated with calcium channel blockers may include hypotension, nausea, tachycardia, and dizziness (Table 2). Fetal and neonatal side effects may include sudden fetal death, tachycardia, hypotension, and fetal distress.

Oxytocin receptor antagonists such as atosiban block the action of oxytocin on inositol triphosphate–induced release of intracellular calcium. A metaanalysis of atosiban studies found that atosiban was associated with an excess of fetal and infant deaths when given before 28 weeks' gestation. Atosiban or other oxytocin receptor antagonists have not been approved for use in the United States. Potential maternal side effects may include nausea and headache (Table 2). Fetal bradycardia and fetal distress have been reported with atosiban (Table 2).

Most placebo-controlled trials of tocolytic medications are underpowered to evaluate the outcomes. Overall, however, women who received any tocolytic agent had a mean time to delivery of approximately 48 hours. Although tocolytic agents are widely used in North America and Europe, several are not approved by the US Food and Drug Administration for this indication (terbutaline, atosiban); conversely, ritodrine is approved for tocolysis of preterm labor but is no longer available for use in the United States. Atosiban, an inhibitor of oxytocin, is the first-line tocolytic agent in Europe.

Although the efficacy of tocolysis has been much debated, it is generally accepted that a 48-hour delay in delivery may facilitate maternal transport and fetal lung maturation after administration of corticosteroids. Tocolytic therapy should be considered in the patient with cervical dilatation less than 5 cm. Successful tocolysis is generally defined by fewer than 4 to 6 uterine contractions per hour without further cervical change. The short-term goal of tocolysis is to continue the pregnancy for 48 hours after corticosteroid administration, the duration of time generally needed to have a maximum

effect. The long-term goal is to continue the pregnancy beyond 34 to 36 weeks' gestation (depending on the institution), at which time fetal morbidity and mortality are significantly reduced and tocolysis can be discontinued. Long-term tocolysis is controversial because of side effects on the mother and infant (Table 2).

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American Board of Pediatrics Content Specification(s):

Know the effects of tocolytic agents used during pregnancy

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April: Question 5

A mother feels a small neck mass in her 1-month-old infant. The infant's examination reveals a round, skin-colored, mobile, nontender, smooth preauricular swelling in the parotid region. You recommend complete excision to prevent potential complications.

Of the following, the MOST common complication of this neck mass is:

1	squamous cell carcinoma
2	fistula formation
3	hypoglossal nerve palsy
4	localized infection
5	osteomyelitis

You selected 4, the correct answer is 4.

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The child in this vignette has a neck mass that is most consistent with a branchial cleft cyst. Infection is the most common complication of branchial remnants and may develop at any time. This infection is typically localized and can lead to an abscess but does not involve adjacent bones. Squamous cell carcinomas have been reported in rare patients with branchial cleft cysts, but this does not present until adulthood. Cysts are typically isolated and do not lead to fistula formation. Hypoglossal nerve palsy is an unusual complication of branchial cysts that is caused by mechanical compression by the cyst.

Branchial cleft cysts, fistulas, and sinuses are embryonic remnants of the four pairs of branchial arches and their intervening clefts (Table).

Table

Table. Derivatives of the Branchial Arches and Intervening Clefts		
Branchial Component	**Mature Structure**	**Anomalies**
First branchial arch	Mandible Maxillary process of upper jaw	Cleft lip Cleft palate Abnormal shape or contour of external ear Malformed internal ossicles
First branchial cleft	Tympanic cavity Eustachian tube	Microtia Aural atresia Cysts (rare) located posterior or anterior to ear or inferior to the earlobe in the submandibular region External openings (uncommon) located inferior to mandible with 1/3 opening into the auditory canal
Second branchial arch and cleft	Hyoid bone Cleft of the tonsillar fossa	Cysts and sinuses (common) in nasopharynx, oropharnyx or tonsillar fossa
Third branchial cleft	Inferior parathyroid glands Thymus	Cysts and sinuses (rare)
Fourth branchial cleft	Superior parathyroid glands	Cysts, fistulas, sinuses (rare)

In fish and amphibians, these structures are responsible for the formation of gills. Branchial cysts, sinuses, and fistulas consist of a tract with no, one, or two opening(s), respectively. While fistulas and sinuses are thought to arise from incomplete obliteration of branchial clefts and pouches during embryogenesis, branchial cysts are believed to arise from the cystic transformation of lymph nodes.

Although all branchial remnants are congenital, the small external openings of fistulas or sinuses are usually not apparent at birth. The cutaneous openings of these remnants may be evident by adjacent skin tags or cartilage remnants. More commonly, patients with fistulas and sinuses present with spontaneous mucoid drainage during infancy or childhood. Compression along the tract may yield further mucoid material exiting from the opening. A cordlike tract may be palpable by hyperextending the child's neck and tightening the skin.

Cysts developing from branchial structures are usually present along the anterior border of the sternocleidomastoid muscle. Although it was previously thought that left-sided cysts are more common than right-sided lesions, further studies have found that branchial cysts occur equally on either side of the neck. In contrast to branchial sinuses and fistulas, branchial cysts usually appear later in childhood and are more difficult to diagnose. Patients present with one of the following: (1) chronic prurulent ear drainage; (2) preauricular swelling in the parotid region; or (3) abscess in the neck. Depending on the size and anatomic extension of the cyst, patients may have dysphagia, dysphonia, dyspnea, or stridor. Cysts may become tender during upper respiratory infections. A branchial cyst can resemble a dermoid or thyroglossal duct cyst, lymphatic nodule, cystic hygroma, or parotid lesion.

Complete excision of the branchial cyst, fistula, or sinus is recommended soon after the diagnosis is made, as long as there is no concurrent inflammation or infection. Inadequate resection is likely to result in recurrence. If the lesion is infected at the time of diagnosis, antibiotics and warm soaks are used to encourage spontaneous drainage of muocoid plugs before definitive excision. If these measures are unsuccessful, a limited incision and drainage procedure may be required to resolve the infection.

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American Board of Pediatrics Content Specification(s):

Recognize the clinical manifestations of branchial cleft cysts

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April: Question 6

A 24-hour-old term infant is being evaluated for discharge. He was delivered by a 22-year-old primigravida African-American woman at 38 weeks' gestation. His birthweight was 3,700 g. Maternal prenatal laboratory findings were normal. The plasma glucose concentration 1 hour after a 50-g glucose challenge test was 116 mg/dL (6.4 mmol/L). The infant has had no problems since birth. He is rooming in with the mother, is feeding well, and has voided and passed meconium. You are discussing the need for and optimal timing of screening for gestational diabetes mellitus (GDM) during this woman's subsequent pregnancies.

Of the following, the BEST time for screening for glucose intolerance in this woman in association with her next pregnancy is:

1	preconception
2	4 to 8 weeks
3	14 to 18 weeks
4	24 to 28 weeks
5	not indicated

You selected 4, the correct answer is 4.

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Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. GDM complicates approximately 4% of all pregnancies in the United States, resulting in approximately 135,000 cases annually. The prevalence may range from 1% to 14% of pregnancies, depending on the population studied. GDM represents nearly 90% of all pregnancies complicated by diabetes.

Clinical recognition of GDM is important because factors such as dietary treatment, insulin, and antepartum fetal surveillance, can reduce GDM-associated perinatal morbidity and mortality. The timing of screening for GDM is important. Because maternal insulin resistance rises progressively during pregnancy, screening too early may miss some patients who will become glucose intolerant later. Screening too late in the third trimester may limit the time during which metabolic interventions can take place. Before 1997, screening for GDM was recommended in all pregnancies. Currently, the screening strategy for GDM is based on an assessment of risk for GDM determined at the first prenatal visit as outlined in Table 1. The woman in this vignette falls into the average-risk category because of her African-American race.

Table 1

Table 1. Screening Strategy for Detecting GDM			
Risk Category	**Criteria**	**Screening Test**	**Screening Timing**
Low risk	*All criteria must be fulfilled* • Members of ethnic group with low prevalence of GDM • No known diabetes in first-degree relatives • Age <25 years • Weight normal before pregnancy • No history of abnormal glucose metabolism No history of poor obstetric outcome	Not indicated	Not indicated
Average risk	Members of an ethnic/racial groups with a high prevalence of diabetes (eg, Hispanic, Native American, Asian, African-American, Pacific islands, indigenous Australian ancestry)	One of the following: • Two step procedure: 50 g GCT followed by a diagnostic OGTT in those with abnormal GCT • One step procedure: diagnostic OGTT on all subjects	24-28 wk
High risk	• Maternal age >25 years • Previous infant > 4 kg • Previous unexplained fetal demise • Marked obesity • Strong family history of type 2 diabetes or GDM • Personal history of GDM • Glucose intolerance o Fasting glucose >140 mg/dL (7.8 mmol) o Random glucose >200 mg/dL (11.1 mmol) • Glucosuria	One of the following: • Two step procedure: 50 g GCT followed by a diagnostic OGTT in those with abnormal GCT • One step procedure: diagnostic OGTT on all subjects	As early in pregnancy as possible

GCT = glucose challenge test; GDM = gestational diabetes mellitus; OGTT = oral glucose tolerance test

The 50-g glucose challenge test (GCT) consists of administration of a 50-g oral glucose load followed by a plasma glucose determination 1 hour later. The patient need not be fasting. Various threshold levels for an abnormal 50-g glucose challenge are in use, including 140 mg/dL (7.8 mmol/L), 135 mg/dL (7.5 mmol/L), and 130 mg/dL (7.2 mmol/L). The sensitivity of the GDM testing regimen depends on the threshold value used. Pregnant women with a GCT result above the selected threshold require a diagnostic oral glucose tolerance test (OGTT). The most commonly used threshold, 140 mg/dL, detects only 80% of patients with GDM and necessitates a 3-hour OGTT in approximately 10% to 15% of patients. Using a challenge threshold of 135 mg/dL improves sensitivity to more than 90% but increases the number of 3-hour OGTTs by 42%.

The diagnostic OGTT is performed in the morning after an overnight fast of 8 to 14 hours after 3 days of unrestricted diet and physical activity. Either a 2-hour (75-g glucose) or a 3-hour (100-g glucose) test can be performed. The diagnostic criteria are shown in Table 2. Two or more values must be met or exceeded for the diagnosis of GDM to be made.

Table 2

Table 2. Criteria for Diagnosis of Gestational Diabetes Mellitus: Venous Plasma Glucose Level*		
Fasting Value	**With 100-g Glucose Load, mg/dL (mmol/L)**	**With 75-g Glucose Load, mg/dL (mmol/L)**
	95 (5.3)	95 (5.3)
1 h	180 (10.0)	180 (10.0)
2 h	155 (8.6)	155 (8.6)
3 h	140 (7.8)	--

* Adapted from Chmait and Moore (2005).

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Chmait R, Moore TR. Endocrine disorders in pregnancy. In: Ballard RA, ed. *Avery's Diseases of the Newborn.* 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005;1:71-82

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American Board of Pediatrics Content Specification(s):

Know the rationale and methods for screening for glucose intolerance during pregnancy

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April: Question 7

A pediatrician has moved her practice to a community with a high rate of human immunodeficiency virus (HIV) infections. She attends a national meeting to learn more about the clinical manifestations of pediatric HIV.

Of the following, children in the United States with a new diagnosis of HIV infection are MOST likely to present with:

1	*Candida* esophagitis
2	cytomegalovirus disease
3	lymphocytic interstitial pneumonitis
4	*Pneumocystis carinii* pneumonia
5	recurrent bacterial infections

You selected 4, the correct answer is 4.

Pneumocystis carinii pneumonia (PCP) is currently the most common first infection that leads to the diagnosis of human immunodeficiency virus (HIV) in children in the United States. Indeed, PCP was the most common (33%) indicator of HIV in 8,086 children younger than age 13 years reported to the Centers for Disease Control and Prevention (CDC) through 1997. Other marker diseases included the following: lymphocytic interstitial pneumonitis (24%), recurrent bacterial infections (20%), _Candida_ esophagitis (16%), and cytomegalovirus disease (8%). These percentages have remained constant (±1%) with an addition of 1,355 new cases through 2005. Children diagnosed with HIV may also present with HIV encephalopathy (17%), _Mycobacterium avium_ infection (9%), severe herpes simplex infection (5%), and cryptosporidiosis (5%).

Pneumocystis carinii (more recently known as _Pneumocystis jiroveci_) pneumonia has been the most common HIV indicator in children since the early HIV epidemic. Since the initiation of PCP prophylaxis in HIV-exposed infants and HIV-infected children in the United States, the incidence of this disease has been slowly decreasing. PCP typically occurs during the first 3 to 6 months of age. Infected children usually present with an acute respiratory illness and cyanosis. The diagnosis can be confirmed by detecting the organism in sputum.

Oral candidiasis is common in healthy newborns and infants. However, HIV-infected children typically have candidal infections beyond infancy, involvement of the pharynx and esophagus, and persistence despite antifungal medications. Disseminated candidiasis is uncommon in HIV-infected children unless the child is receiving total parenteral nutrition or has a central venous catheter.

Cytomegalovirus disease in HIV-infected children can lead to esophagitis, hepatitis, enterocolitis, and/or retinitis. Other commonly encountered viral infections that can occur in HIV-infected children include primary varicella and hepatitis A, B, and C. If these infections occur, HIV-infected children usually have a more fulminant and/or chronic course than children not infected by HIV.

Lymphocytic interstitial pneumonitis, also known as *pulmonary lymphoid hyperplasia*, occurs almost exclusively in the pediatric HIV-infected population. Infants and children may be asymptomatic with isolated radiographic findings of the disease, or they can be severely compromised with exercise intolerance and/or dependence on oxygen and/or corticosteroids. Children with lymphocytic interstitial pneumonia have a greater risk of developing recurrent bacterial and viral infections.

Recurrent bacterial infections, including meningitis, sepsis, and pneumonia are common in children with HIV infection. HIV-infected children with bacterial infections usually require longer courses of treatment than those not infected by HIV. HIV-infected newborns may also have a very-late-onset group B streptococcal disease with a clinical presentation at 3.5 to 5 months of age.

References:

Centers for Disease Control and Prevention (CDC). US HIV and AIDS cases reported through December 1997. HIV/AIDS surveillance report: year-end edition. *MMWR Morb Mortal Wkly Rep.* 1997;9:1-44

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Centers for Disease Control and Prevention. Pediatric HIV/AIDS surveillance (through 2005). Accessed October 11, 2007, at: http://www.cdc.gov/hiv/topics/surveillance/resources/slides/pediatric/

American Board of Pediatrics Content Specification(s):

Understand the clinical manifestations of perinatal HIV infection

PREVIOUS NEXT

April: Question 8

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A male infant was delivered vaginally at 36 weeks' gestation by a 27-year-old primiparous woman with normal prenatal laboratory results. His birthweight was 2,455 g (<10th percentile). His Apgar scores were 7 and 9 at 1 and 5 minutes, respectively. Eight hours after birth, he was noted to have jaundice; his total serum bilirubin concentration at this time was 12.5 mg/dL (213.8 µmol/L) with a conjugated fraction of 7.8 mg/dL (133.4 µmol/L). Laboratory findings were as follows.

Test	Patient Results
Hemoglobin, g/dL (g/L)	10 (100)
Platelets, $\times 10^3$/µL ($\times 10^9$/L)	54 (54)
International normalized ratio	1.08
Fibrinogen, mg/dL (µmol/L)	106 (3.03)
Glucose, mg/dL (mmol/L)	38 (2.1)
Protein, total, g/dL (g/L)	5.4 (54)
Albumin, g/dL (g/L)	1.8 (18)
Aspartate aminotransferase, U/L	206
Alanine aminotransferase, U/L	135
Iron, total, µg/dL (µmol/L)	184 (32.9)
Transferrin, mg/dL (g/L)	192 (1.92)
Iron binding capacity (total), µg/dL (µmol/L)	284 (50.8)
Ferritin, ng/mL (pmol/L)	1,650 (3,707)
Alpha-fetoprotein, ng/mL (µg/L)	104,000

On ultrasonography, the liver appears homogeneous in echotexture without focal abnormality. There is no intra- or extrahepatic biliary ductal dilation. The gall bladder is normal in appearance, without wall thickening.

The T2 sequence on hepatic magnetic resonance imaging shows the left lobe of the liver and the pancreas to be lower in signal intensity than the skeletal muscle, suggesting siderosis.

You counsel the parents regarding the potential outcome for this infant.

Of the following, survival is MOST likely for infants with this condition after:

1	anticoagulant treatment
2	antioxidant cocktail treatment
3	iron chelation treatment
4	liver transplantation
5	supportive management

You selected 4, the correct answer is 4.

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Neonatal hemochromatosis (NH), also known as neonatal iron storage disease, presents with extremely early onset of liver failure, as in the infant in this vignette. NH has an aggressive course and carries a poor prognosis. When not stillborn, infants with NH frequently are premature or are small for gestational age. The pregnancy may be complicated by intrauterine growth restriction, oligohydramnios, placental edema, or sometimes polyhydramnios.

Illness usually is evident within hours after birth; however, some infants have been diagnosed at a few weeks of age. Patients have features of liver failure with hypoalbuminemia, hypoglycemia, coagulopathy, low fibrinogen, and, frequently, thrombocytopenia and anemia. The diagnosis may be suggested by complete or nearly complete saturation of iron-binding capacity, elevated serum ferritin, or by demonstration of extrahepatic iron accumulation using magnetic resonance imaging (MRI) or minor salivary gland biopsy. When measured, transferrin is low, reflecting the impaired synthetic ability of the liver.

Siderosis of the liver is normal in the third trimester but can be distinguished from NH hepatic siderosis by the extrahepatic siderosis with reticuloendothelial sparing. Specifically, although the iron deposition in NH is most notable in the liver, it also is present in the heart, pancreas, exocrine and endocrine organs, intestines, and gastric and salivary glands. Siderosis of extrahepatic sites, including the salivary glands, makes it possible to verify the diagnosis histologically without the need for a liver biopsy.

Because of the paramagnetic influence of ferric ions (Fe^{3+}) on the image signal, MRI can be useful in the diagnostic evaluation of an infant with possible NH. The signal alterations caused by the ferric ions cause shortening of the T1 and, more impressively, the T2 relaxation times. Any tissue containing iron therefore will have low signal intensity. Nodular cirrhosis with severe cholestasis typically is found at the time of biopsy or autopsy.

Neonatal hemochromatosis is nearly universally fatal, and experience with treatment is limited because many die before diagnosis. Deferoxamine therapy is not efficacious, and it has been suggested that its use may potentiate bacterial growth. Deferoxamine combined with an antioxidant cocktail has not proved to be universally successful.

Although experience is very limited, liver transplantation has been successful in treating NH. In one study of 14 infants with NH treated with an antioxidant cocktail, five patients survived to transplantation and three were alive 1 year after transplantation. In most cases, iron overload resolved slowly after transplantation.

Neonatal hemochromatosis has recently been shown to be the result of maternal alloimmune injury. The target protein of the maternal immune response has not been identified, but fetal liver injury is believed to be the result of maternal antibody. Treatment of mothers with a previous pregnancy that resulted in an infant with NH with high-dose intravenous immunoglobulin (IVIG) has been shown to prevent recurrence of disease. In an open trial, women with a previous infant with NH were treated with weekly infusions of IVIG between the 18^{th} week and the end of gestation. Fifteen women were treated through 16 pregnancies; the outcomes were compared with randomly selected previous gestations in each woman. All of the treated pregnancies progressed normally and resulted in infants with normal physical findings and birthweight appropriate for gestational age. Twelve infants had evidence of liver involvement with NH and seven required medical supportive therapy; however, none required transplantation. In contrast, only two of the infants in the previously affected gestations survived without transplantation.

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feature.)

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Smith SR, Shneider BL, Magid M, et al. Minor salivary gland biopsy in neonatal hemochromatosis. *Arch Otolaryngol Head Neck Surg.* 2004;130:760-763

Vohra P, Haller C, Emre S, et al. Neonatal hemochromatosis: the importance of early recognition of liver failure. *J Pediatr.* 2000;136:537-541

Whitington PF, Hibbard JU. High-dose immunoglobulin during pregnancy for recurrent neonatal haemochromatosis. *Lancet.* 2004;364:1690-1698

American Board of Pediatrics Content Specification(s):

Know the etiology and differential diagnosis of metabolic and familial causes of cholestasis in the neonate

Know the various laboratory and radiographic techniques to diagnose the metabolic and familial causes of cholestasis in the neonate

Know the approach to treatment of neonates with metabolic and familial causes of cholestasis in the neonate

PREVIOUS NEXT

April: Question 9

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You are reading a study in the *Journal of Perinatology* by Morkos and colleagues in which an elevated total peripheral neutrophil count in infants with hypoxic-ischemic encephalopathy is associated with compromise of neurodevelopmental outcome. In the statistics section of the publication, the following statement is made: "Differences were considered significant at *P*=.05." This probability limit is often the threshold for statistical significance in clinical as well as basic science research. It means that the "null hypothesis" (that the differences observed occurred only by chance) can be rejected.

Of the following, the best explanation for the use of .05 as the threshold for statistical significance is that it is:

1	a mathematically derived limit of probability
2	a standard commonly accepted by research organizations
3	applicable when studying multiple hypotheses
4	generally thought to be unlikely enough to occur by chance alone
5	the only threshold that has been accepted by scientific editors

You selected 4, the correct answer is 4.

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The use of *P*<.05 as the threshold for statistical significance was originally ascribed to the pioneering statistician RA Fisher. Fisher published tables of statistical probability that were designed to highlight .05 as an important level. He wrote that a 1 in 20 chance that an observation occurred purely by chance was an important threshold that would allow the discovery of useful differences (eg, therapies) without burdening the literature with too many reports of questionable effects. However, in other statements, Fisher suggested other thresholds (such as *P*<.02 and *P*<.01) and often took the *P* value to be a measure of the strength of the argument for rejecting the null hypothesis. He warned that there would be fewer scientific reports in the literature if .01 were the generally accepted criterion.

Over time, the .05 threshold has withstood continuous scrutiny in the biosciences. An informative example follows:

The audience watches while the lecturer flips a coin repeatedly. If the first 2 or 3 tries yield the same answer (eg, "heads"), there is usually little discomfort in the audience with the outcomes so far. However, if the result continues to be the same through the 4^{th} or 5^{th} try, members of the audience usually become skeptical and want to examine the coin. The threshold (either the 4^{th} or 5^{th} coin flip) is fairly consistent from audience to audience.

The probability of getting four heads in a row is $(1/2)^4$ or 0.0625 and for five in a row, it is $(1/2)^5$ or 0.03125. Therefore, around *P*=.05 is where people lose confidence that an outcome is most

likely because of chance.

The .05 or 5% level is not an *extreme* one for rejecting the null hypothesis. The 5% level of significance does not prevent a rejection of the null hypothesis (ie, the result occurs by chance) in error. In fact, such an error occurs on average in 1 of every 20 experiments. An example of an "extremely unlikely" probability is the chance that a particular ticket will win the state lottery (say, *P*=.00001, or 0.001% level). Against these extreme odds, it is unlikely that there will be an error in rejecting the null hypothesis. In this example, the error (winning the lottery) would occur on average in 1 of every 100,000 lottery tickets purchased.

Often, however, good reasons exist for using other thresholds in the pursuit of scientific truth. If, for example, a particular study is investigating more than one hypothesis to explain differences between groups, the chance of finding at least one of the hypotheses statistically significant at the *P*<.05 threshold would be more likely than 5%. In this example, the actual chance of a statistically positive result would be calculated as $1 - (0.95)^n$ using 'n' as the number of hypotheses tested. If the number of variables studied is 4, then the chances of finding at least one that is "significant" at the *P*<.05 level would be 15%. A more reasonable approach for choosing a level of significance in this situation was suggested by Bonferroni, who prescribed dividing the usual threshold by n. In this case, with 4 variables, the new threshold for determining significance would be .05/4 or .0125.

The threshold for rejecting the null hypothesis might be set differently if one were considering the risk of the two types of errors that statistical conclusions can yield. A type I error is defined as rejecting the null hypothesis when it is true. For example, small studies of the use of antenatal phenobarbital to prevent intraventricular hemorrhage showed effectiveness at *P*<.05. However, a large, multicenter trial showed that phenobarbital did not prevent intraventricular hemorrhage. To prevent this error of rejecting the null hypothesis (ie, the effect of phenobarbital was by chance), a smaller *P* value might represent a more prudent threshold.

A type II error can occur in small studies that are not powered to detect the positive effect of a treatment that, in reality, does help. In this situation, the null hypothesis is accepted (ie, no effect) because the *P* value obtained is larger than .05 even though a larger study might show efficacy. Such a preliminary report might discourage investigators from further studies of the treatment and future patients would not benefit from such treatment. This is an argument for conducting studies with enough subjects to detect a small but important effect or for choosing a *P* value greater than .05 in preliminary studies so that further work is still encouraged.

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References:

Dallal GE. Why P=0.05? Accessed July 17, 2007, at: http://www.tufts.edu/~gdallal/p05.htm

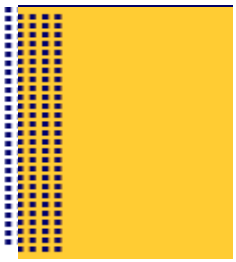
Morkos AA, Hopper AO, Deming DD, et al. Elevated total peripheral leukocyte count may identify risk for neurological disability in asphyxiated term neonates. *J Perinatol.* 2007;27:365-370

Type I and II errors. HyperStat online Web site. Accessed July 17, 2007, at: http://davidmlane.com/hyperstat/A18652.html

American Board of Pediatrics Content Specification(s):

Understand the concept of normal distribution and calculate the standard deviation, the standard error of the mean, and the median, and realize the importance of the *P* value

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



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April: Question 10

A primagravida is referred to you by a perinatologist to discuss the potential effect of her hypothyroidism on the child. Review of her history indicates early-onset hypothyroidism associated with an ectopic, hypoplastic thyroid. She has required supplementation with thyroid hormone. She is a prominent fish merchant, and has heard that the fetal thyroid gland comes from fishlike gills in the embryo. She asks you about this relationship and wants to understand the formation of the thyroid gland.

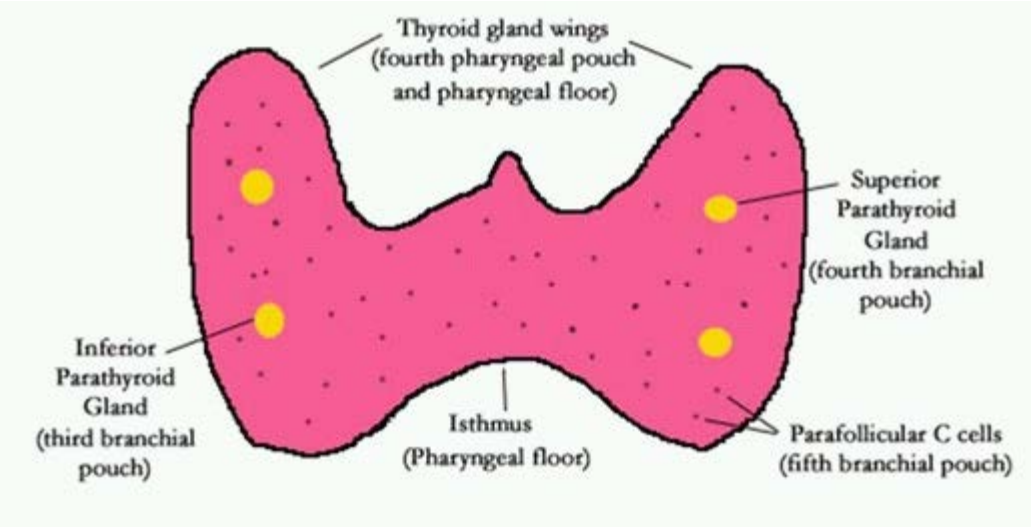
Of the following, the MOST important precursor to the isthmus of the thyroid gland is the:

1	fifth pharyngeal pouch
2	fourth pharyngeal pouch
3	pharyngeal floor
4	Rathke's pouch
5	third pharyngeal pouch

You selected 3, the correct answer is 3.

The thyroid gland comprises several tissues and structures, including the thyroid hormone–secreting follicular cells, the calcitonin-secreting parafollicular C cells, and the four parathyroid glands. These tissues derive from several anlagen (Figure). The bulk of the tissues of the thyroid gland originate in the pharyngeal floor and the fourth pharyngeal pouch, and that portion that forms the isthmus is mainly derived from the pharyngeal floor.

Figure: Posterior view of the thyroid gland tissues and their origins



The gills that are vital for fish and larval amphibians are not needed by air-breathing mammals. When the gills (Greek: *branchia*) form in the mammalian embryo, their structure becomes available for the development of the branchial apparatus. Evolution has played freely with this apparatus, so that the originally simple gill-like structures undergo extensive migration and differentiation in the mammalian embryo before settling on their final function in their final site.

The embryo forms four main branchial arches, as well as two more rudimentary arches, anterior and lateral to the pharynx. The pharynx bulges out between these arches to form four main pharyngeal pouches and a rudimentary fifth. Students often ask how a space, or pouch, can later form a structure; they can be guided by the concept of the resulting structures being formed by the cells lining the pouch, multiplying, and eventually filling in the migrating potential spaces.

The greatest portion of the thyroid gland begins on the pharyngeal floor. It migrates from an area that becomes the posterior aspect of the tongue, leaving a small remnant pit at the base of the tongue called the foramen cecum. The migration of the thyroid diverticulum proceeds caudally along the thyroglossal duct until it reaches the level of the fourth branchial arch. This migration is thought to be linked to the migration of the anlagen of the heart and thymus caudally into the thorax. The midline portion of the thyroid then spreads laterally, and fuses with tissues derived from the fourth branchial pouch, to form the complete thyroid gland by day 50 of gestation. Rarely, remnants of the thyroglossal duct may form midline cysts or sinuses.

The third pharyngeal pouch produces the inferior parathyroid glands, and the fourth pharyngeal pouch produces the superior parathyroid glands. The parathyroid glands migrate with the thyroid anlage and remain on the thyroid's posterior aspect.

The fifth pharyngeal pouch is an ill-defined area incorporated into the caudal end of the fourth pharyngeal pouch to form the ultimobranchial body. This body fuses with the thyroid gland and disperses to form the parafollicular C cells. Although these cells secrete calcitonin, they are labeled "C" because they appear clear on hemotoxylin-eosin staining.

Rathke's pouch is an invagination of the pharyngeal roof. Made of oral ectoderm, it extends toward the neuroectoderm of the infundibulum to form the anterior pituitary gland, which will eventually produce thyroid-stimulating hormone. It was named after Martin Heinrich Rathke, an amiable18th-century German anatomist known for his important work on the comparative anatomy of the embryonic branchial apparatus.

To specifically answer the mother's concern in the vignette: because her hypothyroidism does not involve antithyroid antibodies that cross the placenta, and her hypothyroidism is adequately treated, the likelihood that the pregnancy will be affected is low. The infant likely will not have thyroid problems, and informing her about neonatal screening can reassure her concerns about

her child's development.

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Chmait R, Moore TR. Endocrine disorders in pregnancy. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn.* 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:71-84

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Rose SR. Thyroid disorders. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant.* 8th ed. Philadelphia, Pa: Mosby Elsevier; 2006:1523-1535

American Board of Pediatrics Content Specification(s):

Understand the embryology and normal physiological function of the normal thyroid gland

Know the physiological roles of the hormones and other proteins involved in the regulation of thyroid function

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May: Question 1

A 28-week-gestation female infant was born weighing 1,080 g. She received intravenous parenteral nutrition for the initial 2 weeks after birth. Enteral feedings were begun 5 days after birth but have been stopped several times because of feeding intolerance and a bout with necrotizing enterocolitis. She is currently 5 weeks old, weighs 1,130 g, and is tolerating 110 mL/kg per day of fortified breast milk.

Of the following, former premature infants with postnatal growth restriction are MOST likely, as adults, to have:

1	higher body mass index
2	hypotension
3	insulin resistance
4	malnutrition
5	renal hypertrophy

You selected 2, the correct answer is 3.

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Long-term follow-up studies on the neurodevelopmental outcomes associated with very low birthweight (VLBW) are remarkably encouraging. Although former VLBW infants have more health problems, greater developmental impairment, and lower educational achievement as adults, their self-reported level of self-esteem is similar to that of term controls. As these individuals reach adult years, consequences of being born early are being discovered in other areas of their general health.

Low-birthweight and VLBW infants born prematurely often have insufficient nutrient uptake during the fetal and early neonatal period because of abnormal placental transfer, limitations with parenteral supplementation, and gastrointestinal dysfunction. Often, at term adjusted age, these infants are more underweight for age than they were at birth, a condition called postnatal growth restriction. Upon reaching young adulthood, when compared with term, normally-nourished infants, metabolic differences have been described in former premature and undergrown infants that have been ascribed to the long-term effects of prematurity and/or low birthweight ("The Barker Hypothesis").

The Barker hypothesis suggests that adult disease may originate during fetal life. Furthermore, postnatal growth restriction experienced by most premature and VLBW infants may contribute to or exacerbate adult medical disorders. The low birthweight infant undergoes a marked environmental and nutritional disruption during the time of maximum growth velocity and continuing organogenesis when born prematurely. Both intrauterine and postnatal growth restriction may trigger

adaptations in circulation and/or metabolism that favor the supply of nutrients to the brain at the expense of other organs. Although modest adaptations may affect only fat deposition, resulting in normal head and linear growth, nutrient stress may affect organs such as the kidney, pancreas, liver, and muscle. Several mechanisms involving the hypothalamic-pituitary axis, neuroendocrine axis, renin-angiotensin system, alteration of gene expression (possibly because of oxidative stress), and epigenetic effects on mitochondrial genes have been postulated and are under study.

Epidemiologic studies of former low-birthweight and preterm infants have consistently found altered glucose metabolism and cardiovascular disease later in life. Statistically significant elevations in fasting glucose concentrations, postprandial and fasting insulin concentrations, and insulin resistance index occur among former low-birthweight infants when tested as adults (Table).

Table

Table. Measures of Glucose Metabolism During Adulthood in Former Very-Low-Birthweight (VLBW) Infants*

Measurements	VLBW	Term	*P*
Fasting glucose, mmol/L	4.72	4.67	.08
2-h postprandial glucose, mmol/L	5.34	5.50	.02
Fasting insulin, mU/L	5.61	5.01	.001
2-h postprandial insulin, mmol/L	34.1	25.6	<.001
Insulin resistance index†	1.18	1.04	.001

* Adapted from Hovi and colleagues (2007).

† Insulin resistance by homeostasis model assessment.

Changes in glucose metabolism were noted regardless of intrauterine growth status, suggesting an early neonatal component to the long-term changes in glucose metabolism. Although body mass indices were not found to be different between VLBW and term infants as adults, studies have related earlier emergence of type 2 diabetes to the adiposity rebound—the rapid increase in weight observed after a period of slower growth—that occurs in some infants. This pattern often may be seen after intrauterine growth restriction or postnatal growth restriction. Of note, decreased numbers of pancreatic beta cells and decreased beta-cell mass have been observed, depleting the capacity for insulin secretion to overcome insulin resistance. The degree to which this long-term pattern can be influenced by changes in early nutritional management will only be known as currently treated less malnourished neonates reach adolescence and adulthood.

Altered organogenesis has been noted among VLBW infants. Nephrogenesis continues until 34 to 36 weeks' gestation. Persons with lower birthweights ultimately have fewer nephrons, and newborns are often exposed to potentially nephrotoxic treatments. Renal hypertrophy is not observed. Former low-birthweight infants also have been noted to have a higher incidence of hypertension than normal-birthweight infants. In addition to the kidneys and pancreas, altered growth patterns have been noted in the liver, muscle, and adipose tissue.

feature.)

References:

Barker DJ, Eriksson JF, Forsen T, Osmond C. Fetal origins of adult disease: strength of effects and biological basis. *Int J Epidemiol.* 2002;31:1235-1239

Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischemic heart disease. *Lancet.* 1989;2:577-580

Hovi P, Andersson S, Eriksson JG, et al. Glucose regulation in young adults with very low birth weight. *N Engl J Med.* 2007;356:2053-2063

Ingelfinger JR. Prematurity and the legacy of intrauterine stress. *N Engl J Med.* 2007;356:2093-2095

American Board of Pediatrics Content Specification(s):

Understand how extremes of intrauterine growth affect postnatal nutritional requirements

Recognize the effects of fetal programming on the prevalence of adult disorders

Understand the implications and management of fetal growth restriction

Understand the metabolic consequences of starvation in the neonatal period

Know how to diagnose and manage abnormalities of intrauterine growth rate

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May: Question 2

A 34-hour-old Caucasian male infant delivered at 36 weeks' estimated gestational age is found to be icteric down to the thighs. He is active, alert, and feeding well. Maternal history includes gestational diabetes that was controlled with dietary intervention. In addition, the mother's blood group is O Rh positive with a negative antibody screen. The sibling had no history of neonatal jaundice. The infant is delivered by cesarean section for fetal macrosomia. The infant's birthweight is 4.9 kg. The infant's blood group is B Rh-positive with a positive Coombs' test. Total serum bilirubin concentration at 34 hours of age is 15 mg/dL (257 µmol/L) and the conjugated bilirubin concentration is 0.8 mg/dL (13.7 µmol/L). The reticulocyte count is 9%. Intensive phototherapy is administered and adequate fluid intake is ensured. Serum bilirubin concentration after 2 hours is 16 mg/dL (274 µmol/L) and the serum albumin 2.9 g/dL (29 g/L).

Of the following, the available pharmacologic agent MOST likely to avert the need for exchange transfusion in this infant is:

1	activated charcoal
2	albumin
3	intravenous immunoglobulin
4	phenobarbital
5	zinc mesoporphyrin

You selected 3, the correct answer is 3.

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(Content revised May 19, 2008)

The infant in the vignette has several risk factors for the development of severe unconjugated hyperbilirubinemia, including blood group incompatibility with a positive Coombs' test, gestational age of 36 weeks, male sex, macrosomia, and maternal diabetes. The American Academy of Pediatrics clinical practice guideline published in 2004 provides a framework for the prevention and treatment of severe hyperbilirubinemia in newborn infants of 35 or more weeks of gestation. The mainstay of treatment of unconjugated hyperbilirubinemia is phototherapy and exchange transfusion depending on the age of the infant, total serum bilirubin (TSB) concentration, and presence of risk factors (Table 1). However, several pharmacologic agents can be helpful in the treatment when used appropriately.

Table 1. Risk Factors for Development of Severe Hyperbilirubinemia in Infants of 35 or More Weeks' Gestation (in Approximate Order of Importance)*
Major Risk Factors
Predischarge TSB or TcB level in the high-risk zone
Jaundice observed in the first 24 h
Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (eg, G6PD deficiency), elevated ETCOc
Gestational age 35-36 wk
Previous sibling received phototherapy
Cephalohematoma or significant bruising
Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive
East Asian race†
Minor risk factors
Predischarge TSB or TcB level in the high intermediate-risk zone
Gestational age 37-38 wk
Jaundice observed before discharge
Previous sibling with jaundice
Macrosomic infant of a diabetic mother
Maternal age ≥25 y
Male sex
Decreased risk (these factors are associated with decreased risk of significant jaundice, listed in order of decreasing importance)
TSB or TcB level in the low-risk zone
Gestational age ≥41 wk
Exclusive bottle feeding
Black race†
Discharge from hospital after 72 h

ETCOc = corrected end tidal carbon monoxide; TcB = transcutaneous bilirubin; TSB = total serum bilirubin.
* Adapted from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (2004).
† Race as defined by mother's description.

Administration of intravenous immunoglobulin (IVIG; 0.5-1 g/kg over 2 hours) is recommended in isoimmune hemolytic disease if the TSB concentration is increasing despite intensive phototherapy or if the TSB concentration is within 2 to 3 mg/dL (34-51 mmol/L) of the exchange level. If necessary, this dose can be repeated in 12 to 24 hours. IVIG has been shown to reduce the need for exchange transfusions in Rh and ABO hemolytic disease in which red blood cells are destroyed by an antibody-dependent cytotoxic mechanism mediated by Fc receptor–bearing cells of the neonatal reticuloendothelial system. IVIG may act by nonspecific blockade of Fc receptors.

Reabsorption of unconjugated bilirubin may contribute to a significant portion of hepatic bilirubin load in the newborn period. Frequent milk feeding may slow the rise of TSB concentrations and enhance the bilirubin-reducing effect of phototherapy. Oral administration of nonabsorbable substances that bind bilirubin in the intestinal lumen may reduce enteric absorption of bilirubin, thus reducing peak TSB concentrations in jaundice. Activated charcoal has been used but is effective only when administered during the first 12 hours after birth. Agar has also been shown to be effective in some studies, ineffective in others. Further study of such treatments is needed before recommendations can be made regarding clinical applications. These pharmacologic agents may be no more effective than frequent milk feeding.

Serum albumin levels and the bilirubin-to-albumin (B/A) ratio are recommended as factors to be considered in the decision to initiate phototherapy or perform exchange transfusion.

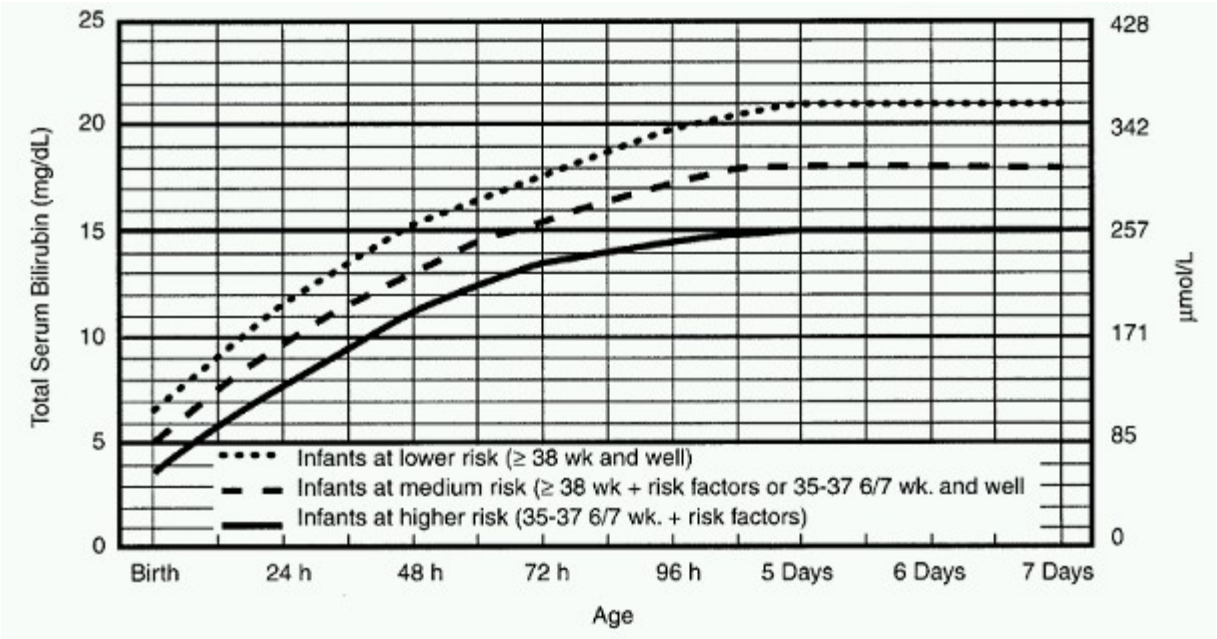
Bilirubin is transported in the plasma tightly bound to albumin, and the portion that is unbound or loosely bound can more readily leave the intravascular space and cross the intact blood-brain barrier. Elevations of unbound bilirubin (UB) have been associated with kernicterus in sick preterm newborns and with transient abnormalities in the auditory brainstem response in term and preterm infants. Clinical laboratory measurement of UB is not currently available in the United States. The ratio of bilirubin (mg/dL) to albumin (g/dL) correlates with measured UB in

newborns and can be used as an approximate surrogate for the measurement of UB. However, this ratio is of limited clinical use because:

- **Both albumin concentrations and the ability of albumin to bind bilirubin vary significantly between newborns.**
- **The risk of bilirubin encephalopathy is a function of a combination of several factors: the TSB concentration, the concentration of UB, and the susceptibility of the cells of the central nervous system to damage induced by bilirubin.**

It is therefore a clinical option to use the B/A ratio together with, but not in lieu of, the TSB level as an additional factor in determining the need for treatment with phototherapy (Figure 1).

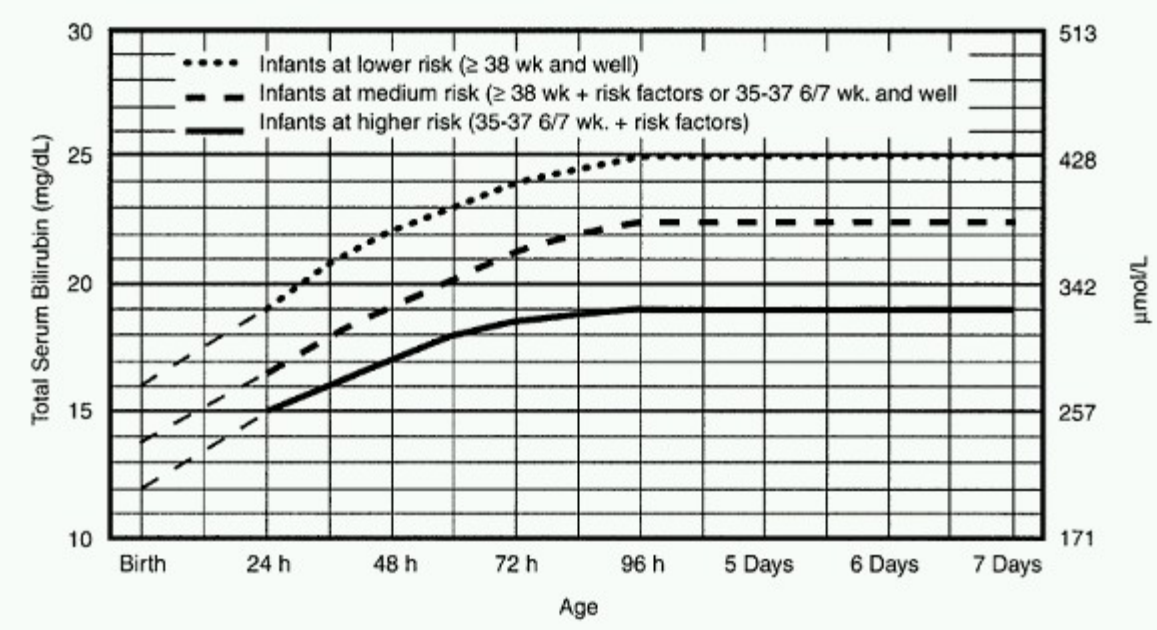
Figure 1: Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation



- **Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.**
- **Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0 g/dL (if measured)**
- **For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.**
- **It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50 mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.**

Guidelines also have been established for exchange transfusion, with differing thresholds depending on the infant's gestational age, TSB, hours since birth, and presence or absence of risk factors.

Figure 2: Guidelines for exchange transfusion in infants 35 or more weeks' gestation



Adapted from the American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (2004).

- **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.**
- **During birth hospitalization, exchange transfusion is recommended if the TSB rises to these levels despite intensive phototherapy.**
- **For readmitted infants, if the TSB level is above the exchange level, repeat TSB measurement every 2 to 3 hours and consider exchange if the TSB remains above the levels indicated after intensive phototherapy for 6 hours.**

If serum albumin concentrations are available, determination of the bilirubin/albumin ratio [TSB (mg/dL) / Albumin (g/dL)] also can be used to assist in determining the threshold at which exchange transfusion is considered (Table 2).

Table 2. B/A ratio at which ET should be considered

Risk Category	B/A Ratio at Which Exchange Transfusion Should be Considered	
	TSB mg/dL/Alb, g/dL	TSB µmol/L/Alb, µmol/L
Infants ≥38 0/7 wk	8.0	0.94
Infants 35 0/7-36 6/7 wk and well or ≥38 0/7 wk if higher risk or isoimmune hemolytic disease or G6PD deficiency	7.2	0.84
Infants 35 0/7-37 6/7 wk if higher risk or isoimmune hemolytic disease or G6PD deficiency	6.8	0.80

B/A = bilirubin-to-albumin ratio; G6PD = glucose-6-phosphate dehydrogenase; TSB = total serum bilirubin.
* Modified from American Academy of Pediatrics (2004).
† If the TSB is at or approaching the exchange level, send blood for immediate type and crossmatch. Blood for exchange transfusion is modified whole blood (red cells and plasma) crossmatched against the mother and compatible with the infant.

Although pretreatment with albumin before exchange transfusion has been shown to increase the efficiency of bilirubin removal by shifting more tissue-bound bilirubin into the circulation, it is *not* routinely recommended because:

- **The total amount of bilirubin removed during an exchange transfusion is only a portion of the total body pool of bilirubin.**
- **Increased bilirubin removal may not significantly alter subsequent concentrations or the need for additional exchange transfusions.**
- **The transient increase in TSB concentration after albumin administration theoretically could increase the risk of kernicterus if local conditions enhance entry of bilirubin into neurons.**
- **Constituents of some albumin solutions may displace bilirubin from its binding sites, potentially increasing the percentage of free bilirubin present in the plasma.**

Phenobarbital has been used as a stimulator of bilirubin conjugation, thus decreasing the severity of unconjugated hyperbilirubinemia:

- **Oral phenobarbital administered to neonates with glucose-6-phosphate dehydrogenase deficiency from the first to fifth day after birth resulted in decreased need for exchange transfusion compared with controls.**
- **Treatment of pregnant women with phenobarbital during the last few weeks of pregnancy resulted in a decreased incidence of severe unconjugated hyperbilirubinemia.**

However, treatment with phenobarbital *cannot* be recommended routinely because:

- **Combining phenobarbital treatment with phototherapy has no advantage, the effect being no greater than that of phototherapy alone.**
- **The administration of phenobarbital to newborns at the time jaundice is first observed or even immediately after delivery is less effective than its administration to the mother during pregnancy for at least 2 weeks before delivery.**
- **Phenobarbital is potentially addictive, may lead to excessive sedation of the newborn, and has other potent metabolic effects in addition to those of bilirubin metabolism.**

For these reasons, phenobarbital is reserved largely for specific high-risk populations. For example, in the unexplained severe hyperbilirubinemia of newborns from the Greek coastal islands, the frequency of kernicterus has been significantly reduced by general administration of phenobarbital to pregnant women during the last trimester.

Synthetic heme analogues such as tin- (Sn) and zinc- (Zn) proto- and mesoporphyrins (MP) competitively inhibit the activity of heme-oxygenase (HO), the rate-limiting enzyme in the production of bilirubin from heme catabolism, thus preventing neonatal hyperbilirubinemia. Human trials with SnMP in preterm neonates have shown a dose-dependent reduction in peak bilirubin concentrations irrespective of gestational age, and a reduction in the need for phototherapy compared with controls. However, SnMP contains a foreign metal, induces the HO-1 promoter, can inhibit other enzymes such as nitric oxide synthase and soluble guanylyl cyclase, and leaves lingering concerns related to potential long-term adverse effects such as suppression of the cytoprotective effects of HO-1 against oxidative stress and inflammation in critically ill neonates. It is not approved by the US Food and Drug Administration for use in neonates.

An alternative compound, zinc porphyrin (ZnPP), has been proposed, but it has a much lower inhibitory potency and it is not well absorbed after oral administration. In nonhuman primates, a single injection of ZnPP (40 mmol/kg of body weight) administered subcutaneously was effective in reducing serum bilirubin concentrations for 12 days. Despite these promising observations, ZnPP can suppress cell proliferation in cultured cells and in tumor models in vivo. Thus, it could potentially cause significant damage to the rapidly proliferating tissues and organs of the neonate. Another potential complication is the induction of HO-1 gene expression. This could result in tachyphylaxis and loss of therapeutic efficacy with repeated doses. These theoretic considerations need to be tested carefully in human cells before the clinical use of ZnPP can be recommended. It is also not approved by the US Food and Drug Administration for use in neonates.

(Content revised May 19, 2008)

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American Board of Pediatrics Content Specification(s):

Know the effect of diabetes mellitus and its treatment on the fetus

Understand the factors that affect the biological properties of bilirubin, including its solubility

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

Understand the factors associated with a decrease in neonatal serum bilirubin concentrations, including those that affect the enterohepatic circulation of bilirubin

Understand the tests that have been used to measure serum bilirubin and the binding of the bilirubin to albumin, and the limitations of these tests

Understand the factors affecting the binding of bilirubin to albumin

Understand the mechanisms by which bilirubin enters the brain

Understand the factors that increase the risk of kernicterus

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

Understand the effect of phenobarbital on bilirubin metabolism and its use in the treatment of hyperbilirubinemia

Understand the effects of drugs on bilirubin metabolism and their use in the treatment of hyperbilirubinemia

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11 November 08

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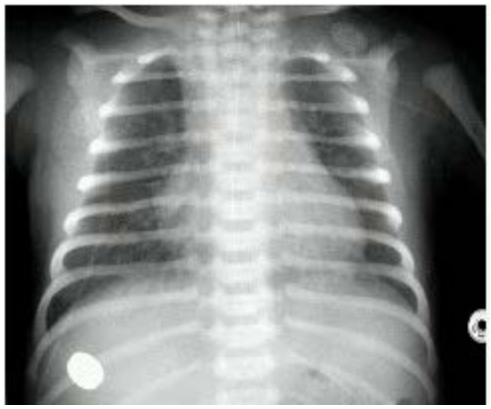
May: Question 3

You are asked to evaluate a 9-hour-old male infant with tachypnea. He was delivered by cesarean birth to a 24-year-old white mother at 38 0/7 weeks' gestation. She had a history of frequent outbreaks of genital herpes before pregnancy and had a vaginal lesion at the time of delivery. Her group B *Streptococcus* status is not known. Her membranes ruptured 1 hour before delivery and the amniotic fluid was meconium stained. She was not in labor. The infant cried immediately after birth and had Apgar scores of 8 and 9 at 1 and at 5 minutes, respectively. He became tachypneic 3 hours after birth after an initial attempt at breastfeeding. When you examine him he has a respiratory rate of 100 breaths per minute. In 30% humidified oxygen from a nasal cannula, he is able to maintain his oxygen saturation above 95%. He has a few subcostal retractions, mild nasal flaring, and an occasional grunt when he is disturbed. Laboratory results are as follows:

Laboratory Test	Patient Result
White blood cell count, /μL (×10^9/L)	14,000 (14)
Differential	
Bands, %	2
Segmented neutrophils, %	64
Lymphocytes, %	26
Monocytes, %	8
Platelet count, ×10^3/μL (×10^9/L)	250 (250)
Capillary blood gas	
pH	7.29
PCO_2, mm Hg	58
PO_2, mm Hg	35

The infant's initial chest radiograph is shown in the Figure.

Figure



Of the following, the MOST effective treatment to reduce the risk of respiratory distress in this neonate would be:

1. chest physiotherapy immediately after delivery

2	maternal glucocorticosteroids before delivery
3	maternal penicillin before delivery
4	maternal valacyclovir beginning at 36 weeks' gestation
5	tracheal suction immediately after delivery

You selected 3, the correct answer is 4.

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Respiratory distress is one of the most frequent reasons for admission of term and late preterm neonates to an intensive care unit. Causes of respiratory distress in the term infant may be pulmonary or nonpulmonary (Table).

Table

Table. Potential Pulmonary Causes for Respiratory Distress in Term Neonates*

Parenchymal conditions
• Transient tachypnea of the newborn • Meconium aspiration syndrome and other aspirations • Respiratory distress syndrome • Pneumonia • Pulmonary edema • Pulmonary hemorrhage • Pulmonary lymphangiectasia
Developmental abnormalities
• Lobar emphysema • Pulmonary sequestration • Cystic adenomatoid malformation • Congenital diaphragmatic hernia • Tracheoesophageal fistula • Pulmonary hypoplasia
Airway abnormalities
• Choanal atresia/stenosis • Laryngeal web • Laryngotracheomalacia or bronchomalacia • Subglottic stenosis
Mechanical abnormalities
• Rib cage anomalies • Pneumothorax • Pneumomediastinum • Pleural effusion • Chylothorax

* Adapted from Flidel-Rimon and Shinwell (2005).

Bacterial or viral pneumonia, respiratory distress syndrome (RDS), meconium aspiration, and transient tachypnea of the newborn (TTN) are common pulmonary causes of respiratory distress in the late preterm and term neonate. The neonate in the vignette has TTN. TTN or “wet lung” is a self-limited disorder generally affecting neonates born at or near term. It occurs in approximately 11 in 1,000 live births and is far more common in neonates born via cesarean section, especially those without labor. Affected neonates with TTN usually present within the first 6 hours after birth with tachypnea and have milder symptoms of respiratory distress than neonates with RDS or pneumonia. Symptoms may include:

- **cyanosis**
- **subcostal retractions**

- nasal flaring
- increased anteroposterior diameter of the chest
- expiratory grunting
- tachypnea

Arterial blood gases may show respiratory acidosis, secondary to air trapping, and hypoxemia. The complete blood count is normal. The chest radiograph and hospital course are usually key to making the diagnosis of TTN. Early radiographic findings may include:

- prominent perihilar streaking
- mild to moderate cardiomegaly
- fluffy densities
- fluid in the minor fissure
- pleural effusions
- hyperinflation with flattening of the diaphragm

Signs and symptoms usually are transient and last for 12 to 24 hours in mild cases and 48 to 72 hours in severe cases.

For effective gas exchange to occur, the alveolar spaces must be cleared of excess fluid. The exact mechanism for clearance of fetal alveolar fluid is still unknown. The expulsion of lung fluid during the "vaginal squeeze" at delivery accounts for only a fraction of lung fluid clearance. Sodium transport is an important mechanism for transepithelial movement of alveolar fluid into the interstitium of the lung where it is subsequently absorbed into the vasculature. Neonates with TTN are more likely to have immature transepithelial sodium transport. High levels of endogenous catecholamines present during labor and at birth are important physiologic regulators of sodium movement across the pulmonary epithelium.

Treatment of TTN is supportive, because symptoms resolve with time. Supplemental oxygen may be required to maintain adequate oxygen saturation. Continuous positive airway pressure or mechanical ventilation is rarely required. Neither chest physiotherapy nor diuretics have been shown to be effective in clearing fluid from the lungs of neonates with TTN.

Herpes simplex virus is a common viral sexually transmitted disease in the United States. Five percent to 10% of women have symptomatic recurrent herpes during their pregnancy, of whom 25% will have an outbreak during the last month of their pregnancy. Because a majority of neonatal herpes results from transmission near delivery, preventive strategies have focused on the peripartum period. Current guidelines recommend a cesarean delivery for all women with active genital herpes lesions or prodromal symptoms at the time of presentation in labor.

Valacyclovir, a prodrug of acyclovir, was developed to improve bioavailability of acyclovir by enhancing absorption from the gastrointestinal tract. A randomized trial has shown that in women with a history of recurrent genital herpes valacyclovir treatment after 36 weeks' gestation reduces herpes simplex virus shedding, recurrent genital herpes, and cesarean delivery (4% in the valacyclovir group and 13% in the placebo group [P = .009]).

Neonates delivered vaginally after labor have the lowest risk of developing TTN. If the mother in the vignette had received valacyclovir treatment beginning at 36 weeks' gestation, her risk of having a herpes outbreak and a cesarean delivery would have been reduced. Thus the risk of TTN in her newborn would be lower.

Antenatal glucocorticosteroid treatment is an established means of reducing the risk of RDS in preterm neonates. The infant does not have clinical or radiographic findings of RDS and the 1994 National Institutes of Health consensus panel guidelines do not recommend antenatal glucocorticosteroids for women beyond 34 weeks' gestational age.

The use of antenatal glucocorticosteroids for the prevention of TTN after an elective cesarean birth is being investigated. A recent pilot study evaluating the efficacy of bethamethasone in preventing respiratory distress in neonates delivered by an elective cesarean section suggested

that two doses of bethamethasone 48 hours before delivery could significantly decrease admissions to the NICU for respiratory distress. Until larger randomized trials are completed, antenatal glucocorticosteroid therapy cannot be recommended to prevent TTN.

Intrapartum intravenous penicillin effectively reduces the risk of group B streptococcal disease among newborns born to women with group B streptococcal vaginal colonization; however, penicillin treatment is required in women whose streptococcal status is unknown only if they deliver before 37 weeks' gestational age, have ruptured membranes for at least 18 hours, or have an intrapartum fever. The mother in the vignette has none of these risk factors. Clinical, laboratory, and radiographic findings of the neonate in the vignette are not compatible with a diagnosis of group B streptococcal pneumonia or septicemia. Intrapartum intravenous penicillin does not prevent TTN.

Passage of meconium in utero occurs in 8% to 20% of all deliveries and meconium aspiration syndrome occurs in about 1% to 4% of deliveries complicated by meconium stained fluid. Resuscitation of neonates born to mothers with meconium-stained fluid is based on their presentation after delivery. Neonates who are not vigorous, as defined by poor respiratory effort, poor muscle tone, and a heart rate less than 100 beats per minute should have their trachea suctioned immediately after delivery. If the infant is vigorous, tracheal suctioning is not required. The neonate in the vignette was vigorous at birth and would not require tracheal suctioning at birth. Clinical, laboratory, and radiographic findings of the neonate in the vignette are not consistent with meconium aspiration syndrome.

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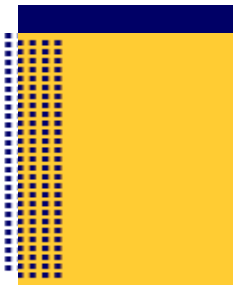
American Board of Pediatrics Content Specification(s):

Recognize the clinical, laboratory, radiographic, and pathologic features of transient tachypnea



of the newborn infant

Determine the prevention and management of transient tachypnea of the newborn infant

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May: Question 4

A 34-year-old primiparous woman is carrying a fetus at an estimated gestational age of 28 weeks. Her history is significant for hypothyroidism secondary to autoimmune thyroiditis diagnosed 4 years earlier for which she is receiving thyroid hormone treatment. She inquires whether the thyroid hormone can cross the placenta and affect the thyroid function of her fetus.

Of the following, the hormone MOST readily transferred across the placenta is:

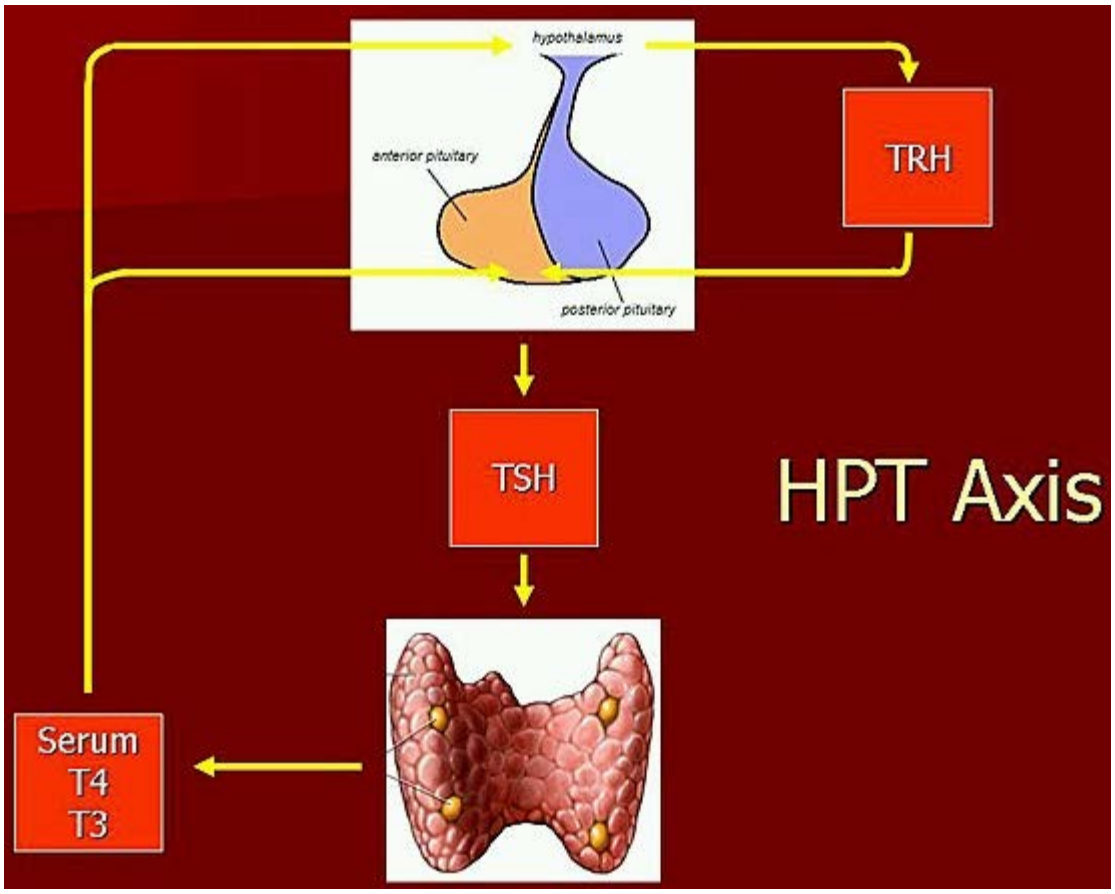
1	reverse triiodothyronine
2	tetraiodothyronine
3	thyroid-stimulating hormone
4	thyrotropin-releasing hormone
5	triiodothyronine

You selected 4, the correct answer is 4.

All forms of thyroid disease are more common in women than in men, and hypothyroidism is not a rare event during pregnancy, occurring in about 2 cases per 1,000 pregnancies. Autoimmune thyroiditis is the most common cause of hypothyroidism among pregnant women. Thyroid microsomal and peroxidase antibodies are positive in 60% to 90% of such cases. These antibodies readily cross the placenta and may cause transient neonatal hypothyroidism by blocking thyroid function.

To understand the placental permeability of hormones related to thyroid function, it is important to examine the hypothalamic-pituitary-thyroid (HPT) axis of thyroid hormone regulation as well as the synthesis of the thyroid hormones. The HPT axis (Figure 1) represents the feedback loop of thyroid hormone regulation.

Figure 1: Hypothalamic-pituitary-thyroid axis



Low circulating concentrations of thyroid hormones stimulate the hypothalamus, specifically the paraventricular nucleus, to secrete thyrotropin-releasing hormone (TRH). The TRH stimulates the thyrotropic cells of the anterior pituitary to secrete thyroid-stimulating hormone (TSH), which induces the secretion of thyroid hormones by the thyroid gland. Conversely, excess thyroid hormones in circulation suppress the hypothalamic TRH, which inhibits the pituitary TSH and lessens the stimulatory effect of TSH on the thyroid gland, reducing the circulating concentrations of thyroid hormones. This dynamic balance maintains concentrations of thyroid hormones in the physiologic range.

Thyroid hormone synthesis involves three critical steps:

- **uptake of iodide**
- **iodination of tyrosine**
- **deiodination of thyronines**

Iodine is absorbed in the alimentary tract in the form of iodide, which is taken up avidly by the thyroid gland under the influence of TSH. Iodination of tyrosine involves incorporation of iodine in specific positions within the tyrosyl ring of thyroglobulin, a glycoprotein synthesized by the endoplasmic reticulum of the thyroid follicle cells. This iodination of tyrosine is catalyzed by the enzyme thyroid peroxidase. The resultant iodotyrosines are monoiodotyrosine (3-iodotyrosine) (Figure 2) and diiodotyrosine (3,5-diiodotyrosine) (Figure 3).

Figure 2: Monoiodotyrosine

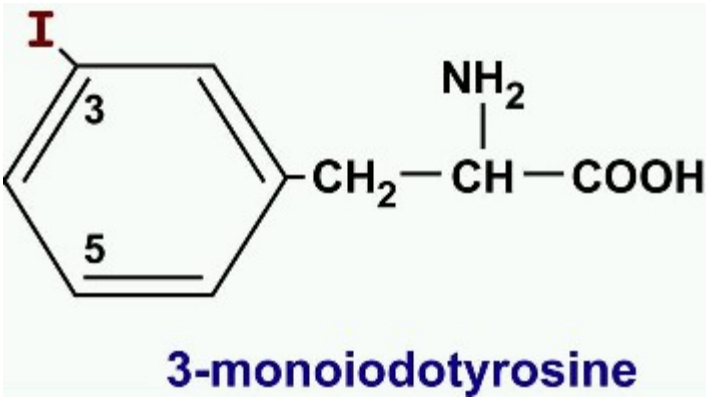
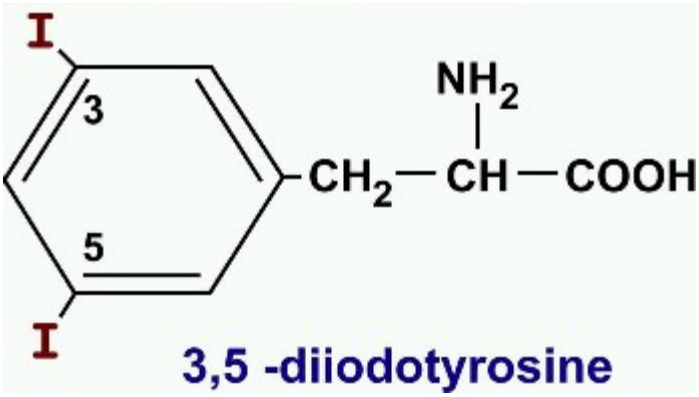
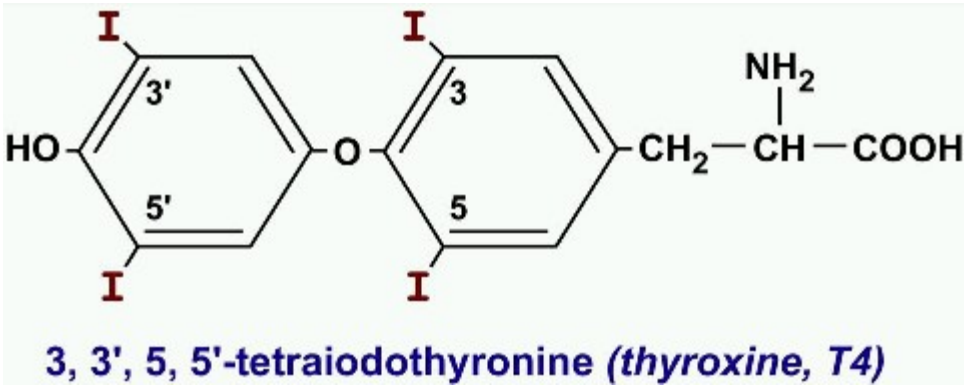


Figure 3: Diiodotyrosine



These iodotyrosines have no hormonal activity. Coupling of the iodotyrosines, under the influence of thyroid peroxidase, results in the formation of iodothyronines. Each iodothyronine has two rings, an inner tyrosyl ring with positions designated as 3 and 5, and an outer phenolic ring with positions designated as 3' and 5'. Tetraiodothyronine (3,3',5,5'-tetraiodothyronine)(thyroxine, T_4) (Figure 4) is the principal product of thyroid hormone synthesis. It has minimal biologic activity and acts mainly as a precursor of active thyroid hormone.

Figure 4: Tetraiodothyronine



Removal of iodine (deiodination) from specific positions in the tyrosyl and phenolic rings of T_4, under the influence of deiodinase, is required for the formation of functional thyroid hormones outside the thyroid gland. Triiodothyronine (3,3',5-triiodothyronine; T_3) (Figure 5) is derived by 5'-deiodination; it is the most biologically active form of thyroid hormone. Reverse triiodothyronine (3,3',5'-triiodothyronine; rT_3) (Figure 6) is derived by 5-deiodination; it is biologically inactive.

Figure 5: Triiodothyronine

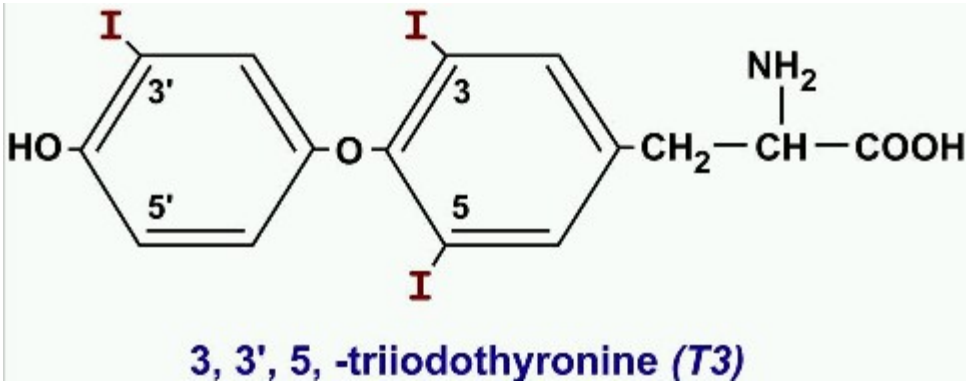
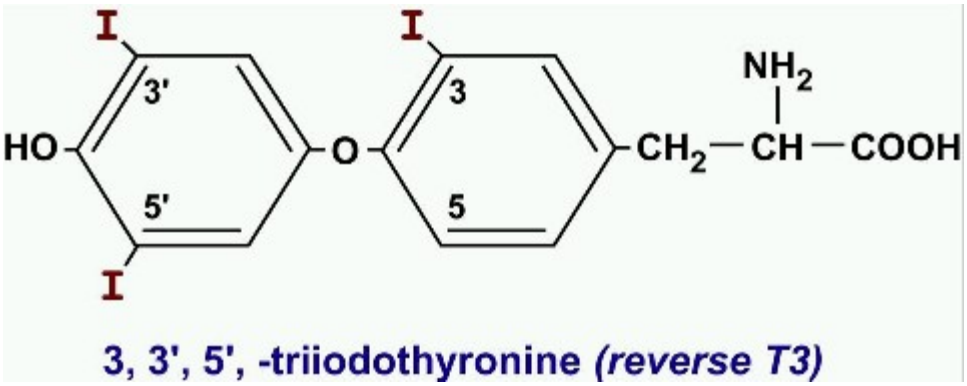


Figure 6: Reverse triiodothyronine



Further deiodination results in the formation of diiodothyronines and monoiodothyronines, which have no biological activity. The process of deiodination of thyronines is critical for balancing thyroid function; 5'-deiodination is predominant when active thyroid hormone is needed, whereas 5-deiodination prevails when thyroid function needs to be suppressed.

Among the hormones related to thyroid function listed in this vignette, TRH has the most placental permeability. Maternal administration of TRH is accompanied by increased concentrations of TSH, T_4, and T_3 in umbilical cord blood, which indicates stimulation of the fetal thyroid. This action of TRH has raised the possibility for maternal intervention with antenatal TRH treatment, used in conjunction with antenatal glucocorticosteroid treatment, to upregulate fetal thyroid function as a means of accelerating fetal lung maturation. In trials conducted before the advent of postnatal surfactant administration, an antenatal combination treatment with TRH and glucocorticosteroid in mothers with impending preterm deliveries was shown to be beneficial in reducing the risk of neonatal respiratory distress. Subsequent trials, after the establishment of surfactant use, however, have shown that a combination of antenatal glucocorticosteroid and postnatal surfactant treatment is effective in reducing the risk of neonatal respiratory distress, and that this benefit is not enhanced further by the addition of antenatal TRH.

The placenta has limited permeability to thyroid hormones. Large doses of T_4 given to the mother produce only minor changes in the concentrations of thyroid hormones in the umbilical cord blood. Much of the placental impermeability is attributed to the presence of 5-deiodinase enzyme in the placenta, which rapidly converts T_4, T_3, and rT_3 into diiodothyronines that have no biologic activity. The placenta is largely impermeable to TSH. The fetus of the woman in this vignette is not likely to be affected by her thyroid hormone treatment during pregnancy.

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American Board of Pediatrics Content Specification(s):

Understand the relationship between fetal and maternal thyroid physiology

Understand the embryology and normal physiological function of the normal thyroid gland

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May: Question 5

A family physician asks you to meet with the parents of a term newborn. They are dairy farmers and want to supplement breastfeeding with cow milk and wish to understand the nutritional impact of substituting or supplementing cow milk for human milk.

Of the following, the substance with a HIGHER concentration in human milk than in cow milk is:

1	alpha-lactalbumin
2	beta-lactoglobulin
3	casein
4	fat
5	phosphate

You selected 4, the correct answer is 1.

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Cow milk is great for newborn cows, but its differences from human milk make it unsuitable for newborn humans. Compared with human milk, cow milk has higher concentrations of protein, sodium, calcium, and phosphate, allowing for the more rapid growth in mass of the calf (Table). Most of the cow milk protein is in the form of casein. Beta-lactoglobulin is the main whey protein of cow milk, but is not found in human milk.

Table

Table. Composition of Human Milk and Cow Milk, per 100 mL

Constituent	Human Milk	Cow Milk
Protein, g	0.9	3.3
Fat, g	3.4	3.4
Carbohydrate, g	6.7	4.8
Sodium, mEq	6	22
Calcium, mEq	340	1,200
Phosphate, mEq	150	930
Osmolarity, mOsm/L	260-300	280
Casein:whey ratio	40:60	80:20

Because of the relative immaturity of the human newborn in relation to other species, human milk has more immunoprotective mechanisms than cow milk. One example of this is the protein alpha-lactalbumin, in greater concentration in human milk than in cow milk. Alpha-lactalbumin, the major whey protein in human milk, has bactericidal, antiviral, and immunomodulatory activities. One of its modulating functions is to reduce release from monocytes of tumor necrosis factor alpha, and interleukins 1, 2, and 6. Another modulating function

is its ability to induce apoptosis in tumor cells. Human milk also has markedly more lactoferrin, lysozyme, and secretory immunoglubulin A, all with anti-infective functions, and all found only in trace amounts in cow milk.

The protein concentration in breast milk correlates with the growth rate of each species, from human (0.9 g/100 mL in mature milk, 2.5 g/100 mL in colostrum) to cow (3.3 g/100 mL in mature milk) to blue whale (13 g/100 mL).

Cow milk protein is 80% casein versus 40% in human milk. Casein is harder to digest by the human neonate than whey, and may not be the best protein to support human brain development because of its abundance of phenylalanine, methionine, and tyrosine residues.

Beta-lactoglobulin is the main whey protein in cow milk. Mouse milk and human milk do not contain beta-lactoglobulin, so it is understandable that human allergy to cow milk is based mainly on reactions to this cow protein.

The total fat concentration in cow and human milk is similar (3.4%-4% by weight), but humans have more essential fatty acids and polyunsaturated fatty acids, such as linoleic acid, linolenic acid, arachidonic acid, and docosohexanoic acid, which are needed for the creation of the brain, retina, and red cell membranes.

Both cow and human milk suspend casein in aggregates called micelles. The negative electrical charge presented on the outside of each micelle helps separate it from other micelles and prevent clumping. In the absence of fat globules, as in skim milk, the proteins may impart some color to milk. The size of the casein micelle (0.1 µm) is just enough to scatter light, especially the shorter blue wavelengths, and causes the bluish tint of skim milk or human colostrum. Riboflavin may give a greenish tint.

The large concentrations of phosphate and calcium in cow milk help construct the rapidly growing calf skeletal mass. When fed to human neonates, however, the excess phosphate of cow milk may cause severe hypocalcemia, tetany, and rickets.

Why not feed cow milk to the human newborn? Because there is the risk of hypocalcemia, essential fatty acid deficiency, cow protein allergy, and gastrointestinal blood loss. The American Academy of Pediatrics recommends that cow milk not be given for the first 12 months after birth.

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American Board of Pediatrics Content Specification(s):

Understand the differences in the nutritional composition of human milk and cow milk

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May: Question 6

An 18-month-old female child is referred to the neurodevelopmental follow-up clinic because of concern regarding her motor development. Her medical history includes preterm birth via emergency cesarean section at 26 weeks' gestation for maternal chorioamnionitis and fetal distress. She received assisted ventilation for 4 weeks after birth. Serial cranial ultrasonography showed evidence of cystic periventricular leukomalacia. She was discharged from the hospital at a chronologic age of 10 weeks. At that time she was receiving fortified formula by bottle and supplemental gavage feeds.

Of the following, the type of cerebral palsy in this child is MOST likely to be spastic:

1	diplegia
2	hemiplegia
3	monoplegia
4	paraplegia
5	quadriplegia

You selected 4, the correct answer is 1.

Cerebral palsy **(CP) is a term used to describe a diverse group of chronic, nonprogressive disorders of movement, posture, and tone resulting from a central nervous system insult during early development. Many factors, both genetic and acquired, have been postulated as causes of CP. These include hypoxic-ischemic injury, structural malformations, vascular disorders, intracranial hemorrhage, infections, hormonal disorders, toxins, trauma, metabolic disease, prematurity, and hemolytic disease of the newborn.**

The clinical manifestations of CP are classified according to their type (spastic, atonic or dyskinetic [athetotic], and ataxic), and the topography of the impairment (quadriplegia, diplegia, hemiplegia, or monoplegia). The proportion of the different types of CP varies from report to report. Approximately 70% of all cases of CP are of the spastic type; 15% are athetotic; 5% ataxic; and the remainder mixed.

Spastic CP **is characterized by upper motor neuron signs such as weakness, hypertonicity, hyperreflexia, clonus, pathologic reflexes, and a tendency to develop contractures. In hemiplegia, one side of the body is chiefly affected, with the arm more affected than the leg. In diplegia, the legs are affected more than the arms, but usually all four extremities are affected. Quadriplegia refers to symmetric impairment of all four extremities. Monoplegia and triplegia are rare. Spastic paraplegia, in which the arms are completely normal, is almost always the result of a spinal cord lesion.**

Atonic CP **is characterized by marked motor delay, decreased tone with hyperextensibility, and mental retardation. The deep tendon reflexes are normal or increased, which distinguishes this condition from anterior horn cell or peripheral nerve disease. This condition appears to be a temporary phase during development; hypertonicity usually supervenes by 4 years of age.**

Dyskinetic CP **manifests as impaired volitional activity and uncontrolled and purposeless movements that disappear during sleep. It is associated with abnormality in the basal ganglia. The more common type is choreoathetoid in which the movements have two components. *Chorea* refers to rapid, variable, jerky motions of proximal muscle groups in the extremities and face, and *athetosis* refers to slow irregular writhing movements of the extremities, face, neck, and trunk. Kernicterus results in choreoathetoid CP, upward-gaze paresis, sensorineural hearing loss, and yellow-stained teeth. Dystonic form of dyskinetic CP involves truncal twisting, facial grimacing, and extremity rigidity resulting from the co-contraction of agonist and antagonist muscle groups.**

Ataxic CP **comprises dysfunction in coordination, gait, and rapid distal movements of the extremities. It is related to a static lesion of the cerebellum and its pathways. It is relatively infrequent and should be a diagnosis of exclusion.**

The neuropathologic antecedents of CP vary considerably with the gestational age of the infant, nature of the insult, and other as yet unidentified factors. Certain basic lesions can be recognized that are correlated with distinct clinical findings (Table).

Table

Table. Distinct Clinical Findings Associated With the Different Types of Lesions

Neuropathologic Feature	Associated Insults	Type of CP	Topography
Preterm infants			
Periventricular leukomalacia	Chorioamnionitis	Spastic	Diplegia
Periventricular hemorrhagic infarction		Spastic	Hemiparesis
Term infants			
Selective neuronal necrosis	HIE	Spastic	Quadriparesis
Status marmoratus	Kernicterus	Dyskinetic	
Periventricular leukomalacia		Spastic	Diplegia
Parasagittal cerebral injury		Spastic	Quadriparesis with upper extremity predominance
Focal and multifocal ischemic cortical injury	Vascular anomalies, vasculopathy, vascular obstruction	Spastic	Hemi- or quadriparesis

CP = cerebral palsy; HIE = hypoxic-ischemic encephalopathy.

The differences in the neuropathologic features of preterm and term infants can be explained on the basis of brain development. Before 32 weeks, the vasculature of the brain is composed of two systems, one that penetrates into the cortex—the *ventriculopedal system*—and another that reaches down to the ventricles, but then curves to flow outward—the *ventriculofugal system*. No vascular anastomoses connect these two systems. The area between these systems, through which the pyramidal tracts pass near the lateral cerebral ventricles, is a vascular watershed area vulnerable to ischemia. Injuries to this area result in spastic diplegia. After 32 weeks, vascular flow shifts toward the cortex. Thus, hypoxic injury after this time primarily damages the cortical region.

In the premature newborn who later presents with CP, periventricular leukomalacia and periventricular hemorrhagic infarction are the most common neuropathologic features.

Periventricular leukomalacia **consists of symmetric, focal necrosis of the white matter dorsal and lateral to the external angle of the lateral ventricles. With the passage of time, cystic cavities may develop in the more severe cases, whereas diminished myelin and dilated lateral ventricles will develop in milder cases. Because the descending motor fibers from the cortex to the lower extremities are closest to the ventricle, these lesions most commonly result in spastic diplegia. Periventricular leukomalacia has a strong association with prolonged rupture of membranes, chorioamnionitis, and neonatal hypotension.**

Periventricular hemorrhagic infarction **consists of asymmetric hemorrhagic necrosis of the periventricular white matter. In addition, there is usually an associated germinal matrix or intraventricular hemorrhage. White matter damage is caused by venous infarction resulting from obstruction of medullary and terminal veins by the germinal matrix or intraventricular hemorrhage. Because these lesions tend to be both large (therefore involving the descending tracts to both the arm and leg) and asymmetric, the common clinical manifestation is spastic hemiparesis.**

In full-term infants, more diverse pathologic patterns are seen, generally in association with hypoxic-ischemic brain injury.

- **S*elective neuronal necrosis,* neuronal loss, and gliosis are found in the neocortex, hippocampus, cerebellum, brainstem, and spinal cord and may be manifested clinically as quadriparesis.**
- ***Status marmoratus* exhibits similar pathologic features localized to the basal ganglia and thalamus, and adds a degree of hypermyelinization to these regions, resulting in a marbled appearance. This lesion is also seen in children with kernicterus. Dyskinetic CP may develop.**
- ***Periventricular leukomalacia*, described in preterm infants, may also be seen in the full-term infant.**
- ***Parasagittal cerebral injury* features necrosis in the superior and medial cortical convexities and adjacent white matter, which is greater posteriorly than anteriorly. The pathogenesis is presumably related to poor perfusion of the arterial border zones and end zones in this region, leading to a spastic quadriparesis with upper-extremity predominance.**
- ***Focal* and *multifocal ischemic cortical injury* shows similar pathologic features but involves a more localized circulatory compromise (single vessel and tributaries) such as might result from vascular anomalies, vasculopathy, or vascular obstruction. Spastic hemi- or quadriparesis is associated with these lesions.**

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American Board of Pediatrics Content Specification(s):

Understand the pattern of neuromotor development with extrapyramidal cerebral palsy

Recognize the most common type of cerebral palsy in infants with hypoxic-ischemic encephalopathy

Recognize the clinical features of spastic quadriplegia, diplegia, and hemiplegia

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May: Question 7

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A 6-day-old, 35-week-gestation daughter of the Director for the Centers for Medicare and Medicaid Services is ready for discharge home. She had transient hypothermia and tachypnea after birth that prompted admission to the neonatal intensive care unit. Breast feedings, although slow, are coordinated and her weight is increasing. She appears well, other than being icteric, and is physiologically stable. You are discussing the infant's medical issues during the hospitalization, outcomes, and the costs of infants born late preterm.

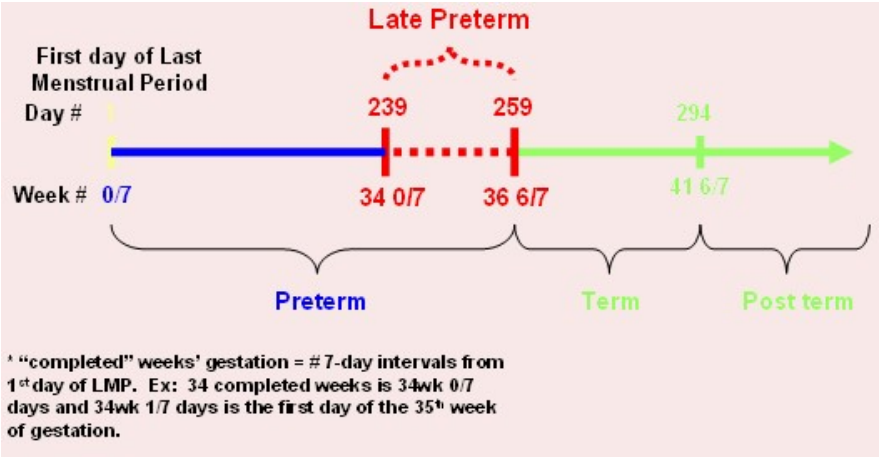
Of the following, late preterm infants in the United States are:

1	decreasing as a percentage of all live births
2	less likely to have difficulties in school than term infants
3	physiologically as mature as term infants
✗ 4	rehospitalized less frequently than infants born more preterm
5	the largest subpopulation of preterm live births

You selected 4, the correct answer is 5.

Late preterm infants are born at 34 0/7 weeks' gestation to 36 6/7 weeks' gestation (Figure 1).

Figure 1: Late preterm definition. (Adapted from Raju et al [2005].)



The term *late preterm* has replaced the use of "near term" because it more accurately reflects the risks associated with birth at this range of gestational ages. This subgroup of preterm infants accounts for 71% of all live *preterm* births (2002), the largest subgroup of preterm births. As a group, the birth rate of late preterm infants is growing more rapidly than all other populations of infants except those born at term (Table 1). Between 1992 and 2002, the rate of increase in late preterm live births was 14.3%, compared with a rate of 20.9% in term infants. The rate of increase in infants born at 40 weeks' gestation (-10.6%) and postterm (-30.5%) has declined such that the median gestational age at birth is now 39 weeks.

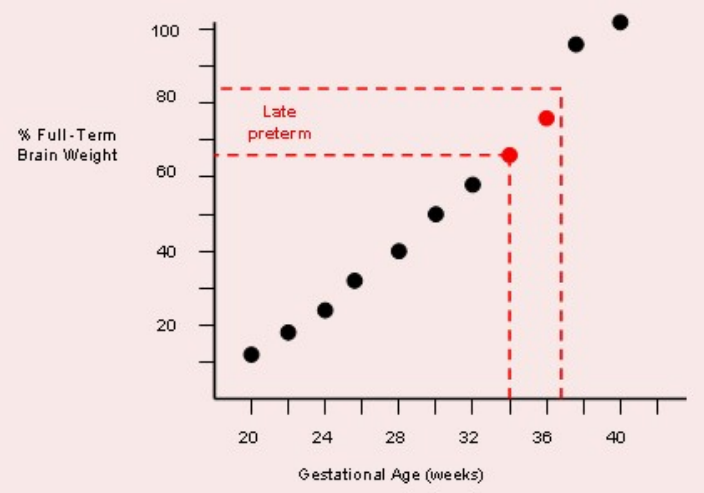
Table 1

Table 1. Gestational Age–Specific Births (All Singleton Live Births), United States*				
Gestational Age, wk	1992, %	1997, %	2002, %	% Change
< 32	1.5	1.4	1.4	−8.7
32-34	2.5	2.5	2.6	+4.0
35-36	**5.6**	**6.0**	**6.4**	**+14.3**
37-39	43.1	47.5	52.1	+20.9
40	23.6	23.0	21.1	−10.6
41-44	23.6	19.5	16.4	−30.5

* From Davidoff MJ. MOD Perinatal Data Center Workshop Optimizing Care and Long-term Outcome of Near-term Pregnancy and Near-term Newborn Infant July 18-19, 2005.

Late preterm infants, such as the infant in this vignette, are mistakenly thought to be physiologically as mature as term infants. For example, the weight of the brain of a 34 weeks' gestation infant is only two thirds (Figure 2) and myelination is only one third that of term infants.

Figure 2: Brain weight versus gestational age. (Adapted from Kinney [2006].)



The finding that late preterm infants as a group do less well in school than term counterparts suggests that neuronal maturation and catch-up brain growth may be delayed or incomplete (Table 2).

Table 2

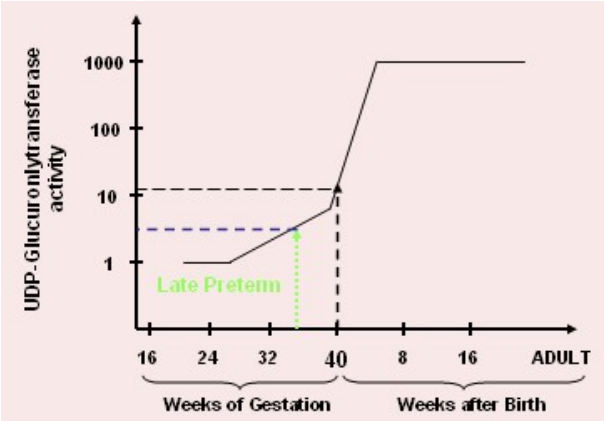
Table 2. School-Age Outcomes and Late Preterm Infants*

Outcome	Age, y	% Near term N = 22,552	% Full term N = 164,628	Adjusted RR (95% CI)
Developmental delay/disability	0-3	4.8	3.2	1.46 (1.42-1.50)
PreK at 3†	3	4.8	4.0	1.18 (1.14-1.21)
PreK at 4†	4	7.7	6.6	1.15 (1.13-1.18)
Not ready to start school	4	4.7	4.1	1.09 (1.05-1.12)
Special education	5	13.6	11.8	1.13 (1.11-1.15)
Retention	5	7.6	6.2	1.11 (1.08-1.14)
Suspension	5	1.3	1.2	0.97 (0.91-1.04)

CI = confidence interval; RR = relative risk.
* From Morse SB, Tang Y, Roth J. [abs 4355] *Pediatr Res.* 2006;1(suppl):158.
† Referral to Florida Part B program, prekindergarten program for children with disabilities.

Glucuronyltransferase activity at birth is about half that of term infants and accounts for a greater propensity for jaundice (Figure 3).

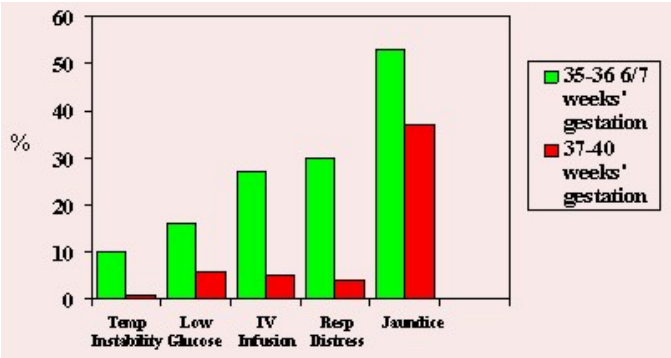
Figure 3: UDP-glucuronyltransferase activity. (Adapted from Kawade and Onishi [1981].)



Furthermore, apnea associated with deglutition and incoordination of oromotor function of late preterm infants contributes to feeding problems. Feeding problems may be masked during the birth hospitalization, especially if breastfeeding, because the infant is not challenged with an adequate volume of milk for several days. This often occurs several days after discharge home. Poor oral intake and low activity of bilirubin enzymes further contribute to the development of jaundice several days after birth.

Complications of preterm birth reflect physiologic immaturity in late preterm infants and result in more frequent admission to neonatal intensive care units than term infants. Common problems include temperature instability, hypoglycemia, need for intravenous fluid administration, respiratory distress, and jaundice (Figure 4).

Figure 4: Late preterm infants: morbidity during birth hospitalization. (Adapted from Wang [2004].)



After discharge from the birth hospitalization, late preterm infants are readmitted more than two to three times as often as term infants. The most frequent reasons are jaundice or possible infection. It appears that late preterm infants born to primiparous mothers who have had complications during the pregnancy, are breastfeeding, and are of Asian–Pacific Islander descent have higher rates of readmission (Table 3).

Table 3

Table 3. Risk Factors for Readmission of Infants Born at 34 to 36 Weeks' Gestation

Characteristic	Morbidity, %	Adjusted RR*	95% CI
Primiparae	7.8	1.5	1.2, 1.7
Asian/Pacific Islander	8.1	1.3	1.0, 1.7
Labor/delivery complications >1	7.1	1.3	1.1, 1.5
Breastfeeding	7.1	1.7	1.4, 2.1

CI = confidence interval; RR = relative risk.

Of all infants born before 36 weeks of gestation and readmitted to the hospital, infants born at 34 and 35 weeks' gestation account for about 55% of the readmissions, 45% of readmission hospital days, and 42% of the total costs of hospital readmissions because of the relatively greater number of births (Table 4).

Table 4

Table 4. Length of Stay and Cost of Readmission of Premature Infants (<36 Weeks' Gestation), California, 1992-2000

Gestational Age, wk	No. (%)	No. of Readmissions (% total)	% Infants Readmitted	No. of Readmissions (% Total)	No. of Hospital Days (% Total)	Average Hospital Days	Cost, Millions $ (% Total)	Cost per Admission, $
≤33	101,362 (38)	17,417 (45)	15 †	24,999 (48)	135,649 (55)	8.8‡	212.8 (58)	8,510
34 – 35	162,521 (62)	21,038 (55)	13	26,739 (52)	111,855 (45)	5.4	157.2 (42)	5,880
Total	**263,883**	**38,455**	**15**	**51,738**	**247,504**	**6.4**	**370.0**	**7,151**

* Adapted from Underwood MA, Danielsen B, Gilbert WM. *J Perinatology* 2007:27:614-619
† 14% at 33 weeks' gestation to 31% at <25 weeks' gestation
‡ 6.5 days at 33 weeks' gestation to 12 days at <25 weeks' gestation

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American Board of Pediatrics Content Specification(s):

Identify perinatal risk factors, including hypoxic ischemic encephalopathy and prematurity, which affect subsequent developmental outcome

Know the type and frequency of school-related and behavior problems in preterm infants

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12 December 08

May: Question 8

A 34-year-old gravida 4 mother was in labor for 14 hours at term and noted to be getting tired. She was supported with an intravenous glucose infusion and, when the fetal heart tones demonstrated persistent variable decelerations, underwent cesarean section. A 2,450-g male infant was delivered with Apgar scores of 4 and 8 at 1 and 5 minutes, respectively. The physical examination findings were unremarkable and he was observed in a transition nursery until 6 hours of age when a blood glucose concentration obtained per nursery protocol was 27 mg/dL (1.5 mmol/L). The infant remained asymptomatic. He was given a nipple feeding and blood glucose concentration rose to 45 mg/dL (2.5 mmol/L) by 12 hours and above 50 mg/dL (2.8 mmol/L) after 24 hours. You conclude that the infant's brain must have been metabolizing alternate fuels to maintain apparently normal neurologic function and consciousness.

Of the following, the source of MOST of the nonglucose energy used by the hypoglycemic brain is:

1	acetoacetic acid
2	beta-hydroxybutyric acid
✗ 3	gamma-aminobutryric acid
4	glutamic acid
5	lactic acid

You selected 3, the correct answer is 5.

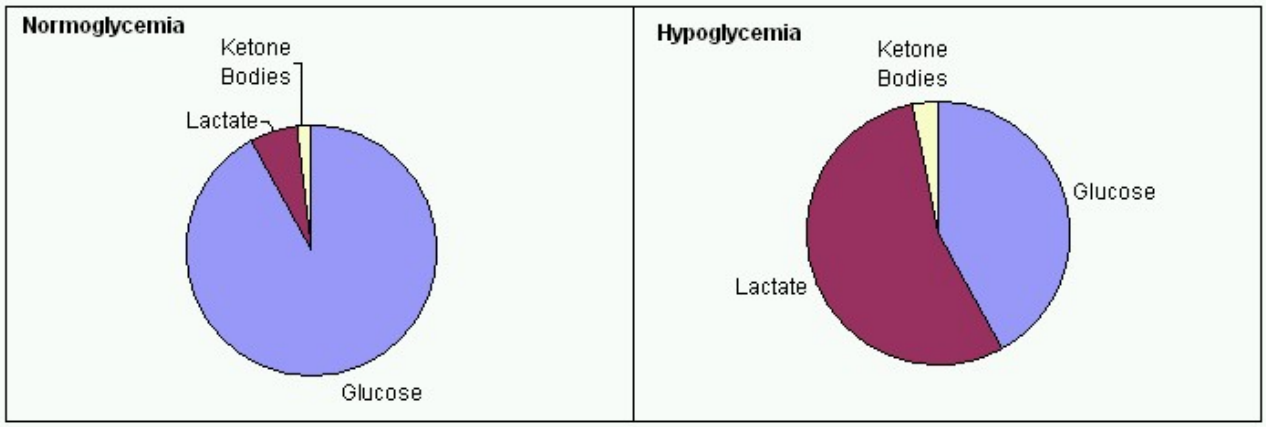
The infant in the vignette had asymptomatic transient hypoglycemia. He had at least three historical risk factors for transient hypoglycemia. These include suboptimal intrauterine growth, signs of perinatal distress, and a maternal glucose infusion around the time of birth. He was treated successfully with oral feedings. If he had any symptoms of hypoglycemia such as irritability, apnea, cyanosis, feeding problems, lethargy, or seizures, parenteral administration of glucose would have been preferred.

Glucose is the main source of energy for the brain in infants and in adults. When blood glucose concentrations are low, however, the brain makes several adaptations to compensate for the shortage of its primary source of energy. First, glucose transport into the brain and its cells is independent of insulin and is facilitated by specific protein transporters (especially GLUT1 and GLUT3). The rate of transport of glucose into brain cells depends on the concentration of the transporter proteins as well as the concentration of blood glucose. Hypoglycemia stimulates increased production of GLUT proteins.

Second, brain cells contain glycogen that can be hydrolyzed to glucose during systemic hypoglycemia, but these stores are limited.

Third, the brain at all ages can use alternative substrates for energy when glucose concentrations are low. The primary alternate substrate is *lactic acid* or lactate. In a neonatal animal model of systemic hypoglycemia, the brain switches from having 95% of its energy derived from glucose during normoglycemia to close to 60% of its energy from lactate during induced hypoglycemia. The brain can also derive energy from ketone bodies (especially acetoacetic acid and beta-hydroxybutyric acid), but ketone concentrations in brain and plasma remain low even during hypoglycemia and account for a small proportion of the energy produced. Blood lactate is elevated at birth in newborns whose mothers receive glucose infusions during labor (Figure).

Figure: Cerebral fuel utilization in normoglycemia and hypoglycemia (adapted from Vannucci and Vannucci [2004]).



Gamma-amino butyric acid (GABA) and glutamic acid (glutamate) are both neurotransmitters in the central nervous system. GABA is the main inhibitory neurotransmitter in term and near-term infants, but it may act as an excitatory neurotransmitter in extremely low-birthweight infants. Glutamic acid (glutamate) is the main excitatory neurotransmitter in the central nervous system. Both GABA and glutamate bind to ion channel receptors on the surface of neurons. They regulate the transmembrane passage of various ions and therefore cell functions. Neither neurotransmitter is used as a source of energy in the brain.

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American Board of Pediatrics Content Specification(s):

Know the fuels used for brain metabolism

Recognize the etiology and clinical manifestations of neonatal hypoglycemia

May: Question 9

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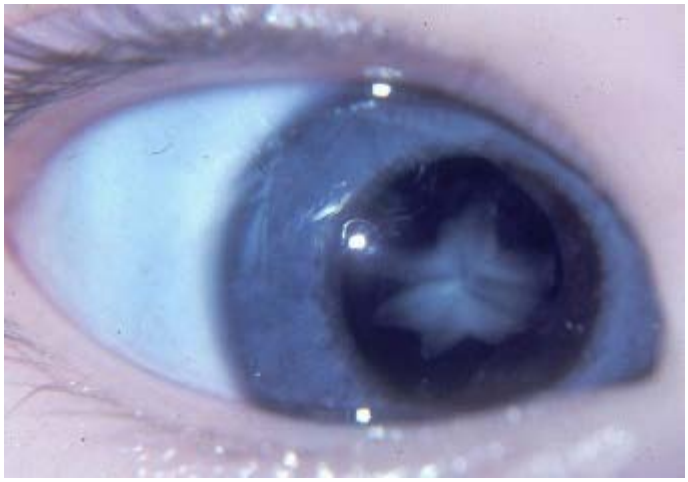
11 November 08

12 December 08

A male infant is examined at 10 days of age. He was born at 35 weeks' gestation after a pregnancy complicated by mild maternal preeclampsia. His birthweight was 2,300 g, and his length and head circumference also were appropriate for his gestational age. He stayed extra days in the hospital because of mild jaundice, treated briefly with phototherapy. His mother reports that he has been breastfeeding and sleeping well. His current weight is 2,250 g. On physical examination, you are unable to elicit a red reflex bilaterally, and note marked leukocoria (Figure). The remainder of the examination findings are normal.

Figure



Of the following, the diagnosis for this infant is MOST likely to be supported by:

1	erythrocyte enzyme studies
2	history of prematurity
3	karyotype
4	ocular examination of the parents
5	serum 7-dehydrocholesterol concentration

You selected 4, the correct answer is 4.

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The red reflex (choroidal light reflex) detects retinal blood vessels appearing as a red glow when viewed through an ophthalmoscope. The presence of a red reflex signifies a lack of obstruction between the external corneal surface and the retina. Leukocoria (white reflex) has many causes, including coloboma, retinoblastoma, and retinal detachment, but is most commonly the result of a cataract. The infant in this vignette has bilateral leukocoria, consistent

with bilateral congenital cataracts.

By definition, a cataract is a nonspecific reaction to a change in lens metabolism leading to lens opacification. The lens, derived from surface ectoderm, grows continuously during life, laying down new lens fibers on its external surface, much like an onion. Processes that alter the glycolytic pathway or epithelial cell mitosis of the avascular lens lead to opacification. The size and shape of a cataract depends on the area of the lens under formation at the time of insult. For example, damage occurring in the early embryonic period leads to opacification in the center of the lens (nuclear cataract), and later periods of damage produce a ringlike opacification (zonular cataract). The visual significance of a cataract depends on the age at onset, location, and morphologic characteristics. Very dense opacifications cause greater visual disturbance, particularly if located in the central axis. Because of associated severe amblyopia and strabismus of the involved eye, unilateral cataracts carry a poorer prognosis for vision than bilateral complete cataracts. Treatment of dense cataracts usually involves lens extraction and subsequent intraocular lens implantation.

Estimates of the prevalence of congenital cataracts range from 1.2 to 6 per 10,000 births, and cataracts are responsible for nearly 10% of all visual loss in children worldwide. Hereditary, inflammatory, and metabolic factors cause most bilateral congenital cataracts. Unilateral cataracts are generally the result of a local ocular phenomenon, including trauma, or a developmental eye abnormality. In addition, cataracts are associated with multiple syndromes, such as Hallermann-Streiff, Pierre Robin, and Rubinstein-Taybi syndromes. However, 60% of unilateral and 40% of bilateral cataracts have no discernible cause.

In developed countries, isolated autosomal dominant (AD) cataracts are most common, and account for 25% of all congenital cataracts. AD cataracts are typically bilateral, of a variety of morphological patterns, and associated with variable expressivity and a high degree of penetrance. Several gene loci have been linked to AD cataracts. Usually there is a clear history of congenital cataracts affecting multiple generations. For all cases of isolated congenital cataracts, as in the infant in this vignette, a thorough family history and ophthalmologic examination of the parents should be done.

Congenital infections, particularly rubella, but also toxoplasmosis, varicella, herpes simplex, and other viruses, account for up to 15% of congenital cataracts. In developing countries, where rates of infection are higher and vaccinations less available, intrauterine infection is the leading cause of congenital cataracts. With congenital rubella syndrome, cataracts occur in 20% of cases, and are usually bilateral. The cataract results from invasion of the lens by the rubella virus, which may remain dormant in the lens material for several years. Microphthalmia, uveitis, and glaucoma are associated ocular findings.

Galactosemia, an inherited deficiency of enzymes for galactose metabolism, is the most common metabolic disorder causing cataracts in infancy. A defect in galactokinase, uridine diphosphate galactose-epimerase, or galactose-1-phosphate uridyltransferase, will result in the conversion of galactose to galactitol in the lens, and a consequent influx of water. This hydration of the lens disrupts the normal packing of the lens fibers, and results in a loss of transparency. Initially, the lens changes appear as a "drop of oil" in the center of the lens. Cataracts associated with galactosemia usually are bilateral, and appear during the first 2 months of age. The removal of galactose from the diet may prevent or reverse initial changes in the lens, but dietary restriction will not completely eliminate the formation of cataracts later in childhood. Classic uridyltransferase deficiency presents early in the newborn period with lethargy, poor feeding, jaundice, hepatomegaly, and in some cases, *Escherichia coli* sepsis. Galactokinase deficiency is associated with cataracts in later childhood and no other manifestations. Erythrocyte enzyme studies and assays of blood galactose are used in the diagnosis of galactosemia. Because the infant in this vignette is well and thriving, it is not likely that galactosemia is the cause of his cataracts.

Prematurity and retinopathy of prematurity have been associated with the development of cataracts. Transient lens opacities have been reported in approximately 3% of low-birthweight infants, who also experienced a high incidence of problems such as respiratory distress, apnea, acidosis, hypothermia, and poor weight gain. The cataracts are bilateral and generally

reversible. Cataracts have also been associated with retinopathy of prematurity, although occurring in only 2% of cases. At 35 weeks' gestation and without illness, it is unlikely that the infant in this vignette has cataracts as a result of prematurity.

Trisomy of chromosomes 13, 18, 21, 10q, and 20p, chromosome translocations, Turner syndrome, and deletion syndromes have all been associated with cataracts. The cataracts are usually bilateral, and occur infrequently. In fact, among infants with trisomy 21, only approximately 1% will develop lens opacification. Because the infant in the vignette has otherwise normal physical examination findings, a karyotypic abnormality is unlikely to be the cause of his cataracts.

Because the lens membrane contains the highest cholesterol content of any known membrane, defects in enzymes of cholesterol metabolism are associated with cataracts. Smith-Lemli-Opitz syndrome, an autosomal recessive deficiency of 7-dehydrocholesterol reductase, results in low cholesterol tissue concentrations, multiple craniofacial and ocular abnormalities, cryptorchidism, developmental delay, growth retardation, and occasionally cataracts. Smith-Lemli-Opitz syndrome can be diagnosed by finding elevated serum 7-dehydrocholesterol concentrations. The infant in this vignette does not exhibit the typical physical anomalies associated with Smith-Lemli-Opitz syndrome, making this an unlikely cause for his cataracts.

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American Board of Pediatrics Content Specification(s):

Recognize the signs of neonatal cataracts

Recognize the conditions associated with neonatal cataracts

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May: Question 10

A 32-year-old woman presents to an emergency room complaining of severe pain with urination and increased urinary frequency. She does not have any flank plain. Numerous white blood cells are identified in the woman's clean catch urine sample. Before the emergency physician prescribes an antibiotic for the woman's presumed urinary tract infection, he asks if she is pregnant. The woman discloses that she is in her 6th week of gestation.

Of the following, the antibiotic with the HIGHEST risk to the fetus is:

1	chloramphenicol
2	ciprofloxacin
3	clindamycin
4	doxycycline
5	gentamicin

You selected 5, the correct answer is 4.

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To assist physicians in prescribing medications to pregnant women, the US Food and Drug Administration (FDA) provides pregnancy category classifications (as defined under *21 Code of Federal Regulations* 201.57) for each medication (Table 1).

Table 1

Table 1. US Food and Drug Administration Pregnancy Categories*	
Pregnancy Category	**Description**
A	• Well-controlled studies in human pregnancies • No adverse effects observed in human pregnancies
B	• Well-controlled studies in human pregnancies • No adverse effects observed in human pregnancies • Adverse effects observed in animal pregnancies OR • No adverse effects observed in animal pregnancies • No well-controlled studies in human pregnancies
C	• No data in human pregnancies • Adverse effects observed in animal pregnancies OR No data in human and animal pregnancies
D	• Adverse effects in human pregnancies • Benefits of drug use may outweigh the associated risks
X	• Adverse effects in human or animal pregnancies • Risks of drug use clearly outweigh any potential benefits

***Defined under 21 Code of Federal Regulations 201.57**
Adapted from: Nahum et al (2006)

The risks of administering medications to a pregnant woman must be assessed separately from the rest of the population because of the potential teratogenic and toxic effects on the developing fetus. Combining human data with animal data, the magnitude of human teratogenic risk for each medication is estimated and categorized by the Teratogen Information Service classification system. The teratogenic potential during human pregnancy ranges from "none," to "unlikely," to "undetermined." Because the amount of data available varies, the teratogenic/toxic potential is also classified by having "good," "fair," "limited," or "very limited" data. The teratogenic risks and the amount of data available are then combined to determine the specific pregnancy category for the medication. Table 2 summarizes the magnitude of human teratogenic risk and the FDA pregnancy category for 11 commonly used antibiotics.

Table 2

Table 2. Placental Transmission and Recommended Pregnancy Dosage/Schedule for Broad-Spectrum Antibiotics

Antibiotic	Magnitude of Human Teratogenic Fetal Risk*	Food and Drug Administration Pregnancy Category
Amoxicillin	• Increased risk of teratogenicity is "unlikely," based on "fair" data	B
Chloramphenicol	• Increased risk of teratogenicity is "unlikely," based on "fair" data • "Therapeutic doses of chloramphenicol are unlikely to pose a substantial teratogenic risk"	C
Ciprofloxacin	• Increased risk of teratogenicity is "unlikely," based on "fair" data • "Therapeutic doses of ciprofloxacin during pregnancy are unlikely to pose a substantial teratogenic risk, but the data are insufficient to state that there is no [increased] risk"	C
Clindamycin	• Increased risk of teratogenicity is "undetermined" based on "limited" data • "Although a small [increased] risk cannot be excluded, a high risk of congenital anomalies in the children of women treated with clindamycin during pregnancy is unlikely"	B
Doxycycline	• Increased risk of teratogenicity is "unlikely," based on "fair" data • "Therapeutic doses of doxycycline are unlikely to pose a substantial risk of fetal malformations, but the data are insufficient to state that there is no [increased] risk" • Increased risk of dental staining is "undetermined" based on "very limited" data	D
Gentamicin	• Increased risk of teratogenicity is "undetermined" based on "limited" data • "A small [increased] risk cannot be excluded, but there is no indication that the risk of malformations in children of women treated with gentamicin during pregnancy is likely to be great"	C
Levofloxacin	• There are no well-controlled studies of the safety and efficacy of levofloxacin in pregnant women	C
Penicillin VK, and Penicillin G	• Increased risk of teratogenicity is "none" based on "good" data	B
Rifampin	• Increased risk of teratogenicity is "unlikely," based on "limited to fair" data • "The data are insufficient to state that there is no [increased] risk"	C
Vancomycin	• Increased risk of teratogenicity is "undetermined" based on "very limited" data	B

***Based on the Teratogen Information Service classification system**
Adapted from: Nahum et al (2006)

The emergency room physician should avoid prescribing doxycycline to the woman in this vignette because of fetal risks. It has been classified in the FDA pregnancy category "D" based on potential adverse effects found in human pregnancies. A study of 1,795 women who had received doxycycline during pregnancy did not report any association with six congenital anomalies (cardiac abnormalities, oral clefts, spina bifida,

polydactyly, limb reduction defects, and hypospadius). However, a larger case-control study of 18,515 doxycycline-exposed pregnancies reported an increased risk for congenital abnormalities (odds ratio [OR] 1.6, 95% confidence interval [CI] 1.1 to 2.3). While infants exposed to some tetracyclines during the second or third trimester have staining of their primary dentition, staining from doxycycline has not been documented. Because the woman in this vignette can be treated effectively with other antibiotics, the benefits of using doxycycline to treat her urinary tract infection do not outweigh the potential risks.

Chloramphenicol is classified in FDA pregnancy category "C." An increased risk of major congenital anomalies for oral administration of chloramphenicol at any time during pregnancy was found in a case-control study of 22,865 infants (OR 1.7, 95% CI 1.2 to 2.6). Both dose-related and idiosyncratic bone marrow toxicity can potentially occur. Caution should be used when prescribing chloramphenical at the end of the third trimester and during labor.

Ciprofloxacin is classified in FDA pregnancy category "C." While the congenital malformation rate was increased to 4.0% to 6.6% in two studies of infants exposed prenatally to ciprofloxacin, a controlled prospective observational study of 200 human pregnancies exposed to ciprofloxacin did not find an increased risk of anomalies.

Clindamycin is classified in FDA pregnancy category "B." Studies have not found an increased congenital malformation rate when infants were exposed to clindamycin during any trimester.

Gentamicin is classified in FDA pregnancy category "C." Studies of infants exposed prenatally to gentamicin have not found an increased risk of congenital anomalies or of hearing deficiencies. However, data are limited and toxicity has been reported in animal studies.

The prescribing physician should also know the characteristic transplacental passage of each medication even if the potential fetal effects are minimal. While antibiotics typically cross the placenta without difficulty, the concentrations in human umbilical cord blood or amniotic fluid may vary compared with maternal serum concentrations. Medication dosages may also need to be altered based on the pregnant woman's ability to metabolize and excrete the drug. Table 3 reviews the placental transmission and possible change in dose of commonly used antibiotics during pregnancy.

Table 3

Table 3. Placental Transmission and Recommended Pregnancy Dosage/Schedule for Broad-Spectrum Antibiotics

Antibiotic	Placental Transmission	Dosage/Schedule Recommendations During Pregnancy
Amoxicillin, Pencillin VK, and Penicillin G	• Crosses the human placenta • Penicillins transferred to the fetus and amniotic fluid reach therapeutic levels	• Shorter dosing interval and/or increased dose have been suggested to attain similar plasma concentrations as for nonpregnant women • Volume of distribution and renal clearance are increased during the 2nd and 3rd trimesters
Chloramphenicol	• Crosses the human placenta • Umbilical cord serum concentrations vary broadly (by 29%-106%) from maternal serum concentrations	• Pharmacokinetics during pregnancy has not been specifically studied • Peak and trough concentrations can be monitored • Unknown whether dose adjustments during pregnancy are necessary
Ciprofloxacin and Levofloxacin	• Crosses the human placenta and concentrates in amniotic fluid	• Maternal serum concentrations are lower in pregnant compared with nonpregnant women • Pharmacokinetics during pregnancy have not been specifically studied • Unknown whether dose adjustments during pregnancy are necessary • 50%-70% of ciprofloxacin dose is excreted in the urine
Clindamycin	• Crosses the human placenta	• Pharmacokinetics during pregnancy are unchanged during 1st, 2nd, and 3rd trimesters
Doxycycline	• Crosses the human placenta	• Pharmacokinetics during pregnancy has not been specifically studied • Enterohepatic recirculation • Unknown whether dose adjustments during pregnancy are necessary
Gentamicin	• Crosses the human placenta	• Increased dosage suggested due to decreased serum half-life in pregnancy and lower maternal serum concentrations • Peak and trough concentrations can be monitored
Rifampin	• Crosses the human placenta	• Pharmacokinetics during pregnancy have not been specifically studied • Unknown whether dose adjustments during pregnancy are necessary • Hepatically deacetylated to active metabolite • Enterohepatic recirculation
Vancomycin	• Crosses the human placenta • Amniotic fluid and umbilical cord blood concentrations during the early 3rd trimester comparable to maternal blood concentrations	• No studies to indicate that vancomycin dosing should be modified during pregnancy • Volume of distribution and plasma clearance are increased

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American Board of Pediatrics Content Specification(s):

Know the effects on the fetus of antibiotics used to treat maternal disorders

PREVIOUS NEXT

June: Question 1

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11 November 08

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During routine prenatal ultrasonography at 22 weeks' gestation, fetal ascites is identified. No other areas of fluid accumulation (ie, no cutaneous edema, pericardial or pleural effusions) or structural abnormalities are found. The fetal echocardiogram is normal. Results of maternal serum and amniotic fluid testing for syphilis, toxoplasmosis, parvovirus, rubella, cytomegalovirus, coxsackievirus, and herpes simplex virus are negative. Maternal blood type is B positive with an antibody negative screen and the karyotype is normal.

Of the following, the MOST likely cause for the isolated ascites in this fetus is:

1	arrhythmia
2	laryngeal atresia
3	meconium peritonitis
4	metabolic storage disease
5	posterior urethral valves

You selected 3, the correct answer is 5.

An infectious or urinary cause is found in approximately one third of fetuses with isolated ascites. Because findings on maternal and amniotic fluid testing for infections are negative, the fetus in this vignette most likely has urinary ascites induced by posterior urethral valves. As time progresses, the fetus in this vignette is at risk of developing a distended bladder with a thickened trabeculated wall. In severe cases, oligohydramnios and/or pulmonary hypoplasia may result. Other obstructive urinary tract abnormalities such as ureteroceles, ureteropelvic junction obstruction, and primary obstructive megaureter, as well as cloacal anomalies, may be associated with fetal ascites, but are less common than posterior urethral valves. Adzick and colleagues reported that 12 of 44 fetuses with urinary tract obstruction had urinary extravasation that was either diffuse (urinary ascites) or localized (perirenal urinoma).

Possible mechanisms for the development of urinary ascites include transudation through the bladder wall; rupture of the fetal bladder; and in cloacal dysgenesis, urine escaping from the hydrocolpos through the fallopian tubes into the abdominal cavity. The formation of urinary ascites in utero may be beneficial because it ameliorates the degree of renal dysplasia by decompressing the high-pressure–obstructed urinary tract.

In addition to urinary tract obstructions, intrauterine infections, such as syphilis, toxoplasmosis, parvovirus, rubella, cytomegalovirus, coxsackievirus, and herpes simplex virus are common causes of isolated fetal ascites. Possible mechanisms include fetal anemia from suppression of erythrocyte production, fetal myocarditis, or fetal hepatitis. Another possible mechanism for infection-induced ascites is

from intrauterine cardiac failure because of direct viral injury to cardiomyocytes. Structural cardiac abnormalities and arrhythmias less commonly lead to isolated fetal ascites by direct cardiac tissue injury. Rather, cardiac defects more commonly lead to ascites because of increased capillary permeability and generalized fluid overload after congestive heart failure.

Laryngeal atresia is a rare congenital anomaly that may present with intrauterine ascites and voluminous lungs. Infants with laryngeal atresia probably develop ascites by obstructing venous return because of the increased intrathoracic pressure created by the overdistended lungs. Resultant esophageal pressure may decrease fetal swallowing of amniotic fluid and lead to polyhydramnios. Other causes of airway obstruction, such as congenital cystic adenomatoid malformation or bronchopulmonary sequestration, may also result in fetal ascites and/or polyhydramnios.

Meconium peritonitis occurs after a small bowel perforation complicating intestinal stenosis, intestinal atresia, or volvulus. The abdominal fluid collection from spillage of small bowel contents is sterile. In addition to the ascites found in approximately 64% of cases, fetuses with meconium peritonitis often have other ultrasonographic findings such as intra-abdominal calcifications (86%), polyhydramnios (71%), and bowel dilatation (46%). Meconium peritonitis is also found in fetuses with cystic fibrosis or a viral infection.

Some metabolic storage diseases can lead to hepatic insufficiency resulting in shifts in colloid osmotic pressure and/or portal hypertension, which, in turn, may result in fetal ascites. Fetuses with Gaucher disease, gangliosidosis, mucolipidosis, mucopolysaccharidosis, or carnitine deficiency may present with ascites.

In addition to urinary tract obstruction, cardiac failure, small bowel perforation, and hepatic insufficiency, two other mechanisms have been implicated in the intrauterine development of fetal ascites. Abnormal lymphatic drainage from a transient blockage or abnormal development of the local lymphatic system can lead to chyloperitoneum. In addition to the distortion of intrahepatic architecture and resultant portal hypertension from the extramedullary erythropoiesis observed in fetuses with anemia, decreased plasma oncotic pressure in anemic fetuses may also lead to isolated ascites. Sometimes, the cause of isolated fetal ascites is not identified and the ascites may resolve spontaneously; other cases may progress to hydrops fetalis.

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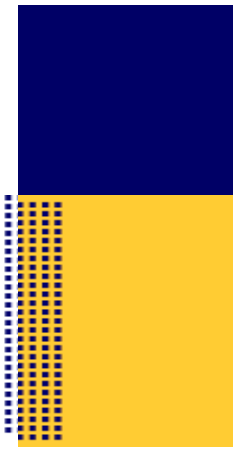

1998;18:963-967

American Board of Pediatrics Content Specification(s):

Identify the etiology and clinical manifestations of neonatal ascites

Know the differential diagnosis and the plan of management of a fetus with nonimmune hydrops

PREVIOUS NEXT

June: Question 2

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12 December 08

An infant is delivered prematurely after induction at 30 weeks' gestation because of worsening preeclampsia. The pregnancy was the result of in vitro fertilization. The Apgar scores are 7 and 8 at 1 and 5 minutes, respectively. The infant weighs 1,100 g (~10th percentile). Her length is 37.5 cm (~10th percentile) and head circumference is 29.5 cm (mean for gestation = 28 cm, standard deviation = 1.5 cm).

Of the following, the head circumference percentile in this infant is closest to:

1	50th
2	60th
3	70th
4	80th
5	90th

You selected 4, the correct answer is 4.

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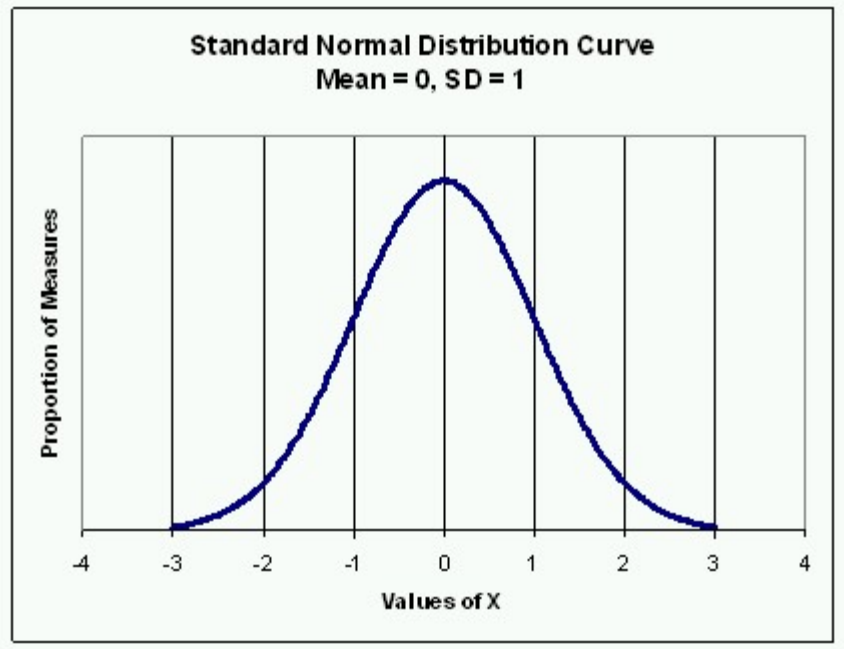
Head circumference measurements for any particular gestational age are distributed normally, as are many biological measures. That is, if you plot the incidences of each value for head circumference in a large population of premature infants of a particular gestational age on the Y axis of a histograph against the circumference values themselves on the X axis, you will obtain a bell-shaped curve. This is known as the normal or Gaussian distribution. The value with the highest incidence corresponds to the middle of the curve and is the mean value of the distribution. The points at which the shoulders of the bell curve make a transition from convex to concave represent a measurement that is one standard deviation (SD) from the mean for the population. In a normal distribution, 68% of the total population is represented by values between -1 SD and +1 SD. At twice that distance from the mean (±2 SD), 95% of the population is included, and at three times (±3 SD), 99.7% of the population is included (Figure).

Figure



The infant in the vignette has a head circumference that is 1 SD above the mean even though her length and weight are relatively low for gestation. This is an example of head-sparing that is more common in instances in which intrauterine growth is inhibited because of placental insufficiency or maternal vascular disease. Because half of any population measures *below* the mean and 34% (half of 68%) is within 1 SD *above* the mean, this infant's head circumference would plot at the 84th percentile line on a fetal growth chart (if such a line were drawn). Of the choices given, the 80th percentile line would be the closest.

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References:

An introduction to Excel's Normal Distribution Functions. Exeluser.com Web site. Accessed July 16, 2007, at: http://www.exceluser.com/explore/statsnormal.htm

Black LS, deRegnier RA, Long J, Georgieff MK, Nelson CA. Electrographic imaging of recognition memory in 34-38 week gestation intrauterine growth restricted newborns. *Exp Neurol.* 2004;190(suppl 1):S72-S83.

How to Generate a Normal Distribution Curve using a Spreadsheet. Exeluser.com Web site. Accessed July 16, 2007, at: http://www.exceluser.com/explore/normalcurve.htm

Narasimhan B. The normal distribution. Accessed July 16, 2007, at: http://www-stat.stanford.edu/~naras/jsm/NormalDensity/NormalDensity.html

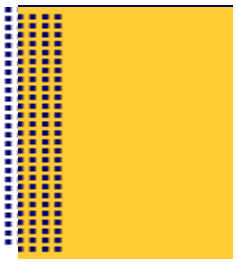
American Board of Pediatrics Content Specification(s):

Understand the concept of normal distribution and calculate the standard deviation, the standard error of the mean, and the median, and realize the importance of the *P* value

Know how to diagnose and manage abnormalities of intrauterine growth rate

Understand the maternal factors that affect intrauterine growth

Understand the placental factors that affect intrauterine growth



June: Question 3

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11 November 08

12 December 08

A 3-week-old term male infant is readmitted for tachypnea and subcostal retractions. His initial birth hospitalization was complicated by transient respiratory distress associated with group B streptococcal sepsis; a small right-sided pleural effusion was present on a chest radiograph. Otherwise, the infant was asymptomatic and he was discharged from the hospital 2 weeks after birth.

Of the following, the MOST likely associated respiratory abnormality in this infant is a:

1	cystic adenomatoid malformation
2	diaphragmatic hernia
3	lobar emphysema
4	pulmonary lymphangiectasis
5	pulmonary sequestration

You selected 3, the correct answer is 2.

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Neonatal group B streptococcal sepsis (GBS) is associated with late-presenting congenital diaphragmatic hernia, as in the infant in the vignette. The diaphragmatic hernia is located on the right in more than 90% of reported cases and is frequently preceded by a right pleural effusion. Symptoms at presentation are usually respiratory with acute respiratory deterioration found in most cases. Nearly two thirds of cases involve male infants, as in patients presenting with early diaphragmatic hernia, and the median gestational age at birth is 37 weeks. Survival after surgical repair is 90%.

The explanation for the association between GBS and late-presenting right diaphragmatic hernia is speculative. One hypothesis associates pneumonia and infection with diaphragm necrosis and rupture; however, diaphragmatic hernia has not been reported with other pathogens. Another hypothesis suggests that positive pressure ventilation, which is required in some cases of GBS, increased intrathoracic pressure, and noncompliant stiff lungs resulting from pneumonia prevent right-sided herniation of liver and intestine initially after birth.

CONTENT SPECIFICATIONS ADDRESSED ABP American Board of Pediatrics

Infection, specifically GBS, has not been associated with cystic adenomatoid malformation of the lung, lobar emphysema, pulmonary sequestration, or pulmonary lymphangiectasis. Cystic adenomatoid malformation of the lung is a hamartomatous change in the terminal bronchioles of the lung resulting in microcystic and macrocystic masses; although presentation is often at birth, small lesions may not cause symptoms and are incidentally discovered.

Lobar emphysema is a pathologic overinflation affecting one lobe of the lung that is caused by intrinsic and extrinsic factors; presentation after the perinatal period, like that found with GBS-associated diaphragmatic hernia, occurs in about half the cases.

Congenital pulmonary lymphangiectasis is a rare form of lymphatic obstruction isolated to the lung. If not associated with congenital heart disease and not extensive, presentation may occur weeks to months after birth. Pulmonary sequestration, characterized as an accessory segment of lung tissue with vascular supply originating from the aorta, is most often discovered incidentally in children and young adults who have had recurrent pneumonia.

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References:

Hansen TN, Corbet A. Anomalies of the airways, mediastinum, and lung parenchyma. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn*. 8th ed. Philadelphia, Pa: Elsevier Saunders; 737-757

Hansen TN, Corbet A. Pulmonary physiology of the newborn. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn*. 8th ed. Philadelphia, Pa: Elsevier Saunders; 634-647

Rescorla FJ, Yoder MC, West KW, Grosfeld JL. Delayed presentation of a right-sided diaphragmatic hernia and group B streptococcal sepsis: two case reports and a review of the literature. *Arch Surg.* 1989;124(9):1083-1086

Strunk T, Simmer K, Kikiros C, Patole S. Late-onset right-sided diaphragmatic hernia in neonates-case report and review of the literature. *Eur J Pediatr.* 2007;166:521-526

American Board of Pediatrics Content Specification(s):

Understand the complications of group B streptococcal infections

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

Recognize the clinical features of congenital malformations of the lung, including congenital pulmonary lymphagiectasis, the cystic lung diseases, such as congenital lobar emphysema, cystic adenomatoid malformation, and mediastinal tumors

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11 November 08

12 December 08

June: Question 4

An infant is transferred to your unit because of depression at birth, respiratory distress, and acidosis. In reviewing the maternal chart, you find a nursing note from the delivery room that "cord gases were sent." You call the laboratory at the referring hospital and receive the following results.

Blood Gases	Umbilical Artery	Umbilical Vein
pH	7.32	7.24
P_{CO_2}, mmHg	40	46
P_{O_2}, mmHg	28	19
Base excess, mEq/L	−4	−4

Of the following, these data are diagnostic for:

1	air bubble contamination
2	duplicated (same vessel) specimens
3	mislabeled specimens
4	prolapsed cord
5	uteroplacental insufficiency

You selected 4, the correct answer is 3.

Do you want to add anything to your Learning Plan?
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Umbilical cord blood analysis is often used to evaluate the blood gas status of the fetus and the function of the placenta. In reviewing umbilical cord blood gases, interpretation is facilitated through analysis of samples from both the umbilical artery and the umbilical vein. The three *directly measured* values are pH, partial pressure of carbon dioxide (PCO_2), and partial pressure of oxygen (PO_2). From these values, bicarbonate (HCO_3^-), base excess (also called *base deficit* and reported as a negative number), and oxygen saturation are *calculated*. Remember that oxygen saturation values are calculated from curves representing adult hemoglobin, in which the hemoglobin dissociation curve is shifted to the right (thereby yielding a lower saturation for a given PO_2) relative to fetal hemoglobin. Because fetal blood is composed of more than 90% fetal hemoglobin at less than 28 weeks' gestation and 75% at term, the calculated saturation values are of little use, because the true oxygen saturation will be higher than the reported value and the exact proportions of adult and fetal hemoglobin are not generally known. Bicarbonate results may be difficult to interpret in the presence of respiratory

acidosis, because the accumulated carbon dioxide will elevate serum bicarbonate as follows:

$$CO_2 + H_2O \Leftrightarrow HCO_3^- + H^+$$

This potentially masks a significant base deficit and metabolic acidosis. For that reason, the base excess/deficit analysis better reflects the true metabolic component of the blood gases.

Normal values [mean (range)] for blood gases are as follows:

Blood Gases	Umbilical Artery	Umbilical Vein
pH	7.28 (7.18-7.38)	7.35 (7.25-7.45)
PCO_2, mmHg	49 (32.2-65.8)	38 (26.8-49.2)
PO_2, mmHg	18 (5.6-30.8)	29 (17.2-40.8)
Base excess, mEq/L	−4 (−0.8-0)	−4 (-8-0)

Before interpretation is possible, several caveats are important. Having specimens from both sources allows for analysis of the function of the placenta (umbilical venous specimen) and of the fetus (umbilical arterial specimen). Accuracy in labeling should be confirmed, not from the labels on the specimen but from the relative relationships between the values. Fetal blood entering the placenta via the umbilical arteries will transfer accumulated carbon dioxide to the mother and receive oxygen from the mother. Thus, umbilical arterial blood will ALWAYS have a higher PCO_2, lower pH, and lower PO_2 than the simultaneously obtained umbilical venous sample. In most cases, the umbilical venous sample will appear a brighter red to the eye. Blood coursing through the placenta has little change in bicarbonate, lactic acid, or other chemicals to affect the base deficit, therefore umbilical venous blood will uniformly have a slightly higher pH because of its lower carbon dioxide concentration. If the base deficit is significantly worse in one vessel than in the other, the more abnormal value will be from the umbilical arterial specimen. Review of the samples from the case in this vignette suggests mislabeling: the specimen labeled umbilical artery has the higher pH, lower PCO_2 and higher PO_2, and must be from the umbilical vein, and vice versa.

Duplicated specimens, because of duplicate sampling of the umbilical vein, most often result in a narrowing of the difference between the samples to less than 0.02 pH units in most cases; the difference, however, will occasionally reach 0.03 pH units. If the values for PO_2 and PCO_2 are similarly close, single-vessel sampling can be suspected, which is estimated to occur in about one of six paired samplings. The specimens in this vignette differ by greater than these amounts, making duplicated vessel sampling unlikely.

Air bubble contamination can easily occur and most dramatically affects the PO_2 value. Umbilical venous blood cannot have PO_2 values exceeding that of a mixed venous (placental blood pool) maternal value, the upper range of which is in the high 40s. Exposure to air, a PO_2 value of 140 mm Hg, can easily result in excessive PO_2 values. The data in this vignette do not suggest air bubble contamination of either specimen.

Pathologic conditions can have predictable effects on the blood gas values obtained at the time of birth. Conditions resulting in partial or total obstruction of umbilical blood flow can result in apparently contradictory values: a critically ill, acidotic, and asphyxiated neonate with unremarkable umbilical vessel values. Prolapse of the umbilical cord may be obvious, with the cord protruding from the introitus, or it may be occult. Because the umbilical vein has a soft pliable wall in contrast to the thicker, less pliable arteries, cord prolapse may result in venous occlusion before arterial flow is interrupted. In this situation, umbilical venous gases would be normal, or nearly so, in the presence of hypoxia, hypercarbia, and acidosis in the umbilical arterial specimen. A pH difference exceeding 0.1 pH units associated with widened gaps in the other values would be consistent with partial obstruction. In the situation of an abrupt umbilical cord prolapse during labor after rupture of the membranes resulting in totally obstructed flow, the fetus and placenta are receiving no flow and the cord blood gases reflect the fetal and placental status just before the obstruction. After correcting for the switched, mislabeled specimens, abrupt and total umbilical cord obstruction can be neither confirmed nor ruled out by the data in this vignette; partial cord obstruction is not likely.

Uteroplacental insufficiency is generally associated with continued but reduced fetal-placental flow over time, when carbon dioxide concentrations will progressively increase and oxygen concentrations will diminish. Although the pH declines, PCO_2 and base deficit rise, and PO_2 drops, the relative relationship between umbilical arterial and venous values persists. Uteroplacental insufficiency is unlikely to result in relatively normal umbilical cord blood gases in association with a depressed fetus or neonate.

Analysis of the umbilical cord gases requires clinical correlation to contribute to the understanding of a patient's condition. Because umbilical vessel blood gas values are stable for up to 1 hour in a double cross-clamped segment of cord even at room temperature, the samples can be obtained, accurately labeled, and sent when time permits, after the infant is resuscitated and stabilized.

References:

Pomerance J. *Interpreting Umbilical Cord Blood Gases.* Pasadena, Calif: BNMG;2004:1-132

Westgate J, Garibaldi JM, Greene KR. Umbilical blood gas analysis at delivery: a time for quality data. *Br J Obstet Gynaecol.* 1994;101:1054-1063

American Board of Pediatrics Content Specification(s):

Understand the interpretation of fetal scalp and umbilical cord blood gas and pH values

PREVIOUS NEXT

June: Question 5

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11 November 08

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A 34-hour-old Caucasian male infant delivered at 38 weeks' estimated gestational age is found to be icteric down to the thighs. He is otherwise active, alert, and feeding well. The mother's blood group is A Rh positive with a negative antibody screen. Maternal history includes two episodes of transient jaundice associated with normal liver function tests. Neither the sibling nor the father has a history of neonatal jaundice. The infant's birthweight is 3.4 kg. Physical examination findings at birth are normal. His total serum bilirubin concentration at 34 hours of age is 15 mg/dL (257 µmol/L), conjugated bilirubin concentration is 0.8 mg/dL (13.6 µmol/L). The reticulocyte count is 3%. The infant is given phototherapy. You are reviewing the pathophysiologic and genetic basis of neonatal hyperbilirubinemia to explain the jaundice in this family.

Of the following, the genetic variation MOST likely to cause hyperbilirubinemia in this child is associated with a(n):

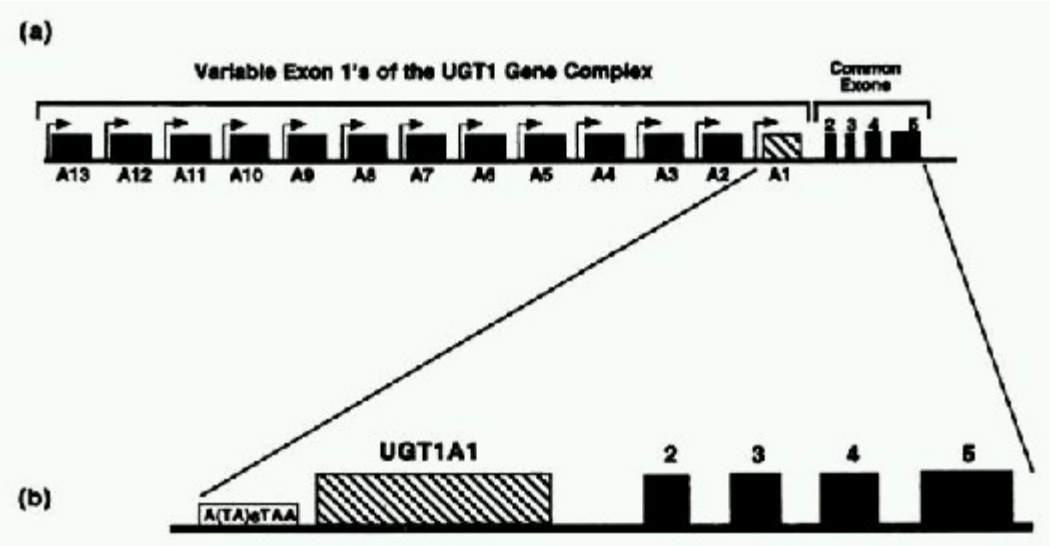
1	deletion in the promoter region of the *heme-oxygenase* gene
2	frameshift mutation in the *heme-oxygenase* gene
3	insertion in the promoter region of the uridinediphosphoglucuronate (*UDP) glucuronyl transferase* gene
4	missense mutation of the *multispecific organic anion transporter* gene
5	nonsense mutation of exon of the *UDP glucuronyl transferase* gene

You selected 3, the correct answer is 3.

The pattern of hyperbilirubinemia described in the vignette is most compatible with Gilbert syndrome, the most common inherited cause of unconjugated hyperbilirubinemia (affecting about 9% of the population). Features consistent with this diagnosis are intermittent jaundice in the mother (especially associated with menstrual periods, overexertion, or stress) absence of hemolysis, and no evidence of underlying liver disease. The genetic defect involves the promoter region of the uridinediphosphoglucuronate (UDP) glucuronyl transferase gene. It can be inherited in an autosomal recessive or dominant manner.

The predominant source of bilirubin is the breakdown of hemoglobin from senescent or hemolyzed red cells. Heme is degraded by heme oxygenase (HO), resulting in the release of iron and the formation of carbon monoxide and biliverdin (Figure 1).

Figure 1: The human UGTI gene locus. (Adapted from Kaplan et al [2003].)



Biliverdin is further reduced to bilirubin by biliverdin reductase. Bilirubin is a weak acid and is neither water soluble nor readily excreted at pH 7.4. It enters the liver where it is conjugated with glucuronic acid by the 1A1 isoform of the enzyme uridinediphosphoglucuronate glucuronosyltransferase (UDP-GT 1A1). Conjugated bilirubin is a polar, water-soluble compound that is excreted into the bile. Conjugated bilirubin is not absorbed from the intestine, but it is relatively unstable and is hydrolyzed to unconjugated bilirubin both nonenzymatically and by the enteric mucosal enzyme ß-glucuronidase. Unconjugated bilirubin is readily and rapidly reabsorbed across the intestinal mucosa to return to the liver via the portal circulation (enterohepatic circulation).

The degradation of heme to biliverdin is catalyzed by *HO*, the rate-limiting step in bilirubin production. Three isoforms of HO have been identified, with HO-1 being the most fully characterized. The HO-1 gene is known as a stress response gene with its expression upregulated by oxidant stress and several transcription factors including glucocorticoids, activator protein–1, and nuclear factor kappa B. Genetic polymorphisms of HO have been described. There is one report of HO-1 deficiency in a 6-year-old boy who presented with growth retardation, hepatic and renal iron deposition, and endothelial oxidative injury.

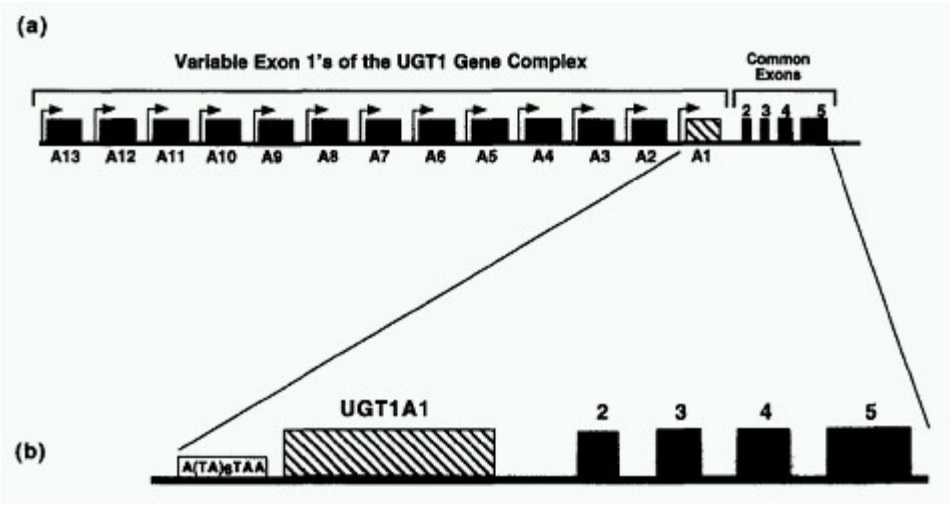
***Biliverdin reductase (BVR)* catalyzes the reduction of biliverdin to bilirubin. To date there are no identified genetic polymorphisms of the *BVR* gene. However, promoter region analysis has revealed recognition sites for AP-1 (an oxidative stress responsive binding site) and P3A (an element involved in embryonic gene expression), suggesting that BVR gene expression may be regulated by oxidizing agents and developmental factors.**

Unconjugated bilirubin is rapidly and selectively taken up across the basolateral membrane of the hepatocyte in part by a carrier-mediated process involving the organic anion-transporting polypeptide-2 (OATP-2). To date, no mutations of the *OATP-2* gene have been identified that might lead to loss of function of this transport protein and contribute to unconjugated hyperbilirubinemia. However, mutations resulting in a deficiency of the cannalicular multispecific organic anion transporter leading to cholestasis have been described in animal models and humans with the Dubin-Johnson syndrome.

Within the hepatocyte, unconjugated bilirubin is conjugated with glucuronic acid via the enzyme activity of UDP-GT 1A1. UDP-GT 1A1 is encoded by variable exons 1s (A1 to A13) and a constant domain (exons 2 to 5) at the UDP-GT locus located in human chromosome 2q37 (Figure 2).

Figure 2: The human UGT1 gene locus. Upper panel: Schematic representation of the genomic structure of the UGT1 gene complex. Lower panel: Exploded view of exon 1A1 and common exons 2–5 of the gene complex that have been identified as sites for genetic mutations associated with absent or decreased UGT activity that cause deficiencies of bilirubin conjugation. (Adapted from Clarke DJ, Moghrabi N, et al. Genetic defects of the UDP-glucuronosyltransferase-1 (UGT1) gene that cause familial non-haemolytic unconjugated

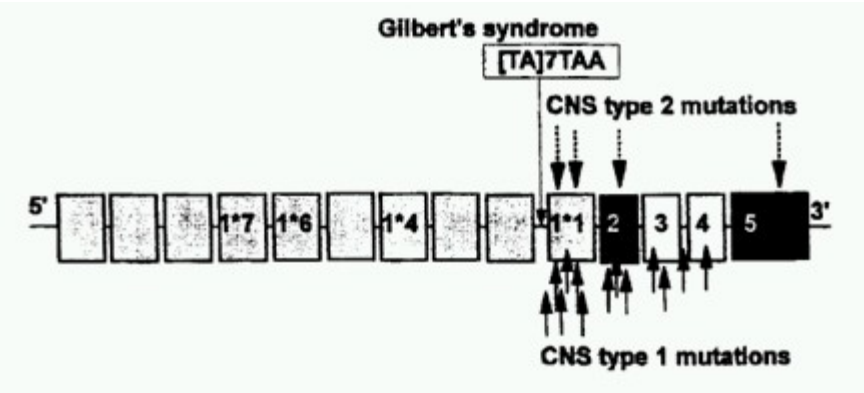
hyperbilirubinaemias. *Clin Chim Acta.* 1997;266(1):63-74; and Kaplan M, Hammerman C, Maisels MJ. Bilirubin genetics for the nongeneticist: hereditary defects of neonatal bilirubin conjugation. *Pediatrics.* 2003;111(4):886-893.)



Bilirubin UDP-GT 1A1 expression in humans is developmentally regulated. In addition, mutations of UDP-GT 1A1 expression result in *indirect hyperbilirubinemia syndromes*, including the Crigler-Najjar type I and II (Arias) syndromes and Gilbert syndrome.

Crigler-Najjar type I is caused by genetic lesions in any of the five exons (1A1, 2, 3, 4, 5) or flanking regions of the UDP-GT 1A1 gene (Figure 3).

Figure 3: The genetic basis of Crigler-Najjar and Gilbert syndromes. CNS indicates Crigler Najjar syndrome. Location of mutations leading to C-N syndrome types 1 and 2 in the coding area of the UGT1 gene. Gilbert syndrome is associated with a variant promoter—(TA)7 TATAA box—in the region of exon 1A1. (Adapted from: Kaplan M, Hammerman C, Maisels MJ. Bilirubin genetics for the nongeneticist: hereditary defects of neonatal bilirubin conjugation. *Pediatrics.* 2003;111(4):886-893.)



Currently, more than 30 different genetic mutations have been identified; typically these are nonsense or 'stop' mutations. The gene frequency for Crigler-Najjar type I is estimated to be 1 in 1,000 individuals. Crigler-Najjar type I syndrome is characterized by marked hyperbilirubinemia and a high risk for kernicterus.

Crigler-Najjar type II or Arias syndrome, however, is typified by more moderate concentrations of unconjugated hyperbilirubinemia as well as low but detectable hepatic bilirubin UDP-GT 1A1 activity. It is mediated by a missense mutation in the *UDP-GT 1A1* gene (Figure 3). In most cases, further UDP-GT 1A1 activity can be induced by phenobarbital administration. The gene frequency for Arias syndrome is also estimated to be 1 in 1,000 individuals.

In Gilbert syndrome, hepatic bilirubin UDP-GT 1A1 activity is reduced to approximately 30% of normal in affected subjects and more than 95% of

their total serum bilirubin is unconjugated. Typically, the unconjugated hyperbilirubinemia in Gilbert syndrome is seen during fasting associated with an intercurrent illness. Gilbert syndrome is common, affecting approximately 9% of the population. The genetic basis for this disorder is the insertion of a two-base-pair (TA) in the TATAA promoter element giving rise to 7 ($A[TA]_7TAA$) rather than the more usual 6 ($A[TA]_6TAA$) repeats in affected subjects. This extra TA repeat ($A[TA]_7TAA$) impairs proper message transcription and accounts for the reduced UDP-GT 1A1 activity. Indeed, as the number of repeats increases, UDP-GT activity decreases. Subjects with Gilbert syndrome are homozygous for the ($A[TA]_7TAA$) variant promoter, providing a unique genetic marker for this disorder. The gene frequency for the expanded $A[TA]_7TAA$ motif is 0.3, resulting in 9% of the general population being homozygous and 42% being heterozygous for the variant promoter. Thus, approximately half of the general population carries a Gilbert promoter on at least one allele. Although Gilbert syndrome is most commonly diagnosed in young adulthood, an association between Gilbert syndrome, as indexed by the variant promoter marker, and neonatal jaundice has been confirmed by several investigators.

Newborn infants with the $A(TA)_7TAA$ polymorphism in the promoter region of UDPGT have higher postnatal serum bilirubin concentrations, an accelerated increase in bilirubin concentrations, and decreased fecal excretion of bilirubin mono and diglucuronides. The importance of the Gilbert genotype to the genesis of neonatal jaundice is particularly apparent when affected newborns either have increased bilirubin production (glucose-6-phosphate dehydrogenase [G6PD] deficiency) or coinherited defects in bilirubin conjugation (mutations in coding region of UDP-GT).

The combination of the Gilbert genotype and G6PD deficiency markedly increases a newborn's risk for hyperbilirubinemia. More specifically, although G6PD-sufficient and G6PD-deficient neonates with a normal UDP-GT promoter showed comparable frequencies (~10%) of significant jaundice (total serum bilirubin >15 mg/dL [>257 µmol/L]), G6PD-deficient neonates who were heterozygous for the Gilbert promoter demonstrated an increased risk for hyperbilirubinemia (31.6%). G6PD-deficient neonates who were homozygous for the Gilbert genotype had a 50% risk for bilirubin concentrations higher than 15 mg/dL. Thus, there is a dose-dependent genetic interaction between G6PD deficiency and Gilbert syndrome that can contribute to the development of neonatal hyperbilirubinemia.

The $A(TA)_7TAA$ variant UDP-GT promoter is significantly more prevalent in breastfed infants who develop prolonged neonatal hyperbilirubinemia.

Recent studies have shown that coinheritance of the Gilbert promoter and a structural mutation in the coding region of UDP-GT can also lead to jaundice. This is true not only for patients who are homozygous for the Gilbert genotype but also for compound heterozygotes of a Gilbert-type promoter and a structural region mutation of UDP-GT 1A1. The importance of this observation is that approximately 50% of the population carry a Gilbert-type promoter on at least one allele. Thus, heterozygous carriers of a UDP-GT coding region mutation have a relatively high probability of carrying a Gilbert-type promoter. Based on the gene frequencies for the Gilbert promoter and structural mutations of the UDP-GT 1A1 gene, it can be predicted that at least 1 in 3,300 infants will be compound heterozygotes for the Gilbert and UDP-GT 1A1 coding region mutations and at risk for significant hyperbilirubinemia. This closely approximates the frequency of total serum bilirubin concentration higher than 30 mg/dL (>513 µmol/L) in recent reports.

References:

Dennery PA, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. *N Engl J Med*.

2001;344(8):581-590

Kaplan M, Hammerman C, Maisels MJ. Bilirubin genetics for the nongeneticist: hereditary defects of neonatal bilirubin conjugation. *Pediatrics.* 2003;111(4):886-893

Mukherjee S. Gilbert syndrome. emedicine.com Web site. Accessed July 27, 2007, at www.emedicine.com/med/topic870.htm

Watchko JF, Daood MJ, Biniwale M. Understanding neonatal hyperbilirubinaemia in the era of genomics. *Semin Neonatol.* 2002;7(2):143-152

Wong RJ, DeSandre GH, et al. Neonatal jaundice and liver disease. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. Philadelphia, Pa: Mosby Elsevier; 2006;2:1419-1450

Wong RJ, Stevenson DK, et al. Neonatal jaundice: bilirubin physiology and clinical chemistry. *Neoreviews.* 2007;8(2):e58-e67

American Board of Pediatrics Content Specification(s):

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

Understand the factors that increase the risk of kernicterus

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

PREVIOUS NEXT

June: Question 6

You are evaluating a 3,000-g birthweight male infant who was born at a local hotel after a 39-week gestation. He was intubated in the field with a 2.5-mm endotracheal tube because of cyanosis and poor respiratory effort. The infant's mother is 28 years old and had prenatal care from an out-of-state clinic. She has three children at home. In the emergency room the 1-hour-old neonate is pink and breathing spontaneously. Heart rate is 140 beats per minute, respiratory rate is 20 breaths per minute, and blood pressure is 65/35 mm Hg. Oxygen saturation is 94% while in room air. The rest of the physical examination findings are unremarkable. Arterial blood gas findings and serum electrolyte concentrations are as follows:

Laboratory Values		Patient Results
Arterial blood gas	pH	7.46
	PCO_2, mm Hg	55
	PO_2, mm Hg	76
	HCO_3, mEq/L (mmol/L)	42 mEq/L
	Base excess, mEq/L (mmol/L)	18 (18)
Electrolytes	Sodium, mEq/L (mmol/L)	130 (130)
	Potassium, mEq/L (mmol/L)	2.8 (2.8)
	Chloride, mEq/L (mmol/L)	82 (82)

Of the following, the mother or rescue squad in this case is MOST likely to report:

1	administration of sodium bicarbonate during resuscitation
2	eating disorder during pregnancy
3	hypoventilation following resuscitation
4	polyhydramnios during pregnancy
5	siblings with cystic fibrosis

You selected 4, the correct answer is 2.

Newborns maintain extracellular pH within a narrow range. The primary systems that maintain pH include the body's buffer systems, the lungs, and the kidney. In utero the placenta is primarily responsible for maintaining extracellular pH.

The infant in this vignette has metabolic alkalosis characterized by elevations in blood pH (>7.45), bicarbonate ([HCO_3]>24 mEq/L [24 mmol/L]), and base excess (>6 mEq/L [6 mmol/L]). Metabolic alkalosis occurs by one of three mechanisms: loss of acid, such as hydrochloric acid from frequent emesis; ingestion of excess base, such as excessive HCO_3 administration during resuscitation; or

contraction of volume by loss of fluids containing more chloride than HCO_3. Metabolic alkalosis within hours of birth is uncommon. The most common causes of metabolic alkalosis in neonates are listed in the Table.

Table

Table. Common Causes of Metabolic Alkalosis in Neonates*	
Acid loss	Vomiting (eg, pyloric stenosis), nasogastric suctioning
Diuretics	Loop, thiazides
Chloride deficiency	Chronic chloride-losing diarrhea, Bartter syndrome, low-chloride formula, cystic fibrosis, congenital adrenal hyperplasia (with hypertension), maternal hypochloremia
Administration of alkali	Bicarbonate, acetate, citrate, lactate

* Adapted from Martin and Fanaroff (2006).

The kidney excretes excess alkali efficiently; however, extracellular volume depletion with chloride or potassium loss can limit HCO_3 excretion and result in metabolic alkalosis. During volume depletion a decrease in glomerular filtration rate reduces the filtered load of HCO_3 and much of the HCO_3 that is filtered is reabsorbed in the proximal tubule in conjunction with avid sodium reabsorption. Volume depletion also increases aldosterone release through the renin-angiotensin system, which increases distal renal tubular absorption of sodium and excretion of both hydrogen ions and potassium. Potassium depletion maintains metabolic alkalosis by stimulating renal ammonia production and reducing movement of hydrogen ions out of the cell.

Maternal and fetal fluid and electrolyte homeostasis are intertwined. Maternal dehydration can result in a reduction in amniotic fluid, which returns to normal with maternal rehydration. Transplacental movement of chloride is bidirectional and almost symmetrical. Although a fetus can maintain normal or near-normal potassium concentrations, even in the face of maternal hypokalemia through the adenosine triphosphatase pump, significant maternal hypokalemia can cause fetal hypokalemia.

Eating disorders, such as anorexia nervosa with bulimia, are often associated with chronic vomiting that can lead to hypochloremic metabolic alkalosis with hypokalemia. Several authors have reported significant hypochloremic metabolic alkalosis, as seen in the infant in this vignette, in neonates born to mothers with chronic metabolic alkalosis from eating disorders. Replacement of fluid and chloride effectively corrects the metabolic alkalosis in the neonates.

A single dose of sodium bicarbonate administered during resuscitation has only a transient effect on the acid-base equilibrium because of the prompt renal response. The markedly elevated serum HCO_3 concentration seen in the infant in this vignette would have required a large dose of intravenous sodium bicarbonate to acutely raise the serum HCO_3 concentration from a normal serum concentration of approximately 20 mEq/L (20 mmol/L). A conservative method of determining the amount of sodium bicarbonate required to treat a base deficit is 0.3 × base deficit × weight (kilograms). In the infant in this vignette, to increase the base excess to 18 mEq/L (mmol/L) would have required at least 16 mEq of exogenous sodium bicarbonate during the resuscitation.

The infant in this vignette had hypochloremic, hypokalemic metabolic alkalosis that was partially compensated. Compensation of acidosis or alkalosis is either respiratory or renal. During metabolic alkalosis, an increase of 1 mEq/L (1 mmol/L) of HCO_3 should result in a 0.2 to 0.9 mm Hg increase in PCO_2. The infant in this vignette had at least a 20 mEq/L (20 mmol/L) increase in serum HCO_3 that resulted in an increase in the PCO_2 of approximately 15 mm Hg, assuming a normal PCO_2 of 40 mm Hg. This compensation is within the range of the expected respiratory compensation of an underlying metabolic alkalosis.

If the infant had acute respiratory acidosis, from pulmonary disease or hypoventilation during resuscitation, for each 1 mm Hg increase in PCO_2, serum HCO_3 should increase by 0.1 mEq/L (0.1 mmol/L). The infant's serum HCO_3 would have risen by at the most 1.5 to 2 mEq/L (1.5-2 mmol/L) above normal. Acute hypoventilation and subsequent acute respiratory acidosis could not explain this

infant's metabolic alkalosis.

Polyhydramnios is seen in mothers of neonates with neonatal Bartter syndrome, which is rare. The primary abnormality in Bartter syndrome is defective chloride reabsorption in the thick ascending limb of the loop of Henle caused by inactivating mutations for genes responsible for regulating electrolyte movement in the ascending limb. A fall in sodium chloride reabsorption results in volume depletion, and enhanced secretion of renin and thus aldosterone. The combination of increased distal flow of sodium chloride and hyperaldosteronism promotes potassium and hydrogen secretion and the development of hypokalemic metabolic alkalosis. Neonatal Bartter syndrome is associated with severe hypercalciuria and nephrocalcinosis, which can be detected in utero. Polyhydramnios, the consequence of polyuria, often leads to premature delivery between 27 and 35 weeks' gestation. Prenatal diagnosis of neonatal Bartter syndrome is based on the striking features of polyhydramnios in a healthy mother and a morphologically normal fetus. The polyuria continues after birth, can last for 4 to 6 weeks, and can be associated with severe fluid and electrolyte abnormalities. The long-term clinical outcome is frequently complicated by nephrocalcinosis and renal failure. Neonatal Bartter syndrome is associated with a distinctive appearance that is characterized by a thin constitution and a triangular facies with a full forehead, large eyes, protruding pointed ears, and a pouting expression from drooping corners of the mouth. The infant in this vignette does not have these features.

Metabolic alkalosis can occur in cystic fibrosis beginning during infancy. Among infants with cystic fibrosis, loss of electrolytes in the sweat leads to volume contraction, hypokalemia, and hyper-reninemia. Because salt losses are limited during the neonatal period, cystic fibrosis does not present with metabolic alkalosis during the first week after birth.

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Mathot M, Maton P, Henrion E, et al. Pseudo-Bartter syndrome in a pregnant mother and her fetus. *Pediatr Nephrol.* 2006;21:1037-1040

Shaer AJ. Inherited primary renal tubular hypokalemic alkalosis: a review of Gitelman and Bartter syndrome. *Am J Med Sci.* 2001;322:316-332

Stulc J. Placental transfer of inorganic ions and water. *Physiol Rev.* 1997;77:805-836

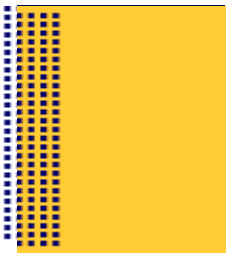
American Board of Pediatrics Content Specification(s):

Know the role of the placenta in the energy metabolism of the fetus, including transfer of glucose, electrolytes, and amino acids to the fetus

Recognize the clinical and laboratory manifestations of electrolyte abnormalities in the neonate

Understand the etiology of metabolic acidosis and metabolic alkalosis in infants

Recognize the clinical and laboratory manifestations of metabolic acidosis and metabolic alkalosis in the neonate



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June: Question 7

A 44-year-old gravida 6 sensitized Rh-negative mother delivers a 3.8-kg male infant by spontaneous vaginal delivery at a level I hospital. The mother was treated with Rh-immune globulin during pregnancy. The infant's Apgar scores were 7 and 9 at 1 and 5 minutes, respectively. The umbilical cord blood was reported to be type O Rh positive, Coombs negative. Jaundice was noted the next morning and became more intense a day later. The serum bilirubin concentration 50 hours after birth was 19.5 mg/dL (333 µmol/L). Physical examination findings, including neurologic assessment, were normal except for generalized jaundice. The infant was transferred to your neonatal intensive care unit for further treatment. Intensive phototherapy and an intravenous infusion of glucose water were started. The bilirubin concentration continued to rise. You need to explain the risks and complications of exchange transfusion to the parents of this otherwise healthy infant with jaundice.

Of the following, the MOST accurate statement about the risks/complications of exchange transfusion is that:

1	calcium infusions during the procedure do not prevent hypocalcemia
2	complications are trivial and transient in healthy infants
3	necrotizing enterocolitis is the most frequent fatal complication
4	rates of risks/complications are the same for sick and well infants
5	thrombocytopenia occurs in fewer than 1% of otherwise healthy infants

You selected 5, the correct answer is 1.

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Guidelines for starting exchange transfusion for hyperbilirubinemia traditionally have been based on an assessment of the risk of the procedure versus the risk of not performing it. In the early 1950s, when most exchange transfusions were performed in infants with Rh isoimmunization (erythroblastosis fetalis), an exchange transfusion was advised when the serum bilirubin concentration reached 20 mg/dL (342 µmol/L). This guideline was established because infants with Rh hemolytic disease with serum bilirubin concentrations of 20 mg/dL or more had about a 5% chance of devastating neurologic disease or death without exchange transfusion. This is similar to the incidence of serious life-threatening complication or death from the procedure at that time.

Today most exchange transfusions are performed for reasons other than Rh isoimmunization, and more data are available about the complications of the procedure. However, because phototherapy has come into general use and most Rh disease has become preventable, the number of exchange transfusions performed has fallen dramatically, resulting in far less experience with the procedure in most hospitals. Procedures that are performed rarely tend to have higher complication

rates, and estimates made when the procedure was more common may be lower than the current complication rate. In addition, there remains considerable uncertainty about the risks of not performing an exchange transfusion at any particular bilirubin concentration, and a resurgence of kernicterus has been documented in the United States and Denmark.

More recently, Hovi and Siimes described 1,069 newborn infants who were treated with 1,524 exchange transfusions for hyperbilirubinemia in the period 1968 to 1981. Transfusion-associated mortality occurred in four infants (3.7/1,000), and serious complications occurred in 14 infants during the procedure and in 5 infants after the procedure (17.8/1,000), making the combined serious risk about 2%. Of the four transfusion-associated deaths, three died of necrotizing enterocolitis. Morbidity and mortality was highest in infants with serious disease before the exchange transfusion. This latter observation was confirmed in a large multicenter trial in the United States.

The latest study of adverse events associated with exchange transfusion was reported by Jackson. He studied 106 infants during a 15-year period ending in 1995. These infants were classified as healthy or ill before the procedure. No deaths occurred among the 81 healthy infants. Five of the 25 ill infants died of complications that could have been caused by or exacerbated by the exchange transfusion. Other complications noted in healthy infants were transient, asymptomatic hypocalcemia (40% of cases) and thrombocytopenia (10%). In this latest study, only one of the infants developed necrotizing enterocolitis, which was not fatal. That infant was ill before the procedure. Therefore, necrotizing enterocolitis is no longer the primary cause of death after exchange transfusion in healthy infants.

Maisels and associates studied the effect of exchange transfusion on serum ionized calcium concentration. Negligible changes occurred with heparinized blood, but blood anticoagulated with citrate regularly produced a profound fall in serum ionized calcium during exchange transfusion. The observed hypocalcemia, however, did not correlate with symptoms. Routine calcium gluconate infusions during the procedure did not prevent ionized hypocalcemia. Serum ionized calcium concentrations returned to normal by 2 hours after exchange transfusion regardless of the use of calcium gluconate infusions during the procedure.

References:

Hovi L, Siimes MA. Exchange transfusion with fresh heparinized blood is a safe procedure. *Acta Paediatr Scand.* 1985;74:360-365

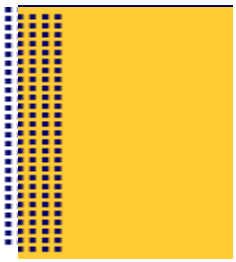
Jackson C. Adverse events associated with exchange transfusion in healthy and ill newborns. *Pediatrics.* 1997;99:e7

Keenan WJ, Novak KK, Sutherland JM, Bryla DA, Fetterly KL. Morbidity and mortality associated with exchange transfusion. *Pediatrics.* 1985;75(suppl):417-421

Maisels MJ, Li T-K, Piechocki JT, Werthman MW. The effect of exchange transfusion on serum ionized calcium. *Pediatrics.* 1974;53:683-686

American Board of Pediatrics Content Specification(s):

Understand the risks and complications of exchange transfusions



June: Question 8

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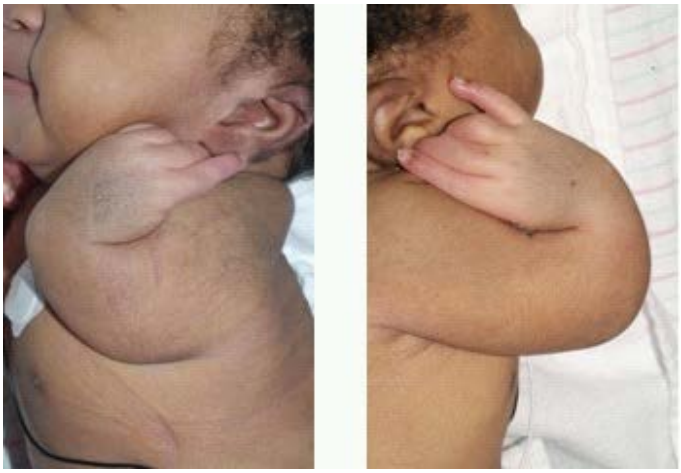
A 3.4-kg male infant was delivered by a 24-year-old primigravida at 38 weeks' gestation. Antenatal course was remarkable for a diagnosis of absent radii bilaterally in the fetus at 20 weeks' gestation. Amniocentesis revealed a normal fetal karyotype. After delivery, physical examination revealed malformed upper extremities (Figure 1); the rest of the physical examination findings were normal.

Figure 1



The infant was vigorous and nursing well. A complete blood count a few hours after birth revealed a total white cell count of 18,000/μL (18×10^9/L), hematocrit of 45%, and platelet count of 47×10^3/μL (47×10^9/L). A skeletal survey was obtained (Figures 2 and 3). Ultrasonographic findings of the brain and heart were within normal limits.

Figure 2

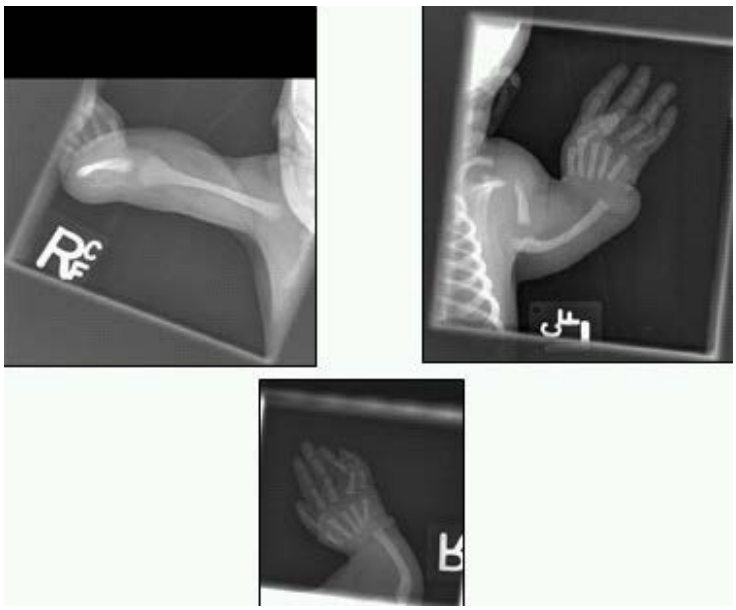
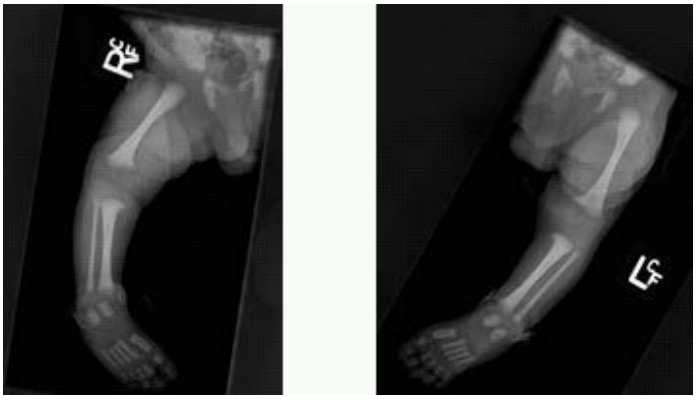


Figure 3



Of the following, the MOST likely diagnosis for the infant in this vignette is:

1	DiGeorge syndrome
2	Fanconi anemia
3	Holt-Oram syndrome
4	thrombocytopenia with absent radii syndrome
5	Wiskott-Aldrich syndrome

You selected 4, the correct answer is 4.

Do you want to add anything to your Learning Plan?
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The infant in this vignette has a constellation of findings (bilateral absent radii, with presence of thumbs bilaterally and thrombocytopenia presenting in the neonatal period) that is sufficient to make a diagnosis of thrombocytopenia and absent radii (TAR) syndrome. Figure 1 shows shortening of both the upper and lower arms. The hands are not seen completely in Figure 1. The skeletal survey in Figures 2 and 3 shows bilateral absence of radii, normal-appearing thumbs bilaterally, hypoplastic ulnae, hypoplastic left humerus, and flexion deformity of the right fourth finger. No other bony abnormality is seen.

The syndrome of thrombocytopenia and absent radii was first described in 1956, and since then, over 100 cases have been reported. Skeletal abnormalities associated with this syndrome are shown in the Table.

Table

Table. Skeletal Abnormalities Associated with the Syndrome of Thrombocytopenia and Absent Radii	
Abnormalities	**% of Cases**
Bilateral absent radii	100
Abnormalities of ulna	
Hypoplasia	100
Bilateral absence	20
Unilateral absence	10
Abnormal humerus	50
Bilateral absence	5-10
Abnormal shoulder joint	
The thumbs are always present but may be hypoplastic	
Lower limb abnormalities	50
Hip dislocation	
Subluxation of knees	
Coxa valga	
Dislocation of patella	
Femoral and tibial torsion	
Abnormal tibiofibular joint	
Ankylosis of knee	
Small feet	
Abnormal toe placement	
Absence of fibula	

Platelet counts in neonates with TAR generally are lower than 50×10^3/µL (50×10^9/L). Bone marrow aspiration reveals a decrease in megakaryocytes; however, this test is not required to make the diagnosis. Half of the patients develop hemorrhagic manifestations in the first week of life and most develop thrombocytopenia by 4 months of age. Patients have mucocutaneous bleeding, especially in the first year of life, when the thrombocytopenia is most pronounced. As infants, these patients may require transfusions of single-donor, irradiated platelets. Approximately 40% of patients die in early infancy as a result of hemorrhage. Thrombocytopenia during infancy can be precipitated by viral illness, particularly gastrointestinal infection. After the first year of life, platelet-transfusion dependence usually diminishes.

"Leukemoid" granulocytosis is seen in 62% of patients, especially during bleeding episodes, and eosinophilia is seen in 53% of patients. Anemia is attributed to hemorrhage and secondary iron deficiency. Although many disorders of hematopoietic failure have an increased risk of malignant transformation, such a risk has not been documented for TAR syndrome. Cow milk protein allergy or intolerance is common in TAR syndrome (47% of cases) and can be a significant problem. Introduction of cow milk may precipitate thrombocytopenia, eosinophilia, and/or leukemoid reactions. Cardiac defects are seen in one third of these patients, the most common being tetralogy of Fallot, atrial septal defect, and ventricular septal defect.

The differential diagnosis of TAR syndrome includes Fanconi anemia, thalidomide embryopathy, Holt-Oram syndrome, Roberts syndrome, and DiGeorge syndrome.

Patients with Fanconi anemia are rarely thrombocytopenic in the neonatal period; rather they develop progressive bone marrow failure as children and adults. Radial abnormalities are seen in only 30% of patients with Fanconi anemia, whereas abnormalities of the radius are *sine qua non* for TAR syndrome. In a patient with TAR syndrome, thumbs are uniformly present in the absence of radii, whereas in Fanconi anemia, absence of the radius always is accompanied by absent thumbs. Despite these differences, it is prudent to test patients with a clinical picture of TAR syndrome for increased chromosomal fragility to formally rule out Fanconi anemia.

Thalidomide embryopathy is associated with osseous abnormalities similar to TAR syndrome; however, thrombocytopenia is not a common finding and maternal intake of this drug in pregnancy is now rare.

Holt-Oram syndrome (hereditary heart disease plus variable skeletal malformations) and Roberts syndrome (tetraphocomelia, cleft lip and palate, intrauterine growth retardation, failure to thrive) are rarely associated with thrombocytopenia.

Thrombocytopenia and radial abnormalities are rarely seen in DiGeorge syndrome and other syndromes belonging to the deletion of chromosome 22q11 spectrum. Chromosomal analysis looking specifically for this deletion should be carried out to exclude this syndrome.

Wiskott-Aldrich syndrome is an X-linked syndrome that is characterized by immunodeficiency, eczema, and thrombocytopenia secondary to decreased production. Often only the thrombocytopenia is recognizable at birth. Skeletal abnormalities are not a feature of this syndrome.

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References:

Check NT. Newborn platelet disorders: Thrombocytopenia and absent radii syndrome. In: Alarcon PA, Werner EJ, eds. *Neonatal Hematology.* New York, NY: Cambridge University Press; 2005;1:219-223

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Jones KL. Radial aplasia-thrombocytopenia syndrome. *Smith's Recognizable Patterns of Human Malformation.* 5th ed. Philadelphia, Pa: WB Saunders; 1997;1:322-323

American Board of Pediatrics Content Specification(s):

Understand the etiologies and pathophysiologies of neonatal thrombocytopenia and thrombocytosis

Understand the clinical manifestations of neonatal thrombocytopenia and thrombocytosis

Understand the treatments of neonatal thrombocytopenia and thrombocytosis

Identify the clinical features and know how to manage congenital anomalies of the upper extremities, such as syndactyly, polydactyly, absent clavicles, absent radius, sprengel deformity, limb reduction

Understand the association between anemia and congenital anomalies

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11 November 08

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June: Question 9

Studies of the process of normal labor and of the pathophysiology of preterm labor suggest that human parturition is regulated by a distinctly human sequence of events. Preterm birth affects 5% to 15% of pregnancies and 70% of neonatal deaths are associated with birth occurring at gestations of 37 weeks or less, making understanding this process essential if effective strategies to prevent preterm labor are to be found.

Of the following, the process MOST uniquely associated with the onset of labor in humans is:

1	dissolution of the maternal corpus luteum
2	fall of maternal circulating progesterone
3	placental expression of corticotropin-releasing gene
4	release of fetal fibronectin into the cervix
5	spontaneous upregulation of the fetal hypothalamic-adrenal axis

You selected 4, the correct answer is 3.

Do you want to add anything to your Learning Plan?
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Unique to humans, timing of labor and birth is regulated through placental expression of the gene for corticotropin-releasing hormone (CRH). In humans and in great apes, CRH concentrations rise throughout pregnancy and peak at the time of delivery. Labor and delivery follow a period of exponential rise of CRH associated with a simultaneous decrease in concentration of CRH-binding protein. CRH receptors have been identified in maternal and fetal pituitary and adrenal glands. In addition, myometrial tissue in the mother and lung tissue in the fetus have CRH-binding sites.

Increases in CRH concentrations and bioavailability result in release of corticotropin by the maternal and fetal pituitary glands and secretion of cortisol by the maternal and fetal adrenal glands. Cortisol, whether secreted by the fetus or received from the mother, further stimulates the expression of the CRH gene by the placenta, causing added CRH secretion through this positive feedback system.

The *rate of increase* of CRH is considered to be the critical variable and the most accurate predictor of onset of labor. When comparing pregnancies at similar gestation, large differences in absolute CRH concentration are noted. Therefore individual CRH concentrations have a low sensitivity in predicting onset of labor.

Following the secretion of CRH and increased cortisol concentrations, a number of other events facilitate the process of parturition:

- **Myometrial CRH receptors change from a form facilitating relaxation of myometrial cells into a form linked to activate contraction.**

Oxytocin and prostaglandin F2 alpha are potentiated.
- Maternal and fetal adrenal glands produce dehydroepiandrosterone sulfate, a substrate for placental estrogens which stimulate uterine contractions.
- Surfactant and surfactant protein is synthesized and released into the amniotic fluid.
- Proinflammatory effects of prostaglandins and macrophages are stimulated by surfactants and surfactant protein A.
- Prostaglandin H2 synthetases in the chorion and amnion are activated.
- Cyclooxygenase-2 (COX-2) activity increases, which raises the concentration of prostaglandin E2, which becomes more proinflammatory as chorionic prostaglandin dehydrogenase synthesis decreases.
- Prostaglandin-mediated release of metalloproteinases weakens the membranes.
- Breakdown of the junction between the fetal membranes and decidua caused by inflammatory infiltrates and metalloproteinases results in the release of the adhesive protein fetal fibronectin into vaginal fluids.

Labor is also associated with changes in the myometrium needed to progress from growth accommodation (distention not producing contraction) to progressive, stronger contractions sufficient to produce birth. Three processes that enhance contractions have been identified:

- Promotion of myocyte contractility through enhancement of actin-myosin interactivity as CRH receptors in the myometrium change from the inhibitory form (BRHR1*alpha*) to a form stimulating the *Galpha*q contractile pathways.
- Increase in the excitability of myometrial cells associated with decline in the activity of $beta_2$ and $beta_3$ sympathomimetic receptors that function to open potassium channels and suppress contractility.
- Promotion of synchrony of myometrial cell contractions through the actions of connexin 43, prostaglandin F2*alpha*, and calcium.

Progesterone withdrawal is associated with a change from growth accommodation to stretch-induced contraction. In contrast to the process in many mammals, in humans, progesterone concentrations do not fall at the onset of labor. A functional withdrawal of progesterone activity accompanies modifications of the progesterone receptors A, B, and C. Decreases in several progesterone receptor coactivators result in reduced biologic activity of progesterone in the human at the onset of labor. The progesterone antagonist RU486 will initiate labor at any time during pregnancy.

Although inflammation has a major role in CRH initiation of labor, primary inflammation may initiate labor and do so without an increase in CRH. This effect may be mediated through factors such as COX-2 or interleukin-8.

In humans, the functions of the corpus luteum are assumed by the placenta early in pregnancy. Parturition in goats is dependent on dissolution of the maternal corpus luteum.

Although sheep are used for a number of perinatal physiological studies, parturition in sheep is dependent on processes initiated by the fetal hypothalamus, pituitary, and adrenal glands.

Human birth is a unique and complicated process. Understanding preterm birth may be enhanced with increased knowledge of the physiologic effects of the many epidemiologic factors related to preterm birth.

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References:

Behrman RE, Butler AS, eds. *Preterm Birth: Causes, Consequences, and Prevention.* Washington, DC: National Academies Press; 2007:169-206

Smith R. Parturition. *N Engl J Med*. 2007;356:271-283

American Board of Pediatrics Content Specification(s):

Understand the physiological and molecular biological characteristics of normal labor

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June: Question 10

A 7-day-old female neonate, whose birthweight was 868 g and estimated gestational age at birth was 26 weeks, has evidence of hypothyroxinemia on newborn screening. Confirmatory laboratory tests of thyroid function reveal the following plasma concentrations.

Thyroid Function Test	Patient Results (SI Values)	Reference Ranges
Total thyroxine, µg/dL (nmol/L)	3.8 (49)	8.0-16.0 (103-206)
Total triiodothyronine, ng/dL (nmol/L)	58 (0.9)	80-200 (1.2-3.1)
Free thyroxine, ng/dL (pmol/L)	0.9 (12)	2.0-4.0 (27-54)
Free triiodothyronine, pg/mL (pmol/L)	2.4 (3.7)	3.0-7.0 (4.6-10.8)
Thyroid-stimulating hormone, µU/mL (mU/L)	2.8 (2.8)	0.5-5.0 (0.5-5.0)
Thyroxine-binding globulin, mg/dL (nmol/L)	0.8 (128)	1.5-3.0 (240-480)

You are discussing with medical students the regulation of thyroid function during fetal life and its implications in infants delivered prematurely.

Of the following, the mechanism of regulation of fetal thyroid function EARLIEST to mature during gestation is:

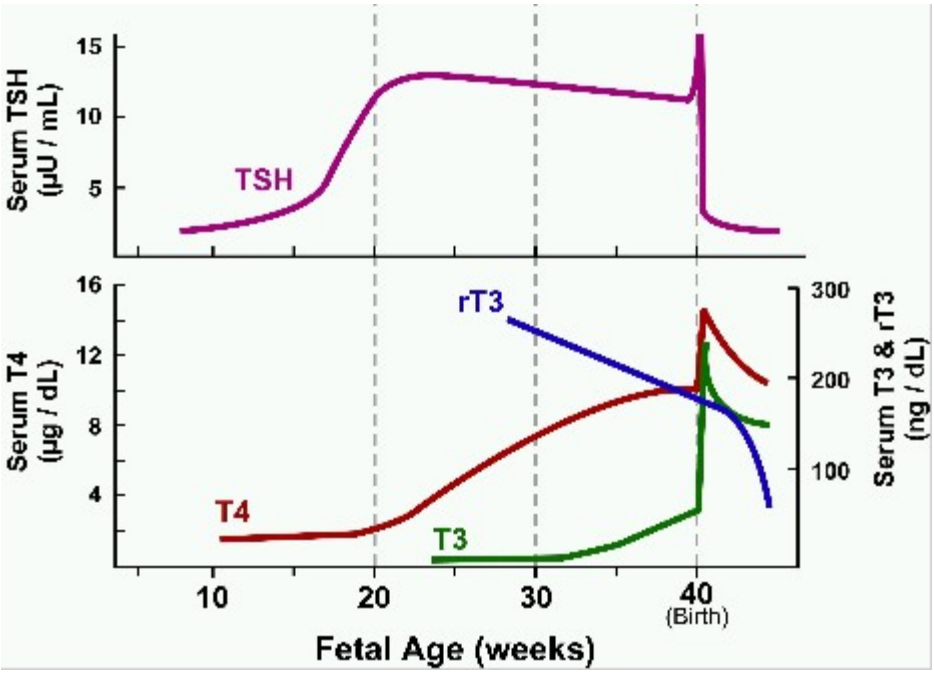
1	alternate pathways of thyroid hormone metabolism
2	deiodination of iodothyronines
3	hypothalamic-pituitary-thyroid axis
4	thyroid hormone binding proteins
5	Wolff-Chaikoff iodide regulation

You selected 4, the correct answer is 1.

The infant in this vignette has low plasma concentrations of total and free thyroid hormones, thyroid-stimulating hormone (TSH), and thyroxine-binding globulin (TBG), which are characteristic of transient hypothyroxinemia of prematurity. This disorder is a result of immature development of fetal thyroid function.

During fetal life, thyroid hormones are unmeasurable until approximately 20 weeks of gestation (Figure 1).

Figure 1: Thyroid hormones during human fetal development



Thyroid hormone tetraiodothyronine (thyroxine, T_4) appears at approximately 20 weeks of gestation and its plasma concentration increases linearly thereafter until term. Thyroid hormone triiodothyronine (T_3) appears at approximately 30 weeks of gestation and its plasma concentration increases linearly thereafter until term. The appearance of TSH and increase in its plasma concentration during gestation precedes the rise in circulating concentrations of thyroid hormones. In contrast to T_4 and T_3, the plasma concentration of reverse triiodothyronine (rT_3) is high during fetal life and declines with advancing gestation. These findings suggest that the regulation of fetal thyroid function—promotion of an optimal balance between production and disposal of thyroid hormones—is developing during fetal life and, in general, the mechanisms for preventing thyroid hormone excess are developed earlier than those for preventing thyroid hormone deficiency.

Among the mechanisms of regulation of fetal thyroid function, the alternate pathways of thyroid hormone metabolism mature earliest, by approximately 19 weeks of gestation. These pathways include T_4 conjugation with sulfate or glucuronide, T_4 deamination and decarboxylation, and ether-link cleavage. Among these pathways, the production of sulfate conjugates, catalyzed by the enzyme phenol sulfotransferase, is the major disposal pathway for both T_4 and T_3. T_4 sulfate is detectable in human fetal blood by 19 weeks of gestation.

To understand thyroid function regulation by deiodination of iodothyronines, it is important to examine the synthesis of the thyroid hormones. Thyroid hormone synthesis involves three critical steps: uptake of iodide, iodination of tyrosine, and deiodination of thyronines. The thyroid uptake of iodide from the circulating pool of iodide is under the influence of TSH. The iodination of tyrosine involves incorporation of iodine in specific positions within the tyrosyl ring of thyroglobulin, a glycoprotein synthesized by the endoplasmic reticulum in thyroid follicle cells. This iodination of tyrosine is catalyzed by the enzyme thyroid peroxidase. The resultant iodotyrosines are monoiodotyrosine (3-iodotyrosine) (Figure 2A) and diiodotyrosine (3,5-diiodotyrosine) (Figure 2B). These iodotyrosines have no hormonal activity.

Figure 2A

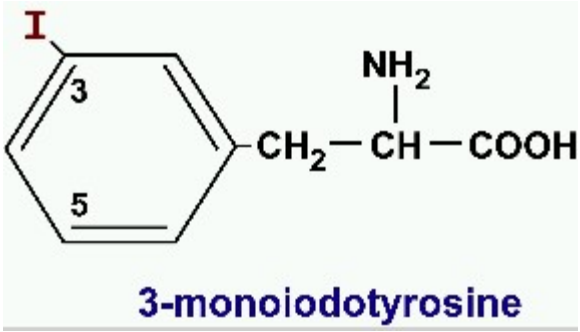
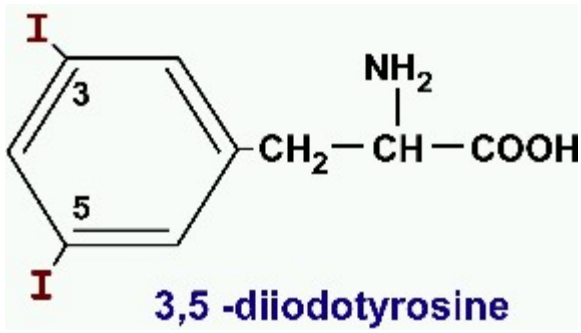
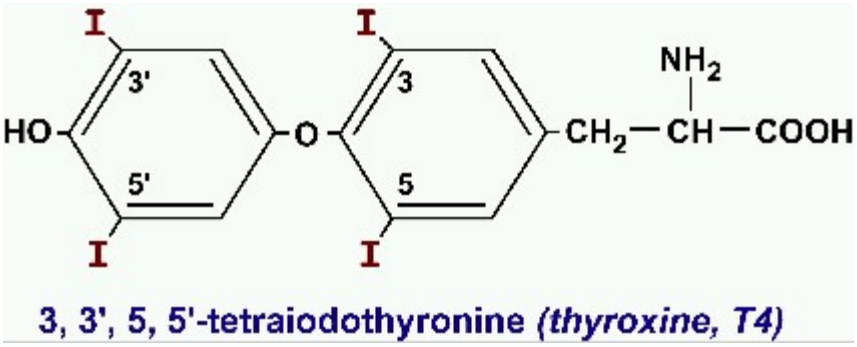


Figure 2B



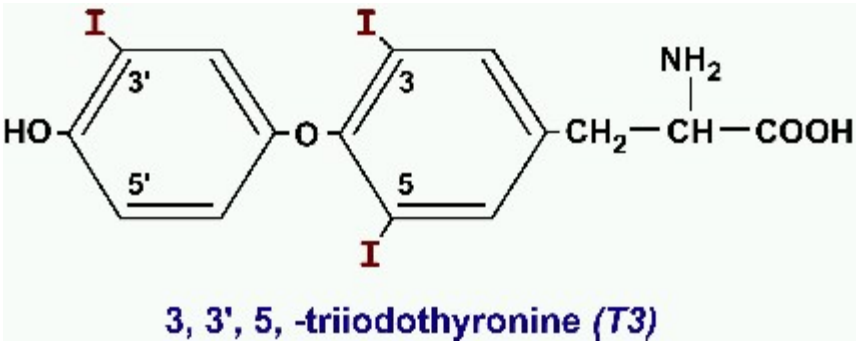
Coupling of the iodotyrosines, under the influence of thyroid peroxidase, results in the formation of iodothyronines. Each iodothyronine has two rings, an inner tyrosyl ring with positions designated as 3 and 5, and an outer phenolic ring with positions designated as 3'and 5'. T_4 (3,3',5,5'-tetraiodothyronine) (Figure 2C) is the principal product of thyroid hormone synthesis.

Figure 2C



It has minimal biologic activity and acts mainly as a precursor of active thyroid hormone. Removal of iodine (deiodination) from specific positions within the tyrosyl and phenolic rings of T_4, under the influence of deiodinase, is required for the formation of functional thyroid hormones. T_3 (3,3',5-triiodothyronine) (Figure 2D) is derived by 5'-deiodination; it is the most biologically active form of thyroid hormone.

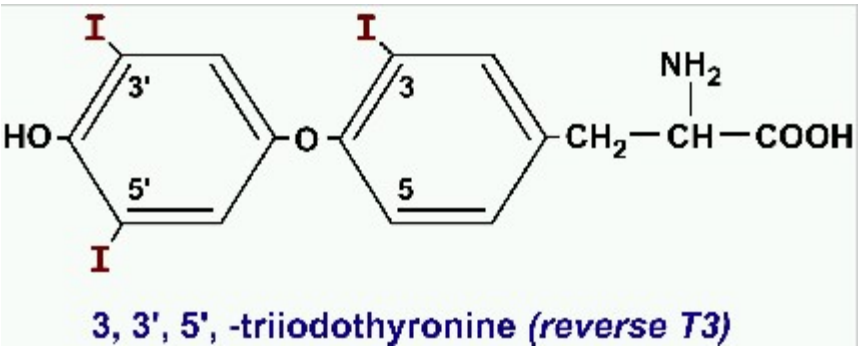
Figure 2D



3, 3', 5, -triiodothyronine *(T3)*

rT_3 (3,3',5'-triiodothyronine) (Figure 2E) is derived by 5-deiodination; it is biologically inactive. Further deiodination results in the formation of diiodothyronines and monoiodothyronines, which have no biological activity.

Figure 2E

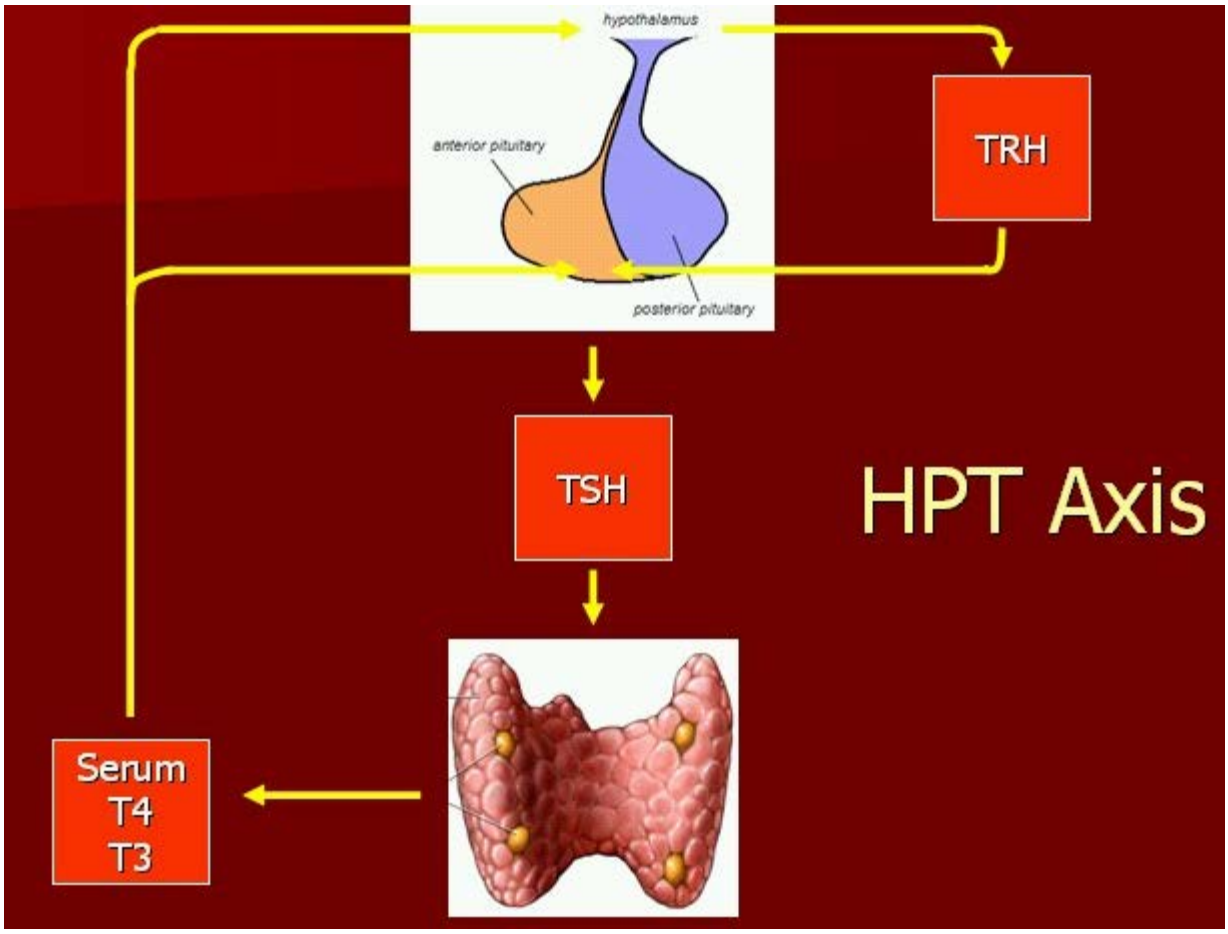


3, 3', 5', -triiodothyronine *(reverse T3)*

The process of deiodination of thyronines is critical for balancing thyroid function; 5'-deiodination is predominant when active thyroid hormone is needed, whereas 5-deiodination prevails when thyroid function needs to be suppressed. Fetal thyroid metabolism early in gestation is oriented largely to production of inactive hormones via predominant 5-deiodination of T_4 to rT_3. The 5'-deiodination of T_4 to active T_3 does not manifest until approximately 30 weeks of gestation, increasingly around the time of birth.

The hypothalamic-pituitary-thyroid (HPT) axis (Figure 3) represents a feedback loop of thyroid hormone regulation. According to this axis, low circulating concentrations of thyroid hormones stimulate the hypothalamus, specifically the paraventricular nucleus, to secrete thyrotropin-releasing hormone (TRH).

Figure 3: Hypothalamic-pituitary-thyroid axis



The TRH stimulates the thyrotropic cells of the anterior pituitary to secrete TSH. The TSH stimulates the thyroid gland to restore the circulating concentrations of thyroid hormones within the normal range. Conversely, excess thyroid hormones in circulation suppress the hypothalamic TRH, which inhibits the pituitary TSH and lessens the stimulatory effect of TSH on the thyroid gland, normalizing the circulating concentrations of thyroid hormones. This central regulation of thyroid function via the HPT axis does not appear until approximately 26 weeks of gestation in the human fetus; it matures during the third trimester of pregnancy. The low plasma concentration of TSH in the face of low plasma concentrations of all thyroid hormones in the infant in this vignette is consistent with immaturity of the HPT axis.

Most of the circulating thyroid hormones are bound to plasma proteins. Only about 0.03% of total T_4 and 0.3% of total T_3 is present in free or unbound form. The major thyroid-hormone-binding proteins are TBG, transthyretin, and albumin. The normal distribution of T_4 among these proteins is approximately 80% bound to TBG, 15% bound to transthyretin, and 5% bound to albumin. This protein binding of thyroid hormones serves at least two functions. First, by creating a flexible extrathyroidal reservoir of thyroid hormones, the thyroid-hormone-binding proteins serve to safeguard the body from the effects of abrupt fluctuations in hormonal secretion and disposal. Second, by imparting macromolecular properties to the small iodothyronine molecules, the thyroid-hormone-binding proteins may limit the urinary loss of these iodothyronines. The hepatic synthesis of thyroid-hormone–binding proteins matures during the third trimester of pregnancy in the human fetus, making a preterm infant vulnerable to fluctuations in thyroid function and to urinary loss of thyroid hormones.

Iodide, the principal substrate of the thyroid follicle cell in the synthesis of thyroid hormones, regulates its own metabolism and, consequently, thyroid function, independent of TSH. This iodide regulation, called Wolff-Chaikoff regulation, involves the capacity of the thyroid follicle cell to increase iodide trapping in the presence of low plasma iodide concentrations, and to decrease iodide trapping in the presence of iodide excess. Upon uptake of iodide by the thyroid follicle cell, its oxidation to iodine, mediated by thyroid peroxidase, is a critical prerequisite for iodination of tyrosine in thyroid hormone synthesis. In the mature thyroid follicle cell, iodide can self-regulate its own oxidation to iodine depending on the status of the thyroid function.

This thyroid autoregulation develops only after 36 to 40 weeks of gestation in the human fetus. The preterm infant, thus, is unable to regulate the thyroid function in the presence of iodide deficiency or excess.

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References:

Fisher DA, Polk DH. Thyroid disease in the fetus, neonate, and child. In: DeGroot LJ, ed. *Endocrinology.* 3rd ed. Philadelphia, Pa: WB Saunders; 1995:783-798

Polk DH, Fisher DA. Fetal and neonatal thyroid physiology. In: Polin RA, Fox WW, Abman SH, eds. *Fetal and Neonatal Physiology.* 3rd ed. Philadelphia, Pa: WB Saunders; 2004:1926-1933

Refetoff S, Nicoloff JT. Thyroid hormone transport and metabolism. In: DeGroot LJ, ed. *Endocrinology*. 3rd ed. Philadelphia, Pa: WB Saunders; 1995:560-582

American Board of Pediatrics Content Specification(s):

Know the physiological roles of the hormones and other proteins involved in the regulation of thyroid function

Understand the proper use of laboratory tests (including screening tests) in the diagnosis of thyroid dysfunction

Understand the causes of transient hypothyroidism in the neonate

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July: Question 1

You are called to the operating room for an emergency cesarean section of a mother who just had a seizure. The obstetrician hands you a full-term hypotonic infant making only weak respiratory efforts. After an appropriate resuscitation, the infant is pink with a normal heart rate and perfusion, but still somewhat hypotonic. Over the next few hours, the weakness is accompanied by poor feeding, apnea, decreased bowel sounds, and no meconium production. Skin turgor, urine output, and serum glucose concentration are normal. Among other diagnoses, you suspect an electrolyte abnormality.

Of the following, the MOST appropriate treatment for this infant is:

1	calcium, insulin, and glucose
2	extra fluids, calcium, and loop diuretics
✗ 3	extra free water
4	normal saline, loop diuretics, hydrocortisone
5	phenylbutyrate and benzoate

You selected 3, the correct answer is 2.

The most likely electrolyte abnormality in this infant is hypermagnesemia. The treatment most likely to benefit a symptomatic child with hypermagnesemia includes fluids, calcium, and loop diuretics. The other treatment choices are important for cases involving hyperkalemia, hypernatremia, hypercalcemia, or hyperammonemia.

Magnesium ion passes freely across the placenta. Equilibration of maternal and fetal serum concentrations occurs with a 2-hour delay. The normal serum magnesium concentration is between 1.6 mEq/L (1.6 mmol/L) and 2.1 mEq/L (2.1 mmol/L). The most common cause of hypermagnesemia in the newborn is maternal administration of magnesium for preeclampsia, or eclampsia as in this vignette. Other causes of hypermagnesemia include renal failure, rhabdomyolysis, hypothyroidism, and excess magnesium administered by antacids, laxatives, or parenteral nutrition.

Signs and symptoms of hypermagnesemia vary by serum magnesium concentration, and neonates often are affected at lower concentrations than children or adults (Table).

Table

Table. Selected Signs and Symptoms of Hypermagnesemia	
Serum Concentration, mEq/L	**Signs and Symptoms**
3-8	Sedation
	Facial flushing
	Hypotension
	Electrocardiographic changes
5-15	Respiratory depression
	Apnea
	Ileus
	Loss of deep-tendon reflexes
	Weakness
	Coma
20-30	Cardiac arrest

Serum concentrations correlate only approximately with tissue levels and clinical signs. Signs in the neonate can last from hours to days. The elimination half-life of magnesium in premature infants with adequate urine output may be as long as 40 hours. Changes on the electrocardiogram may include sinus bradycardia; prolonged PR, QRS, and QT intervals; atrial fibrillation; heart block; and asystole. Signs and symptoms can be potentiated by the addition of weak neuromuscular blocking agents, such as gentamicin. Death has been reported in some cases, mainly from cardiac arrhythmias.

Treatment of hypermagnesemia in a neonate with good urine output requires supportive care, as well as the removal of any intravenous source of the magnesium. Severe symptomatic cases, especially those with cardiac arrhythmias, may benefit from supplemental fluid administration and loop diuretics to promote magnesium excretion. Intravenous calcium acts as a temporary magnesium antagonist and may reverse arrhythmias and electrocardiographic abnormalities. Exchange transfusion and dialysis have been used successfully in severe cases.

Calcium, insulin, and glucose are used to treat severe hyperkalemia. Bicarbonate and cation exchange resins have also been used. Weakness, ileus, and apnea, as in this vignette, are not common signs of hyperkalemia.

Extra free water in the total daily fluids, as the main treatment mode, is important in the treatment of hypernatremia. Hypernatremic neonates are often hypovolemic, and so may also require volume expanders such as normal saline. Calcium and diuretics, potentially useful for the infant in this vignette with hypermagnesemia, are not ordinarily part of the treatment of a neonate with hypernatremia. Clinical signs of hypernatremia may include irritability and hyperpnea, not present in this vignette.

Normal saline, loop diuretics, and hydrocortisone are part of the treatment of hypercalcemia. Hypercalcemia may present with poor feeding, lethargy, and constipation, as in this vignette. It is unlikely to present in the delivery room, and even less likely than hypermagnesemia, given the probable treatment of the mother with magnesium after her seizure.

Benzoate and phenylbutyrate are useful agents for the treatment of hyperammonemia. They provide alternative pathways for the excretion of waste nitrogen. Benzoate is transaminated from glycine to form hippuric acid, eliminating one nitrogen in the urine. Phenylbutyrate causes one glutamine to form phenylacetyl-glutamine, eliminating two nitrogens. Although transient hyperammonemia may manifest as hypotonia on the first day after birth, as in this vignette, it is unlikely to manifest in the delivery room.

References:

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Bringhurst FR, Demay MB, Krane SM, Kronenberg HM. Bone and mineral metabolism in health and disease. In: Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson JL, eds. *Harrison's Principles of Internal Medicine.* 16th ed. New York, NY: McGraw-Hill; 2005:2238-2249

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Lipsitz PJ, English IC. Hypermagnesemia in the newborn infant. *Pediatrics.* 1967;40:856-862

Robin 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

American Board of Pediatrics Content Specification(s):

Understand the etiology, clinical manifestations, and approach to therapy of hypermagnesemia

Recognize and diagnose the metabolic disorders that lead to coma

Know how to recognize inadequate or excessive water intake by analyzing water intake, urine output, weight change, and serum sodium concentration

Understand the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of the urea cycle

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July: Question 2

A 25-year-old human immunodeficiency virus (HIV)–positive woman delivers a full-term male infant. Although she has followed all of the current recommendations to minimize the vertical transmission of HIV, she remains distraught about the possibility of infecting her son. She would like to know whether her infant is infected with HIV as soon as possible using the most reliable test(s).

Of the following, the MOST reliable test for HIV in this infant is:

1	DNA polymerase chain reaction (PCR) at 4 weeks of age
2	enzyme-linked immunosorbent assay at 4 weeks of age
3	HIV p24 antigen detection at 2 weeks of age
4	RNA PCR using cord blood
5	viral blood culture at 2 weeks of age

You selected 4, the correct answer is 1.

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The most reliable method to diagnose human immunodeficiency virus (HIV) in the infant in this vignette is direct detection of the virus in peripheral blood mononuclear cells using DNA polymerase chain reaction (PCR). PCR assays should not be performed on cord blood because of the possibility of contamination with maternal blood. An infant who has a positive HIV DNA PCR result in the first 2 days after birth has probably been infected in utero while an infant with a positive test result first noted between 2 and 6 weeks after birth has most likely been infected during the intrapartum period. Approximately 93% of HIV-infected newborns have detectable HIV DNA by 2 weeks of age, and almost all infected newborns have a positive DNA PCR result by 1 month of age. PCR testing for HIV can be performed using dried blood spots as well as whole blood samples. Because of the reagent cost and processing time for dried blood spot testing, it is currently preferable to test whole blood.

At present, to assess for HIV infection in HIV-exposed infants in the United States, it is recommended that an HIV DNA PCR assay be performed during the first 48 hours after birth, at 1 to 2 months of age, and at 2 to 4 months of age. If an infant has a positive result at anytime, DNA PCR testing should be repeated on a second blood sample as soon as possible to confirm the diagnosis. If this second blood sample is also positive, the infant is infected. If two separate blood samples obtained at or after 1 month of age and again after 4 months of age are both negative on DNA PCR assay in nonbreastfed infants, HIV infection can be reasonably excluded. To definitively confirm seroreversion (ie, negative immunoglobulin G [IgG] HIV antibody concentrations), HIV antibody testing at 12 to 18 months can also be performed. Because breastfeeding infants can acquire HIV postpartum, DNA PCR testing should

be repeated 4 to 6 weeks after the last milk exposure; this is not relevant to the United States population because breastfeeding is not recommended in HIV-positive women.

Assays that measure HIV antibodies, such as enzyme-linked immunosorbent assay (ELISA) or Western blot analysis, measure IgG antibodies. Thus, these antibody assays are not reliable in the diagnosis of HIV in a newborn because all newborns will acquire HIV IgG antibodies transplacentally and will have a positive test result, regardless of their HIV infection status. However, IgG antibody testing in the newborn period may be helpful if the mother's HIV status is unknown; a positive HIV IgG test using blood from the cord or postnatally indicates that the infant was exposed to HIV. IgG antibody testing can also be helpful in diagnosing HIV in children over age 18 months because maternal antibodies have been eliminated from the circulation of most infants by this time. While a positive HIV IgG test is not helpful in the diagnosis of HIV in newborns, a negative IgG antibody test before 18 months of age can exclude HIV infection.

While testing for HIV IgM antibodies is more sensitive in diagnosing HIV infection, it is not an ideal test in newborns. IgM antibody testing is problematic because of interference with large amounts of maternally acquired IgG antibodies. Furthermore, IgM production occurs during a brief period and some HIV-infected infants have a limited IgM response. Antibody assays for IgA levels are promising and currently being investigated.

Detection of HIV p24 antigen is less sensitive than the HIV DNA PCR assay. The inability to consistently detect p24 antigen in infants may be attributable to a low amount of circulating p24 antigen in an asymptomatic infant. High concentrations of p24 antibody complexing with the antigen may further prevent the detection of antigen alone. This last obstacle may be avoided by using a new assay that first dissociates the p24 immune complex before measuring p24 antigen amounts, but this test requires further study.

Quantitative or qualitative RNA PCR assays are not recommended for routine testing of infants and children younger than 18 months of age because a negative result cannot definitively exclude HIV infection. However, HIV RNA PCR testing is the preferred method of diagnosis to identify non-B subtype HIV-1 infections. The HIV RNA PCR test is also currently useful to quantify the amount of virus to help assess the progression of the disease.

Viral detection using blood culture is expensive and not available at all laboratories. A positive result may require up to 1 month for confirmation. Viral isolation may be unreliable because it requires replication competence of the virus. In addition, viral isolation may be negative in some children who are asymptomatic or have markedly elevated suppressor lymphocytes.

References:

American Academy of Pediatrics. Human immunodeficiency virus infection. In: Pickering LK, ed. *Red Book: 2006 Report of the Committee on Infectious Diseases.* 26th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2006:378-401

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Maldonado YA. Acquired immunodeficiency syndrome in the infant. In: Remington JS, Klein JO, Wilson CB, et al, eds. *Infectious Diseases of the Fetus and Newborn Infant*. 6th ed. Philadelphia, Pa: Elsevier Inc; 2006:667-692

Palumbo P. Laboratory findings in HIV infection in infancy. *Clin Perinatol.* 1994:21:109-124

American Board of Pediatrics Content Specification(s):

Understand the diagnostic criteria of perinatal HIV infection

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July: Question 3

An infant with a birthweight of 3,200 g is born at 40 weeks' gestation. At 48 hours of age, you perform a neurologic examination.

Of the following, the finding MOST likely to represent nervous system dysfunction in this infant is:

1	absent patellar tendon reflex
2	ankle clonus of 5 to 8 beats
3	brisk pectoralis reflex
4	crossed adductor response
5	extensor plantar response

You selected 5, the correct answer is 1.

Assessment of deep tendon reflexes (DTRs) contributes to the neurologic examination of the newborn infant. In the absence of nervous system dysfunction, DTRs should always be elicitable in the term newborn. DTRs may be difficult to elicit in the triceps, variably obtainable at the biceps, and present at the patellar and Achilles tendons. In the newborn, the DTR easiest to elicit involves the pectoralis major. In the preterm infant, DTRs are elicitable by 27 weeks' gestation, and generally are less intense than in the term infant.

Deep tendon reflexes are qualified as absent, hypoactive, normal, or hyperactive. In the newborn infant, the response is often normally brisk or hyperactive. Absent or hypoactive DTRs occur with myopathies, neuropathies, and cerebellar disorders. Upper motor neuron lesions typically present with normal or increased DTRs. Detecting asymmetry in response is more useful than precisely qualifying the intensity of the reflex.

Ankle clonus is frequently elicited in the newborn, and it is enhanced during crying and hyperexcitable states. In the absence of other abnormal neurologic signs, up to 8 to 10 beats of symmetric clonus should be accepted as normal in the newborn infant. Newborn clonus is transient, and more than a few beats of clonus beyond 3 months of age suggests dysfunction of the corticospinal tracts.

Tapping the patellar tendon or the thigh adductors (medial aspect of the knee) may produce contraction in the opposite extremity, known as a crossed adductor response. Although a normal finding in the first months after birth, a crossed adductor response beyond 6 to 8 months of age suggests central nervous system dysfunction.

In the newborn, the plantar response is considered of limited value, because of competing reflexes and relative inconsistency of the response. In older infants, a positive Babinski reflex, extension of the great toe with fanning of the other toes, follows stimulation of the lateral aspect of the sole of the foot. However, in the newborn, the plantar response is normally extensor for the first month, and usually throughout the first year. Competing reflexes in the newborn stimulated by contact with the foot, such as with an examiner holding the foot to perform the plantar response, contribute to inconsistency in the finding. Nociceptive withdrawal and contact avoidance, stimulated by stroking of the dorsum of the foot, promote an extensor response. In contrast, plantar grasp and the positive supporting reflex, both elicited by pressure on the plantar aspect of the foot, promote flexion at the toes. A distinctly asymmetrical extensor plantar response, or persistence beyond infancy, suggests corticospinal tract impairment.

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References:

Kuban KC, Skouteli HN, Urion DK, Lawhon GA. Deep tendon reflexes in premature infants. *Pediatr Neurol*. 1986;2:266-271

Swaiman KF. Neurologic examination of the term and preterm infant. In: Swaiman KF, Ashwal S, Ferriero DM, eds. *Pediatric Neurology, Principles & Practice*. 4th ed. Philadelphia, Pa: Mosby Elsevier; 2006:47-64

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

American Board of Pediatrics Content Specification(s):

Recognize normal deep tendon reflexes (DTRs) in the newborn infant

Know that unsustained clonus is common in newborn infants

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July: Question 4

A 4-day-old, 35-week-gestation male infant with intrauterine growth restriction is referred to you for evaluation and management of mixed hyperbilirubinemia. His mother is being treated with thyroxine after thyroid ablation 5 years ago for Graves disease. Delivery was vaginal and uncomplicated. After birth, the infant is found to be symmetrically growth restricted with marked hepatosplenomegaly, petechiae, icterus, and small anterior fontanel (0.5 cm diameter). Tachypnea and tachycardia are also present. He is vigorous and no congenital anomalies are present. Stools are pale white in color. Laboratory and radiology investigations available include the following:

Laboratory Test	Patient Result
Total bilirubin	Markedly elevated
Conjugated bilirubin	Markedly elevated (55% of total)
Unconjugated bilirubin	Moderately elevated
Transaminases	Minimally elevated
Alkaline phosphatase	Elevated
γ-glutamyl transferase	Normal
Ammonia	Elevated
International normalized ratio	Elevated
Partial thromboplastin time	Elevated
Platelets	Low
Fibrinogen	Low
Ferritin	Normal
Transferrin saturation	Normal
Galactose-1-phosphate uridyl transferase activity	Normal
α_1-antitrypsin	Normal
Sweat chloride	Normal
Free thyroxine	High
Thyroid-stimulating hormone	Low
Chest radiograph	Mild cardiomegaly, diminished vascularity
Echocardiogram	Mild pulmonary hypertension
Abdominal sonogram	Normal, gallbladder present, no dilation of hepatic ducts, biliary sludge, or choledochal cyst
Bacterial cultures	No growth
Viral serologies and cultures	Negative

Of the following, the study that is MOST likely to confirm the diagnosis in this infant is:

1	*ABCB11* gene mutation analysis (lymphocytes)
2	cytomegalovirus culture (urine)
3	fumarylacetoacetate hydroxylase activity (lymphocytes)

4	*Jagged-1* gene mutation analysis (lymphocytes)
5	thyroid-stimulating antibody concentration (serum)

You selected 1, the correct answer is 5.

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The presence of thyroid-stimulating antibodies in the infant in this vignette will confirm the diagnosis of congenital hyperthyroidism. Maternal Graves disease, high thyroxine concentration, and low thyroid-stimulating hormone concentration raise suspicion about congenital hyperthyroidism as the cause for the clinical findings in this infant. Intrauterine growth restriction, cardiomegaly associated with congestive heart failure, hepatosplenomegaly, small anterior fontanel, petechiae, goiter, proptosis, hyperkinesis, diarrhea, and poor growth are reported in neonates with this disorder.

Infants born to mothers receiving antithyroid medications, such as propylthiouracil, may become biochemically and clinically hyperthyroid during the first weeks after birth as the antithyroid medications are metabolized. In contrast, infants born to mothers whose thyroid gland has been ablated may become hyperthyroid in utero because of the ongoing production and transplacental passage of thyroid-stimulating antibodies by the mother, as occurred in the infant in this vignette.

Cholestatic jaundice is an unusual finding in congenital hyperthyroidism. Although the mechanism is unclear, the cholestasis improves with treatment and recovery from hyperthyroidism. Immaturity of bile formation and flow in neonates is reflected by impaired hepatic uptake of bile salts (the primary stimulus for bile flow), smaller bile salt pool size, and lower rates of absorption in the ileum (versus the adult). These deficiencies are described by the term *physiologic cholestasis* (or *physiologic hypercholanemia) of infancy*. It is likely that pituitary hormones affect bile synthesis and flow because of the association of cholestasis with hypopituitarism. However, the specific effect of pituitary hormones, specifically thyroxine, on bile metabolism is yet to be determined.

It could be conjectured that the taurine conjugated bile acids and precursors that predominate in the fetus, rather than the glycine conjugates that predominate in the older child and adult, may be overproduced in response to the hypermetabolic response to high thyroxine concentrations. These taurine-conjugated bile acids may then accumulate because of immature bile metabolism in the neonate and impair the metabolic and cellular functions of the hepatocyte.

The presence of intrauterine growth restriction, coagulopathy, and elevated liver function results, including the conjugated fraction of bilirubin, is consistent with a number of congenital infections, including cytomegalovirus, toxoplasmosis, human immunodeficiency virus, parvovirus B19, and herpes simplex. Absence of maternal or placental evidence of congenital infection usually prompts a search for the other common and easily evaluated causes for neonatal cholestasis, especially if early recognition and treatment are important to reduce morbidity. The causes of neonatal cholestasis include:

- **biliary atresia (most common)**
- **other obstructive biliary tract disorders (such as choledochal cysts, paucity of bile ducts)**
- **inherited disorders (such as a_1-antitrypsin deficiency, cystic fibrosis)**
- **bacterial infections (such as sepsis and urinary tract infections)**
- **galactosemia**
- **hypothyroidism**
- **idiopathic hepatitis**

If clinical or laboratory studies are inconclusive or suggestive of other diagnoses, additional

evaluation is indicated for other inborn errors of metabolism (such as tyrosinemia, fructosemia, peroxisomal disorders, progressive familial intrahepatic cholestasis, bile salt synthetic defects, congenital hemochromatosis), endocrinopathies (such as hypopituitarism, hyperthyroidism), syndromes (such as Alagille syndrome), and toxic exposures (such as drugs, parenteral nutrition).

ABCB11 **gene mutation analysis determines the presence of mutations in the gene responsible for progressive familial intrahepatic cholestasis type 2 (PFIC2). The** ***ABCB11*** **gene is responsible for the activity of the bile salt export pump located on the canalicular membrane of the hepatocyte. Like progressive familial intrahepatic cholestasis type 1 (*PFIC1*, mutation of the *ATP8B1* gene), *PFIC2* is inherited in an autosomal recessive pattern and the spectrum of disease can be variable. However, severe cholestasis with pruritus, malabsorption, greasy stools, and failure to thrive may present in the first months after birth. If untreated, cirrhosis, hepatic failure, and death may occur during infancy or early childhood. The diagnosis is usually determined on clinical and laboratory findings with low or normal concentrations of g-glutamyltranspeptidase (GGT). In most disorders that cause cholestasis, GGT is elevated. Cholestasis with hyperthyroidism is one of the few disorders associated with normal or low GGT, as in the infant in this vignette.**

Isolation of cytomegalovirus (CMV) from fibroblast tissue cultures of urine or saliva is the standard reference method to determine the presence of CMV. Modifications of the tissue culture method by the addition of monoclonal antibodies to CMV-specific early antigens (shell vial assay, microtiter plate immunofluorescent antibody assay) may allow diagnosis to be established within 24 hours. Such modifications have shown high sensitivity and specificity. DNA hybridization methods are reliable but limited if the titer of virus is less than 10^3 infective doses per milliliter. The polymerase chain reaction amplification method for detecting CMV in many tissue or body fluid specimens is highly sensitive and specific. A modification for use of dried filter paper specimens is also available for retrospective diagnosis. Detection of antigenemia using CMV-specific monoclonal antibodies is also available but sensitivity and specificity are not superior to other methods. Serologic analysis of the immune response to CMV is complicated by individual variations in development of IgG and IgM antibodies and lower sensitivity and specificity than viral culture methods.

A diagnosis of tyrosinemia type 1 is confirmed by measurement of fumarylacetoacetate hydroxylase activity in lymphocytes, erythrocytes, or liver biopsy specimens. A presumptive diagnosis is determined by the onset in early infancy of hepatic failure, hepatomegaly, hemorrhage, vomiting, hypoglycemia, Fanconi-like syndrome (normal anion gap acidosis, hyperphosphaturia, hypophosphatemia), mixed hyperbilirubinemia, and elevations of serum transaminases and a-fetoprotein (even in cord blood specimens suggesting in utero liver dysfunction). These findings usually are precipitated by an intercurrent illness and catabolic state. Increased plasma tyrosine and methionine concentrations and elevated serum and urine succinylacetoacetate and succinlylacetone are diagnostic. Tyrosinemia type 1 is rare (1:110,000 live births) outside Quebec, Canada (1:1,846 live births), transmitted in an autosomal recessive fashion, treatable with 2-(nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione and liver transplantation, and carries a high risk of hepatocellular carcinoma (37% of cases).

Alagille syndrome is diagnosed with *Jagged-1* mutation analysis. Eighty-eight percent of affected individuals have abnormalities in the *Jagged-1* gene. Fluorescence in situ hybridization for microdeletions of chromosome 20p12 will detect another 7% of affected patients and mutation analysis of the *NOTCH2* gene in present is 1% of affected individuals. Alagille syndrome is inherited as an autosomal dominant disorder and is characterized by:

- **Chronic cholestasis**
- **Peripheral branch pulmonary stenosis and other cardiac defects**
- **Paucity of bile ducts (beginning in childhood)**
- **Butterfly vertebrae and other skeletal abnormalities**
- **Characteristic facies (broad forehead, deep-set eyes, triangular facies)**
- **Eye abnormalities (posterior embryotoxon = prominent Schwalbe ring in the anterior chamber of the eye)**

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References:

Beroukhim RS, Moon TD, Felner EI. Neonatal thyrotoxicosis and conjugated hyperbilirubinemia. *J Maternal-Fetal Neonatal Med.* 2003;13(6):426-428

Dryden C, Simpson JH, Hunter LE, Jackson L. An unusual cause of neonatal coagulopathy and liver disease. *J Perinatol.* 2007;27(5):320-322

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Rezvani I. an approach to inborn errors of metabolism. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*. 17th ed. Philadelphia, PA: WB Saunders Co; 2004:397-433

Sheehan AG, Martin SR, Stephure D, Scott RB. Neonatal cholestasis, hypoglycemia, and congenital hypopituitarism. *J Pediatr Gastroenterol Nutr.* 1992;14(4):426-430

Stagno S, Britt W. Cytomegalovirus infections. In: Remington JS, Klein JO, Wilson CB, Baker CJ, eds. *Infectious Diseases of the Fetus and Newborn Infant*. 6th ed. Philadelphia, Pa: Elsevier Saunders; 2006:740-781

Viallard JF, Tabarin A, Neau D, Longy-Boursier M. Hyperthyroidism with severe intrahepatic cholestasis. *Dig Dis Sci.* 1999;44(10):2001-2002

American Board of Pediatrics Content Specification(s):

Identify the effect of maternal immunologic disease with transplacental passage of immunoglobulins and its treatment on the fetus

Understand the relationship between fetal and maternal thyroid physiology

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

Recognize the effects on the fetus of maternal endocrine disorders (other than diabetes mellitus) and their management

Identify the etiology and clinical manifestations of congenital hyperthyroidism

Know the laboratory features and treatment of congenital hyperthyroidism

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

Understand the diagnostic criteria of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Ebstein-Barr virus, and varicella virus

Know the various laboratory and radiographic techniques to diagnose metabolic and familial causes of cholestasis in the neonate

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July: Question 5

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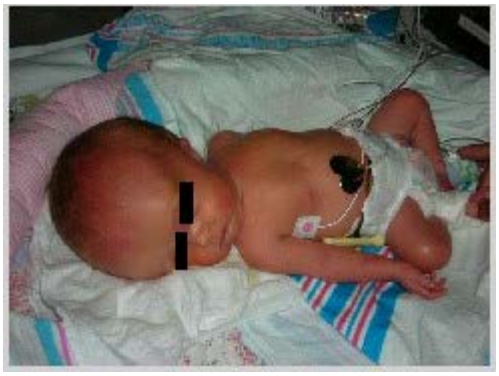
A 2,947-g female infant is born at 32 weeks' gestation. Physical examination reveals macrocephaly. Her head circumference measures 43.4 cm (>90th percentile). She does not have other dysmorphic physical features (Figure 1).

Figure 1: Infant with macrocephaly



Magnetic resonance imaging of her brain demonstrates agenesis of the corpus callosum, hydrocephalus, and a dilated fourth ventricle. The cerebellum is small, the cerebellar vermis is absent, and a large posterior fossa cyst is present (Figures 2 and 3).

Figure 2: Magnetic resonance image of brain demonstrating markedly enlarged lateral ventricles, absence of the corpus callosum, and a large posterior fossa cyst

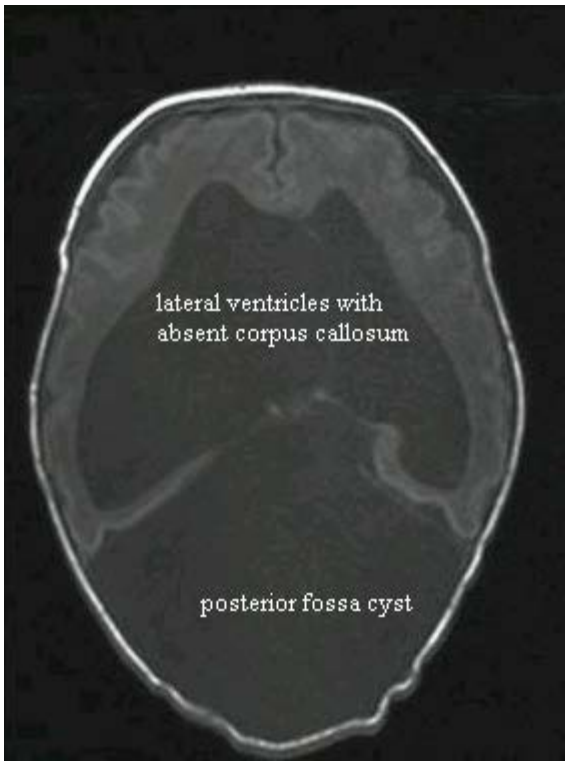
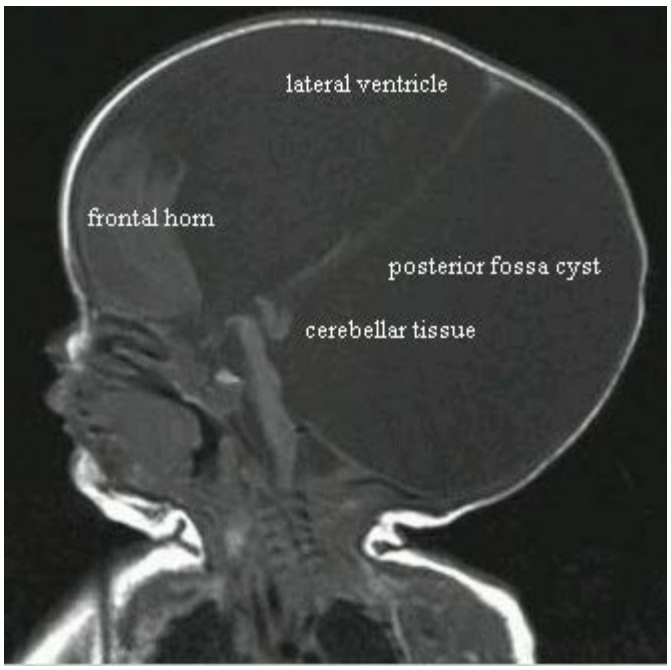


Figure 3: Magnetic resonance image of brain demonstrating markedly enlarged lateral ventricles, large posterior fossa cyst, and a small amount of cerebellar tissue



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

1	aqueductal stenosis
2	arachnoidal cyst
3	Arnold-Chiari malformation
4	Dandy-Walker malformation
5	Joubert syndrome

You selected 3, the correct answer is 4.

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Hydrocephalus refers to ventricular enlargement, and is classified as obstructive (noncommunicating) or communicating. Cerebrospinal fluid (CSF) is secreted by the choroid plexus, and is generally absorbed by the arachnoid villi. Impaired CSF absorption leads to CSF accumulation and consequent ventricular enlargement or hydrocephalus. Obstruction of CSF flow can occur at any point in the pathway, including the foramen of Monro, aqueduct of Sylvius, fourth ventricle outlets (foramina of Luschka and Magendie), basal cisterns, and the arachnoid villi. In communicating hydrocephalus, CSF accumulates as a result of impaired absorption or obstruction within the subarachnoid space over the cerebral hemispheres.

The major causes of congenital hydrocephalus are aqueductal stenosis (33% of cases); Arnold-Chiari malformation with myelodysplasia (28%); "communicating" hydrocephalus (22%); Dandy-Walker malformation (7%); and other conditions, such as intrauterine infection, tumor, and hemorrhage (10%). Obstructive hydrocephalus is typically permanent, and a diversionary shunt is the preferred treatment.

The infant in the vignette has hydrocephalus and intracranial findings consistent with a diagnosis of Dandy-Walker malformation. Imaging of her brain demonstrates cystic dilation of the fourth ventricle, abnormal development of the cerebellar vermis, and hydrocephalus, the three major abnormalities comprising Dandy-Walker malformation (Figures 2 and 3). Enlargement of the posterior fossa and elevation of the tentorium are also distinguishing features of Dandy-Walker malformation. Associated CNS abnormalities, such as agenesis of the corpus callosum and neuronal migration defects, occur in as many as 70% of cases. Hydrocephalus with occipital prominence is a dominant clinical feature, but may not develop until later in the first year or rarely until adulthood. Management of the hydrocephalus involves shunting both the fourth ventricular cyst and the lateral ventricles. The long-term outcome of Dandy-Walker malformation is related to the severity of both the malformation and associated anomalies. Among infants with a postnatal diagnosis of Dandy-Walker malformation, the mortality is 10% and impaired cognitive development occurs in 25% to 75% of survivors. Dandy-Walker variant refers to the condition of vermian hypoplasia and cystic dilation of the fourth ventricle, without associated enlargement of the posterior fossa or hydrocephalus.

Aqueductal stenosis is the most common cause of congenital hydrocephalus, accounting for approximately one third of cases. Obstruction at the aqueduct of Sylvius results in marked enlargement of the third and proximal ventricles. The posterior fossa and cerebellar findings of Dandy-Walker malformation are not seen with aqueductal stenosis. Most cases of aqueductal stenosis are nonfamilial, but an X-linked variety associated with adducted thumbs, agenesis of the corpus callosum, and severe cognitive deficiencies has been associated with a mutation in the neural cell adhesion molecule L1CAM. In addition, aqueductal stenosis has been seen with the VACTERL association in an X-linked or autosomal recessive inheritance pattern.

Intracranial arachnoid cysts are benign, nongenetic developmental cysts that occur within the arachnoid membrane, and may obstruct CSF flow. Common locations for arachnoid cysts include the Sylvian fissure (66% of cases), the sellar region, and the posterior fossa. Arachnoid cysts of the posterior fossa can be difficult to distinguish from other cystic malformations of the posterior fossa, such as the Dandy-Walker malformation. However, the cerebellar abnormalities associated with Dandy-Walker malformation are not characteristic of arachnoid cysts.

Arnold-Chiari malformation (type II, occurring with myelodysplasia) is associated with obstructive hydrocephalus because of aqueductal compression and fourth ventricle outlet obstruction. The major features of the Chiari-II malformation include inferior displacement of the medulla and fourth ventricle, elongation and thinning of the upper medulla and lower pons, inferior displacement of the lower cerebellum through the foramen magnum, and a variety of bony defects of the occiput and upper cervical spine. Unlike Dandy-Walker malformation,

posterior fossa fluid collections are not characteristic of the Arnold-Chiari malformation.

Joubert syndrome is a disorder of autosomal recessive inheritance marked by agenesis or severe hypoplasia of the cerebellar vermis, and is also known as familial vermian agenesis. Clinical features include ataxia, hypotonia, oculomotor apraxia, dysregulation of breathing, and mental retardation. Although the fourth ventricle is enlarged with Joubert syndrome, the lack of both hydrocephalus and enlargement of the posterior fossa are features that distinguish this disorder from Dandy-Walker malformation.

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References:

Gleeson JG, Dobyns WB, Plawner L, Ashwal S. Congenital structural defects. In: Swaiman KF, Ashwal S, Ferriero DM, eds. *Pediatric Neurology, Principles & Practice*. 4th ed. Philadelphia, Pa: Mosby Elsevier; 2006:363-490

Pattisapu JV. Etiology and clinical course of hydrocephalus. *Neurosurg Clin North Am*. 2001;36:651-659

Volpe JJ. Neural tube formation and prosencephalic development. In: *Neurology of the Newborn.* 4th ed. Philadelphia, Pa: WB Saunders; 2001:3-44

American Board of Pediatrics Content Specification(s):

Be able to differentiate the familial/genetic features of neurology disorders associated with increased head circumference

Understand the etiology, familial/genetic features, and abnormalities associated with hydrocephalus

Understand the treatment of hydrocephalus

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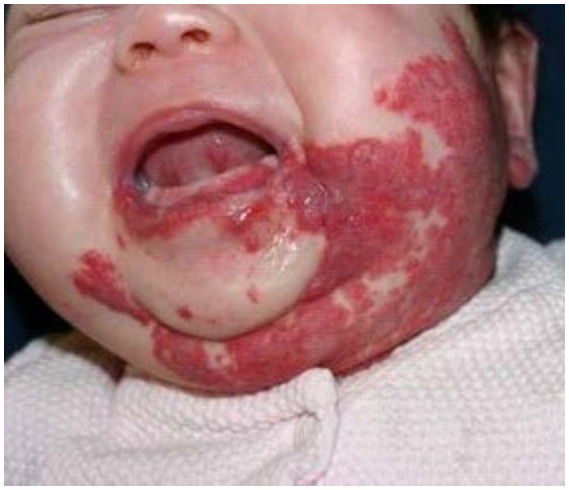
July: Question 6

A full-term infant is born with a large, erythematous facial lesion in a beardlike distribution (Figure).

Figure



A cleft in the sternum and a supraumbilical raphe are discovered on physical examination.

Of the following, the diagnostic evaluation that RARELY uncovers an abnormality in this syndrome is:

1	echocardiography
2	magnetic resonance imaging of the brain
3	ophthalmology examination
4	renal ultrasonography
5	upper airway endoscopy

You selected 4, the correct answer is 4.

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Infants with large, segmental plaquelike hemangiomas on the face, as in the infant in the vignette, may have PHACE syndrome. PHACE syndrome is a neurocutaneous syndrome defined by the presence of a large, segmental *h*emangioma in association with one or more congenital malformations involving structures of the *p*osterior fossa, *a*rterial and cerebral vasculature, *c*ardiac anatomy, and *e*ye. (Table).

Table. PHACE(S) Syndrome

Posterior fossa defects	• Dandy-Walker complex • Cerebellar hypoplasia or atrophy • Dysgenesis/agenesis of the vermis
Hemangioma	• Segmental facial hemangiomas
Arterial Anomalies	• Aneurysm of the left subclavian artery • Atresia of the right carotid artery • Calcified cerebral aneurysms
Cardiac Anomalies	• Coarctation of the aorta • Complex aortic arch anomalies • Ventricular septal defects • Atrial septal defects • Tetralogy of Fallot
Eye abnormalities	• Microphthalmos • Retinal vascular abnormalities • Persistent fetal retinal vessels • Optic nerve atrophy • Iris hypertrophy or hypoplasia • Exophthalmos • Colobomas • Excavated optic disc anomalies
Sternal cleft, supraumbilical raphe, or both	• Ventral developmental defects (sternal clefting or supraumbilical raphe)

An 'S' may be added to the end of PHACE(S) because sternal clefting and supraumbilical raphe are commonly present. Generally the kidneys are not involved and few infants manifest the entire constellation of anomalies. Physical examination and imaging studies of the brain, cerebral vasculature, heart, and eye are most relevant to establish the diagnosis of PHACE syndrome. Because the kidneys are usually normal, renal ultrasonography is not likely to detect a structural abnormality.

PHACE syndrome is not rare; 20% of all facial hemangiomas and 2% to 3% of all hemangiomas are a part of the PHACE spectrum. Eighty percent of cases occur in females. Cervicofacial mandibular or "beard" distribution hemangiomas may involve the upper airway. Posterior fossa abnormalities may be associated with developmental delays, motor delays, and pituitary dysfunction. PHACE syndrome is more common than the rare, sporadic Sturge-Weber syndrome, another neurocutaneous syndrome that includes nevus flammeus of the face, unilateral angiomatosis of the meninges, and vascular abnormalities of the choroid of the eye.

Specific more common abnormalities by organ or site found in patients with PHACE syndrome are listed in the Table.

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References:

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Frieden IJ, Reese V, Cohen D. PHACE syndrome: the association of posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities. *Arch Dermatol.* 1996;132(3):307-311

Metry DW, Haggstrom AN, Drolet BA, et al. A prospective study of PHACE syndrome in infantile hemangiomas: demographic features, clinical findings, and complications. *SO Am J Med Genet A*. 2006;140(9):975-986

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American Board of Pediatrics Content Specification(s):

Know how to diagnose hemangiomas

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July: Question 7

An infant born at 38 weeks' gestation is evaluated for low birthweight (1,820 g). Length is at the 10th percentile and head circumference at the 50th percentile on the growth chart. The infant's mother is a 28-year-old primigravida, whose pregnancy has been complicated by severe preeclampsia.

Of the following, the outcome MORE likely to be found later in life in the infant in the vignette than in infants with normal growth is:

1	growth hormone deficiency
2	insulin resistance
3	mental retardation
4	short stature
5	subcutaneous adiposity

You selected 5, the correct answer is 2.

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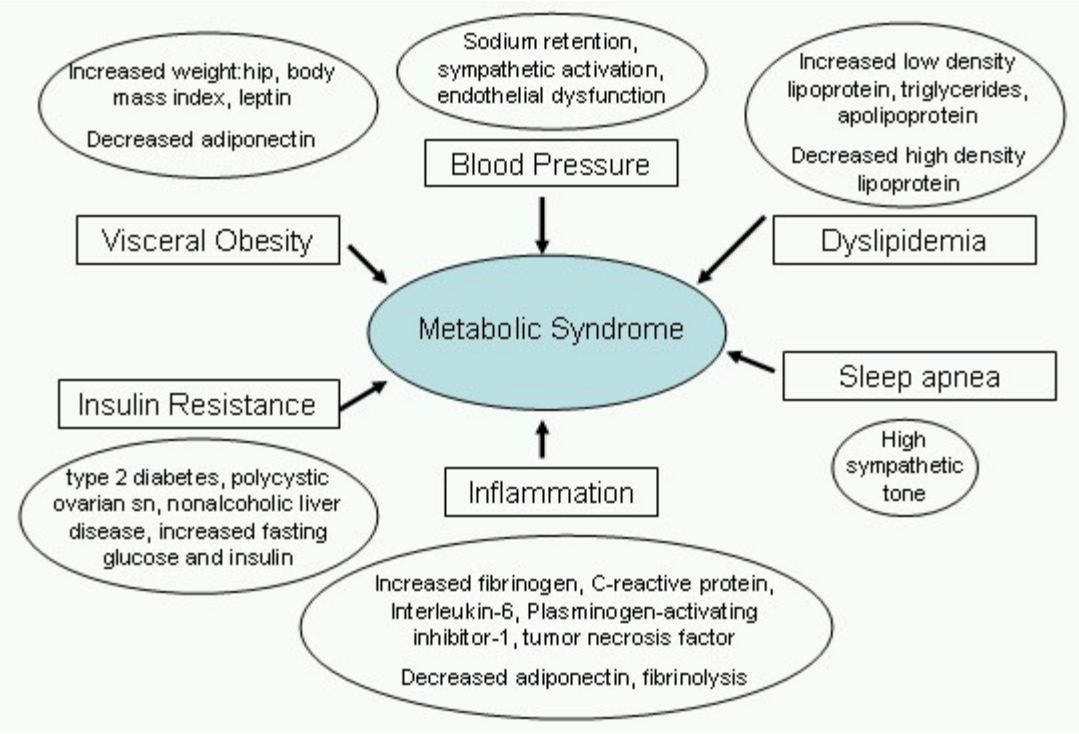
The metabolic syndrome, although variably defined, is composed principally of insulin resistance, hyperinsulinemia, visceral adiposity, dyslipidemia, and systemic hypertension. Ischemic heart disease and overt type 2 diabetes mellitus may develop. Systemic inflammation, hypercoagulability, and endothelial dysfunction are also observed in the spectrum of this disorder. About 20% to 30% of adults are affected and the prevalence is increasing. Teenagers are also being diagnosed with the metabolic syndrome at an alarming frequency. Because morbidity and mortality during adulthood are substantial, research and development of strategies to prevent or treat associated pathophysiologic aberrations are receiving emphasis by neonatologists and internal medicine specialists alike.

Multiple metabolic and physiologic abnormalities underlie the metabolic syndrome. Insulin resistance and abnormal adipose tissue metabolism are common, but not essential, features (Figure 1).

Figure 1: Pathogenic mechanisms contributing to the metabolic syndrome (adapted from Batsis et al [2007])

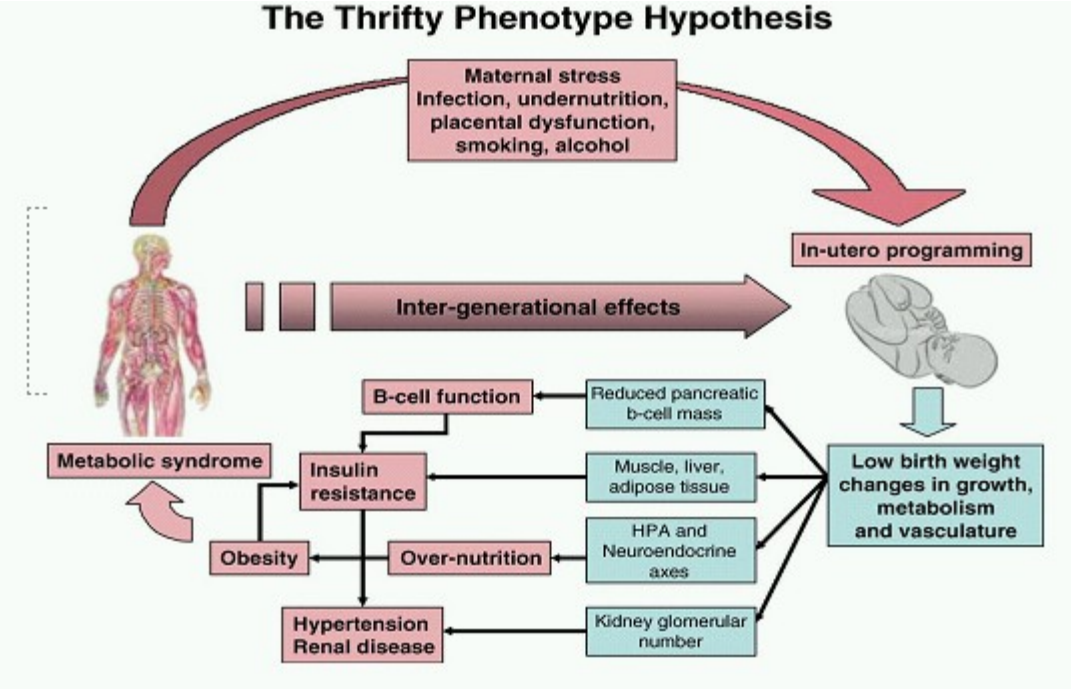


A large body of epidemiologic and animal model evidence indicates that low birthweight, especially presenting as intrauterine growth restriction (IUGR) as in the infant in this vignette, is associated with a high risk for developing the metabolic syndrome and its complications. The risk for metabolic syndrome in small-for-gestational-age infants during young adulthood is low (2.3%) but is sixfold higher than in those who were appropriate for gestational age (0.4%). Landmark studies have demonstrated associations between low birthweight and obesity, hypertension, hypertriglyceridemia, cardiovascular disease (myocardial infarction, stroke), impaired glucose tolerance, and type 2 diabetes mellitus.

It is important to recall that size at birth is a poor proxy for IUGR. Small size is associated with many causes, not all of which may have implications for adult disease. For example, infants whose birthweights are lower than the 10th percentile on growth grids are often constitutionally small but do not have IUGR. These normal-growth but small infants may not be at higher risk for adult morbidity than those born with IUGR. Additional research is needed to clarify which populations of infants born "small" are at risk for "adult" diseases.

The underlying mechanisms for later development of metabolic syndrome in infants with IUGR are unclear. These mechanisms likely involve fetal programming of metabolic pathways and organ development in response to limited nutrient/oxygen delivery and pathologic insults (Figure 2).

Figure 2: The thrifty phenotype hypothesis (reprinted with permission from Fernandez-Twinn and Ozanne [2006])



The "thrifty phenotype" hypothesis describes in utero programming of fetal metabolic systems and physiologic adaptations in response to life-threatening maternal stress, infection, undernutrition, placental dysfunction, and exposure to alcohol and tobacco. After birth, these metabolic and physiologic adaptations then become a liability during times of nutrient excess.

Changes in the hypothalamic-pituitary-adrenal axis are hypothesized to play a pivotal role in fetal adaptations but oxidant stresses also likely play important roles. The combination of increased fetal catabolism and subsequent metabolic reprogramming causes growth restriction. Specific findings in affected infants include reduction in pancreatic beta-cell mass and function; growth hormone hypersecretion (induces insulin resistance); abnormal muscle, liver, and fat development (visceral rather than subcutaneous adiposity); changes in adrenal and neuroendocrine production; and reduction in glomerular number. Genetic and epigenetic changes occur and account, in part, for risk transmission through subsequent generations of offspring. Insulin resistance, hypertension, visceral adiposity, and other findings of the metabolic syndrome result. As the infant grows, occult physiologic and metabolic abnormalities exist but overt signs and symptoms may only become apparent or be triggered during the teenage years and adulthood.

An interesting parallel has been described between full-term infants with IUGR and extremely preterm infants. Both experience undernutrition during the last "trimester" of fetal life. The preterm infant fails to grow during the first weeks after birth because of limited nutrient intake and medical illness. During this time, low concentrations of insulinlike growth factor 1 (IGF-1), an important regulator of growth, stimulate excessive secretion of growth hormone. The adrenal hormone axis is often upregulated because of stress and, combined with a large supply of growth hormone, causes insulin resistance. The addition of exogenous glucocorticoids exacerbates these pathophysiologic phenomena. In the presence of overnutrition and inhibition of important adipocyte metabolic pathway components (such as beta$_3$-adrenoreceptors), fat is preferentially deposited in visceral sites within the mesentery and abdomen rather than in subcutaneous sites. This gives infants the appearance of truncal obesity with relatively thin extremities. Protein supplementation to raise IGF-1 levels has the potential to reduce growth hormone hypersecretion and insulin resistance. Supplementation with very-long-chain polyunsaturated fatty acids (such as eicosapentaenoic acid and docosahexaenoic acid) has been found to reduce production of proinflammatory mediators that also cause insulin resistance. Additional protein and very-long-chain fatty acid supplementation are promising interventions to mitigate the evolution of the physiologic impairments that may lead to the metabolic syndrome in recovering preterm infants and full-term infants with IUGR.

Although there are conflicting reports, infants who are born at term and severely growth

restricted are found to have IQs similar to those of infants with normal growth. Nevertheless, such infants with IUGR are at higher risk for school failure because of behavioral disorders (especially attention deficit disorder) and learning disabilities. In contrast, preterm infants with severe IUGR have higher rates of cognitive, motor, and neurologic deficits than preterm infants without IUGR. Interestingly, such infants have lower rates of cerebral palsy.

Growth patterns in infants with IUGR vary with the cause of the growth restriction. Infants with moderate IUGR and uncomplicated medical courses, such as the infant in the vignette, usually reach normal height. In comparison, infants with severe IUGR are frequently shorter and lighter through adolescence.

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References:

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Yeung MY. Postnatal growth, neurodevelopment and altered adiposity after preterm birth-from a clinical nutrition perspective. *Acta Paediatr.* 2006;95:909-917

American Board of Pediatrics Content Specification(s):

Recognize that there may be a period of catch-up growth in SGA infants

Understand the differences in body composition between SGA, LGA, and AGA infants

Know the nutritional requirement before and during pregnancy and the impact on fetal growth and development

Understand the complications and management of fetal growth restriction

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July: Question 8

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A 19-year-old Amish woman delivered her first infant at home after 36 weeks of gestation by dates; he was good sized and healthy in all respects. He began breastfeeding and urinated frequently during the first few days, but did not have a stool for 36 hours. Breastfeeding was difficult, and on the third day the infant refused to eat and became sleepy. He was seen by a physician who noted jaundice. The infant's serum bilirubin concentration was 28 mg/dL (479 µmol/L).

The infant was transferred immediately to a tertiary care nursery where he was found to have alternating irritability and lethargy, as well as newly developed opisthotonus. Laboratory investigation showed a total serum bilirubin concentration of 32 mg/dL (547 µmol/L), negligible conjugated bilirubin concentration, and no evidence of a hemolytic process or infection. The infant started receiving intensive phototherapy. Albumin (1 g/kg) and glucose water were infused intravenously while an exchange transfusion was being arranged.

Of the following, the only TRUE statement about acute kernicterus in this infant is that:

1	exchange transfusion cannot reverse the process
2	hearing loss is not commonly associated
3	lack of feeding/nutrition is an added risk
4	seizures are a common finding
5	serum bilirubin concentration is a sensitive predictor

You selected 2, the correct answer is 3.

The infant in the vignette is demonstrating an early to intermediate phase of acute kernicterus. He has severe unconjugated hyperbilirubinemia along with alternating irritability and lethargy, opisthotonus (retrocollis), and poor feeding. Such infants commonly fail hearing assessments. If allowed to go on without treatment, the syndrome would progress to shrill cry, fever, and deep stupor or coma. Later stages of acute bilirubin encephalopathy include seizures, although uncommon, and death. If not treated promptly, life-long devastating neurologic dysfunction, dental dysplasia, and deafness might result.

The risk factors for kernicterus described in the vignette include an inexperienced mother, breastfeeding, late prematurity, male gender, poor feeding, and a lack of professional contact/supervision or screening for jaundice in the first days after birth. Poor feeding leads to hyperbilirubinemia through enhanced enterohepatic reabsorption of bilirubin.

Initial treatment of the infant in the vignette included albumin, glucose water, and intense phototherapy. All of these are temporizing measures in anticipation of definitive therapy (ie, exchange transfusion). Albumin,

an important natural defense against bilirubin toxicity, binds bilirubin tightly in the extracellular fluid and prevents transfer of bilirubin to cells including brain cells. Premature infants tend to have lower serum albumin concentrations than term infants. Glucose water is given to stimulate insulin release. Insulin, in turn, reduces the concentration of free fatty acids in circulation. Free fatty acids are the most abundant natural competitors for bilirubin binding sites on albumin, making any particular concentration of bilirubin more toxic. Free fatty acids are present in high concentrations when infants are fasting.

Phototherapy converts some of the lipid-soluble toxic form of bilirubin (in which the double bonds connecting the outer pairs of pyrrole rings are in the *cis* configurations) to a nontoxic stereoisomer by changing the *cis* double bonds to the *trans* configuration. This transformation is temporary and exposes one or both of the proprionic acid side chains of bilirubin, previously neutralized by internal hydrogen bonding, to the aqueous milieu. These stereoisomers are then water-soluble and unable to cross cell membranes and produce toxicity.

Exchange transfusion has been documented to reverse the toxic effects of bilirubin in animals and in human infants. This does not happen every time an exchange transfusion is performed on an infant with signs of kernicterus, but is worth trying as soon as possible when such an infant is identified. The success or failure is probably related to the length of time the brain cells were exposed to toxic concentrations of bilirubin.

The serum bilirubin concentration, regardless of the presence of hemolytic disease, is a poor predictor of bilirubin toxicity. Even in the early studies of Rh disease, concentrations of 20 mg/dL (342 µmol/L) were associated with only a 5% incidence of kernicterus. Concentrations about twice that high were associated with less than a 50% incidence of the disease. Therefore, measuring the total serum bilirubin concentration is not a very sensitive test for risk. It has been suggested that measurement of the free (unbound) bilirubin concentration would be much more sensitive, but this concept has not been accepted widely and the test is not generally available.

Do you want to add anything to your Learning Plan?
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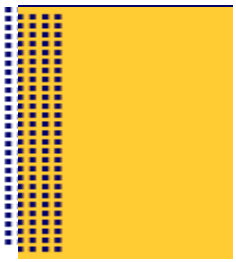
American Board of Pediatrics Content Specification(s):

Describe the clinical features of acute bilirubin encephalopathy in newborn infants



July: Question 9

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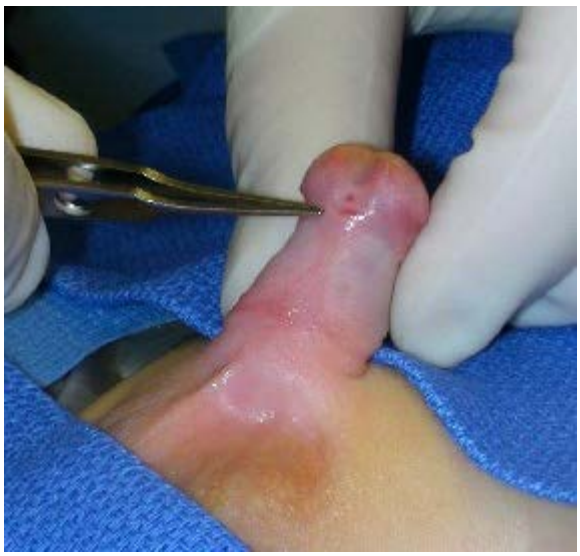
11 November 08

12 December 08

During rounds with the residents in the newborn nursery, you are asked to see a full-term infant born to a 25-year-old white mother. The mother's pregnancy was uncomplicated. Because of previous pregnancy losses, chorionic villus karyotype was performed and parents were told it was normal. Prenatal ultrasonography performed at 18 weeks' gestation was normal, but parents did not want to know the predicted fetal sex from either study. The infant's abnormal physical finding is seen in the Figure. The chorionic villous sampling result was 46,XY, according to the prenatal records.

Figure



Of the following, the statement that MOST accurately describes details about the evaluation and management of the infant is that:

1	circumcision is recommended in the neonatal period
2	cryptorchidism increases risk of intersexuality
3	meatal obstruction is common
4	renal ultrasound should be obtained
5	surgical repair is usually done by 2 months of age

You selected 2, the correct answer is 2.

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The infant in this vignette has penile hypospadias. Hypospadias is a common congenital anomaly of the penis in which the urethra opens proximal to its normal position at the tip of the

glans. Hypospadias, following cryptorchidism, is the second most common genital abnormality in male infants, occurring with an incidence of 0.3% to 0.8% of live births. The incidence of hypospadias has doubled since the 1960s for unknown reasons.

The anatomic location of approximately 87% of hypospadias anomalies are glandular or coronal, 10% are penile, as in the neonate in the vignette, and 3% are penoscrotal or perineal. The anatomy of a penis with hypospadias is similar to that of a normal penis except on the ventral aspect where the foreskin and urethral spongiosum are absent.

Formation of the male external genitalia is a complex process involving genetic programming, cell differentiation, hormonal signaling, enzyme activity, and tissue remodeling. Hypospadias occurs because of an arrest of urethral formation. The urethral opening can be found anywhere along the ventral midline from the perineum to the glans depending on the time during embryogenesis when fusion of the urethral folds ceases. The exact cause of hypospadias is still not known in most cases. In fewer than 5% of patients, hypospadias can be attributed to defects in androgen metabolism (5-alpha-reductase type II deficiency), androgen receptors, or known genetic factors.

Hypospadias is usually identified during the initial examination. The penile raphe is displaced from the midline and the glans tilts downward (chordee). The meatus may be the size of a pinhole but is usually not obstructed. Micturition from the ventrally placed meatus confirms the diagnosis.

Anomalies that may accompany hypospadias include meatal stenosis, hydrocele, inguinal hernia, and cryptorchidism. Evaluation of a newborn with hypospadias may include the following:

- a family history of hypospadias, endocrine, or intersex problems
- a history of possible maternal progestin or estrogen exposure
- examination to evaluate the hypospadias (urethral meatus location, chordee, scrotal folds, phallus length, presence of gonads)
- identification of other congenital abnormalities
- radiographic studies of the kidneys and pelvis if the hypospadias appears to be part of a malformation syndrome

A male infant without cryptorchidism, as in this vignette, who has an isolated urethral opening on the glans or shaft of a normal-sized phallus rarely has a dilemma of gender identity; evaluation for endocrinopathies or intersex disorders are generally not required. Cryptorchidism is defined by the failure of one or both testes to descend completely into the scrotum (at least 4 cm below the pubic crest in a term infant weighing more than 2.5 kg).

Disorders resulting in ambiguous genitalia, such as congenital adrenal hyperplasia in a virilized female, must be considered if the gonads are not palpable and especially if the defect is low on the shaft or scrotum. Congenital adrenal hyperplasia can yield marked virilization making chromosomal diagnosis essential in all cases of ambiguity with cryptorchidism. If the gonads are not palpable in a male (46,XY) neonate with hypospadias, risk of intersexuality approaches 50%. The likelihood of intersexuality is also increased among male neonates whose meatus is positioned in the scrotum or perineum.

Because cryptorchidism may result from insufficient androgen, it is not surprising that hypospadias and intersex disorders may coexist. Approximately 8% of boys with hypospadias have at least one undescended testicle with the incidence varying with the severity of hypospadias. Only 5% of genetically male neonates with distal hypospadias, as in this vignette, have cryptorchidism, compared with 32% of neonates with proximal lesions.

Hypospadias, often associated with cryptorchidism, occurs in a number of syndromes. The neonate in the vignette has mild hypospadias, defined as glandular or penile, and no other dysmorphic features. Isolated penile hypospadias without other genital abnormalities or dysmorphic features is unlikely to be associated with a chromosomal abnormality.

In the past, boys with hypospadias routinely underwent intravenous pyelography, voiding cystourethrography, and renal ultrasonography as part of their evaluation. However, even with severe hypospadias the arrest in development is after the eighth week of gestation, when the urethral bud joins the metanephros. The likelihood of detecting an upper urinary tract anomaly is low, with clinically significant abnormalities found in fewer than 5% of neonates with hypospadias. Radiographic studies may be helpful in boys who develop a urinary tract infection or those whose anomaly is part of a malformation syndrome.

The only treatment for hypospadias is surgical repair of the defect. The goal of surgical correction is to create a penis with normal function and appearance. Because the spectrum of severity is wide, ranging from glandular to perineal, and the shaft may be straight or significantly curved, it is not surprising that more than 300 operative techniques for hypospadias repair have been described. Depending on the severity of the lesion, surgical techniques can be applied sequentially or in combinations beginning at 6 months in an otherwise healthy newborn. In severe cases requiring a two-stage procedure, the second stage is performed at least 6 months after the initial repair. Neonatal circumcision is contraindicated in such cases because foreskin tissue is often used in the repair process.

Do you want to add anything to your Learning Plan?
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American Board of Pediatrics Content Specification(s):

Know how to evaluate and manage an infant with hypospadias and epispadias

Know how to evaluate and manage an infant with cryptorchidism

Know the etiology and diagnosis of an infant with ambiguous genitalia, including congenital adrenal hyperplasia

PREVIOUS NEXT

July: Question 10

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11 November 08

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A woman presents at 26 weeks' gestation with preterm labor and intact membranes. Although she has several concerns regarding the fetal effects of antenatal steroids, she is convinced of the benefit of accelerating lung maturity and reducing neonatal respiratory distress.

She is given a course of betamethasone. The contractions subside spontaneously after 18 hours, at which time her cervix is dilated 2 cm. Two days later she is sent home and asked to return in 5 days for a repeated course of betamethasone. She continues to have concerns about the effect of medicines given to her on the short- and long-term developmental outcomes of her fetus.

Of the following, premature infants exposed to multiple courses, as opposed to a single course, of antenatal corticosteroids are MORE likely to have:

1	blindness
2	cerebral palsy
3	deafness
4	hypertension
5	intrauterine growth restriction

You selected 5, the correct answer is 5.

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The efficacy of antenatally administered corticosteroids to enhance fetal lung maturity among infants born after 26 weeks' up to 34 weeks' gestation has been demonstrated in studies from the 1970s. These early studies repeatedly indicated benefit in reduction of incidence and severity of respiratory distress syndrome among infants delivered 1 to 7 days after maternal treatment. Many mothers had not yet delivered at 7 days, raising questions about the safety of repeated courses of antenatal steroids and the impact on maternal, neonatal, and longer-term childhood outcomes. As repeated dosing became a prevalent practice, animal studies raised concerns about abnormal brain development and fetal growth.

Recent analyses of the short- and longer-term effects on infants and young children of repeated doses of antenatal steroids have demonstrated the following effects among infants exposed to multiple courses as compared with those exposed to a single course:

- **Short-term**
  - **Intrauterine growth restriction**
  - **Significant reductions in respiratory distress syndrome, surfactant administration, mechanical ventilation, and severe neonatal lung disease**
- **Early childhood**
  - **No significant difference in somatic measurements at 24 to 36 months of age**
  - **No difference in pulmonary morbidity**

- Similar Bayley Developmental Index scores
- Higher rates of attention problems
- Similar risks for blindness and deafness
- Similar rates of cerebral palsy

Although no statistically significant difference exists, a trend toward greater risk for cerebral palsy in the study using higher maternal dosing (betamethasone: 12 mg given twice versus 11.4 mg given once) and among infants who had been exposed to multiple courses of treatment raises concern of a dose-dependent effect. These concerns led investigators to different conclusions regarding the approach to repeated dosing. Those who gave their patients the lower dose, and whose study showed no relationship between cerebral palsy and the number of courses of treatment, recommend repeated courses of antenatal corticosteroids for mothers who remain at risk of preterm delivery. Those who used the larger dosing regimen do not recommend repeated courses, but if repeated courses are given, lower weekly dosing is the preferred strategy.

Studies to date have examined infants in the early preschool developmental stages. Follow-up into school age, adolescence, and adulthood will enlighten us regarding more subtle or delayed impacts of repeated cortiocosteroid courses.

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Stiles AD. Prenatal corticosteroids: early gain, long-term questions [editorial]. *N Engl J Med.* 2007;357:1248-1250

Wapner RJ, Sorokin Y, Mele L, et al. Long-term outcomes after repeat doses of antenatal corticosteroids. *N Engl J Med.* 2007;357:1190-1198

American Board of Pediatrics Content Specification(s):

Know the medications, indications for, and complications of drugs used to enhance fetal lung maturity

Understand the timing of the biochemical maturation of the lung and the factors affecting this timing

Understand the prevention of RDS

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11 November 08

12 December 08

August: Question 1

A female infant with a birthweight of 4,785 g was delivered by a 34-year-old multiparous obese Native American woman whose pregnancy was complicated by gestational diabetes. An emergency cesarean section was performed for shoulder dystocia. Physical examination reveals a large-for-gestational-age infant with Erb palsy.

Of the following, fetal macrosomia in diabetic pregnancies is MOST characterized by its:

1	detectability by ultrasound in the first trimester
2	higher risk among mothers with pregestational type 1 diabetes
3	lack of impact on growth velocity after 2 weeks of age
4	lower risk for shoulder dystocia than nondiabetic macrosomia
5	reduction by strict glycemic control in second and third trimesters

You selected 2, the correct answer is 5.

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***Macrosomia*, defined as birthweight above the 90th percentile for gestational age or birthweight greater than 4,000 g occurs in 15% to 45% of diabetic pregnancies compared with 8% to 14% of normal pregnancies. It is a risk factor for intrapartum injury (shoulder dystocia, brachial plexus palsy, and asphyxia) and for cesarean delivery.**

As hypothesized by Pedersen, the increase in fetal growth in a diabetic pregnancy is the result of increased maternal glucose concentrations. Glucose crosses the placenta and results in fetal hyperglycemia and subsequent hyperinsulinemia. This hyperinsulinemia affects primarily insulin-sensitive tissues such as fat. The risk of macrosomia is similar for all classes of diabetes (type 1, type 2, and gestational), suggesting that first-trimester metabolic control has less effect on fetal growth than glycemic regulation in the second and third trimesters. Postprandial blood glucose concentrations in the second and third trimesters of pregnancy are strongly predictive of both birthweight and overall percentage of macrosomic infants. Furthermore, it has been shown that strict glycemic control in the second and third trimesters may reduce the fetal macrosomia rate to near baseline. However, other authors have shown that macrosomia is determined primarily by early diabetes control and suggested that strict blood glucose control in the first and second trimesters may reduce the incidence of large-for-gestational-age infants.

The macrosomic infant of a diabetic mother (IDM) follows a unique pattern of in utero growth compared with fetuses in euglycemic pregnancies. During the first trimester, no differences in size between diabetic and nondiabetic fetuses are detectable by ultrasound measurements. However, after 24 weeks (20 weeks in one study) the abdominal circumference of the fetus of a

diabetic pregnancy begins to grow at a rate above normal because of deposition of fat in the abdominal and interscapular areas and visceral organ hypertrophy (liver, heart, adrenals, pancreas). Of significance, head and femur growth of IDM fetuses are similar to those of normal fetuses.This central deposition of fat is a key characteristic of diabetic macrosomia and combined with the lack of increase in head size, is responsible for the higher incidence of shoulder dystocia in these cases. Among infants with birthweights more than 4,000 g, the incidence of shoulder dystocia is 16% in diabetic pregnancies compared with 3% among nondiabetic pregnancies.

The higher growth velocity seen in fetal life during a diabetic pregnancy may extend into childhood and adult life. By 8 years of age, approximately half of the IDMs are above the 90th percentile for weight. It is believed that offspring of a diabetic pregnancy have a permanent derangement of glucose-insulin kinetics, resulting in a higher incidence of impaired glucose tolerance and type 2 diabetes.

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References:

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Raychaudhuri K, Maresh MJ. Glycemic control throughout pregnancy and fetal growth in insulin-dependent diabetes. *Obstet Gynecol.* 2000;95:190-194

American Board of Pediatrics Content Specification(s):

Know the effect of diabetes mellitus and its treatment on the fetus

Know the causes of maternal and neonatal complications and the management of abnormal presentations, such as breech, shoulder dystocia, etc

Understand the implications of fetal macrosomia

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11 November 08

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August: Question 2

You are reviewing the complications experienced since birth by a 7-year-old male child who is presenting for a follow-up. After being discharged from the birth hospitalization at 65 days of age, the child has had persistent respiratory distress requiring supplemental oxygen, chronic mild pulmonary hypertension, and severe gastroesophageal reflux requiring intensive medical and surgical intervention. The child has remained small but growing at the fifth percentile for weight, length, and head circumference; gastrostomy feedings were required during infancy. Oral aversion complicated feeding until 2 years of age. Partial bowel obstruction at 4 years of age was successfully managed with gastric decompression and intestinal rest. Hearing loss was diagnosed at 2 years of age; audiologic screening was passed at the end of the birth hospitalization. Neurologic, developmental, and behavioral outcomes have been normal. A chest radiograph shows a small left pleural effusion that has remained unchanged for the last several years. Ventilation-perfusion scan shows normal ventilation but reduced perfusion of the left lung.

Of the following, the MOST likely primary neonatal diagnosis in this child is:

1	bronchopulmonary dysplasia
2	congenital cystic adenomatoid malformation
3	congenital diaphragmatic hernia
4 ✗	meconium aspiration syndrome
5	pulmonary hypoplasia

You selected 4, the correct answer is 3.

The child in the vignette has experienced many of the complications associated with his neonatal diagnosis, congenital diaphragmatic hernia (CDH). He required a long birth hospitalization and has had chronic lung disease, pulmonary hypertension, gastroesophageal reflux, failure to thrive, oral aversion, bowel obstruction, and late-onset hearing loss. Persistent small pleural effusion and diminished left lung perfusion are also present. Although not presented in the vignette, the child was treated with extracorporeal membrane oxygenation for severe respiratory failure, required prolonged mechanical ventilation, and had a patch placed for a large diaphragmatic defect, all important risk factors for complications associated with CDH.

Pulmonary dysfunction after CDH repair is associated with chronic lung disease (33%-50% at discharge), bronchospasm, pulmonary hypoplasia, pulmonary hypertension, and aspiration associated with gastroesophageal reflux. Chronic lung disease often improves with time. The presence of pulmonary hypertension and small pleural effusion in the child in the vignette suggests that chronic lung disease is complicated by one or more of the other pathophysiologic factors, most likely pulmonary hypoplasia.

The ipsilateral lung in patients with diaphragmatic hernia and severe hypoplasia may enlarge with time but is characterized by increased alveolar size rather than increased alveolar number. Furthermore, pulmonary vascular growth and development is stunted; this pulmonary vascular hypoplasia accounts for the abnormally diminished perfusion of the hypoplastic ipsilateral lung in patients with diaphragmatic hernia.

Gastroesophageal reflux (45%-90% of cases), foregut dysmotility, esophageal ectasia, esophagitis, and hernia recurrence (8%-50%) also may complicate the recovery of infants and children after CDH repair. These problems occur because of the presence of abnormal hiatal anatomy, displaced angle of His, and, occasionally, gastric herniation.

Other frequently experienced complications of CDH include failure to gain weight (40% of cases have weight less than the fifth percentile at 2 years of age); poor oromotor skills/oral aversion; late-onset hearing loss (~50% of cases present late); abnormal neurologic, developmental, and behavioral outcomes (~33%); pectus abnormalities (21%-48%); and scoliosis/kyphosis (10%-27%). Some of these complications are worsened by additional congenital anomalies or high risk factors such as severe respiratory failure and treatment with extracorporeal membrane oxygenation. About 40% of infants with CDH have additional anomalies, two-thirds being congenital heart defects.

Multidisciplinary follow-up of infants with CDH is warranted because of the many complications that may occur. Ideally, follow-up occurs in a multidisciplinary clinic where subspecialists collaborate and coordinate the care with the primary pediatrician. Such clinics are not universally available. Furthermore, because of the wide

variation in outcomes and number of complications in patients with CDH, follow-up must be tailored to the individual. Some children will require extensive ongoing evaluation and interventions whereas many will require relatively limited ongoing care in addition to that provided in the patient's medical home. A schedule for follow-up of patients with CDH was published by the American Academy of Pediatrics (Table).

Table

Table. Recommended Schedule of Follow-up for Infants With CDH*

Findings	Before Discharge	1-3 mo After Birth	4-6 mo After Birth	9-12 mo After Birth	15-18 mo After Birth	Annual Through 16 y
Weight, length, occipital-frontal circumference	X	X	X	X	X	X
Chest radiograph	X	If patched	If patched	If patched	If patched	If patched
Pulmonary function testing			If indicated		If indicated	If indicated
Childhood immunizations	As indicated throughout childhood					
RSV prophylaxis	RSV season during first 2 years after birth (if evidence of chronic lung disease)					
Echocardiogram and cardiology follow-up	X	If previously abnormal or if on supplemental oxygen	If previously abnormal or if on supplemental oxygen	If previously abnormal or if on supplemental oxygen	If previously abnormal or if on supplemental oxygen	If previously abnormal or if on supplemental oxygen
Head computed tomography or magnetic resonance imaging	If • abnormal finding on head ultrasound; • seizures/abnormal neurologic findings†; or • ECMO or patch repair	As indicated	As indicated	As indicated	As indicated	As indicated
Hearing evaluation	Auditory brainstem evoked response or otoacoustic emissions screen	X	X	X	X	Every 6 months to age 3 y, then annually to age 5 y
Developmental screening evaluation	X	X	X	X		Annually to age 5 y
Neurodevelopmental evaluation	X			X		Annually to age 5 y
Assessment for oral feeding problems	X	X	If oral feeding problems	If oral feeding problems	If oral feeding problems	If oral feeding problems
Upper gastrointestinal study, pH probe and/or gastric scintiscan	Consider for all patients	If symptoms	If symptoms	Consider for all patients	If symptoms	If symptoms
Esophagoscopy		If symptoms	If symptoms	If symptoms or if abnormal gastrointestinal evaluations	If symptoms	If symptoms
Scoliosis and chest wall deformity screening (physical examination, chest radiograph, and/or computed tomography of the chest)				X		X

CDH = congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation;
RSV = respiratory syncytial virus.
***The neurosensory tests performed and frequency of surveillance may differ among infants with CDH because of variability in neurologic, developmental, and physiologic impairments. Follow-up should be tailored to each infant.**
†Muscle weakness, hypotonia, hypertonia, or other abnormal neurologic sign or symptom.

Congenital cystic adenomatoid malformation of the lung (CCAM) is a hamartomatous overgrowth of the terminal bronchioles with cyst formation and absence of alveolar development. Hydrops, mediastinal shift, and microcystic CCAM are risk factors for fetal death and long-term morbidity. Although prenatal shunt placement, drainage, and, in rare cases, fetal excision, have been successful for a few infants, fetal mortality with these risk factors remains high.

Postnatal mortality in infants with CCAM also is high (~26% of cases) for infants presenting with symptoms at birth. Long-term complications in survivors include frequent infections, bronchospasm, slow growth, and, infrequently, pectus deformity. Other complications of illness likely reflect severity of illness, presence of prematurity, and associated congenital anomalies (~20% of cases) in infants with CCAM. Ventilation-perfusion scans show symmetric reduction in ventilation and perfusion in infants who had hydrops and lobectomy (23%-42% of cases). The symmetric ventilation-perfusion abnormalities contrast with the predominant perfusion abnormalities found after repair of CDH, as seen in the child in the vignette.

Extremely premature infants have many long-term complications similar to those found in infants with CDH (feeding problems, bronchopulmonary dysplasia, gastroesophageal reflux, hearing loss—usually detected in the birth hospitalization). However, developmental, behavioral, and cognitive function deficits are more frequent and symmetric abnormalities in lung function predominate. Pulmonary hypertension into childhood is unusual. Late-onset hearing loss, pectus deformities, and scoliosis/kyphosis are infrequent complications associated with extreme prematurity and bronchopulmonary dysplasia.

Infants who survive after meconium aspiration may have long-term residual lung dysfunction. Like preterm infants, however, lung function usually improves with age. Late-onset hearing loss may occur, especially if extracorporeal membrane oxygenation is required. Developmental disabilities generally depend on severity of illness and complications associated with critical care.

Pulmonary hypoplasia is associated with conditions causing oligohydramnios, external compression of the fetal thorax, cystic lung disease, internal compression from herniated bowel or other abnormal internal thoracic structures (such as pleural effusions, massive cardiomegaly, and large mediastinal tumors), and absent or ineffective fetal breathing associated with abnormal neurologic conditions. Long-term outcomes are, as in other critically ill infants with respiratory failure, most often associated with severity of illness, complications associated with life-support interventions, and presence of congenital anomalies.

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American Board of Pediatrics Content Specification(s):

Recognize the clinical features of infants who require a complete developmental assessment

Plan appropriate therapy for an infant with extrapulmonary causes of respiratory distress, such as diaphragmatic hernia, diaphragmatic paralysis, and cord transaction

Know the prenatal, perinatal, and neonatal risk factors associated with hearing impairment

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August: Question 3

A 35-day-old 27-week-gestation male infant is receiving full feedings and caffeine citrate. He experiences an increase in apneic events over the past 8 hours. He has been less active over the last 24 hours and he has gastric residuals with his last three feedings. His axillary temperature is 38.4°C. Blood pressure, respiratory rate, and heart rate are normal. A physical examination shows decreased muscle tone and a mildly full abdomen. A complete blood cell count is normal. A blood culture is obtained and antibiotics are initiated pending culture results. A urine sample obtained by catheterization because of abdominal distention reveals the following:

Characteristics	Patient Results
Color	Yellow
Appearance	Cloudy
Specific gravity	1.020
Nitrate	Negative
White blood cell count, /hpf	5
Red blood cell count, /hpf	3-5
Bacteria	Many

hpf = high-powered field.

Of the following, the MOST accurate statement regarding the diagnosis of urinary tract infections (UTI) among hospitalized neonates is that:

1	a colony count of 10^2/mL from a catheterized specimen confirms the diagnosis
2	any concentration of bacteria found in a suprapubic tap specimen is abnormal
3	group B *Streptococcus* is the most common cause of UTI
4	males are less often affected than females
5	UTI rarely presents without pyuria

You selected 2, the correct answer is 2.

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The incidence of urinary tract infections (UTIs) varies from 0.1% to 1% among all neonates. The incidence is higher (4%-10%) among low-birthweight neonates. Among infants in a neonatal intensive care unit, UTIs most often will occur 72 hours after birth or later.

Signs of UTI in neonates are varied and can be nonspecific. The most frequent signs of an acute UTI among hospitalized neonates are fever and/or signs associated with sepsis. Although approximately 15% to 30% of neonates with a UTI have bacteremia, it is not clear whether the UTI is the cause or the result of the bacteremia. Hospitalized neonates may also have a less acute course. Signs and symptoms can be entirely

absent, or they may be limited to nonspecific findings such as poor weight gain, apnea, altered temperature control, or abdominal distention with feeding intolerance and vomiting. Fever may be present intermittently. Gross hematuria is rare. Jaundice and hepatomegaly may be presenting features. Jaundice during a UTI is frequently of sudden onset and clears rapidly after antimicrobial therapy is started. Hyperbilirubinemia as the only sign of a UTI in otherwise healthy neonates is rare.

A urinary tract infection should be considered in hospitalized neonates with signs of sepsis, as well as those with nonspecific signs. Diagnosis of a neonatal UTI can be made only through a properly obtained urine culture. The suprapubic bladder tap is the single best source of obtaining urine specimen for culture. Isolation of any bacteria from a bladder tap should be considered abnormal. Complications of a suprapubic bladder tap are rare, even among low-birthweight neonates. The most common complication, occurring in 0.6% of neonates is transient gross hematuria that usually resolves within 24 hours. Rare complications may also include bowel perforation, peritonitis, abdominal wall abscess, and sepsis. A suprapubic aspiration should not be performed if the neonate has recently voided, has abdominal distention, has poorly defined anomalies of the urinary tract, or has a hematologic disorder that might increase risk of severe bleeding.

Catheterized specimens can be used to obtain a urine sample. A concentration of at least 10^3 colony-forming units per milliliter of urine obtained by a catheter represents significant bacteriuria in neonates. Samples collected in a bag are inappropriate for culture.

Organisms that are associated with neonatal UTI are similar to those that cause neonatal sepsis. Pathogens responsible for hospital-acquired UTI include gram-negative organisms such as *Escherichia coli, Klebsiella and Enterobacter* species; *Enterococcus* species; *Candida;* and coagulase-negative staphylococci. The organisms causing UTI among hospitalized neonates have changed during the last 30 years. Infection with coagulase-negative staphylococci is now one of the primary causes of nosocomial UTI among hospitalized neonates. Group B *Streptococcus* may be isolated from the urine of neonates with group B streptococcal sepsis, but primary UTI caused by group B *Streptococcus* is unusual.

Urinary tract infection is more common among male neonates. The increased risk of UTI noted in uncircumcised males is likely responsible for the preponderance among males that is evident during the first year after birth. The increased risk among uncircumcised male infants is associated with an increase in the number and types of periurethral bacterial flora. Uncircumcised males have higher total urethral bacterial colony counts of uropathogenic organisms. With age, as the foreskin is more easily retracted during hygiene, both the excessive periurethral flora and the frequency of UTI in uncircumcised males decreases.

Healthy neonates without a UTI may have white blood cell counts as high as 25/μL in males to 50/μL in females in a voided specimen. Clinical significance of the presence of pyuria in low-birthweight neonates has not been well studied; however, neither the presence nor absence of pyuria in a suprapubic tap or catheter specimen, is reliable evidence for or against a UTI among infants younger than 3 months of age. Although pyuria was significantly associated with urine colony counts in a series of infants with documented UTI, it was present in only 69% of infants with a UTI whose colony counts were less than 10^5 colonies/mL. In a second series of infants with documented UTIs, 27% had fewer than 10 white blood cells per microliter in urine samples obtained from a suprapubic tap.

When starting treatment for neonates with a suspected nosocomial UTI, antimicrobial agents should be given intravenously because of the high rate of bacteremia. Sterilization of the urine can be documented with a urine culture repeated 36 to 48 hours after initiation of appropriate antibiotics. Neonates with persistent bacteriuria must be evaluated for an abscess or urinary

obstruction. Ten days of therapy usually is sufficient for uncomplicated hospitalized neonates whose urine is sterilized within 48 hours. Parenteral therapy is administered for at least 5 to 7 days in uncomplicated cases. Rapidity of clinical and microbiologic response, the presence of bacteremia, or anatomic abnormalities are used to determine if parenteral antibiotics can be changed to oral agents for the remainder of the treatment. A follow-up urine culture performed approximately 7 days after completion of an antibiotic course can document effectiveness of treatment.

The American Academy of Pediatrics recommends renal ultrasonography and voiding cystourethrography after the first UTI in infants 2 to 24 months of age. Because of limited research, similar practice guidelines are not available for low-birthweight neonates. In a series of 62 neonates with UTI, 79% had a normal renal ultrasound during their first UTI. Transient mild renal pelvic dilation was noted in 30%. Two cases had significant abnormalities of the kidney. Vesicoureteral reflux was present in 14% of neonates who underwent voiding cystourethrography 6 weeks after the UTI. Larger studies are needed to evaluate the usefulness of radiographic studies among hospitalized neonates with a UTI.

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American Board of Pediatrics Content Specification(s):

Understand the causes and differential diagnosis of urinary tract infections

Understand the clinical and laboratory features of urinary tract infections

Understand the treatment and complications of urinary tract infections

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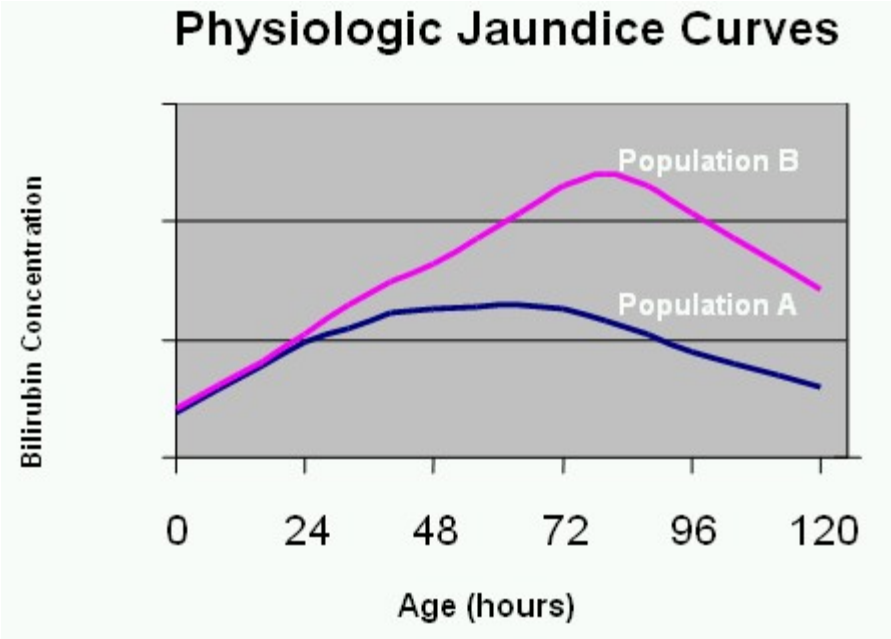
August: Question 4

Physiologic jaundice has been defined as bilirubinemia of the newborn in which the hour-specific bilirubin concentrations do not exceed 2 standard deviations above the population mean. However, unlike serum potassium or hemoglobin concentrations, bilirubin concentrations for a defined population depend on specific genetic and environmental factors resulting in a unique physiologic jaundice curve. Population mean curves are presented below for two representative populations.



Of the following, the pair of categories BEST represented by the graph is:

Response	Population A	Population B
1	Asian-American	African-American
2	Females	Males
3	Formula-fed	Breastfed
4	Term	Postterm
5	White	Black

1	Asian-American; African-American
2	Females; Males
3	Formula-fed; Breastfed
4	Term; Postterm
5	White; Black

You selected 5, the correct answer is 3.

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Physiologic jaundice (nonpathologic jaundice or physiologic bilirubinemia) is the typical rise and fall in serum bilirubin concentration seen in newborn infants in the first week after birth. Before birth, the fetus produces bilirubin, detoxifies (conjugates) it, and excretes it through the biliary tree into the fetal gut. A portion of conjugated bilirubin is then hydrolyzed (deconjugated) and reabsorbed from the fetal intestines. The placenta is responsible for clearing bilirubin from the fetal circulation. Bilirubin, however, does accumulate in the meconium before birth.

Physiologic jaundice results from a temporary imbalance between bilirubin production and excretion. Production is enhanced in the newborn because the half-life of the red blood cell is shorter (~90 days) than the 120-day life span of the adult red blood cell. Bilirubin excretion depends on uptake and conjugation (detoxification) of bilirubin. Uptake of bilirubin into the hepatocyte is facilitated by a cytosolic receptor-carrier protein called ligandin, which has a higher affinity for bilirubin than serum albumin. Conjugation is effected by bilirubin-UDP-glucuronosyl transferase (UGT), an enzyme that is bound to the endoplasmic reticulum. In normal newborns excretion is somewhat hampered by (1) a likely reduction in ligandin and (2) a moderate reduction in bilirubin-UDP-glucuronosyl transferase A1A (UGT). In addition, normal infants exhibit an enterohepatic circulation of already excreted conjugated bilirubin that is deconjugated by a glucuronidase enzyme in the newborn gut and then reabsorbed.

All of the aforementioned conditions combine to raise the serum bilirubin concentration from about 2 mg/dL (34 µmol/L) at birth to about 6 mg/dL (103 µmol/L) by 2 to 4 days of age in white and African-American infants. Asian-American neonates tend to reach higher bilirubin values (up to 10-14 mg/dL [171 to 239 µmol/L]) a bit later in the first week possibly because of a higher prevalence of UGT gene promoter variations and inherited red blood cell abnormalities. The serum bilirubin concentrations of normal newborns tend to return to adult concentrations by 7 to 10 days of age as feeding increases, UGT activity and ligandin concentrations increase, and the enterohepatic recirculation of bilirubin decreases.

The physiologic jaundice curves for girls and boys are very similar, as are those for white infants compared with black infants. Postterm infants tend to have lower peak serum bilirubin concentrations, possibly because of an accelerated development of UGT activity.

The physiologic jaundice curve, however, is not the same for formula-fed infants as for breastfed infants. Breastfed infants tend to have higher peak bilirubin concentrations than formula-fed infants. This might be because of reduced feeding volumes and the presence of active ß-glucuronidase (which hydrolyzes conjugated bilirubin and enhances the reabsorption of bilirubin) in human milk.

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American Board of Pediatrics Content Specification(s):

Understand the course of physiologic jaundice of the newborn infant

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August: Question 5

A term, 3.9-kg female infant, delivered by cesarean section following partial placental abruption, is limp and unresponsive at delivery. Apgar scores are 2, 3, 3, 3, 4, and 6 at 1, 2, 5, 10, 20, and 25 minutes, respectively. By 25 minutes after birth following resuscitation, assisted breathing is no longer needed and weak spontaneous movements of the arms and legs are observed. An umbilical cord arterial gas measurement indicates a pH of 7.01 and base deficit of 21 mEq/L (21 mmol/L).

Sixty minutes after delivery, the infant is pink in 40% hood oxygen and vital signs are: heart rate 165 beats per minute, respiratory rate 65 breaths per minute, and rectal temperature 38.3°C. Neurologic findings include a hyperalert appearance with staring, mydriatic pupils, low muscle tone, and weak Moro reflex. She needs nasal and oral suctioning to remove secretions.

Ninety minutes after delivery, you counsel the family that she has experienced a period of hypoxia-ischemia because of early separation of the placenta. As you discuss her current status and care needs, they interrupt and ask, "Our baby won't have cerebral palsy, will she?"

Of the following, the response that BEST reflects her risk for cerebral palsy is, "I don't know. We will have a better idea after we see how she recovers during the next hours and days. The MOST encouraging current finding is that she is/has:

1	a body temperature of 38.3°C
2	breathing spontaneously
3	female
4	hyperalert
5	large for her gestation

You selected 2, the correct answer is 2.

Long-term outcome prediction shortly after an episode of apparent hypoxia-ischemia may be difficult because of poor positive and negative predictive values of clinical findings. Yet, prognostication is important for making decisions about immediate observation and treatment, neuroprotective interventions, and transfer for subspecialty care.

For the infant in the vignette, a delay in specific prognostication is recommended to evaluate the clinical severity of her neurologic insult, the effect on other organ systems, and results of magnetic resonance imaging. However, certain features of her current physical examination findings and course correlate with her risk for mortality and long-term impairment. Although the placental abruption, decreased fetal movement, a nonreassuring fetal heart rate pattern, and need for delivery room resuscitation are highly consistent with a hypoxic insult, the duration

and severity of the insult and its secondary effects on her brain are unknown.

Among infants experiencing hypoxic-ischemic encephalopathy (HIE), the risks for death or long-term disability have been correlated with three clinical parameters during the birth experience: (1) need for chest compressions for more than 1 minute; (2) delay of spontaneous respirations for more than 30 minutes; and/or (3) presence of base deficit of 16 mEq/L (16 mmol/L) or more anytime in the first 4 hours after birth.

The infant's heart rate response to positive pressure ventilation was sufficient to avoid chest compressions, and her recovery of spontaneous breathing by 25 minutes improves her prognosis. Although these observations provide a window of hope, her history and large base deficit are concerning for a 64% risk of death or severe disability from the hypoxic/ischemic insult (Table 1).

Table 1

Table 1. Clinical Predictors of Death or Severe Disability	
Number of Predictors	Risk: Death or Severe Disability (%)
0	46
1	64
2	76
3	93

Hyperpyrexia potentiates the impact of hypoxia and ischemia on acute brain injuries in adults, older children, and newborn infants. Encephalopathic infants (not treated with hypothermia) who exhibited pyrexia had significantly greater risk for adverse outcomes than those who did not (odds ratio: 3.2; 95% confidence interval: 1.2-8.4; *P*=.028). Although the effect of the elevated body temperature on the infant in the vignette is not known, the temperature elevation is unlikely to predict a reduced risk for cerebral palsy.

Among infants requiring delivery room resuscitation, the radiant warmer provides a valuable venue for observation, resuscitation, and thermoregulation. Recent observations have demonstrated that approximately one-third of infants with moderate to severe neonatal encephalopathy exhibited rectal temperature of 38°C or higher during the first 3 days after birth. Increased metabolic activity because of seizures, the actions of inflammatory cytokines, and radiant warmer malfunction or limitations to detect core temperature in some infants may contribute to the development of pyrexia.

Sarnat and Sarnat described three stages of encephalopathy, which have been adapted for use in the early neonatal period and which have the best correlation with long-term outcome (Table 2). Because neonatal encephalopathy worsens during reperfusion, serial evaluations are important to ascertain the maximal degree of involvement.

Table 2

Table 2. Sarnat and Sarnat Staging Criteria for Neonatal Encephalopathy*			
Criterion	**Stage I**	**Stage II**	**Stage III**
Consciousness	Hyperalert	Obtunded	Stuporous
Tone/posture	Good tone, mild distal flexion	Hypotonic, strong distal flexion	Flaccid, occasionally decerebrate
Stretch reflexes	Increased	Increased	Decreased or absent
Suck	Weak	Variably weak to absent	Absent
Moro reflex	Strong	Weak	Absent
Pupils	Mydriatic	Miotic	Variable, anisochoria, poor light response
Heart rate	Tachycardia	Bradycardia	Variable
Respiratory secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal or decreased	Increased	Variable
Seizures (clinical)	None	Common	Uncommon

* Adapted from Sarnat and Sarnat (1976).

The hyperalert appearance of the infant in the vignette may be deceptive, especially to families. Her examination findings meet the criteria for stages I and II, and her age (90 minutes) makes her too young to render an accurate prognosis. In infants who continue in Sarnat stage I, the condition generally resolves in a day or so, and those infants whose course involves only a period of hyperalertness or hyperexcitability without hypotonia or seizures have a high likelihood of being normal. Stage II findings may last up to 2 weeks' after birth, and often are accompanied by seizures. Overall, these infants have a 20% to 35% risk for disabilities; normal outcome becomes more likely if the neurologic examination has normalized by age 1 week. Abnormalities consistent with Sarnat and Sarnat stage III may last hours to weeks, and are infrequently accompanied by seizures. The risk of mortality is 75%, with impairment occurring in nearly all survivors.

Although the incidence of neonatal encephalopathy is higher in boys, there are no data suggesting a prognostic benefit for girls. No data suggest that sex factors into the response to therapeutic interventions for HIE.

In recent controlled studies of therapeutic hypothermia, an adverse effect of larger body weight on prognosis was found in control infants. For each 100-g increase in body weight, the risk of an adverse outcome was significantly increased (odds ratio 1.06; 95% CI 1.01-1.12). The relatively larger size of the infant in the vignette is not a favorable prognostic sign.

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American Board of Pediatrics Content Specification(s):

Know the neonatal manifestations of asphyxia that predict the likelihood of cerebral palsy

Know the incidence of cerebral palsy in high-risk infants such as those with extreme prematurity, hypoxic-ischemic encephalopathy, and symptomatic congenital infection

Know the prenatal, perinatal, and neonatal risk factors associated with the development of cerebral palsy

PREVIOUS NEXT

August: Question 6

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An infant was born at 27 weeks' gestation and is now 5 days old. She has a clinically significant patent ductus arteriosus. The infant's resident calls you to report that no urine has been detected since indomethacin treatment was started 12 hours ago. You review the reasons for oliguria and the pathophysiology involving the renin-angiotensin system in preterm infants with the resident.

Of the following, the peptide MOST active in the lung is:

1	angiotensin I
2	angiotensin II
3	angiotensin-converting enzyme
4	angiotensinogen
5	renin

You selected 4, the correct answer is 3.

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A primary function of the renin-angiotensin system is maintenance of blood pressure and fluid volumes (Figures 1 and 2).

Figure 1: Renin-angiotensin system

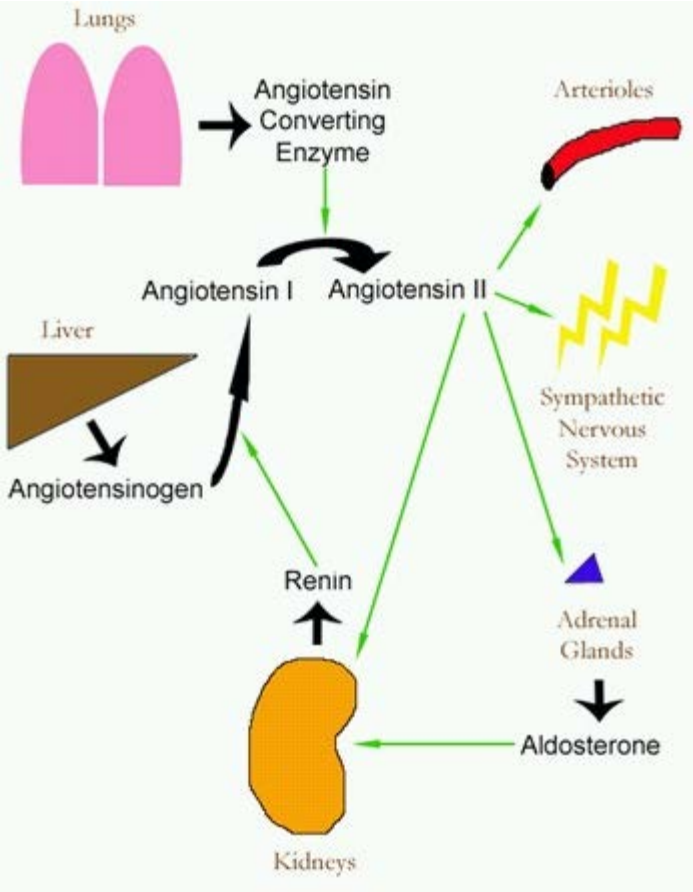
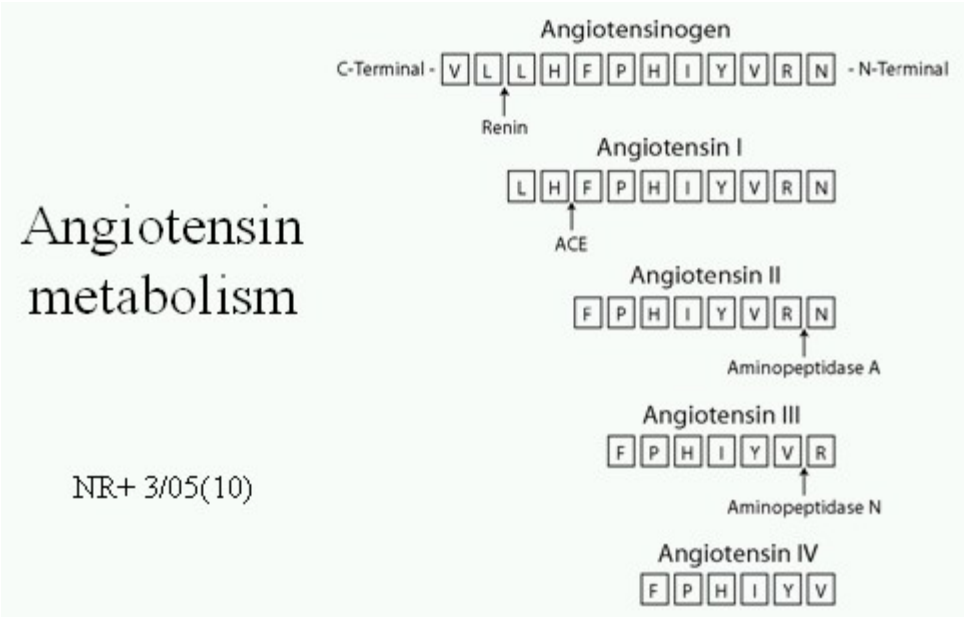


Figure 2: Elements of the renin-angiotensin system



When stimulated by a drop in blood pressure, the renin-angiotensin system becomes fully active in about 20 minutes. This system also responds to small changes in blood volume, and effects changes in water and sodium retention to maintain homeostasis. The main elements of the system are peptides acting in various body tissues. The main site of action of angiotensin-converting enzyme is the lung.

Renin is a proteolytic glycoprotein made of 340 amino acid residues. It is made and stored in the juxtaglomerular apparatus of the kidney. The stimuli for its release are decreased perfusion pressure in the afferent arterioles, decreased sodium reabsorption through the macula densa, or

beta-adrenergic stimulation by the sympathetic nervous system. Angiotensin II inhibits renin secretion. The half-life of renin in the circulation is 15 minutes.

Angiotensinogen, or renin substrate, is an a_2-globulin made mainly in the liver. It is a glycoprotein with a molecular weight of 55 to 60 kD, containing 452 amino acid residues. It is split in the circulation by renin to form angiotensin I. Oral contraceptives with estrogen are thought to induce hypertension by increasing serum concentrations of angiotensinogen.

Angiotensin I is a decapeptide made from angiotensinogen in the circulation. It has only a mild vasoconstrictive effect. It serves mainly as a precursor for angiotensin II.

Angiotensin-converting enzyme is a glycoprotein with 1,277 amino acid residues and a molecular weight of 170 kD. It rapidly converts angiotensin I to the vasoconstrictor angiotensin II, and helps in the breakdown of the vasodilator bradykinin. It is made by endothelial cells of the vascular system, and is concentrated in the endothelial cells of the lungs.

Angiotensin II is an octapeptide made from angiotensin I by cleavage with angiotensin-converting enzyme. It is a strong vasoconstrictor, 40 times more potent than norepinephrine and 100 times more potent than angiotensin I. It acts within seconds after an acute dose, but is degraded within minutes. It acts on the arterioles to cause an increase in total peripheral resistance, and on the veins to augment venous return to the heart. It increases norepinephrine release from sympathetic nerves. In the kidneys, it stimulates the proximal tubule to reabsorb sodium. It causes the adrenal gland to make more aldosterone, which also increases salt and water retention.

The oliguria caused by indomethacin likely has two explanations. The first involves vasopressin. In the kidney of the premature neonate, prostaglandin E inhibits fluid retention caused by vasopressin and renin-angiotensin peptides. Indomethacin blocks the production of prostaglandin E, thereby allowing vasopressin and renin-angiotensin peptides to effect fluid retention and oliguria. Before the renin-angiotensin system can downregulate, the potent action of vasopressin combines with the normal action of the renin-angiotensin system to conserve water and cause oliguria.

A second explanation for the neonatal oliguria with indomethacin is based on the observation that indomethacin redistributes renal blood flow away from the mature nephrons of the inner cortex, toward the immature nephrons of the outer cortex. These nephrons have only a limited capacity to excrete sodium and water.

Oliguria associated with indomethacin use is not changed by the concurrent use of dopamine or furosemide, but may be reversed in experimental animal models with the use of a vasopressin inhibitor.

The short answer to the resident in the vignette is that indomethacin disturbs the balance in the kidneys between prostaglandins and the renin-angiotensin system, and between prostaglandins and vasopressin.

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Norwood VF, Fernandez LG, Tufro A, Gomez RA. Development of the renin-angiotensin system. In: Polin RA, Fox WW, Abman SH, eds. *Fetal and Neonatal Physiology.* 3rd ed. Philadelphia, Pa: Elsevier Saunders; 2004:1249-1256

American Board of Pediatrics Content Specification(s):

Understand the pathway and control of angiotensin peptide production

Know the actions of the components of the renin-angiotensin system

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11 November 08

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August: Question 7

A 27-year-old woman with a history of mild asthma develops significant nasal congestion and wheezing at 11 weeks of pregnancy. She contacts her obstetrician to establish a treatment plan.

Of the following, the type of medication presenting the MOST risk to the fetus in the first trimester is an:

1	inhaled beta$_2$-agonist
2	inhaled corticosteroid
3	inhaled mast cell stabilizer
4	oral decongestant
5	oral methylxanthine

You selected 5, the correct answer is 4.

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The primary goal of asthma treatment during pregnancy is to prevent maternal hypoxic episodes and maintain fetal oxygenation. Instead of treating pregnant women with asthma when they become symptomatic, it is preferable that these women receive preventive pharmacologic therapy, regardless of the presence or absence of respiratory symptoms. Indeed, women with severe and poorly controlled asthma are at greater risk for preeclampsia, need for cesarean delivery, premature delivery, and/or delivery of a growth-restricted infant. Treatment of pregnant women with asthma must be individualized and may include frequent lung function assessments, avoidance of triggering factors, a maintenance regimen, and aggressive treatment of exacerbations.

Rhinitis, sinusitis, and gastroesophageal reflux may exacerbate symptoms of a pregnant asthmatic woman. Thus, the woman in this vignette should receive treatment for her nasal congestion. However, in the first trimester she should avoid using oral decongestants because they have been associated with gastroschisis, intestinal atresia, and hemifacial microsomia. Rather, she should use an inhaled decongestant or corticosteroid.

The short-acting inhaled beta$_2$-agonist albuterol rapidly relieves acute bronchospasm by relaxing smooth muscle cells and serves as a bronchoprotective agent prior to exercise. Data on using long-acting beta$_2$-agonists (eg, salmeterol and formoterol) during pregnancy are limited. Studies have not demonstrated an advantage of systemic beta$_2$-agonists (eg, epinephrine and terbutaline) over aerosols.

By decreasing airway inflammation and hyperresponsiveness, inhaled corticosteroids are the most effective long-term medication to control asthma. Studies have found that inhaled corticosteroid treatment significantly reduces the number of asthma exacerbations and improves

lung function during pregnancy. No studies to date have found any increase in congenital malformations or other adverse perinatal outcomes with the use of inhaled corticosteroids. Of the five inhaled corticosteroids that are currently available in the United States, budesonide is the preferred medication to use during pregnancy.

In contrast to inhaled corticosteroid use during pregnancy, use of oral corticosteroids during the first trimester is associated with an increased risk for isolated cleft lip (0.3% compared with 0.1% in the general population). In addition, oral corticosteroid treatment during pregnancy is associated with a higher incidence of preeclampsia, preterm delivery, and low-birthweight infants. While it is difficult to separate the effects of severe or uncontrolled asthma from medication-induced complications, other agents are preferred because of better safety data and similar effectiveness.

Cromolyn sodium is an inhaled mast cell stabilizer with an excellent safety profile in pregnant women. It functions by blocking the early- and late-phase response to allergens and minimizes airway responsiveness. Cromolyn sodium is sometimes used to treat mild persistent asthma in pregnancy. However, it is less effective than inhaled corticosteroids in reducing the symptoms of asthma.

Oral methylxanthines have antiinflammatory actions, possibly mediated by inhibiting leukotriene production. Although the most commonly used oral methylxanthine, theophylline, has been shown to be safe in randomized controlled trials, patients report side effects (such as insomnia, heartburn, palpitations, nausea, tachycardia) and often discontinue the medication. If used during pregnancy, low doses are recommended because of its potential transplacental passage, and serum theophylline concentrations should be monitored. However, because it is not effective for the treatment of acute exacerbations, it is only indicated for pregnant women with chronic asthma.

In addition to the aforementioned agents, leukotriene modifiers can be used to treat asthma symptoms. These arachidonic acid metabolites are thought to reduce bronchospasm and mucous secretion as well as increase vascular permeability. However, minimal data are currently available on the use of these agents during pregnancy.

Based on the effectiveness and potential side effects of these asthma medications, a stepwise pharmacologic approach is recommended to treat pregnant women with chronic asthma. During acute exacerbations, the dose, frequency, and number of these medications can be increased. For women with mild asthma, albuterol is the preferred inhaled beta$_2$-agonist. However, if this short-acting agent is being used daily, additional long-term therapy with a chronic low-dose inhaled corticosteroid is warranted. Women with moderate persistent asthma symptoms should receive the recommended inhaled corticosteroid budesonide. For women with moderate asthma who require additional treatment, the options include a low-dose inhaled corticosteroid with a long-acting beta$_2$-agonist or a medium-dose inhaled corticosteroid only. Women with severe persistent asthma should receive a high-dose inhaled corticosteroid and a long-acting inhaled beta$_2$-agonist. Of note, cromolyn and theophylline are no longer preferred first-line medications to treat asthma in pregnancy.

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American Board of Pediatrics Content Specification(s):

Know the effect of maternal acute and chronic pulmonary disease and their management on the fetus

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11 November 08

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August: Question 8

A 26-week-gestation premature female infant is born after spontaneous labor and rupture of membranes. Her mother was healthy before the onset of labor and had no history of a thyroid disorder. The birthweight was 900 g. The infant had respiratory distress that was treated with three doses of surfactant and severe hypotension that was treated with dopamine and hydrocortisone. She was supported with assisted ventilation for the first 10 days and had persistent oxygen dependency. She was treated for suspected pneumonia and/or sepsis. A state screening test conducted at 3 days of age and before any transfusion reveals a thyroxine (T_4) concentration of 2.8 µg/dL (36 nmol/L), just below the normal range for age, and a normal thyroid-stimulating hormone (TSH) concentration of 19 mIU/L. Confirmatory serum studies are ordered, including T_4 and free thyroxine (FT_4). The FT_4 concentration was in the low-normal range.

Of the following, the MOST appropriate management plan at this time would be to:

1	follow clinically; no need to recheck values if no signs or symptoms
2	initiate L-thyroxine treatment and continue for life
3	initiate L-thyroxine treatment; discontinue in 3 years
4	recheck TSH at 2 weeks and 6 weeks; if TSH becomes abnormal, treat
5	recheck TSH in 2 weeks; if TSH still normal, no further testing needed

You selected 4, the correct answer is 4.

Congenital hypothyroidism occurs in 1 in 3,000 to 1 in 4,000 newborn infants. It is either primary, when it involves a disorder of the thyroid gland itself (malformation or inborn error of thyroid synthesis), or secondary, involving a disorder of thyrotropin (TSH) production or release (central). The primary form occurs more frequently and is usually associated with elevated serum TSH values soon after birth. The latter is usually accompanied by other pituitary hormone deficiencies.

Most infants with an initially low thyroxine (T_4) and normal TSH concentration have a normal free thyroxine (FT_4) concentration and subsequent thyroid function test results are normal. Some experts have suggested following them clinically for signs of hypothyroidism. However, some of these infants have true hypothyroidism, which will result in irreversible mental retardation; therefore, the preferred management is to repeat laboratory studies until the infant is clearly hypothyroid (elevated TSH) or is at least 6 weeks old, because the delay in TSH elevation may persist until then. L-thyroxine therapy should not be started for a low T_4 value during significant illness because these low values may represent the euthyroid sick syndrome, in which case thyroxine treatment may be harmful.

Some infants with normal TSH but low T_4 values may have true thyroid insufficiency. This profile is seen in 3% to 5% of newborn infants. The pattern may result from hypothalamic immaturity and is most commonly seen among preterm infants. Low T_4 with normal TSH may also occur in central hypothyroidism (1 in 25,000 to 1 in 50,000 newborn infants) or with true primary hypothyroidism and delayed TSH elevation (1 in 100,000 newborns, but more prevalent among very-low-birthweight infants).

Primary congenital hypothyroidism with delay in TSH elevation also can be seen in infants who have significant illnesses that are often associated with exposure to exogenous iodine (from povidone antiseptic or intravenous contrast solutions), glucocorticosteroids, dopamine, and/or antibiotics. The duration of the delay in TSH elevation has been reported to vary from 11 to 176 days among very-low-birthweight infants, but rarely exceeds 6 weeks. Among term infants with delayed TSH increase, the delay varied from 3 to 94 days and congenital heart disease is more common than otherwise expected. Once the TSH rises, L-thyroxine replacement therapy is recommended.

If T_4, FT_4, and TSH concentrations are all low, then central or secondary hypothyroidism should be considered. Isolated TSH-releasing hormone deficiency may cause low-normal T_4 and low or normal TSH concentrations. Central hypothyroidism has been reported in association with severe birth trauma or asphyxia, often with other pituitary hormone deficiencies.

A few infants with abnormal screening values will have true transient hypothyroidism. These infants have transient elevation of TSH, unlike the infant in the vignette, and will have normal serum T_4 and TSH concentrations later. This condition occurs in 1 in 50,000 newborns in North America. It also is more common in premature infants but can occur in apparently healthy term infants. This condition can be caused by intrauterine exposure to antithyroid medications, maternal antibodies to thyrotropin receptors, abnormal thyrotropin receptors (mutations), iodine deficiency during pregnancy, or recent exposure to excess iodides. These causes can be identified by obtaining an appropriate history.

Because transient hypothyroidism can interfere with brain development, this condition requires thyroid replacement therapy. To help decide whether the condition is transient or permanent, the thyroid medication can be stopped for at least a month after the third birthday. This will not interfere with long-term neurodevelopment and should help the clinician decide whether it is necessary to continue replacement therapy.

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Larson C, Hermos R, Delaney A, Haley D, Mitchell M. Risk factors associated with delayed TSH elevations in congenital hypothyroidism. *J Pediatr.* 2003;143:587-591

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American Board of Pediatrics Content Specification(s):

Understand the causes of transient hypothyroidism in the neonate

Understand the proper use of laboratory tests (including screening tests) in the diagnosis of thyroid dysfunction

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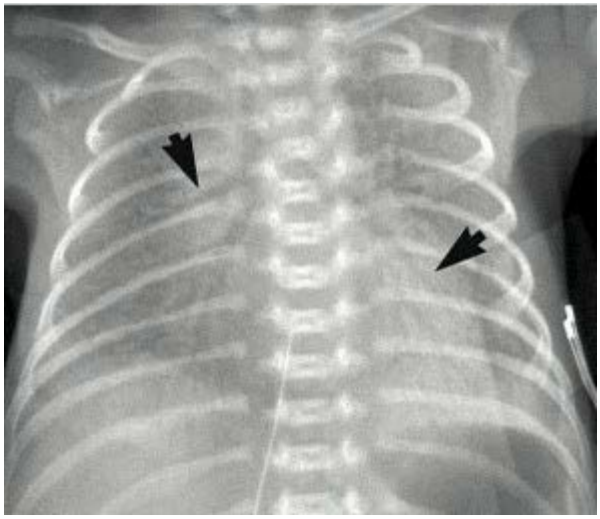
August: Question 9

A 30-week-gestation infant is born precipitously and has respiratory distress at 30 minutes of age. You suspect the respiratory distress syndrome of prematurity, and obtain a chest radiograph (Figure).

Figure: Chest radiograph of a newborn with respiratory distress syndrome. Note the ground-glass appearance to the lung-fields. Arrows point to air bronchograms (from AAP PREP Self-Assessment, Item 238A, courtesy of Brian Carter, MD)



You note air bronchograms (arrows) and a ground-glass appearance of the lung-fields on the radiograph.

Of the following, the basic gas law that BEST explains the ground-glass appearance is the law of:

1	Boyle
2	Charles
3	Dalton
4	Laplace
5	Poiseuille

You selected 2, the correct answer is 4.

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The basic gas laws are useful to understand respiratory physiology. Boyle's law relates gas

pressure and volume. Charles's law relates volume and temperature. Dalton's law relates the partial pressures in a gas mixture to the total pressure. Poiseulle's law relates gas flow through a tube to the tube radius. Laplace's law relates pressure to surface tension and radius of curvature. Of these, Laplace's law applied to the small airways of the neonatal lung best explains the microatelectasis that produces the ground-glass appearance of the respiratory distress syndrome on chest radiography.

Laplace's law states that the gas pressure in a circumscribed volume increases directly with the surface tension at the gas-fluid interface, and inversely with the radius of curvature. As a mammalian lung deflates, the small airways collapse before the alveoli. A small airway with a high surface tension pulling on its surface will close at a higher air pressure than a similar small airway with a low surface tension, as expected by the Laplace law.

Pulmonary surfactant serves to lower the surface tension of small airways and keep them patent at low air pressures. A lack of surfactant causes the small airways to collapse and prevents air from entering the more distal alveoli. Alveolar air is then resorbed and the alveoli collapse. Air is redirected to small airways that have either some surfactant or a larger radius of curvature. The collapse of a large number of small airways causes the diffuse microatelectasis of the respiratory distress syndrome and the ground-glass appearance on radiography.

The Laplace law was applied in the past to the individual alveolus, erroneously assuming independent alveoli of spherical shape and constant curvature. Alveoli are, instead, interdependent, with flat polygonal surfaces. Radial traction from neighboring alveoli and the lung matrix resists alveolar collapse. The two-bubble model of Laplace's law applied to independent spherical alveoli is no longer presented in current texts.

Boyle's law states that, given a constant temperature, the product of a gas's pressure and its volume is constant. Charles's law states that, given a constant pressure, the ratio of a gas's volume to its temperature is constant. These relationships are often combined with the laws of Gay-Lussac and Avogadro to give the familiar ideal gas law:

$$PV = nRT$$

where P is the pressure in pascals, V is the volume in cubic meters, n is the number of moles of gas, R is the ideal gas constant (8.315 J/mol/K), and T is the temperature in Kelvins. The ideal gas law allows calculations of gas exchange and ventilation, including the basic observation that delivering more gas to a lung (increasing n) will cause an increase in P or V or both.

Dalton's law states that the total pressure of a mixture of gases is the sum of each gas's partial pressure. This law is used in the alveolar gas equation when the partial pressure of water vapor at body temperature (47 mm Hg) is subtracted from the barometric pressure.

Poiseuille's law relates laminar flow in a tube to several factors. It is often reduced to the concept that the flow varies directly with the fourth power of the radius. This is useful to keep in mind when considering a change to a larger endotracheal tube. A change in inner diameter, from 2.5 mm to 3.0 mm, under the theoretical conditions of an ideal Newtonian gas and laminar flow, allows a doubling of gas exchange for the same pressure. In the cardiovascular system, it is more efficient to regulate blood flow by varying the diameter of a blood vessel than by varying blood pressure. Vasodilation by 50% will increase the blood flow by a factor of 5. A decrease in vessel diameter by 30% will reduce blood flow to one-quarter of its previous rate.

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Jobe AH. Lung development and maturation. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal Perinatal Medicine Diseases of the Fetus and Infant.* 8th ed. Philadelphia, Pa: Mosby Elsevier; 2006:1069-1087

Mortola JP. Mechanics of breathing. In: Polin RA, Fox WW, Abman SH. *Fetal and Neonatal Physiology.* 3rd ed. Philadelphia, Pa: WB Saunders; 2004:864-870

Prange HD. Laplace's law and the alveolus: a misconception of anatomy and a misapplication of physics. *Adv Physiol Educ.* 2003;27:34-40

American Board of Pediatrics Content Specification(s):

Understand the basic gas laws and how they apply to the clinical setting

Understand the pathophysiology of RDS

Recognize the radiographic features of RDS

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11 November 08

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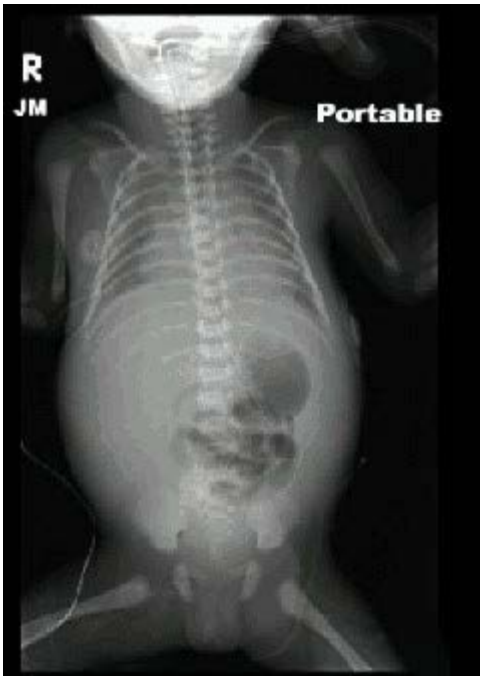
August: Question 10

A female infant is born at 38 weeks' gestation via repeat cesarean section to a 34-year-old woman with two healthy children. The pregnancy was normal. Membranes ruptured at home during early labor. Birthweight is 3.8 kg, and Apgar scores are 8 and 9 at 1 and 5 minutes, respectively. Physical examination reveals persistent tachypnea and a nontender, rounded, full abdomen. There are no abdominal masses, organomegaly, or visible bowel loops. Chest radiograph is normal except for poor inflation of the lungs. Abdominal radiograph shows loops of bowel of normal size collected into the center of the abdomen on the supine view (Figure). A sample of abdominal fluid is obtained and sent to the laboratory for studies.

Figure



Of the following, the measurement MOST likely to assist in identifying the cause of this infant's condition is:

1	creatinine concentration
2	eosinophil count
3	glucose concentration
4	sodium concentration
5	specific gravity

You selected 2, the correct answer is 1.

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Ascites is an abnormal collection of fluid in the intraperitoneal cavity. It is an uncommon finding in newborn infants. When present, the fluid may represent a transudate or an exudate. The "common" types of isolated neonatal ascites are chylous ascites, presumably associated with congenital malformations of lymph drainage, and abdominal fluid secondary to perforation of the gastrointestinal tract, urinary tract, or biliary tract. However, sepsis, congenital infection, congenital heart disease, ovarian cyst, pancreatic cyst, or severe liver disease including storage disease can also result in ascites. Rarely, ascites has been caused by erosion of an umbilical vein catheter into the peritoneum.

Most infants with isolated ascites have abdominal distention at birth. In some cases, neonatal ascites first appears after birth. In any case, the fluid may be under enough pressure to interfere with breathing. Infants with ascites occurring as part of a more generalized fluid retention problem such as hydrops fetalis are not included in this discussion of ascites.

Ascites may be identified on fetal ultrasonography. After delivery, radiographic signs of ascites include abdominal distention often without distention of bowel loops. The abdomen appears more or less opaque, sometimes with separation of loops of bowel. Often gas-containing bowel is seen in the center of the abdomen on a supine view. The liver appears denser than the background opacity of the abdomen. Abdominal ultrasonography can also identify free fluid.

Urinary ascites is a common form of ascites and results from lower urinary tract obstruction at the lower ureter, the bladder, or the posterior urethra. Such obstruction often results in perforation of the upper urinary tract. A voiding cystourethrogram is helpful in identifying the point of obstruction. The infant in this vignette had a ureterocele obstructing the ureter and a resultant tear in the caliceal fornix. Urinary ascites is often accompanied by systemic acidosis, elevated blood urea and creatinine concentrations, electrolyte abnormalities, and possibly a history of oligohydramnios. Severe bilateral obstruction can lead to Potter syndrome. Most affected infants are male. Elevated creatinine in the ascitic fluid is diagnostic of this form. Urinary drainage and correction of the obstruction are the mainstays of management along with correction of the fluid and electrolyte imbalances. Despite the apparent success of this management, some patients may develop end-stage renal disease before adolescence.

In utero gastrointestinal tract perforation can present as neonatal ascites (also known as meconium ascites). Diagnostic clues include:

- **calcifications in the abdomen**
- **abdominal mass or distended bowel**
- **history of polyhydramnios**

The diagnosis is confirmed when meconium is found in the ascitic fluid. Management includes abdominal surgery to find and correct the obstruction and perforation. These infants should undergo an evaluation for cystic fibrosis because meconium peritonitis can be the first sign of cystic fibrosis.

Chylous ascites is the most common neonatal form of ascites, and it is often difficult to manage. With chylous ascites, the peritoneal fluid can be clear initially, but it becomes cloudy or milky once oral feedings are started. This fluid contains a high concentration of triglycerides especially after feeding and a high lymphocyte count (>75% of peritoneal cells). The eosinophil count is not affected. Surgical causes of chylous ascites include malrotation, volvulus, and neoplasia. Most cases, however, are thought to be associated with lymphatic malformations. Treatment consists of a diet rich in medium-chain triglycerides or intravenous alimentation allowing for bowel rest for 2 to 4 weeks. Prognosis is usually good. However, intractable cases have been treated with peritoneovenous shunts.

Biliary ascites is also a rare form of neonatal ascites. It is usually associated with mild

conjugated hyperbilirubinemia. These infants often have feeding problems in addition to their ascites. The diagnosis is confirmed if the ascitic fluid has an increased concentration of bilirubin. Nuclear medicine imaging of the biliary tree can demonstrate free radionuclide outside the biliary tree and intestines. Drainage of the biliary tree through a cholecystostomy tube is usually effective in allowing the perforation to heal.

Measuring electrolytes, specific gravity, or glucose concentration in ascitic fluid does not help to identify the underlying cause in most cases. Hyponatremia is common regardless of the cause. A high glucose concentration, along with the presence of a central venous catheter, would indicate possible migration of the catheter into the peritoneum. The infant in this vignette did not have such a catheter.

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American Board of Pediatrics Content Specification(s):

Identify the approaches to diagnosis and management of neonatal ascites

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11 November 08

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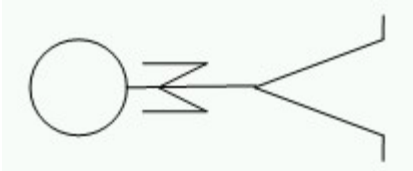
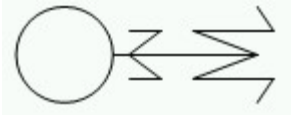
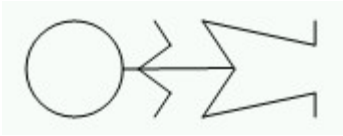
September: Question 1

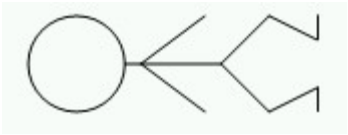
An infant is born at 36 weeks' gestation, and appears healthy. At 24 hours of age, you perform a neurologic examination.

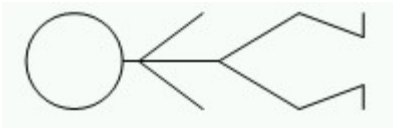
Of the following, the figure MOST likely to represent the resting posture in this infant is:

1 

2 

3 

4 

5 

You selected 2, the correct answer is 3.

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Muscle tone and posture are important components of the motor examination of the newborn, because abnormalities may suggest central nervous system (CNS) and/or neuromuscular dysfunction. Operationally, passive tone is defined as the resistance to movement, experienced by the examiner, while the infant's relaxed limbs are gently manipulated about the joints. Active tone, in contrast, is associated with voluntary or spontaneous movements of the infant, and is generally higher than passive tone. Hypotonia refers to decreased resistance to passive movement, and is more common than hypertonia, or increased resistance.

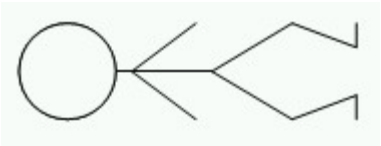
Posture of the limbs at rest is determined, in part, by the tone of various muscles, and is useful

in the assessment of tone. Hypotonia may be indicated by unusual posture, such as the “frog leg” configuration, in which the supine infant's lower extremities are externally rotated and abducted.

However, assessment of tone and the dependent resting posture must be made in the context of gestational age, as a caudocephalic progression of the development of tone occurs in the last 3 months of gestation. With increasing maturity, the fetus passes from a hypotonic posture dominated by extension, to one with increased appendicular and axial flexor tone, first in the lower extremities and then in the upper extremities.

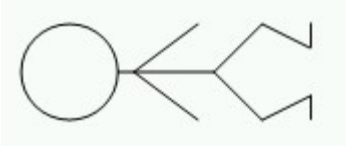
At 28 weeks' gestation, there is minimal resistance to passive range of motion. At rest in the supine position, the arms and legs are extended or very slightly flexed (Figure 1).

Figure 1



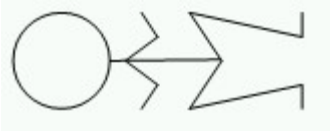
By 32 weeks' gestation, distinct flexor tone becomes apparent in the lower limbs, and the legs are now slightly flexed (Figure 2).

Figure 2



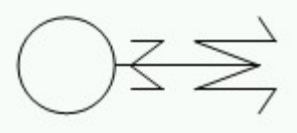
By 36 weeks' gestation, as in the vignette, flexor tone in the lower extremities is strongly developed, and some flexor tone is detectable in the upper limbs (Figure 3).

Figure 3



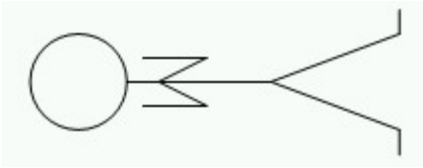
At 40 weeks' gestation, strong flexor tone exists in all limbs, in addition to adduction (Figure 4).

Figure 4



At any gestational age, opisthotonic posturing (Figure 5), with marked leg extension and strong arm flexion, deviates from the normal evolution of tone, and suggests underlying CNS abnormality.

Figure 5



The progressive maturation of tone and posture, in addition to neurologic features such as reflexes, has been mapped, and is useful both in assessing gestational age and in the neurologic evaluation at varying gestational ages. An example of the use of this neurologic mapping in the day-to-day assessment of infants is the tool by Dubowitz and Dubowitz (first published in 1981, and revised by Dubowitz and colleagues in 1999.)

Tone can also be assessed by gentle manipulation of the infant's limbs. Passive supination, pronation, flexion, and extension of the limbs, and gentle shaking of the hands and feet are common means of assessing tone. The measurement of limb angles has been used to assess tone as well. As an example, the popliteal angle is measured by maximum extension of the leg at the knee with the hip fully flexed. The popliteal angle decreases from 180 degrees at 28 weeks' gestation to less than 90 degrees at term.

In addition, responses to multiple maneuvers reflecting tone have been mapped to gestational age. Examples include:

- **Scarf sign: Performed by wrapping the infant's arm across its chest toward the neck on the contralateral side; in the preterm infant, the elbow reaches the opposite shoulder, but is not brought beyond midline in the term infant.**
- **Ventral (horizontal) suspension: The infant's trunk is supported in the outstretched prone position, with observation of the back, limb flexion, and head position in relation to the trunk; the term infant will hold the head erect, and flex the limbs against gravity, while holding the back straight; the infant of 32 weeks' gestation or less will droop against gravity.**
- **Traction maneuver (head lag): The infant is pulled toward sitting posture by traction on both wrists; the head lags with considerably little resistance until after 30 weeks' gestation, but by term, the head follows the trunk before falling forward.**
- **Vertical suspension: The infant is held upright by the axillae; the premature infant will slip through the hands of the examiner, while the term infant will hang firmly.**

Of interest, the term newborn infant demonstrates a consistent preference for position of the head toward the right side. This preference has not been associated with differences in lighting, care practices, or other factors, but is thought to reflect a normal asymmetry of cerebral function in the newborn.

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American Board of Pediatrics Content Specification(s):

Distinguish between active and passive tone

Identify the various maneuvers used to evaluate extremity, shoulder, hip, trunk, and neck tone

Know the normal pattern of evolution of extremity and axial (neck and trunk) tone from fetus through infancy

Characterize the normal resting posture of term and preterm infants at varying gestational ages

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September: Question 2

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11 November 08

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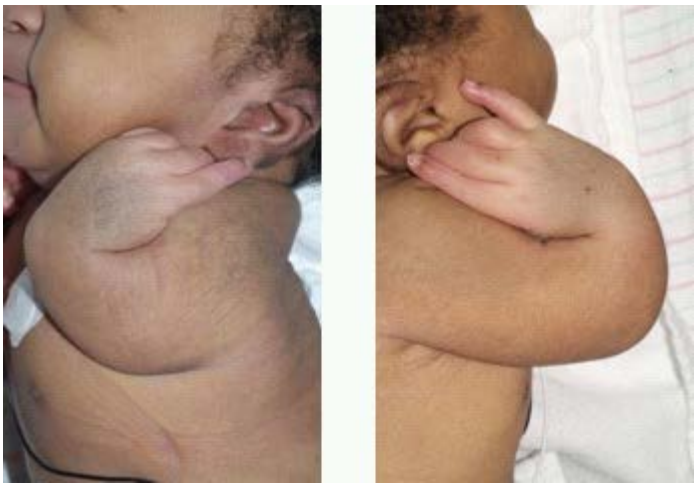
A 3.4-kg male infant was delivered by a 24-year-old primigravida mother at 38 weeks' gestation. The antenatal course was remarkable for a diagnosis of absent radii bilaterally in the fetus at 20 weeks' gestation. Amniocentesis revealed a normal fetal karyotype. After delivery, physical examination revealed malformed upper extremities (Figure 1); the rest of the physical examination findings were normal.

Figure 1



The infant was vigorous and nursing well. A complete blood count several hours after birth revealed a total white blood cell count of 18,000/μL (18×10^9/L), hematocrit of 45% and platelet count of 47,000×10^3/μL (47×10^9/L). A skeletal survey is obtained (Figures 2 and 3). Ultrasonographic findings of the brain and heart were within normal limits.

Figure 2

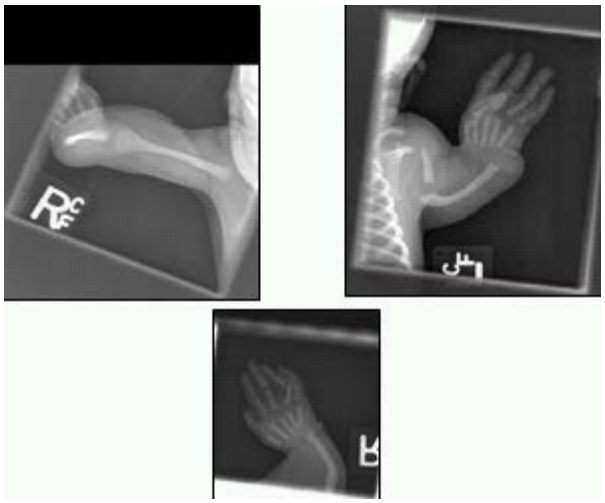
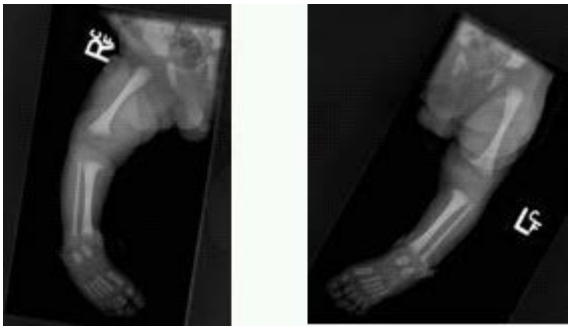


Figure 3



Of the following, this condition is characterized by:

1	cow milk protein allergy in infancy
2	leukemia in adult life
3	lifelong need for platelet transfusions
4	thrombopoietin deficiency
5	X-linked recessive inheritance

You selected 4, the correct answer is 1.

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The infant in the vignette has thrombocytopenia and absent radii (TAR) syndrome. Figure 1 shows shortening of both the upper and lower arms. The hands are not seen completely in Figure 1. The skeletal survey in Figures 2 and 3 shows bilateral absence of radii, normal-appearing thumbs bilaterally, hypoplastic ulnae, hypoplastic left humerus and flexion deformity of the right fourth finger. No other bony abnormality is seen.

The syndrome of thrombocytopenia and absent radii was first described in 1956 and, subsequently, more than 100 cases have been reported. Skeletal abnormalities associated with this syndrome are shown in the Table.

Table

Table. Skeletal Abnormalities Associated with the Syndrome of Thrombocytopenia and Absent Radii	
Abnormalities	**% of Cases**
Radial abnormalities	
Bilateral absent radii	100
Ulnar abnormalities	
Hypoplasia	100
Bilateral absence	20
Unilateral absence	10
Abnormal humerus	50
Bilateral absence	5-10
Abnormal shoulder joint	
The thumbs are always present but may be hypoplastic	
Lower limb abnormalities	50
Hip dislocation	
Subluxation of knees	
Coxa valga	
Dislocation of patella	
Femoral and tibial torsion	
Abnormal tibiofibular joint	
Ankylosis of knee	
Small feet	
Abnormal toe placement	
Absence of fibula	

Cow milk protein allergy or intolerance is common in TAR syndrome (47% of cases) and can be a significant problem. Introduction of cow's milk may precipitate thrombocytopenia, eosinophilia, and/or leukemoid reactions. The cause for this association is unknown.

Platelet counts in neonates with TAR syndrome generally are lower than $50{,}000\times10^3$/μL (50×10^9/L). Bone marrow aspiration reveals a decrease in megakaryocytes; however, this test is not required to make the diagnosis. Defective signal transduction through the thrombopoietin receptor (c-mpl) pathway for megakaryocyte production has been suggested as the cause of thrombocytopenia. Thrombopoietin concentrations have been reported to be normal or high in several case series.

Infants with TAR syndrome may have mucocutaneous bleeding, especially during the first year of life, when the thrombocytopenia is most pronounced. Half of the patients develop hemorrhagic manifestations in the first week after birth and most develop thrombocytopenia by 4 months of age. As infants, these patients require transfusions of single-donor, irradiated platelets. About 40% of patients die in early infancy as a result of hemorrhage. Thrombocytopenia during infancy can be precipitated by viral illness, particularly gastrointestinal infection. After the first year of life, platelet-transfusion dependence usually diminishes. Corticosteroids, intravenous immunoglobulin, and splenectomy have been tried, but the beneficial effects for TAR-associated thrombocytopenia have been inconsistent. Successful treatment with interleukin 6 and erythropoietin has been described in one case each.

"Leukemoid" granulocytosis is seen in 62% of patients, especially during bleeding episodes, and eosinophilia is seen in 53% of patients. Anemia is attributed to hemorrhage and secondary iron deficiency. Although many disorders of hematopoietic failure have an increased risk of malignant transformation, such a risk has not been documented for TAR syndrome; however, two cases of leukemia in TAR syndrome have been reported.

Cardiac defects are seen in one third of these patients, the three most common being tetralogy of Fallot, atrial septal defect, and ventricular septal defect.

The inheritance pattern of TAR syndrome in limited case series is reported to be autosomal recessive. However, the incidence among siblings of 1:7 is lower than the expected rate. Both males and females are affected, but there is a predominance among females, thus making a X-linked recessive pattern of inheritance unlikely.

Do you want to add anything to your Learning Plan?
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References:

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Jones KL. Radial aplasia-thrombocytopenia syndrome. *Smith's Recognizable Patterns of Human Malformation.* 5th ed. Philadelphia, Pa: WB Saunders; 1997;1:322-323

American Board of Pediatrics Content Specification(s):

Understand the etiologies and pathophysiologies of neonatal thrombocytopenia and thrombocytosis

Understand the clinical manifestations of neonatal thrombocytopenia and thrombocytosis

Understand the treatments of neonatal thrombocytopenia and thrombocytosis

Identify the clinical features and know how to manage congenital anomalies of the upper extremities, such as syndactyly, polydactyly, absent clavicles, absent radius, sprengel deformity, limb reduction

Understand the association between anemia and congenital anomalies

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11 November 08

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September: Question 3

A family decides to adopt a special-needs orphan from another country. The only available history is that the child, now 7 years old, was dropped off as an infant and has had a static neurologic disorder ever since. She had poor dentition when she was a toddler in spite of good dental care, but her secondary teeth are sound. Her present condition is represented in this video.* Her adoptive parents are interested in knowing the cause of her problems with a view toward helping her as much as possible to attain the maximum of her future potential.

Of the following, the MOST likely disorder in this child is:

***Note that the video may stop/restart once during initial play and thereafter loop for repeat viewing.**

1	bilirubin encephalopathy
2	glutaric aciduria, type I
3	hypoxic-ischemic encephalopathy
4	Lesch-Nyhan disease
5	Wilson disease

You selected 3, the correct answer is 1.

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The child in this vignette has a static condition characterized by choreoathetosis (involuntary uncoordinated jerky and twisting movements) and sensorineural deafness with a history of poor primary dentition in spite of good dental care. She has at least three of the typical findings of chronic bilirubin encephalopathy. Chronic bilirubin encephalopathy, the long-term outcome of acute bilirubin encephalopathy, is characterized by variable severities of extrapyramidal abnormalities and spasticity (typically choreoathetosis), auditory neuropathy with hearing loss, abnormalities of upward gaze, and enamel hypoplasia of deciduous teeth. Intelligence is usually normal, and seizures, if they occur at all, appear in the neonatal period and tend to resolve over time.

Glutaric aciduria, type 1, is a neurometabolic disorder resulting from a deficiency of glutaryl-CoA dehydrogenase, the enzyme responsible for the breakdown of lysine, hydroxylysine, and tryptophan. Accumulation of intermediate products such as glutaric acid in the brain leads to progressive macrocephaly, ataxia, dystonia, and choreoathetosis. Regression of developmental milestones, seizures, and strokelike episodes are common. Deafness and problems with primary dentition are not typical of this disorder.

Hypoxic-ischemic encephalopathy (HIE) can lead to cerebral palsy. However, only 12% to 24%

of children with cerebral palsy have a history of intrapartum asphyxia. Such children have problems similar to those seen in this vignette including spasticity and less commonly choreoathetosis. Choreoathetosis tends to appear later in children affected by HIE (mean age at onset = 12.9 years). Intelligence is often spared. However, dentition is not affected directly by this condition and deafness is less prevalent.

Lesch-Nyhan syndrome (LNS) is a rare, X-linked recessive genetic disorder caused by a deficiency of the enzyme *hypoxanthine-guanine phosphoribosyltransferase* (HPRT). It is extremely rare in girls. HPRT deficiency causes accumulation of uric acid leading to symptoms of severe gout, poor muscle control, and moderate intellectual disability, which appear in the first year after birth. A striking feature of LNS is persistent lip and finger biting beginning in the second year. These children exhibit facial grimacing and involuntary repetitive writhing movements of the arms and legs. Deafness is not described as part of LNS.

Wilson disease (WD) is a rare genetic disorder in which excessive amounts of copper accumulate in the body. The buildup of copper leads to damage in the kidneys, brain, and eyes. Although copper accumulation begins at birth, symptoms of the disorder appear later in life. The most characteristic symptom of WD is the Kayser-Fleischer ring, a rusty brown ring around the cornea of the eye that can be best viewed using an ophthalmologist's slit lamp. The primary problem associated with WD is acute and/or chronic liver damage, which starts in late childhood or early adolescence. In some individuals, the first symptoms may occur in adulthood, and include slurred speech (dysarthria), difficulty in swallowing (dysphagia), and drooling. Other symptoms may include tremors of the head, arms, or legs; poor muscle tone, and persistent muscle contractions leading to abnormal postures, twisting, and repetitive movements (dystonia); and slowness of movements (bradykinesia). Deafness and dental problems are not described.

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American Board of Pediatrics Content Specification(s):

Know the clinical features of chronic bilirubin encephalopathy

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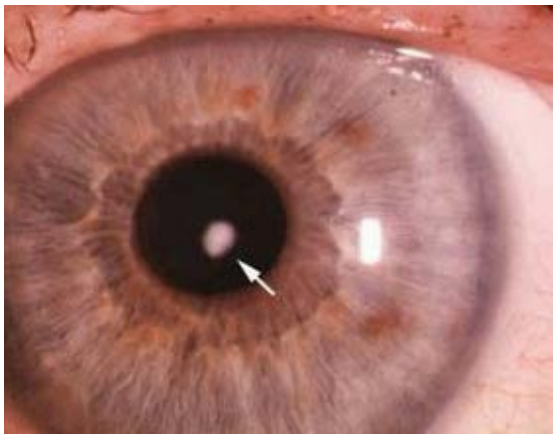
11 November 08

12 December 08

September: Question 4

During an eye examination to screen for retinopathy of prematurity, the ophthamologist reports that she did not get a good look at the entire retina of the left eye because of the lesion depicted in Figure 1.

Figure 1



The right eye is normal. During his stay in the neonatal intensive care unit, the 45-day-old 28-week-gestation infant has had respiratory distress that required ventilatory support, a short course of hydrocortisone for hypotension, and mild conjugated hyperbilirubinemia that has improved during the past 2 weeks. He is tolerating fortified breast milk feeds. Maternal history and prenatal laboratory evaluation are significant for well-controlled gestational diabetes.

Of the following, the MOST likely cause of this neonate's eye finding is:

1	galactosemia
2	hereditary
3	idiopathic
4	rubella infection
5	steroid exposure

You selected 4, the correct answer is 3.

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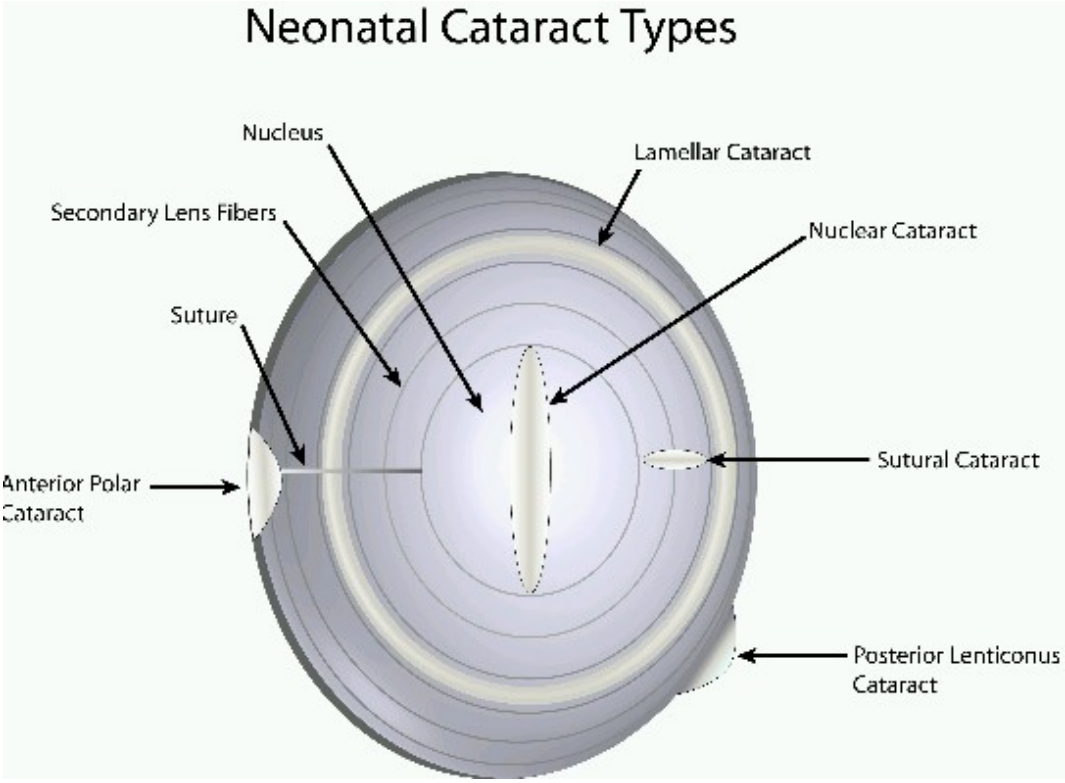
The eye lesion in the infant in this vignette is a cataract. Cataracts occur with an incidence of 1.2 to 6 per 10,000 live births and account for about one-tenth of cases of childhood blindness. Through an ophthalmoscope using the 0-diopter lens, the red reflex can be obtained by viewing the pupil from approximately 1 m. If an opacity in the lens obstructs the reflection of light from the red fundus, the reflex will appear black. An irregular density from an incomplete cataract can produce an

irregular reflex. The abnormality can be localized to the lens by looking through a +10-diopter lens at a distance of about 30 cm from the infant. The abnormality in the lens will appear in focus in the plane of the pupil. Abnormalities of the vitreous will come into focus posterior to the pupil. Moving slightly to one side or the other while viewing the lesion in the lens will help to estimate the depth of the lesion. Definitive evaluation of cataracts requires a slit-lamp examination of a dilated pupil.

Pediatric cataracts are most often classified based on morphologic findings as zonular, polar, lenticonus, and membranous (Figure 2).

Figure 2: Saggital view of neonatal lens



Zonular cataracts are located in one zone of the lens and can be nuclear, lamellar, or sutural. Polar cataracts involve either the central anterior or posterior capsule of the lens as well as the underlying lens. Posterior or anterior lenticonus is the result of a defect in the lens capsule with bulging and opacification of the underlying lens. Membranous cataracts occur as the result of resorption of the lens and are often associated with congenital rubella.

Cataracts may also be grouped according to suspected causes. The presence of cataract(s) should initiate an evaluation while considering many of the potential causes and associations, a few of which are listed in Table 1.

Table 1

Table 1. Classification of Congenital Cataracts by Causes*	
Category	**Associated Findings or Causes**
Idiopathic	Unknown
Isolated	None
Associated with ipsilateral ocular disorder	Microphthalmia, persistent hyperplastic primary vitreous, aniridia, anterior chamber dysgenesis syndromes, retinopathy of prematurity, ectopia lentis, posterior lenticonus, intraocular tumor
Intrauterine infection	Rubella, cytomegalovirus, varicella-herpes zoster, herpes simplex, toxoplasmosis, syphilis
Intrauterine drug exposure	Chlorpromazine, corticosteroids, sulfonamides, vitamin D, vitamin A
Systemic prenatal/perinatal disorders	Galactosemia, galactokinase deficiency, hyperglycinuria, sialidosis, α-mannosidosis, sorbitol dehydrogenase deficiency, hypocalcemia (idiopathic), hypoparathyroidism or pseudohypoparathyroidism, marginal maternal galactokinase deficiency, maternal diabetes
Hereditary–isolated	Autosomal dominant, autosomal recessive, or X-linked recessive
Hereditary associated with systemic disorder or dysmorphic syndrome	• Chromosomal: Trisomy 13, 18, 21, Turner syndrome, deletion chromosome 5 • Skeletal disease: Conradi-Hünermann syndrome, rhizomelic chondrodysplasia punctata, Stickler syndrome, Camfak syndrome • Syndactyly, polydactyly or other digital syndrome: Rubinstein-Taybi syndrome, Ellis-van Creveld syndrome, Bardet-Biedl syndrome • Central nervous system disorder: Cereboro-oculo-facial-skeletal syndrome, Martsolf syndrome, Zellweger syndrome, Marinesco-Sjögren syndrome, Smith-Lemli-Opitz syndrome, Norrie disease • Muscle disorder: Myotonic dystrophy, cataract, lactic acidosis and cardiomyopathy • Renal disease: Lowe syndrome, Alport syndrome • Mandibulo-facial syndromes: Hallerman-Streiff syndrome, Nance- Horan cataract-dental syndrome • Dermatologic disorder: Congenital icthyosis, cataract, alopecia, sclerodactyly, Schafer syndrome, Siemen's syndrome, incontinentia pigmenti

*** Adapted from Rahi and colleagues (2000).**

In several large published series, idiopathic cataract, or one without a recognized cause, is the most commonly reported form of congenital cataract. Approximately half of all congenital cataracts are idiopathic. A unilateral cataract, as present in the neonate in the vignette, is likely to be idiopathic; however, because it can also occur with an ipsilateral ocular disorder such as microphthalmia, aniridia, or retinopathy of prematurity (Table 2), a careful ophthalmologic examination is required.

Table 2

Table 2. Congenital Cataracts		
Findings	**Unilateral Cataracts, %**	**Bilateral Cataracts, %**
Associated Findings		
None	47	61
Systemic disease	6	25
Ocular abnormalities	47	14
Causes		
Idiopathic	92	38
Hereditary	6	56
Infections and other perinatal conditions	2	6

*** Adapted from Fallaha and Lambert (2001).**

Galactosemia, an inborn error of galactose metabolism, is caused by a deficiency of galactose-1-phosphate uridyl-transferase (classic galactosemia), galactokinase, or uridine diphosphate-galactose-4-epimerase. Affected

neonates may have normal eyes at birth, only to develop cataracts during the first 2 months after birth. Because galactosemia is a systemic disorder, associated cataracts are usually bilateral. Cataracts may be zonular or appear as vacuoles and in classic cases, are described as a "drop of oil" in the center of the lens. Cataracts associated with galactosemia are caused by the accumulation of galactose and galactitol in the lens. Most state screening programs test for classic galactosemia. Because classic galactosemia is found on newborn screening and usually has a rapid onset that may include lethargy, hypoglycemia, conjugated hyperbilirubinemia, and in some cases *Escherichia coli* sepsis, it is an unlikely cause of the unilateral cataract found in the infant in the vignette.

Bilateral neonatal cataracts are more likely to be inherited than are unilateral cataracts (Table 2). They are most often inherited as an autosomal dominant disorder, but in rare cases, may be inherited as an autosomal recessive trait, particularly among offspring of consanguineous relationships. A number of genes, most of which code for lens proteins, may be involved in cataract formation. A family history and examination of parents and siblings will be useful in determining whether neonatal cataracts are familial.

If the cataracts are not inherited and are bilateral, a careful prenatal and postnatal history as well as selected laboratory studies are required to determine the cause of cataracts. Congenital infections such as toxoplasmosis, cytomegalovirus, herpes simplex, syphilis, and rubella have been associated with cataracts. Cataracts are present in approximately 20% of children with a congenital rubella infection. The cataracts are usually bilateral and present as total or near-total opacities in a smaller-than-normal lens. The eye is often small and the retinal pigment epithelium may have "salt and pepper" changes. Glaucoma and anterior uveitis may be present. Maternal immunity to rubella conveys protection to her fetus and the congenital rubella syndrome does not occur, making congenital rubella an unlikely cause of the unilateral cataract in the infant in the vignette.

Prednisone use has been shown to increase the risk of bilateral cataract formation in children with asthma. A short course of hydrocortisone has not been shown to be associated with unilateral cataract formation in neonates.

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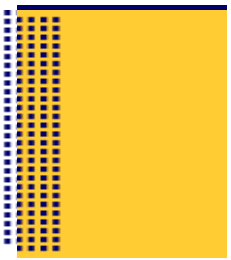
American Board of Pediatrics Content Specification(s):



Recognize the signs of neonatal cataracts

Recognize the conditions associated with neonatal cataracts

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September: Question 5

A 4.5-kg full-term male infant, who is delivered by emergency cesarean section, requires oxygen supplementation. You are reviewing the mechanisms of oxygen transport and delivery with the housestaff.

Of the following, the MOST accurate statement regarding oxygen kinetics in the newborn infant is that:

1	anaerobic metabolism begins when intramitochondrial O_2 is less than 40 mm Hg
2	oxygen consumption for normal neonates is approximately 6 mL/kg per minute
3	oxygen extraction ratio in normal newborns is approximately 40%
4	PaO_2 is the most important measurement to assess oxygenation in ill newborns
5	there is a linear relationship between O_2 delivery and consumption

You selected 5, the correct answer is 2.

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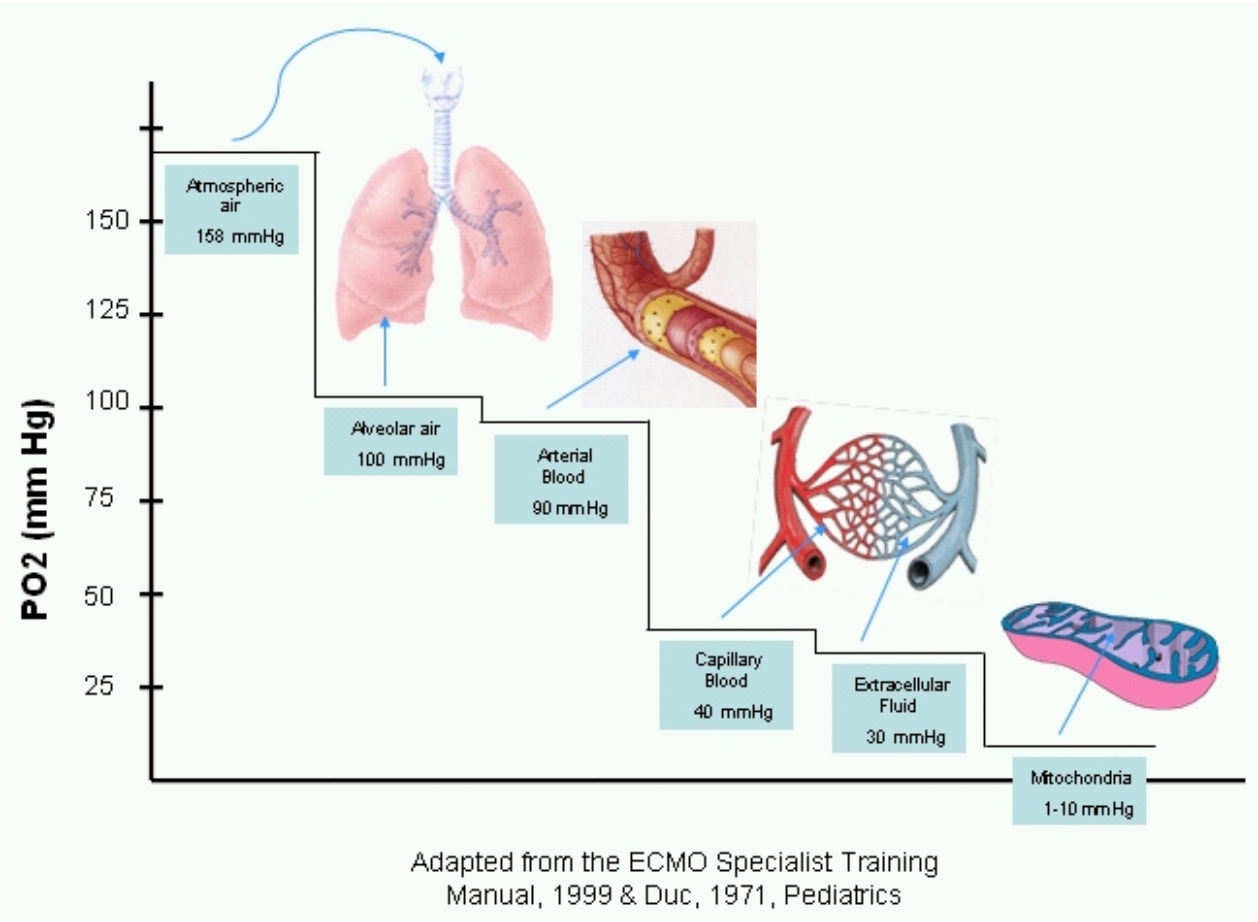
Oxygen (O_2) consumption in normal neonates is approximately 6 mL/kg per minute. Understanding oxygen dynamics requires review of the movement of oxygen from the ambient or inhaled environment to the intracellular environment.

Gas exchange in the human body can be divided into two types: pulmonary and tissue respiration. Pulmonary respiration refers to the gas exchange between blood and inspired gas, while tissue respiration refers to the exchange of O_2 and carbon dioxide (CO_2) at the cellular level. O_2 passes from the atmosphere to the cells along a continuous diffusion concentration gradient (Figure 1).

Figure 1: Oxygen Gradient from the Inspired Air to the Cells



Adapted from the ECMO Specialist Training Manual, 1999 & Duc, 1971, Pediatrics

Oxygen makes up 21% of ambient air, which at sea level represents a partial pressure of 158 mm Hg. As the air is delivered to the distal airways and alveoli, PO_2 decreases by dilution with CO_2 and water vapor, and by uptake into the blood. Under ideal conditions, when ventilation and perfusion are well matched, the alveolar PO_2 will be approximately 100 mm Hg. This can be derived from the following alveolar gas equation:

$$PaO_2 = (\text{Barometric pressure} - \text{partial pressure of water vapor}) \times FiO_2 - PaCO_2/R$$

Where

PaO_2 is the partial pressure of O_2 in the alveolar gas

$PaCO_2$ is the partial pressure of CO_2 in the arterial blood as an estimate of alveolar gas

R is the respiratory quotient

The partial pressure of CO_2 in the alveoli is nearly identical to the amount of CO_2 physically dissolved in the arterial blood, or $PaCO_2$. The respiratory quotient is the ratio of CO_2 excretion to O_2 uptake. It ranges from 0.8 to 1.0 depending on the diet. Thus, in normal infants, the PaO_2 is 100 to 110 mm Hg. Under normal conditions, there is complete equilibration of alveolar gas and capillary blood. In some diseases, the diffusion barrier for gas transport may be increased, and the alveolar-end-capillary PO_2 gradient may be increased. The PO_2 in arterial blood is further reduced by venous admixture (shunt) and the addition of mixed venous blood from the pulmonary artery, which has a PO_2 of approximately 40 mm Hg. A combination of a small diffusion barrier, ventilation-perfusion mismatches, and the shunt fraction produces the alveolar-to-arterial oxygen gradient, which is normally 10 to 12 mm Hg when air is breathed and 30 to 50 mm Hg when 100% oxygen is breathed.

Oxygen is delivered to the tissue capillary beds by the circulation and again follows a gradient out of the blood, through the extracellular fluid, and into cells. The final gradient drives O_2 from the

extracellular fluid (PO_2 = 30 mm Hg) to the cytoplasm of the individual cell (PO_2 = 6-10 mm Hg). Although the PO_2 at the site of cellular oxygen utilization, or the mitochondria, is not known, oxidative phosphorylation can continue at a PO_2 of only a few millimeters of mercury. When the mitochondrial PO_2 falls below about 1 mm Hg, aerobic metabolism stops and the less efficient anaerobic pathway of glycolysis becomes responsible for the production of cellular energy.

In the blood, O_2 is carried primarily in chemical combination with hemoglobin and is to a small extent dissolved in solution. Thus, oxygen content (CaO_2) of blood can be expressed as follows:

$$CaO_2 = (HbO_2) + (\text{Dissolved } O_2)$$

Where HbO_2 is O_2 bound to hemoglobin, and Dissolved O_2 is the O_2 in solution.

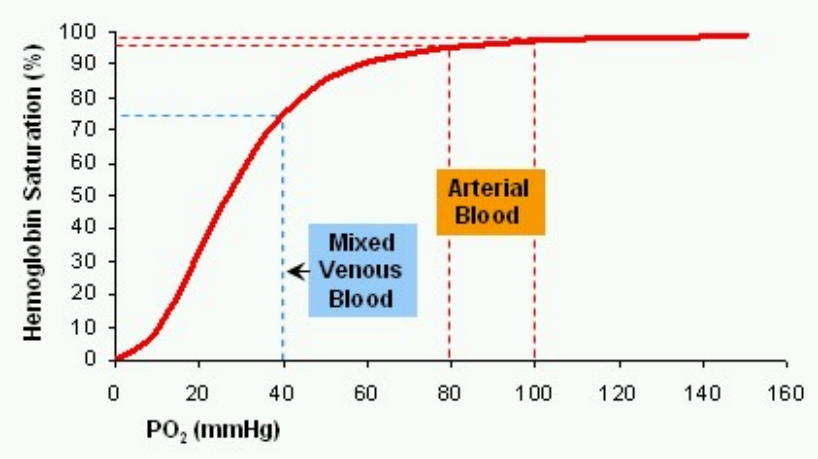
The amount of O_2 carried in the blood by hemoglobin depends on the hemoglobin concentration, percentage of hemoglobin saturation, and O_2 capacity of hemoglobin. Mathematically, this is expressed as follows:

$$HbO_2 = (\text{g \% Hb}) \times (O_2 \text{ capacity}) \times (\text{\% saturation})$$

Hemoglobin O_2-carrying capacity is a constant that represents the maximum amount of O_2 that can be carried by a gram of hemoglobin. This value is 1.34 mL/g of hemoglobin.

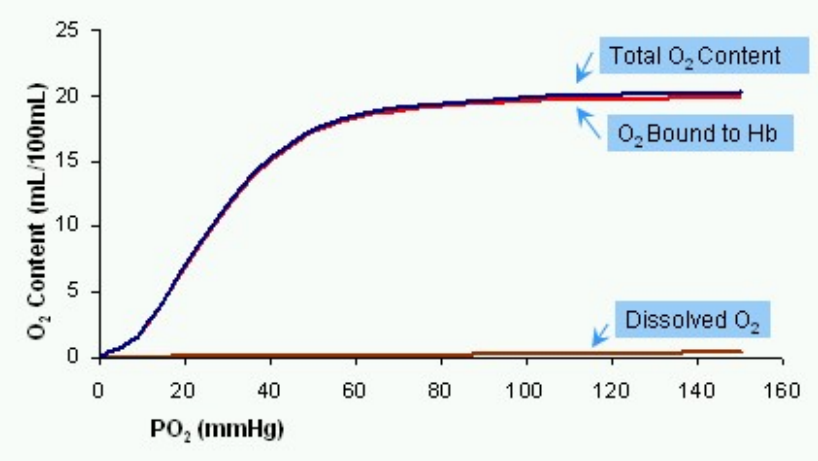
The relationship between arterial oxygen tension (PO_2) and amount of O_2 combined with hemoglobin, or hemoglobin saturation, is sigmoidal over the physiologic range (Figure 2).

Figure 2



Hemoglobin is almost fully saturated at PO_2 of 80 to 100 mm Hg. Hemoglobin-bound O_2 accounts for the majority of the O_2 content in blood (Figure 3).

Figure 3



Only a small amount of O_2 is dissolved in the plasma (Figure 3). This amount is directly proportional to PO_2 from 0 to 600 mm Hg. At 38°C, 0.003 mL of O_2 is dissolved in 100 mL of plasma per mm Hg of O_2.

Dissolved O_2 = (0.003 × PO_2) mL/100 mL of plasma

Assuming that a normal full-term newborn infant has a hemoglobin concentration of 15 g in 100 mL of blood, and that arterial blood is normally 100% saturated, the oxygen-carrying capacity of the blood (CaO_2) is:

CaO_2 = (HbO_2) + (Dissolved O_2)

=[(g % Hb) × (O_2 capacity) × (% saturation)]+ Dissolved O_2

CaO_2 = (15) × (1.34) × (1.0) + (0.003 × 100)

= 20.10 + 0.3

= 20.4 mL per 100 mL arterial blood

The amount of O_2 delivered to the tissues (DO_2) is dependent on the CaO_2 and cardiac output (CO). Assuming that the normal newborn CO is approximately 120 mL/kg per minute, the amount of O_2 that can be delivered to the systemic circulation is calculated as follows:

O_2 delivered = (CO) × (CaO_2)

= (120 mL/kg/min) × (0.204 mL O_2/mL blood)

= 24.48 mL O_2/kg/min

The O_2 content is rarely measured directly for clinical applications, and it is standard practice to describe blood oxygenation in terms of PaO_2 or hemoglobin saturation. However, O_2 content is the more important measurement in the physiologic treatment of critically ill patients.

Oxygen consumption can be calculated as the product of the arteriovenous oxygen content difference multiplied by the CO (the Fick equation):

Oxygen consumption (VO_2) = Arterial O_2 delivery – Venous O_2 delivery

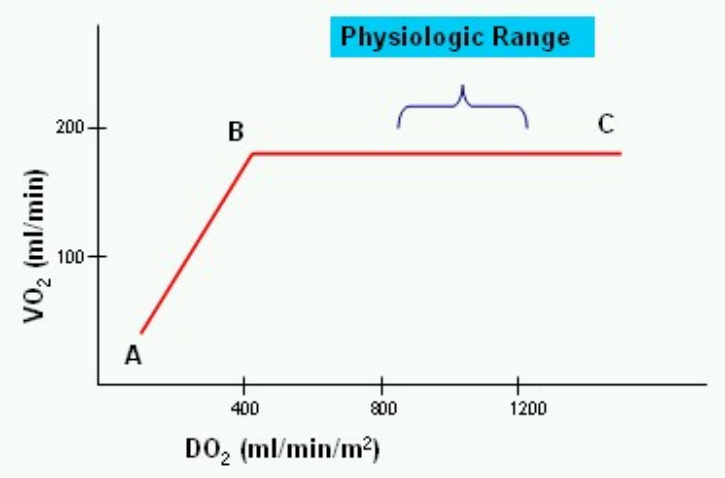
= CO (CaO_2 – CvO_2)

where CvO_2 is the content of O_2 in mixed venous blood.

Under normal circumstances, a neonate's O_2 consumption is approximately 6 mL/kg per minute and the body extracts O_2 at a rate of 6 mL/kg per minute from the approximately 24 mL/kg per minute that is delivered to the systemic circulation. Therefore, the normal DO_2 is four to five times the V_TO_2 regardless of patient size (Figure 4) and 20% to 25% of the O_2 has been removed by the time it

returns to the heart.

Figure 4



Adapted from Ouelette, 2005, Chest

The mixed venous blood thus is 75% to 80% saturated. In general, a measured mixed venous saturation of 70% to 75% represents adequate tissue O_2 delivery. In patients in whom mixed venous saturation can be directly monitored (eg, patients receiving extracorporeal membrane oxygenation), the goal is to keep the mixed venous saturation in the normal physiologic range of 70% to 75%. Mixed venous blood hemoglobin saturation reflects the oxygen extraction ratio, and therefore it is the most important indicator for treating critically ill patients. If the arterial blood is fully saturated, the venous saturation decreases in proportion to the amount of O_2 extracted from the blood. Thus, if the O_2 extraction ratio is 20%, the venous saturation will be 80%; if the oxygen extraction ratio is 33%, the venous saturation will be 67%.

The normal relationship between DO_2 and V_TO_2 is biphasic (Figure 4). Above a *critical threshold* (point B in Figure 4), VO_2 is independent of DO_2. Below this threshold value, VO_2 decreases in a linear fashion with a decrease in DO_2. The critical threshold for DO_2 has been identified to be 3 to 5 mL/kg per minute or a ratio of DO_2 to V_TO_2 less than 2:1. However, the relationship of DO_2 to V_TO_2 may change during the course of a critical illness.

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Simon BA, Moody EJ, Johns RA. Therapeutic gases: oxygen, carbon dioxide, nitric oxide, and helium.

In: Brunton LL, ed. *Goodman and Gilman's The Pharmacologic Basis of Therapeutics*. 11 ed. New York, NY: McGraw-Hill; 2006

American Board of Pediatrics Content Specification(s):

Know the causes of arterial hypoxemia in a patient with a structurally normal heart and how to differentiate among them using measurements of arterial blood gas tensions

Understand the basic gas laws and how they apply to the clinical setting

Understand the various factors affecting oxygen uptake, transport, and delivery, including the blood and circulation

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September: Question 6

A full-term infant was born by cesarean section after several attempts at vaginal delivery with forceps assistance. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Initial physical examination revealed a depressed region over the right parietal bone; the infant was otherwise clinically stable, with a hematocrit count of 51.3% (0.51).

Of the following, the NEXT step in the evaluation of a suspected skull fracture in this infant is:

1	computed tomography of the head
2	magnetic resonance imaging study of the head
3	plain radiography of the skull
4	transillumination of the head
5	ultrasonography of the head

You selected 2, the correct answer is 3.

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Depressed skull fractures can occur from compression of the skull—either after forceps application or against the ischial spines or the pubic symphysis. Usually such fractures result from inward collapse of the calvarial bones. Injury of the intracranial structures (dural attachments and major vessels) may result in hemorrhage. On clinical examination, an underlying fracture should be suspected when there is an obvious and palpable bony defect. Plain radiography is the diagnostic test of choice in such cases.

Computed tomography (CT) remains the primary imaging choice in acute situations, and would be the correct choice if this infant demonstrated clinical or laboratory signs of hypovolemia, acute anemia, or coagulopathy. CT is most reliable for detecting extracerebral (subdural and subarachnoid) and posterior fossa (cerebellar or subdural) hemorrhage. Whereas normal vascular grooves, lacunar skull, and ripple lines (soft-tissue folds in the scalp) may be mistaken for fractures on plain radiography, CT scans may be helpful in these circumstances. Given the known risks (exposure to ionizing radiation) associated with CT scans, this is not the imaging modality of choice for initial evaluation of a stable infant with a suspected skull fracture.

The National Cancer Institute is encouraging providers to perform CT scans only when absolutely necessary. According to their recommendations, radiologists should review the indications and be available for consultation before every pediatric scan. Some reports suggest up to 30% of CT scans performed in the pediatric population are unnecessary. Radiation doses from a single pediatric head CT scan can range from about 30 mSv to 60 mSv; three scans would be expected to triple the cancer risk of a single scan.

Transillumination of the skull is a valuable aid in determining the degree of hydrocephalus and in the diagnosis of hydranencephaly, as well as unilateral hygromata and Dandy-Walker syndrome. It is a low risk procedure, but it has little benefit in diagnosing skull fractures.

Although CT is more reliable, high-resolution ultrasonography using transfontanelle and transcranial approaches, including the mastoid view, can detect extracerebral and posterior fossa hemorrhage, including subdural hemotomas. While ultrasonography may provide important screening information, particularly with regard to hemorrhage and trauma, it is currently not the screening modality of choice to detect or to evaluate skull fracture.

Magnetic resonance imaging (MRI) is not the imaging modality of choice in acute situations in which skull fracture is suspected; the procedure is time consuming and neonates often require sedation to reduce motion artifact. Nonetheless, MRI frequently provides superior diagnostic specificity compared with CT or ultrasonography for delineating hemorrhagic processes, including staging of hemorrhage and clot formation based on hemoglobin breakdown. In the presence of an atypical or unexplained intracranial hemorrhage, MRI may distinguish hemorrhagic infarction from hematoma.

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References:

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Brenner, David J., Hall, Eric J.Computed tomography: an increasing source of radiation exposure. *N Engl J Med.* 2007;357:2277-2284

Johnson JH, Figueroa R, Garry D, Elimian A, Maulik D. Immediate maternal and neonatal effects of forceps and vacuum-assisted deliveries. *Obstet Gynecol*. 2004;103:513-518

National Cancer Institute, Division of Cancer Epidemiology and Genetics. Radiation risks and pediatric computed tomography (CT): a guide for health care providers. Rockville, MD: National Cancer Institute. Accessed January 21, 2008, at http://www.nci.nih.gov/cancertopics/causes/radiation-risks-pediatric-CT

American Board of Pediatrics Content Specification(s):

Understand the indications for and limitations of various neuroimaging studies (including ultrasonography, magnetic resonance imaging study, positron emission tomography, and near infrared spectroscopy), and be able to recognize normal and abnormal structures

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September: Question 7

You are meeting with the family of a term male infant who presented with abdominal distention associated with ileal atresia, for which an ileostomy was done. The colon was small. Although he had no pulmonary difficulties, cystic fibrosis was suspected based on the clinical presentation and confirmed with sweat chloride and genetic studies. After you present the need for referral to the cystic fibrosis clinic for ongoing nutritional support using pancreatic enzymes and for careful respiratory management, the family inquires about the future for patients having cystic fibrosis.

Of the following, the prognostic statement MOST consistent with the diagnosis of cystic fibrosis is that:

1	azoospermia will result in infertility
2	endocrine pancreatic function will remain normal
3	expected median survival is 25 years
4	osteopenia affects most adult patients
5	pancreatic enzyme supplements will prevent malnutrition

You selected 4, the correct answer is 4.

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Cystic fibrosis (CF) is the most common life-shortening autosomal recessive condition affecting the white population. Four percent of whites carry one of the over 800 mutations of the CF gene on chromosome 7. The incidence of CF (per live births) varies in different ethnic groups: 1 in 2,500 in whites, 1 in 17,000 in blacks, 1 in 9,200 in Hispanics, and 1 in 90,000 in Asians.

The genetic abnormality causing CF affects the function of the cystic fibrosis transmembrane conductance regulator (CFTR). Residing on the apical membrane of epithelial linings of the airways, biliary tree, intestines, pancreatic ducts, vas deferens, and sweat ducts, CFTR enables the transport of chloride at these sites and downregulates the resorption of sodium from secreted fluids. Individuals lacking CFTR function have insufficient fluid secretion combined with sodium/fluid resorption, resulting in hyperviscous secretions that may contain protein precipitates as well. Cells lacking CFTR fail to produce normal amounts of nitric oxide synthetase-2; the resultant reduction in nitric oxide contributes to increased sodium resorption, exaggerated inflammatory responses, and decreased bacterial killing. Other properties affected by CFTR abnormality include increased binding sites for *Pseudomonas* and upregulated proinflammatory pathways.

Diagnostic tests focus on the *CFTR* gene or its dysfunction: sweat chloride concentration exceeding 60 mEq/L (60 mmol/L); presence of two known CF mutations of the *CFTR* gene; or abnormal bioelectric testing of CFTR function in nasal epithelium. Currently, in most states,

newborn screening is indirect, in that it involves measurement of immunoreactive trypsinogen in blood (elevated in CF). Although most infants having CF will have positive test results, 80% of these results are false positive, requiring confirmation of the diagnosis with sweat testing or genetic testing. In the neonatal period, sweat testing has technical difficulties because of the low volume of sweat. Adequate sweat samples for testing usually are available after 1 month of age. Commercial genetic testing can identify almost all of the CF alleles, but some families with CF have unique (or private) mutations that are not detected with current tests. Delayed diagnosis will become less frequent as newborn screening becomes more effective and universal, making genetic counseling for CF a regular part of neonatal practice.

Of patients who have CF, 15% present with symptoms in the neonatal period, the most common manifestation being meconium ileus. Ninety percent of patients with meconium ileus have CF. Patients with either jejunal or ileal atresia have a 15% to 30% risk of CF, leading to the diagnosis of the infant in this vignette. An occasional patient will present with prolonged jaundice, the exact mechanism for which is unknown.

Although most individuals with CF are diagnosed by age 3 years, the initial presentation of CF can be subtle so that 1 in 20 cases is not diagnosed before age 16 years. Three elements define the CF phenotype, any one of which should lead to evaluation for CF: chronic sinopulmonary disease, gastrointestinal disease and/or malnutrition, and obstruction of the vas deferens (males).

The strongest determinant of survival and quality of life is pulmonary health. At birth, the lungs are histologically normal. Abnormality of the CFTR protein results in defective sodium and water balance resulting in shallow surface liquid layers, more viscous secretions, and in the lung, decreased ability to clear infected secretions. The endobronchial chronic infection and inflammatory changes result in bronchial damage with relative alveolar sparing. Bronchial mucous plugging, combined with infection and inflammation, ultimately results in bronchiectasis, initially involving the upper lobes and progressing to all the lobes of the lungs. Current long-term strategies include airway clearance using mechanical techniques, mucolysis (dornase alpha and hypertonic saline), inhaled antibiotics, antiinflammatory agents, and systemic antibiotics for exacerbations. Lung function is monitored regularly using forced expiratory volume, and 1% to 4% loss of lung capacity per year can be expected, even with treatment. Lung transplantation is reserved for the most severely affected patients and is performed on about 1.5% of the adult population with CF each year. The early and aggressive pulmonary treatment regimen in association with nutritional management has increased median survival to 36.9 years (2006 data) with 43% of all patients with CF now being older than 18 years of age.

Among infants with intact intestinal tracts, pancreatic exocrine insufficiency will be present in 90% of individuals. CF often presents as failure to thrive in an infant with good appetite and frequent foul-smelling stools. Treatment with pancreatic enzymes (amylase, lipase, and protease) lessens the impact of chronic malabsorption and should be begun early, but most patients will have chronic fat malabsorption. Because the acid-neutralizing effect of pancreatic secretions is diminished, use of acid inhibitors may augment the effect of orally administered pancreatic enzymes. Strategies such as high-caloric and high-sodium meals, supplementation with fat-soluble vitamins, and night-time tube feedings may be used. Nevertheless, patients with CF generally are somewhat undernourished with body mass indices lower than expected.

Vitamin D deficiency and decreased bone mineral content are common, affecting two-thirds of adults with CF. Osteoporosis results from combined effects of vitamin D malabsorption, inflammatory cytokines, low testosterone concentration, general malnutrition, and direct effect of the CFTR mutation on bone development. Deficiencies of vitamin K and vitamin E can occur. If vitamin E is necessary for shortened red blood cell survival or for peripheral neuropathy, the water-soluble form is needed.

In adults, distal intestinal obstruction syndrome can result from accumulation of solid stool at the ileocecal junction, where it normally should be liquid. Especially of concern among patients who are malnourished, not taking sufficient pancreatic enzyme supplementation, swallowing large volumes of mucous, and/or taking narcotics, treatment involves rehydration of the stool with osmotic laxatives or enemas. Adult patients with CF also present increased risk for cirrhosis, cholelithiasis, and nephrolithiasis, all suspected to be sequelae of CFTR dysfunction.

Adherent stools can create a lead point for intussusception, and poor tissue quality in the perirectal area can lead to rectal prolapse.

Congenital bilateral absence of the vas deferens (CBAVD) affects 99% of males with CF, resulting in obstructive aspermia. Eighty percent of CBAVD is associated with mutations of the *CFTR* gene. Although the vas is not patent, spermatogenesis is normal, and men with CF have fathered children through microepididymal sperm aspiration and in vitro fertilization. Fertility in females with CF is unaffected. Because CF is autosomal recessive, offspring of individuals with CF are usually not affected. Genetic testing of both parents can assess the risk for individual couples.

In addition to the pancreatic exocrine dysfunction, by adulthood, 20% to 30% of patients with CF have pancreatic endocrine dysfunction as the islets of Langerhans become strangulated by ongoing pancreatic fibrosis, resulting in CF-related diabetes. In this condition, release of insufficient amounts of insulin results in postprandial hyperglycemia, which may be precipitated by stresses such as pregnancy, treatment with corticosteroids, or pulmonary exacerbations. Because both insulin and glucagon are suppressed, diabetic ketoacidosis is rare. Management with short-acting insulin rather than with caloric restriction is needed to avoid worsening malnutrition. Recognition of and treatment for CF-related diabetes is important because of the association of poor diabetic control with neutrophil dysfunction, malnutrition, and risk for mortality.

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American Board of Pediatrics Content Specification(s):

Know the long-term outcome and survival of infants with various congenital abnormalities

Understand the clinical manifestations and pathophysiology of cystic fibrosis in the newborn infant

Understand the diagnosis of cystic fibrosis in newborn infants

Understand the disorders for which molecular genetic studies are clinically indicated, such as cystic fibrosis

Know the recurrence risks of various single-gene disorders

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September: Question 8

A 4-week-old male infant born at 34 weeks' gestation is admitted to the hospital with moderate respiratory distress. Upon admission, the infant's oxygen saturation in room air is 85%. He is afebrile with a respiratory rate of 75 breaths per minute. His physical examination is significant for copious yellow nasal secretions, moderate retractions, nasal flaring, and expiratory wheezing. Cardiorespiratory monitoring documents two spells of apnea. A chest radiograph displays hyperinflation with perihilar infiltrates. As the examining physician, you suspect a diagnosis of respiratory syncytial virus infection.

Of the following, the indicator MOST preferred to diagnose respiratory syncytial virus infection in this infant is:

1	confirmation by polymerase chain reaction
2	detection of viral antigens
3	elevation of serum antibodies
4	identification of viral ribonucleic acid
5	isolation of the virus by culture

You selected 5, the correct answer is 2.

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The infant in this vignette has classic manifestations of respiratory syncytial virus (RSV) infection. While a presumptive diagnosis of RSV infection is acceptable in the outpatient setting, hospitalized infants usually require a definitive diagnosis because isolation of RSV-infected patients will prevent viral spread to other hospitalized patients. Large amounts of the virus are found in the respiratory droplets of infected individuals, therefore the use of nasopharyngeal secretions is ideal for confirmation of RSV infection. If this cannot be obtained, a nasopharyngeal or throat swab can also be used. Tracheal aspirate or bronchiolar lavage fluid samples from intubated patients can also be analyzed for RSV.

CONTENT SPECIFICATIONS ADDRESSED ABP American Board of Pediatrics

Most clinical laboratories use antigen detection assays to diagnose RSV infection. These assays are rapid and include immunofluorescent or enzyme immunoassay techniques. They are reliable and accurate, offering specificity and sensitivity in the 80% to 95% range. Results are reported within a few hours. Antigen detection assays are currently the preferred method to diagnose RSV infection.

Although detection of RSV by polymerase chain reaction (PCR) is possible, it is not available commercially. In the future, multiplex reverse transcriptase PCR technology may enable the diagnosis of multiple simultaneous respiratory pathogens.

Serum antibody levels may not be reliable to diagnose RSV infection because of the presence of maternal RSV antibodies that were passed to the infant during pregnancy; this explains the low sensitivity of serologic diagnosis among young infants. Even in adults, serum antibodies often are not diagnostic because repeated infections lead to a stable and sustained RSV-specific antibody level.

Respiratory syncytial virus genomic ribonucleic acid has recently been identified in the laboratory using fluorescent oligonucleotide probes. Because these probes can attach to the live virus, it is possible to visualize the virus as it replicates and infects cells. In the future this technology may assist in the early diagnosis of RSV infection, perhaps before the development of any symptoms.

Respiratory syncytial virus can also be identified with plaque morphology with syncytium formation in culture. While this viral culture provides a definitive diagnosis, RSV isolation requires between 4 and 14 days. Because RSV is a labile virus, the culture sensitivity may vary. For these reasons, isolation of RSV by culture is not the preferred method for diagnosing RSV infection.

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References:

American Academy of Pediatrics. Respiratory syncytial virus. In: Pickering LK, ed. *Red Book: 2006 Report of the Committee on Infectious Diseases.* 26th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2006:560-566. November 6, 2007, at: http://aapredbook.aappublications.org/cgi/content/full/2006/1/3.107

Barr FE, Graham BS. Clinical features and diagnosis of respiratory syncytial virus infection. UpToDate.com Web site. Accessed November 6, 2007, at: http://www.uptodateonline.com/utd/content/topic.do?topicKey=pedi_id/20617&selected= (subscription required)

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Santangelo PJ, Bao G. Dynamics of filamentous viral RNPs prior to egress. *Nucleic Acids Res.* 2007;35:3602-3611

American Board of Pediatrics Content Specification(s):

Understand the clinical manifestations and diagnostic criteria of neonatal infections with respiratory syncytial virus

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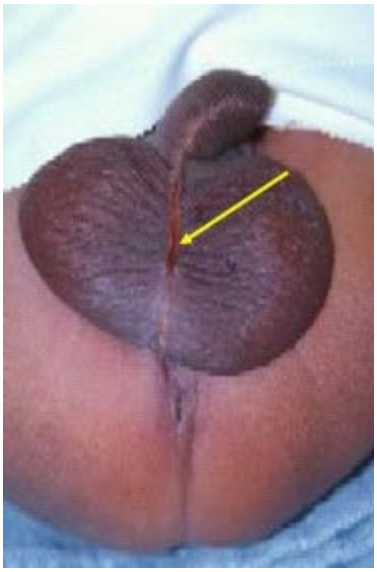
September: Question 9

You are called in to evaluate a full-term newborn. The mother's pregnancy and delivery were uncomplicated. During your examination of the rectum and genitalia you note the abnormalities shown in Figure 1 (courtesy of Casey Calkins, MD, Milwaukee, Wis).

Figure 1



The infant's physical examination findings are normal. You observe meconium coming from the base of the scrotum (Figure 1, Arrow). A red rubber catheter placed in the rectal opening can only be advanced 0.5 cm. You discuss evaluation plans with the infant's parents and the importance of quickly determining the reason for meconium leaking from the scrotum.

Of the following, the INITIAL diagnostic study in this infant would be:

1	abdominal ultrasonography
2	contrast enema
3	spinal magnetic resonance imaging
4	upper gastrointestinal series
5	voiding cystourethrography

You selected 1, the correct answer is 1.

Do you want to add anything to your Learning Plan?
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The neonate in the vignette has an imperforate anus, a malformation that varies widely in

appearance. Imperforate anus occurs in 1 of 4,000 to 5,000 live births and is slightly more common among male infants. Recurrence risk in families with an isolated case is approximately 1%. Imperforate anus may occur as part of a genetic syndrome or as a sporadic abnormality.

More than 80% of boys with an imperforate anus have a fistula that connects the rectum to the bladder (rectovesical), the prostatic urethra (rectoprostatic), or bulbar urethra (rectobulbar) of the urinary tract. If the fistula opens onto the skin along the midline raphe, as it did in the infant in the vignette, it is called a perineal fistula. In the infant, the lowest aspect of the rectum opens along the midline raphe (Figure 1, Arrow) anterior to the center of the external sphincter. The more proximal aspect of the rectum remains within the sphincter muscles. The perineal fistula can be located anywhere along the midline raphe. In fewer than 5% of neonates with an imperforate anus the rectum ends in a blind pouch without a fistula, and 50% of these infants have Down syndrome.

Three variants of imperforate anus are seen in females: perineal fistula, vestibular fistula, and a cloaca. The rectum opens on the skin anterior to the anal dimple in the perineal fistula variant and the posterior aspect of the introitus outside the hymen in the vestibular fistula variant. A cloaca is a congenital anomaly in which the rectum, vagina, and urethra open into a common channel of variable length.

Although certain associated defects may require urgent treatment, most cases of imperforate anus do not require immediate surgical repair. Managing life-threatening complications caused by associated anomalies and determining whether a diverting colostomy is required are two issues that need to be addressed during the initial evaluation. The initial evaluation and management of a neonate with an imperforate anus generally includes an abdominal and pelvic ultrasound, a radiograph of the spine including anteroposterior and lateral views of the sacrum, a cardiac evaluation, and insertion of a nasogastric tube (Figures 2 and 3). Subsequent evaluation and management vary based on the infant's sex.

Figure 2: Male neonate with an anorectal malformation (adapted from *Principles and Practice of Pediatric Surgery* [2005])

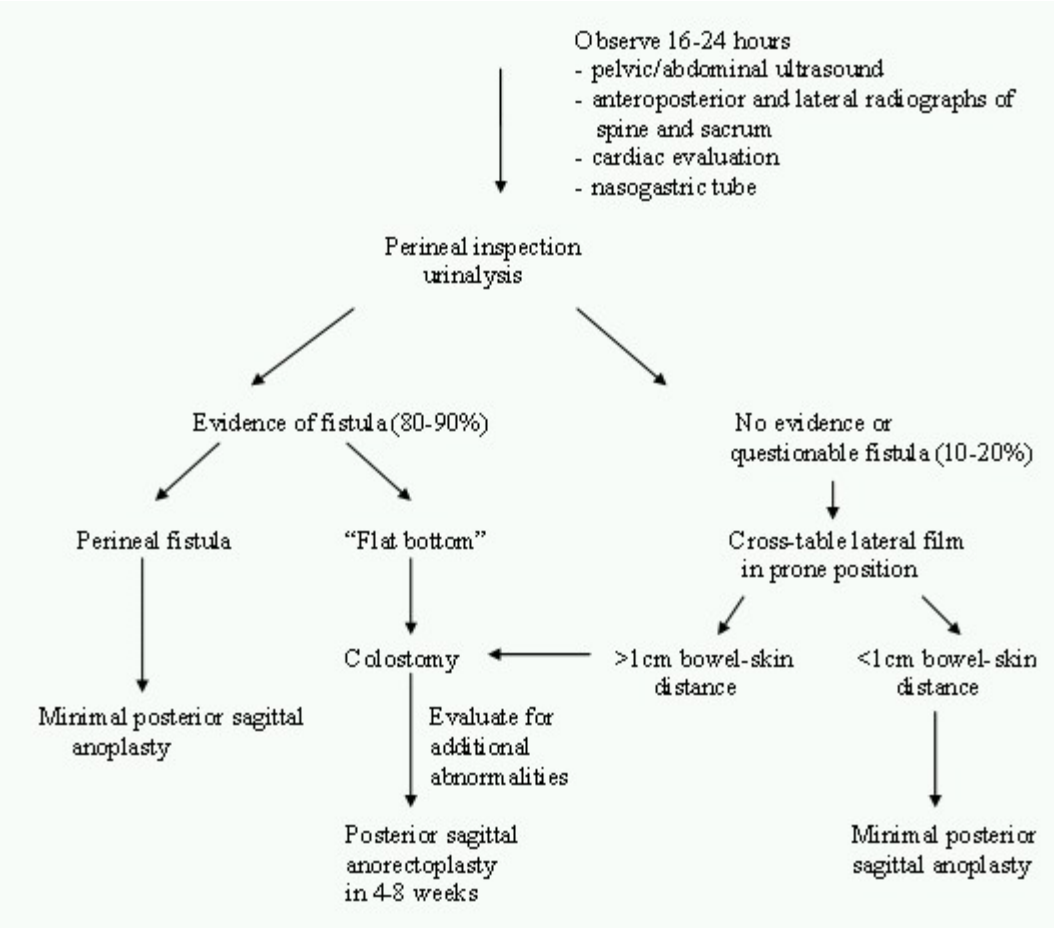
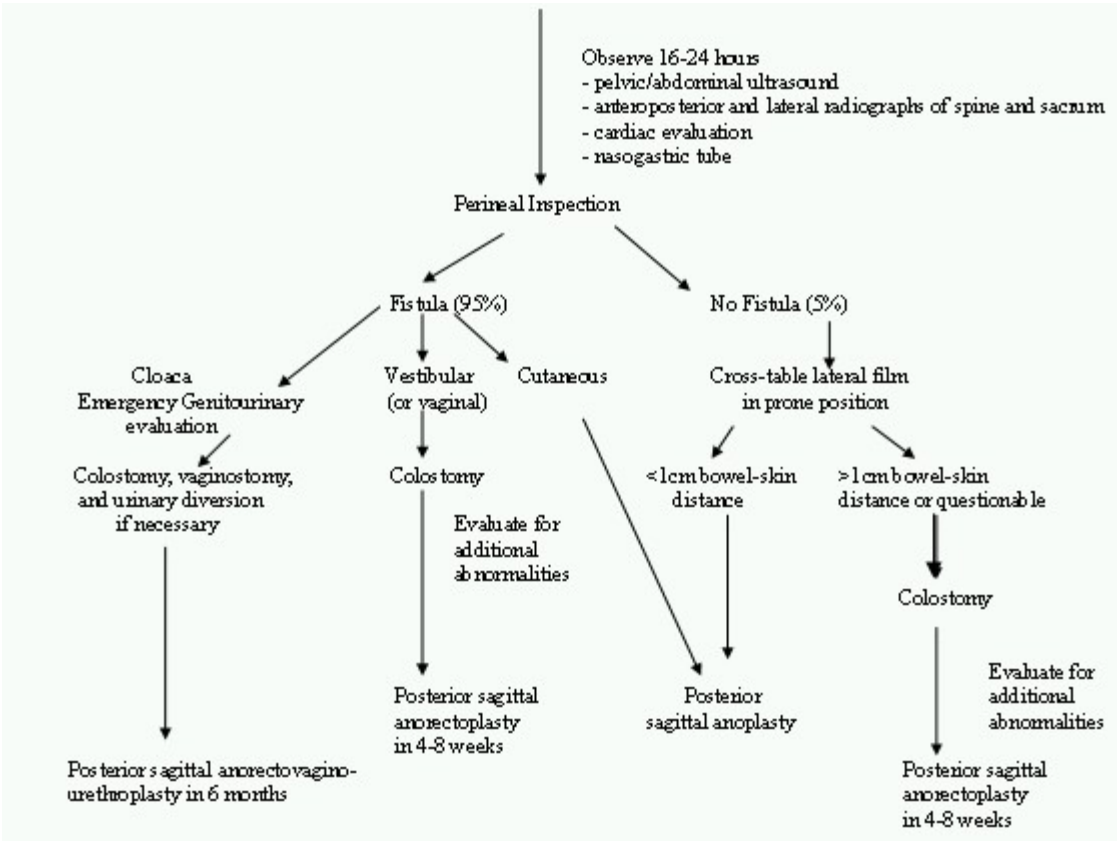


Figure 3: Female neonate with an anorectal malformation (adapted from *Principles and Practice of Pediatric Surgery* [2005])



The arrested migration of the mesoderm in the caudal eminence and abnormal resorption of the cloacal membrane are likely embryologic causes of the imperforate anus; therefore, other tissues derived from mesoderm can also be affected. The tissues derived from the paraxial and lateral mesoderm plate include the genitourinary, skeletal, muscular, and gastrointestinal system. Among neonates with imperforate anus, 22% to 72% have associated malformations, the most common of which are genitourinary malformations. Genitourinary malformations occur in 20% to 54% of cases and may include the following:

- **absent, dysplastic, or horseshoe kidneys**
- **hydronephrosis**
- **hypospadias**
- **bifid scrotum**

Fewer than 10% of neonates with perineal fistulas, as present in the infant in the vignette, have genitourinary anomalies. In contrast, 90% of infants with high fistulas (cloaca, rectobladder) have associated genitourinary anomalies compared with 30% of cases with lower fistulas (rectourethral, rectovestibular). Abdominal ultrasonography performed during the initial evaluation (Figures 2 and 3) will help identify genitourinary abnormalities, which may alter management. Voiding cystourethrography may be reserved for those infants in whom hydronephrosis is identified on ultrasonography.

Gastrointestinal malformations associated with imperforate anus may include the following:

- **esophogeal atresia**
- **duodenal atresia**
- **Hirschsprung disease**

Gastrointestinal anomalies may occur independently or as part of the VACTERL association. If a nasogastric tube can be passed into the stomach, the common forms of esophogeal atresia are absent. In the absence of bilious emesis or an abnormal abdominal radiograph, a contrast study of the upper gastrointestinal tract is not indicated during the initial evaluation (Figures 2 and 3). Although Hirschsprung disease may occur with imperforate anus, it is rare, especially among neonates with low fistulas. A biopsy can be performed at the time of definitive repair or during colostomy if Hirschsprung disease is suspected. A contrast study of the lower intestinal tract to outline the fistula is not necessary during the initial management of a male infant with imperforate anus.

Infants with imperforate anus with a high fistula have a higher risk of vertebral anomalies. Examples of the types of vertebral anomalies that are found include the following:

- **partial or complete lumbosacral agenesis**
- **hemivertebrae**
- **agenesis of thoracic vertebrae**
- **scoliosis**
- **hemisacrum or scimitar sacrum**
- **asymmetric sacrum**
- **posterior protruding sacrum**
- **agenesis of the coccyx**

Sacral abnormalities occur in as many as 45% of neonates with imperforate anus. The severity of the sacral anomaly is correlated with the prognosis for bowel and bladder function. If two or more sacral vertebrae are missing, the prognosis is poor for normal bowel and bladder function following repair.

At least one study reported a 38% incidence of spinal cord abnormalities among infants with anal-rectal malformations. Approximately 25% of cases of imperforate anus are associated with a tethered cord. Spinal cord abnormalities associated with imperforate anus include the following:

- **tethered cord**
- **dural sac stenosis**
- **narrow spinal canal**

diastemeningocele, meningocele
- intraspinal teratoma
- neurogenic bladder

Spinal cord abnormalities are also more common among neonates with high fistulas. A lumbosacral spine evaluation with plain radiographs will help delineate skeletal abnormalities. Pelvic ultrasonography is most often performed in infants younger than 3 months of age, especially those with low fistulas, to detect abnormalities of the vertebrae, spinal cord, or canal. Spinal magnetic resonance imaging (MRI) is recommended in neonates with complex defects, myelodysplasia, cloacal exstrophy, or abnormal sacral anatomy. An MRI should also be considered in an infant with a bladder fistula, a presacral mass, hemivertebrae, or a genitourinary anomaly. MRI is rarely required as part of the initial evaluation unless ultrasound or spine radiographs are abnormal.

Other rare syndromes are associated with imperforate anus. For example, cat eye syndrome, associated with trisomy or tetrasomy 22pter?q11, presents with anal atresia and ocular coloboma. Ophthalmology consultation may be warranted.

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American Board of Pediatrics Content Specification(s):

Understand the embryology of rectal and anal malformations and associated anomalies

Understand the diagnosis of rectal and anal malformations and associated anomalies

Understand the management of rectal and anal malformations and associated anomalies

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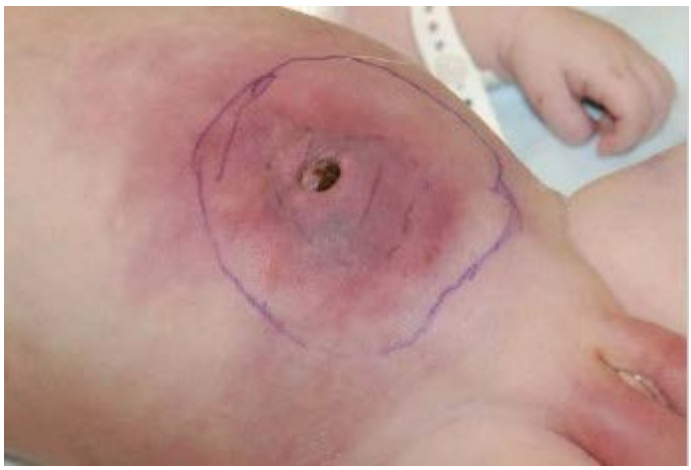
September: Question 10

You attend the cesarean delivery of a 34-week-gestation boy for a nonreassuring fetal heart rate pattern. The amniotic fluid is foul-smelling. Blood cultures are obtained and the child is treated with ampicillin and gentamicin. The complete blood count at birth is normal, cultures remain negative, and antibiotics are stopped 48 hours after birth. He looks well, does not need mechanical respiratory support, and easily tolerates increasing feeding volumes. On the sixth day, his condition deteriorates and he exhibits a purulent discharge with redness for several centimeters around the base of the umbilical cord (Figure 1).

Figure 1: Omphalitis in a neonate (from Evered and Anderson [2007])



Cultures of the purulent material, the blood, and the cerebral spinal fluid grow mixed flora that include a *Bacteroides* species.

Of the following, the antibiotic to which *Bacteroides* is MOST likely to be sensitive is:

1	ampicillin
2	clindamycin
3	gentamicin
4	metronidazole
5	vancomycin

You selected 4, the correct answer is 4.

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Omphalitis is a serious but rare skin manifestation of a *Bacteroides* infection in the neonate. Other serious infections with *Bacteroides* are also rare, including pneumonia, meningitis,

peritonitis, and endocarditis. Infections with *Bacteroides* are often polymicrobial, necessitating multiple antibiotics. Antibiotic regimens often include drugs, such as gentamicin, directed not at *Bacteroides* but at the facultative anaerobes that facilitate the proliferation of *Bacteroides*. *Bacteroides* species of the lower gastrointestinal tract, the group of *Bacteroides* most often associated with omphalitis, are regularly resistant to many antibiotics. Of the antibiotics listed, metronidazole is most likely to be effective.

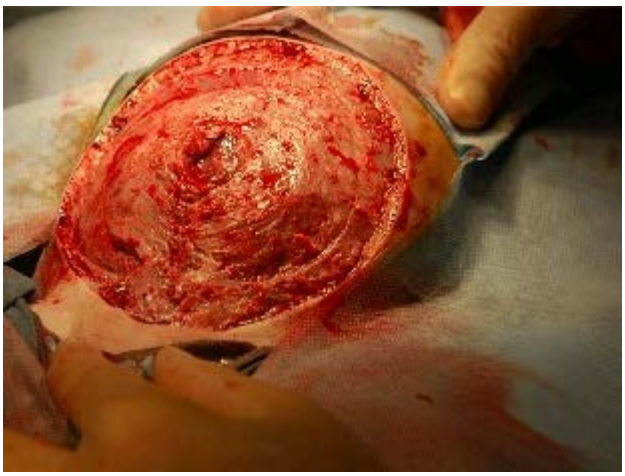
Omphalitis in the neonate is polymicrobial in approximately three-quarters of cases. The organisms most commonly responsible are *Staphylococcus, Streptococcus, Escherichia coli, Klebsiella,* and *Clostridium.*

Bacteroides comprises a group of anaerobic gram-negative pleomorphic rods that are part of the normal flora of the respiratory, gastrointestinal, and genitourinary tracts. *Bacteroides fragilis* is found in human stool at a concentration of 10^{11} per gram, compared with 10^{8} per gram for the facultative anaerobes such as *Escherichia coli*. Although some early studies found that up to 20% of all cases of significant bacteremia were caused by *Bacteroides* or other anaerobes, more recent studies suggest their involvement in only 2% to 6% of cases of bacteremia. In neonates, possible sites of *Bacteroides* infection include the oral cavity, respiratory tract, skin, conjunctivae, heart valves, meninges, peritoneum, and gastrointestinal tract including the liver.

Bacteroides infections are different from other gram-negative infections. The cell-wall lipopolysaccharide of *Bacteroides* has little endotoxin activity and so does not immediately cause the fever and shock that is typical of other gram-negative organisms. The reliance on mixed fermentation for energy results in short-chain fatty-acid products and a foul-smelling discharge. *Bacteroides* can survive in oxygen because of its production of superoxide dismutase, but it does better in the presence of facultative anaerobes that can use up all available oxygen. In this way, *Bacteroides* thrives in mixed infections such as peritonitis after bowel injury. The difficulty in performing cultures of anaerobic specimens often leads to a delay in treatment and a high mortality rate; one study found a *Bacteroides fragilis* mortality rate of 34%. Rapid tests, such as fluorescent in-situ hybridization, are in the realm of the research laboratory.

Treatment of *Bacteroides* infections often involves surgical drainage or débridement (Figure 2) in combination with antibiotics.

Figure 2: Débridement of omphalitis (from Evered and Anderson [2007])



Gentamicin is not effective against *Bacteroides*, but is often included in treatment regimens to eliminate the facultative anaerobes such as *Escherichia coli* that help produce and maintain an anaerobic environment. Ampicillin is useful for some infections with anaerobes, such as sinusitis or pneumonia, but not for *Bacteroides*, which often produce beta-lactamase. Vancomycin resistance is one of the defining traits of the genus.

Drugs effective against *Bacteroides* include clindamycin, chloramphenicol, metronidazole, imipenem, and ampicillin-clavulinate. *Bacteroides* isolates are clindamycin-resistant about 10% of the time. Metronidazole resistance is rare.

Anaerobes such as *Bacteroides* species are also found in the mixed flora of bacterial vaginosis. Bacterial vaginosis occurs in 10% to 25% of pregnancies, and is a risk factor for preterm birth. Bacterial vaginosis responds best to regimens that include antianaerobe antibiotics such as metronidazole and clindamycin. The use of antibiotics to treat bacterial vaginosis and prevent preterm birth has been examined using randomized controlled trials, with inconsistent results.

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American Board of Pediatrics Content Specification(s):

Understand the epidemiology, pathogenesis, and prevention of perinatal *Bacteroides* infections

Understand the clinical manifestations, diagnostic criteria, treatment, and complications of perinatal *Bacteroides* infections

Understand the causes and differential diagnosis of omphalitis

Understand the clinical and laboratory features, treatment and complications of neonatal omphalitis

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October: Question 1

A pregnant woman at 39 weeks' gestation feels uterine contractions every 4 minutes. As you wait for the delivery, you are reviewing with the obstetrician the hormonal responses during labor.

Of the following, induction of labor in this woman is MOST likely to occur by suppressing the function of:

1	corticotropin-releasing hormone
2	estrogen
3	oxytocin
4	progesterone
5	prostaglandins

You selected 5, the correct answer is 4.

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During parturition, the uterus must change from a relaxed to a powerful rhythmic contractile muscle. Removal of mechanisms that maintain uterine quiescence and recruitment of factors that promote uterine contractility mediate this transition. As the fetus grows and uterine enlargement ceases at the end of the third trimester, the increasing tension on the uterine wall also contributes to the onset of parturition. In addition, inflammatory cytokines entering the cervix and metalloproteases degrading the cervical collagen contribute to cervical ripening. Understanding the complex pathways involved in human parturition has been complicated by a lack of an animal model, because animals have significant mechanistic differences of labor compared with humans. Indeed, we are only recently beginning to understand the intricate hormonal influences on human labor. The precise molecular signals that trigger these hormonal changes are still unknown, but are probably mediated by fetal, placental, and maternal pathways.

During pregnancy progesterone maintains the uterus in a relaxed state. A withdrawal of progesterone function is essential for inducing labor in the woman in this vignette. Because circulating progesterone concentrations remain stable during labor, the functional suppression of progesterone is probably mediated by decreases in progesterone receptors as labor begins. In addition, progesterone receptor coactivators decrease with the onset of labor, perhaps further attenuating progesterone function. By limiting progesterone function, uterine myocyte attachment to the intercellular matrix increases, leading to an activation of mitogen-associated protein kinases and uterine contractility. The consequence of progesterone withdrawal is evident by the effect of administering the progesterone antagonist mifepristone, also known as RU-486, which can induce labor at any

time during pregnancy.

Increasing maternal plasma corticotropin-releasing hormone (CRH) concentrations are strongly associated with the timing of delivery; CRH concentrations increase exponentially with advancing gestation and peak at the time of delivery. CRH is produced by the placenta and incites the maternal and fetal pituitary glands to release corticotropin, leading to the release of cortisol from the maternal and fetal adrenal glands. Increased cortisol concentrations stimulate further CRH production by the placenta; this continuous positive feedback creates an exponential rise in CRH production. Cumulatively, these hormonal increases lead to fetal lung maturation and a change in amniotic fluid proteins, phospholipids, and myometrial receptor expression, which help to precipitate labor and delivery. In addition, CRH influences other hormones involved in parturition by enhancing the estrogen effects on the uterus; increasing prostaglandin production by the amnion, chorion, and decidua; and potentiating the oxytocin effect on the uterus.

Estrogens contribute to human parturition by increasing the strength of uterine contractions. This effect is mediated by estrogen-induced upregulation of myometrial gap junctions and uterotonic receptors. Not surprisingly, circulating maternal estrogen concentrations increase before the onset of labor.

Oxytocin is a potent inducer of uterine contractility. While maternal serum oxytocin concentrations remain stable during parturition, uterine oxytocin receptors increase 300-fold. Evidence suggests that the effects of oxytocin may be mediated by increased myometrial calcium and/or a greater sensitivity of the myometrium to intracellular calcium. In addition, in vitro data suggest that oxytocin stimulates the production of prostaglandin F_{2a} , leading to further myometrial contractility.

Concentrations of E and F prostaglandins in amniotic fluid and maternal plasma and urine increase before the onset of labor. Prostaglandins play a central role in synchronizing uterine contractions, ripening the cervix, and increasing the myometrial sensitivity to oxytocin. Whereas prostaglandin F_{2a} is thought to be important in initiating uterine contractility, prostaglandin E_2 seems to play an important role in cervical ripening and rupture of fetal membranes.

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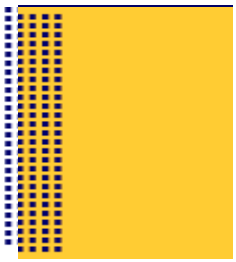
American Board of Pediatrics Content Specification(s):

Understand the physiologic and molecular biological characteristics of normal parturition

Understand the physiological and molecular biological characteristics of normal labor



Understand the effects of normal labor on uteroplacental physiology and its effects on the fetus

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October: Question 2

A 3-day-old female infant, whose birthweight was 680 g at an estimated gestational age of 24 weeks, has the following laboratory data:

Laboratory Data	Patient Results (SI Values)
Arterial blood gas measurements	
pH	7.22
Partial pressure of oxygen, mm Hg (kPa)	78 (10.4)
Partial pressure of carbon dioxide, mm Hg (kPa)	44 (5.9)
Base deficit, mEq/L (mmol/L)	10 (10)
Serum electrolytes	
Sodium, mEq/L (mmol/L)	135 (135)
Potassium, mEq/L (mmol/L)	4.9 (4.9)
Choride, mEq/L (mmol/L)	111 (111)
Bicarbonate, mEq/L (mmol/L)	17 (17)

The infant is breathing spontaneously in a fraction of inspired oxygen of 0.30 and has received no methylxanthines, indomethacin, or diuretics. She is receiving trophic enteral feeds of expressed breast milk at 8 mL/kg per day and supplemental parenteral nutrition for a total fluid intake of 130 mL/kg per day. Urine measurements are: output 72 mL/kg per day, pH 7.6, and glucose ++.

Of the following, the PRINCIPAL site of developmental immaturity in the nephron in this infant is:

1	collecting duct
2	distal tubule
3	glomerulus
4	loop of Henle
5	proximal tubule

You selected 5, the correct answer is 5.

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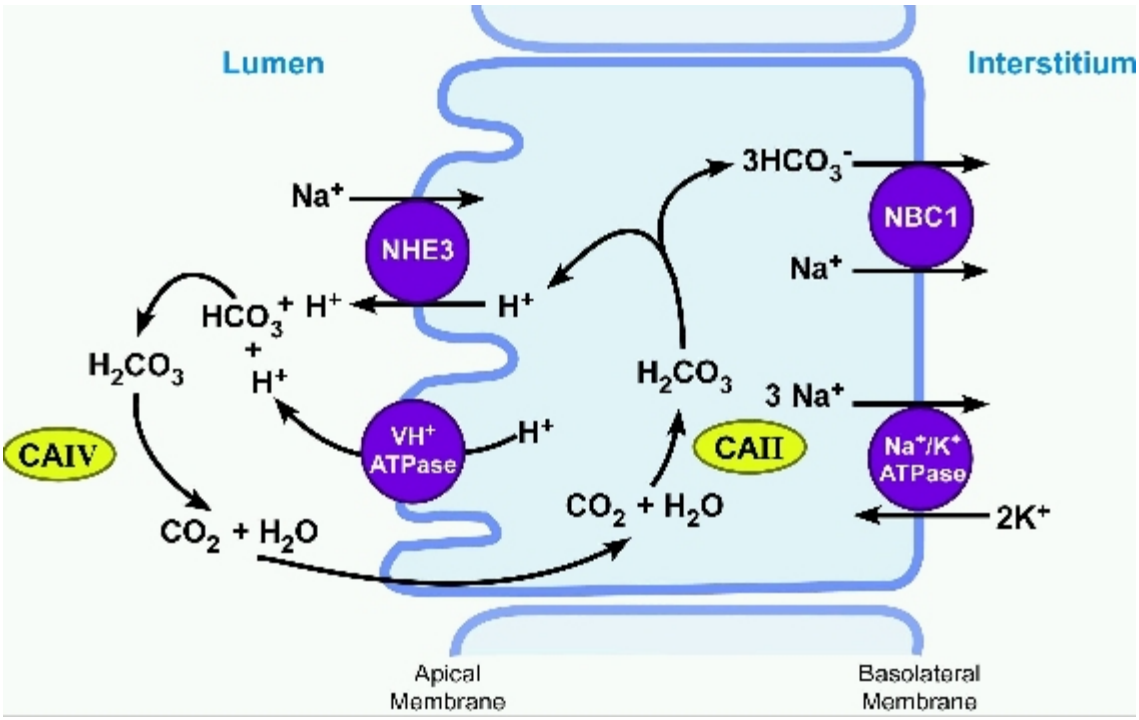
The extremely preterm infant in this vignette has evidence of metabolic acidosis. The major renal contributor to metabolic acidosis is immaturity of the proximal tubule, which results in urinary loss of bicarbonate, glucose, phosphate, and amino acids. Other contributors to metabolic acidosis include exogenous intake of acid largely from arginine and cysteine in parenteral nutrition and inadequate intake of base equivalents from enteral milk feeding. Pathologic causes of metabolic acidosis include patent ductus arteriosus, dehydration, sepsis,

hypoxemia, intraventricular hemorrhage, anemia, shock, gastrointestinal losses, and metabolic disorders such as cystinuria, tyrosinemia, galactosemia, and fructose intolerance.

The principal site of developmental immaturity in the nephron as a cause of metabolic acidosis in this infant is the proximal tubule. Cells of the proximal tubule absorb sodium via an apical membrane Na^+/H^+ antiporter (NHE3) (Figure 1).

Figure 1: Proximal tubule cell: acid-base homeostasis



The action of this antiporter, coupled with that of another apical membrane vacuolar H^+ATPase, results in extrusion of H^+ into the lumen of the proximal tubule. An apical membrane enzyme, carbonic anhydrase IV, catalyzes the conversion of extruded H^+ and filtered HCO_3^- into H_2CO_3, and further into CO_2 and H_2O. The latter diffuse into the proximal tubule cell, where a cytosolic enzyme, carbonic anhydrase II, catalyzes the reconversion of CO_2 and H_2O into H_2CO_3, and further into H^+ and HCO_3^-. The H^+ is extruded into the lumen as mentioned before, whereas the HCO_3^- is transferred across the basolateral membrane into the interstitium via a Na^+/HCO_3^- cotransporter (NBC1).

Immaturity of the proximal tubule accounts for impaired excretion of H^+ in the form of phosphate-buffered titratable acid and through generation of ammonium. This defect in urinary acidification frequently is accompanied by impaired absorption of electrolytes (sodium, potassium, chloride), minerals (calcium, phosphate), and nutrients (glucose, lactate, amino acids). The urinary acidification improves with advancing gestational and postnatal age.

The glomerular filtration rate (GFR), as measured by inulin clearance studies in the human infant, is low at birth, especially in preterm neonates. It is estimated at 13 mL/min per 1.73 m^2 surface area at gestational age of 28 weeks and at 20 mL/min per 1.73 m^2 at term. The GFR increases rapidly in the first month after birth to values estimated at 27 mL/min per 1.73 m^2 in the preterm neonate and at 42 mL/min per 1.73 m^2 in the term infant. This postnatal increase in GFR is attributed to:

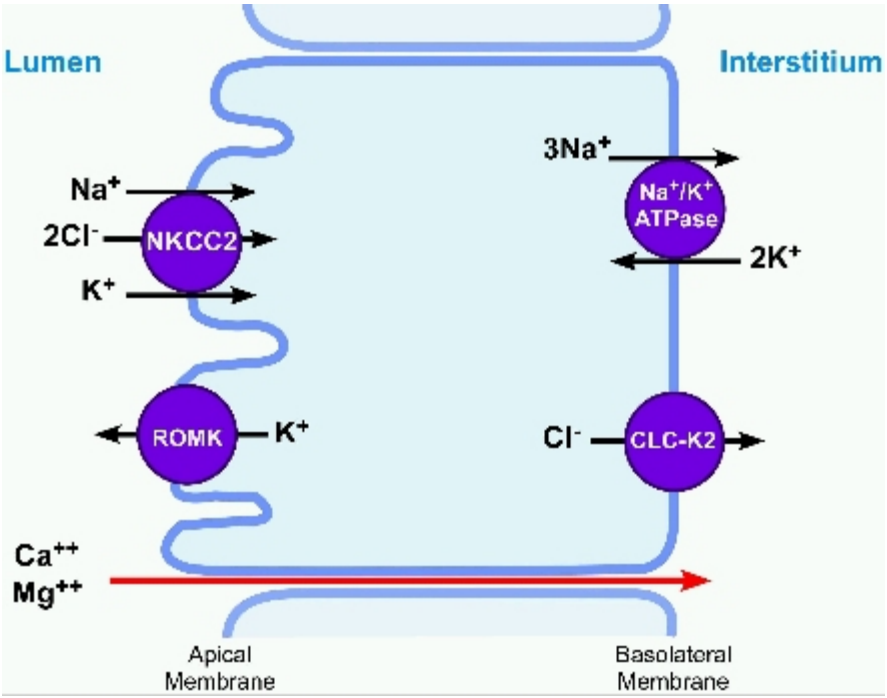
- **decrease in renal vascular resistance and consequent increase in renal blood flow**

- **increase in systemic blood pressure and consequent increase in glomerular capillary hydrostatic pressure, and**
- **increase in filtration coefficient associated with an increase in both glomerular basement membrane surface area and permeability**

Immaturity of the glomerular function by itself is not a common cause of metabolic acidosis. However, under pathologic conditions such as hypoxemia, ischemia, hypovolemia, hypotension, ventilation abnormalities, and renal failure, the impaired glomerular function can contribute to metabolic acidosis.

Cells of the medullary thick ascending loop of Henle absorb sodium via an apical membrane $Na^+/K^+/2Cl^-$ transporter (NKCC2) (Figure 2).

Figure 2: Loop of Henle cell: calcium and magnesium absorption

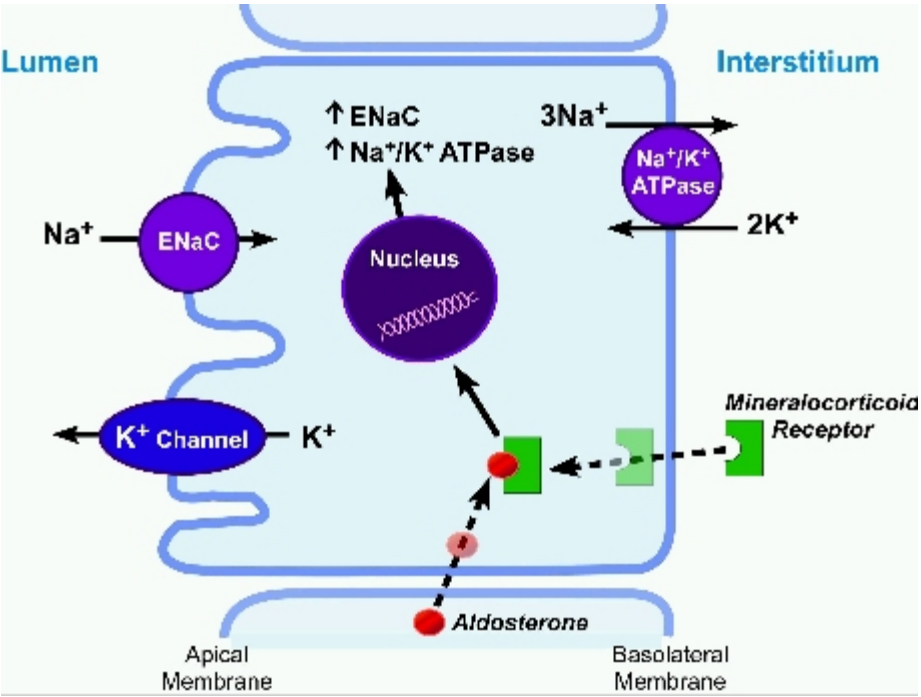


The sodium is then transported across the basolateral membrane into the interstitium via the Na^+/K^+ ATPase. The chloride is transported from the cytosol into the interstitium via a basolateral Cl^- channel (CLC-K2). The potassium is recycled primarily into the urinary space via a lumenal K+ channel (ROMK). The combined activities of apical ROMK and basolateral CLC-K2 result in a lumen-positive transepithelial potential difference that drives paracellular absorption of cations, principally calcium and magnesium. Immaturity of the loop of Henle accounts for impaired absorption and consequent urinary loss of calcium and magnesium.

The distal tubule, in conjunction with the collecting duct, is important for water homeostasis. When the water intake is low and/or the water loss is excessive, the permeability of the distal tubule under the influence of arginine vasopressin from the posterior pituitary is increased, thereby promoting reabsorption of water. Conversely, when the water intake is high and/or the water loss is decreased, the distal tubule remains impermeable to water, thereby inhibiting reabsorption of water. Immaturity of the distal tubule accounts for impaired water homeostasis.

Cells of the collecting duct absorb sodium via an apical membrane Na^+ channel (ENaC) (Figure 3).

Figure 3: Collecting duct cell: sodium-potassium exchange



The sodium is then transported across the basolateral membrane into the interstitium via the Na^+/K^+ ATPase. In addition, collecting duct cells express an apical membrane K^+ channel that allows potassium to exit from the cells into the lumen of the nephron. Both sodium absorption and potassium excretion are closely linked and reciprocal. The ENaC expression is modulated by aldosterone, an adrenal mineralocorticosteroid hormone. The aldosterone binds to the mineralocorticoid receptor, which then increases the nuclear transcription of both ENaC and Na^+/K^+ ATPase. The resultant effect is increased renal absorption of sodium and renal excretion of potassium. Immaturity of the collecting duct accounts for potassium retention and resultant hyperkalemia. Nonoliguric hyperkalemia is observed in 30% to 50% of extremely preterm neonates, particularly in the first 48 to 72 hours after birth.

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American Board of Pediatrics Content Specification(s):

Know the changes in glomerular and tubular function that occur during development, including the handling of glucose, sodium, potassium, calcium, and phosphate

Understand the etiology of metabolic acidosis and metabolic alkalosis in infants

Recognize the clinical and laboratory manifestations of metabolic acidosis and metabolic alkalosis in infants

Recognize the causes, diagnosis, and treatment of renal tubular acidosis in the neonate

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11 November 08

12 December 08

October: Question 3

A 35-day-old male infant, whose gestational age at birth was 29 weeks, is being treated in your nursery. His birthweight was 780 g (<10th percentile), length was 38 cm (50th percentile), and occipital-frontal circumference was 28 cm (75th percentile). The infant has had an uncomplicated course other than respiratory distress requiring continuous positive airway pressure for 1 day. Currently, he has occasional apnea and is receiving enteral nutrition through an orogastric tube. You are meeting with the infant's parents who are interested in knowing what the long-term implications of low birthweight are for such infants.

Of the following, the problem this infant is MOST likely to have when he reaches adulthood is:

1	attention deficit disorder
2	hypoglycemia
3	internalizing behaviors
4 (selected)	systemic hypotension
5	tall stature

You selected 4, the correct answer is 1.

Important developmental priorities during adolescence and adulthood include socialization, individuation from peers, abstract thought, emancipation, and career-building. Infants born small and/or preterm may have behavioral, medical, and cognitive disorders that can impede such developmental transitions and complicate the health of individuals through the adult years of life.

Attention deficit/hyperactivity disorder (ADHD) is observed in about 20% of individuals born with a low birthweight (LBW), preterm, or with intrauterine growth restriction (IUGR). Attention deficit is the most frequent abnormal psychiatric outcome for such infants and because symptoms only abate in 30% to 70% of individuals by adulthood, a significant number of adult lives may be affected. For comparison, the prevalence of ADHD in normal birthweight individuals is 6% to 7% during late childhood. Internalizing behaviors (such as anxiety, depression, withdrawal, somatic concerns) and externalizing behaviors (such as delinquency, aggressiveness) are less prevalent than ADHD in LBW and preterm infants.

The relative risk of ADHD in very-low-birthweight infants (<1,500 g) such as the infant in this vignette is 2.64 (95% confidence intervals [CI] 1.85-3.78) compared with controls. In moderately LBW individuals (1,500-2,500 g), the risk of ADHD is also significantly increased (odds ratio 1.8 [95% CI 1.08-2.9]). Other conditions during infancy associated with ADHD are shown in Table 1.

Table 1. Conditions Associated with Attention Deficit/Hyperactivity Disorder*
Low birthweight
Prematurity
Birth complications
Prenatal alcohol or drug use
Meningitis/encephalitis
Central nervous system trauma
Cyanotic congenital heart disease
Genetic disorders
Syndromes: Turner, Klinefelter, Fragile X, Williams
Neurofibromatosis type 1
Inborn errors of metabolism

* Adapted from Worley and Wolraich (2005).

Preterm and LBW individuals have a relative preponderance of inattention problems (such as poor concentration, distractibility, forgetfulness, disorganization, slow mental processing) in contrast to other individuals with ADHD in whom hyperactive behaviors are predominant. Rather than flitting from one activity to the next, adults are more likely to be fidgety, restless, speak excessively, or blurt out inappropriate comments. Such symptoms underlie difficulties with academic achievement, poor work performance, risk-taking behaviors (such as drug use, criminal activity), driving problems, and relational discord.

Males are more frequently reported to be affected by ADHD (some estimates as high as 12:1) than females. Such reports likely overestimate the male preponderance because male patients, with their hyperactivity and impulsivity symptoms, are identified more readily than females, who are affected more often by inattention.

The following three major subtypes of ADHD have been identified:

- **inattentive type**
- **hyperactive-impulsive type**
- **combined type (inattention and hyperactivity-impulsivity)**

The diagnosis of ADHD requires a thorough neuropsychologic and medical evaluation; interviews with parents, teachers, and colleagues; physical examination; and behavior rating scales. The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) developed by the American Psychiatric Association lists the diagnostic criteria for ADHD (Table 2).

Table 2. DSM-IV Diagnostic Criteria for Attention-Deficit/Hyperactivity Disorder
Either 1 or 2
1. Six, or more, of the following symptoms of inattention have persisted for at least 6 months and the patient is maladaptive, with behavior inconsistent with developmental level
• often fails to give close attention to details or makes careless mistakes in school work, work, or other activities
• often has difficulty sustaining attention in tasks or play activities
• often does not seem to listen when spoken to directly
• often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not related to oppositional behavior or failure to understand instructions)
• often has difficulty organizing tasks and activities
• often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
• often loses things necessary for tasks or activities (eg, toys, school assignments, pencils, books, or tools)
• is often easily distracted by extraneous stimuli
• is often forgetful in daily activities
2 Six, or more, of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months and the patient is maladaptive, with behavior inconsistent with developmental level
• Hyperactivity:
o often fidgets with hands or feet or squirms in seat
o often leaves seat in classroom or in other situations in which remaining seated is expected
o often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
o often has difficulty playing or engaging in leisure activities quietly
o is often "on the go" or often acts as if "driven by a motor"
o often talks excessively
• Impulsivity
o often blurts out answers before questions have been completed
o often has difficulty awaiting turn
o often interrupts or intrudes on others (eg, during conversations or games)

* Adapted from Simms (2004).

Important conditions for a diagnosis of ADHD include the following:

- **Signs of hyperactivity, impulsiveness, and inattention that caused impairment before 7 years of age**
- **Evidence of impairment in two or more settings (home, work, school)**
- **Clear evidence of impairment in social, academic, or occupational functioning**
- **Symptoms that do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder and are not better related to another mental disorder (such as mood disorder, anxiety disorder, dissociative disorder, or personality disorder)**

The causes for the heterogeneity of symptoms that comprise the diagnosis of ADHD are unclear. Although studies in twins have demonstrated the importance of genetic and environmental causes for ADHD, fetal, biochemical, and medical conditions likely contribute. Morphologic and functional brain differences have been identified including a size reduction in regions or structures important for attention: corpus callosum, basal ganglia (inhibition of automatic responses), frontal lobes (distraction filtering), and cerebellar vermis (motivation regulation).

Dopamine plays an inhibitory function in neuronal pathways that regulate attention. With insufficient dopamine concentrations in affected regions of the brain, neuronal activity will not be repressed and attention will be unmodulated. The role of dopamine in attention disorders

has been proven in studies showing stimulants to be clinically effective in increasing extracellular dopamine concentrations and in animal studies demonstrating an imbalance between dopamine and norepinephrine in the prefrontal cortex. Candidate genes critical for attention have not been identified. The dopamine D_4 receptor gene function is associated with performance on tasks assessing attention, short-term memory, and executive function but no clinical correlation with ADHD has yet been demonstrated.

Medical complications, such as asthma and cerebral palsy, often become less problematic during adolescence and adulthood. However, individuals born LBW and IUGR are at a sixfold higher risk of developing metabolic syndrome as adults than those with normal birthweight and appropriate growth (2.3% versus 0.4%, respectively). Metabolic syndrome is characterized by insulin resistance (hyperglycemia), hyperinsulinemia, visceral adiposity, dyslipidemia, and systemic hypertension. Ischemic heart disease and overt type 2 diabetes mellitus may develop. Systemic inflammation, hypercoagulability, and endothelial dysfunction are also observed in the spectrum of this disorder. The presence of ADHD along with these medical complications or other significant morbidities identified during childhood (such as mental retardation, psychiatric disorders, cerebral palsy) may compound the clinical effect on adult functioning of former preterm and small infants.

The mechanisms responsible for the metabolic syndrome in LBW and infants with IUGR likely involve fetal programming of metabolic pathways and organ development in response to limited nutrient/oxygen delivery and pathologic insults. The “thrifty phenotype” hypothesis describes in utero programming of fetal metabolic systems and physiologic adaptations in response to life-threatening maternal stress, infection, undernutrition, placental dysfunction, and exposure to alcohol and tobacco. After birth, these metabolic and physiologic adaptations become a liability during times of nutrient excess.

Growth patterns in infants with IUGR vary with the cause of the growth restriction. Infants with moderate IUGR with uncomplicated medical courses, such as the infant in this vignette, usually achieve normal height. In comparison, infants with severe IUGR frequently remain shorter and lighter through adolescence.

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American Board of Pediatrics Content Specification(s):

Identify the perinatal risk factors, including hypoxic-ischemic encephalopathy or prematurity which affect subsequent development

Know the type and frequency of school-related and behavioral problems in preterm infants

Understand the prenatal, perinatal, and neonatal risk factors associated with school and behavior problems

Know the significance of delay in development in one or more streams of development

Understand the complications and management of fetal growth restriction

Identify the clinical features of attention deficit disorder with and without hyperactivity

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11 November 08

12 December 08

October: Question 4

You are treating a 10-day-old male infant who has *Haemophilus influenzae* type b pneumonia and sepsis with intravenous cefotaxime. He was born at 39 weeks' gestation. He was discharged after a 2-day stay in the newborn nursery, only to return to the emergency department 7 days later with fever and tachypnea. The mother lives with her husband, their 10-month-old daughter, and her pregnant 20-year-old sister. The 10-month-old daughter attends day care and has received two doses of *Haemophilus influenzae* type b conjugate vaccine. The unit's infection control nurse approaches you to discuss chemoprophylaxis for index case contacts.

Of the following, the individual MOST likely to require rifampin chemoprophylaxis is the:

1	day care worker
2	emergency room nurse
3	index case
4	mother
5	pregnant aunt

You selected 1, the correct answer is 4.

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***Haemophilus influenzae* is the pathogen responsible for pneumonia and sepsis in the neonate in the vignette. *H influenzae* is the second most common cause of gram-negative early-onset sepsis in very-low-birthweight neonates. Isolates are classified by the presence of one of six antigenically distinct capsular serotypes a through f, or as nontypable nonencapsulated strains.**

Before the introduction of the *H influenzae* type b conjugate vaccine in 1988, *H influenzae* type b was the leading cause of bacterial meningitis among children younger than 5 years of age. The introduction of the vaccine led to dramatic declines in the incidence of invasive *H influenzae* type b disease; currently it occurs primarily in underimmunized children or infants too young to have completed the primary immunization series. The incidence of invasive disease caused by other serotypes has not changed substantially in the United States.

Most strains responsible for neonatal infections are nontypable and beta-lactamase negative. Nontypable *H influenzae* disease occurs primarily in premature neonates and can be associated with significant mortality. In contrast, invasive *H influenzae* type b disease is rare in neonates; presumably because anticapsular IgG antibody is passively transferred to the fetus and confers protection during the first months after birth. An invasive *H influenzae* type b infection can develop in neonates born to mothers who lack anticapsular antibodies at the time of delivery. Because nontypable *H influenzae* or *H influenzae* type b may colonize the maternal genital tract, risk factors such as preterm labor, prolonged rupture of

membranes, or chorioamnionitis are associated with early-onset disease. Late-onset (occurring more than 2 days after birth) invasive *H influenzae* type b disease may also develop in neonates exposed to household contacts colonized with *H influenzae* type b.

In neonates, clinical syndromes associated with *H influenzae* include sepsis, respiratory distress syndrome, meningitis, soft tissue or joint infection, otitis media, and mastoiditis. Pneumonia caused by *H influenzae* is acquired at or immediately after birth following aspiration of infected amniotic fluid or secretions from the birth canal. Signs of respiratory distress, including tachypnea, dyspnea, grunting, nasal flaring, intercostal retractions, coughing, cyanosis, rales, and decreased breath sounds may be present at the onset of illness or develop later in the course. Because organisms responsible for pneumonia in the newborn period are similar to those causing sepsis, initial antimicrobial treatment is also similar. After culture results and antimicrobial sensitivities are available, antibiotic treatment can be reevaluated.

In the past, asymptomatic nasopharyngeal colonization by *H influenzae* type b was common, occurring in 3% to 5% of children under 6 years of age. Even though pharyngeal colonization by *H influenzae* type b organisms has fallen since the introduction of the *H influenzae* type b conjugate vaccine, the American Academy of Pediatrics (AAP) guidelines still call for rifampin chemoprophylaxis for certain contacts of the index case of invasive *H influenzae* type b (Table).

Table. Guidelines for Rifampin Chemoprophylaxis for Contacts of Index Cases of Invasive *Haemophilus influenzae* Type b (Hib) Disease*

- For all household contacts† in the following circumstances:
  - Household with at least one contact <4 years of age who is unimmunized or incompletely immunized‡
  - Household with a child <12 months of age if the child has not received the primary series
  - Household with an immunocompromised child, regardless of that child's Hib immunization status
- For nursery school and child care center contacts, regardless of age, when ≥2 cases of Hib invasive disease have occurred within 60 days
- For index case, if <2 years of age or member of a household with a susceptible contact and treated with a regimen other than cefotaxime or ceftriaxone , chemoprophylaxis usually is provided just before discharge from hospital

* Adapted from *Red Book: 2006 Report of the Committee on Infectious Diseases* (2006).
† Defined as people residing with the index patient or nonresidents who spent 4 or more hours with the index case for at least 5 of the 7 days preceding the day of hospital admission of the index case.
‡ Complete immunization is defined as having had at least 1 dose of conjugate vaccine at 15 months of age or older; 2 doses between 12 and 14 months of age; or a 2- or 3-dose primary series when younger than 12 months, with a booster dose at 12 months of age or older.

Chemoprophylaxis is not recommended after infections caused by nontypable *H influenzae.* In two randomized, placebo-controlled trials, rifampin effectively eliminated *H influenzae* type b from the nasopharynx of household contacts of children with invasive *H influenzae* type b. Nursery and child care center contacts also may be at increased risk of secondary disease, but the magnitude of this risk as well as the efficacy of rifampin in preventing disease in child care centers have not been established.

The AAP recommends rifampin prophylaxis for all household members, regardless of age, if at least one household contact younger than 12 months of age has not received the three-dose primary series of the *H influenzae* type b conjugate vaccine. The mother, father, and the sister of the index case should receive a 4-day course of rifampin (20 mg/kg once daily; maximum 600 mg). The dose is not well established for infants younger than 1 month of age, but a lower dose of 10 mg/kg is recommended. In addition to rifampin chemoprophylaxis, the incompletely immunized sister of the index case should receive a dose of the vaccine. Because most secondary cases in households occur during the week after hospitalization of the index case, rifampin prophylaxis should be started as soon as possible. Rifampin chemoprophylaxis is not indicated for pregnant women.

Exposure time with the index case is an important factor in determining whether chemoprophylaxis is required for household and nonhousehold members. Significant household contacts, as defined by the AAP, are people residing with the index patient or nonresidents who spent at least 4 hours with the index case for at least 5 of the 7 days before hospitalization. Medical caregivers of the index case, such as the emergency department nurse who cared for the neonate in this vignette, do not need chemoprophylaxis.

Day care center contacts, regardless of age, should receive rifampin prophylaxis when at least two cases of invasive *H influenzae* type b have occurred at the center during a 60-day period. Caregivers and day care attendees of the sister's day care do not require rifampin prophylaxis.

The index case should receive rifampin chemoprophylaxis if he or she is younger than 2 years of age and received a treatment regimen other than cefotaxime or ceftriaxone. In most cases, treatment of invasive *H influenzae* type b with cefotaxime or ceftriaxone will eradicate *H influenzae* type b colonization, eliminating the need for index case chemoprophylaxis. The neonate in this vignette was treated with cefotaxime and thus does not require chemoprophylaxis.

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American Board of Pediatrics Content Specification(s):

Understand the epidemiology, pathogenesis, and prevention of neonatal infection with *Haemophilus influenzae*

Understand the clinical manifestations and diagnostic criteria of neonatal infection with *Haemophilus influenzae*

Understand the treatment and complications of neonatal infection with *Haemophilus influenzae*

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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11 November 08

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October: Question 5

A 3.5-kg, full-term infant required resuscitation following a cesarean section delivery. The mother had experienced a gush of fluid at home 40 minutes before her arrival in the hospital. A loop of umbilical cord was observed in the vagina and the fetal heart rate was 58 beats per minute. The infant's heart rate was low after birth, but recovered to a normal rate after 30 seconds of positive pressure ventilation. Spontaneous respiratory efforts began after 10 minutes of assisted ventilation. Apgar scores at 1, 2, 5, 10, and 15 minutes are 3, 3, 4, 6, and 6, respectively.

Umbilical vessel and infant blood gases are consistent with abrupt total cord occlusion (Table 1)

Table 1. Umbilical Vessel and Blood Gas Findings

	pH	PCO_2	PO_2	Base Deficit
Umbilical artery (cord)	7.28	52	15	4
Umbilical vein (cord)	7.32	46	26	3
Arterial blood gases (infant)	7.03	42	110	21

Clinical examination 75 minutes after delivery reveals that the infant has mild hypotonia with distal flexion, a “staring gaze” with open pupils, absent suck, active stretch reflexes, weak Moro reflex, and a strong tonic neck reflex—all indicative of neonatal encephalopathy, stage I to II in the modified criteria of Sarnat and Sarnat.

You are considering brain cooling for perinatal asphyxia and neonatal encephalopathy but would like additional information about the severity of the neurologic insult. You are considering the predictive value of available information or ancillary studies to help you make a recommendation.

Of the following, the MOST useful prognostic indicator of the severity of neonatal encephalopathy in the 75-minute-old infant in the vignette is :

1	Apgar score
2	Sarnat staging
3	computed tomography
4	electroencephalography
5	magnetic resonance imaging

You selected 5, the correct answer is 2.

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feature.)

The infant in the vignette has experienced a hypoxic-ischemic insult following an acute perinatal event and she shows signs of encephalopathy. Mild encephalopathy is generally self-limited and the prognosis for long-term neurologic and developmental recovery is good. In contrast, profound encephalopathy is associated with high rates of death or severe disability.

Differentiation of moderate or moderate/severe encephalopathy from mild encephalopathy is important to determine the eligibility of the infant in the vignette for therapeutic hypothermia. In this case, the most informative assessment of the severity of current neural involvement is clinical staging using criteria developed by Sarnat and Sarnat, and modified for use in the very early neonatal period.

Sarnat and Sarnat described three stages of encephalopathy, which have been adapted for use in the early neonatal period. At this age, staging using the Sarnat and Sarnat criteria (modified for use shortly after birth) provides the best correlation with long-term outcome (Table 2).

Table 2. Sarnat and Sarnat Staging Criteria for Neonatal Encephalopathy

Criterion	Stage I	Stage II	Stage III
Consciousness	Hyperalert	Obtunded	Stuporous
Tone/posture	Good tone, mild distal flexion	Hypotonic, strong distal flexion	Flaccid, occasionally decerebrate
Stretch reflexes	Increased	Increased	Decreased or absent
Suck	Weak	Variably weak to absent	Absent
Moro	Strong	Weak	Absent
Pupils	Mydriatic	Miotic	Variable, anisochoria, poor light response
Heart rate	Tachycardia	Bradycardia	Variable
Respiratory secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal or decreased	Increased	Variable
Seizures (clinical)	None	Common	Uncommon

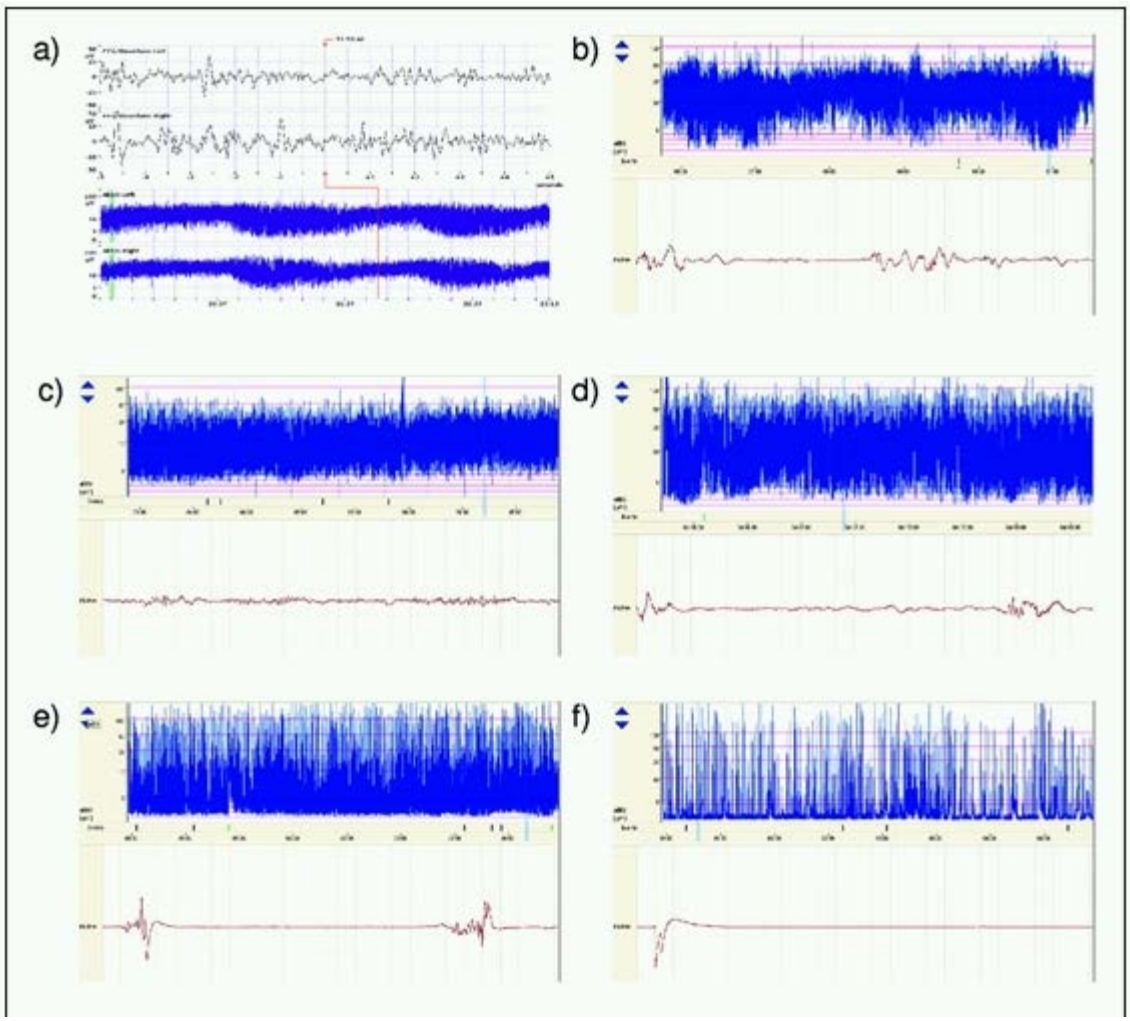
Because neonatal encephalopathy may worsen during reperfusion, serial evaluations are important to ascertain the maximal degree of involvement.

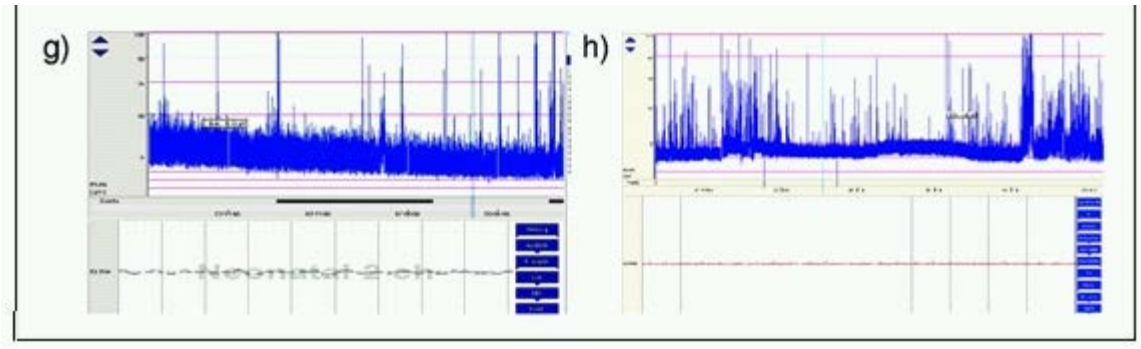
The hyperalert appearance of the infant in the vignette may be deceptive, especially to families. Her examination findings meet the criteria for stages I and II, and her age makes her too young to render an accurate prognosis. Infants who continue in Sarnat stage I generally recover normal neurologic function within a day or two. Infants who demonstrate only a period of hyperalertness or hyperexcitability without hypotonia or seizures have a high likelihood of normal long-term neurologic and developmental outcome. Findings of Sarnat and Sarnat stage II may last up to 2 weeks' of age, and often are accompanied by seizures. Such infants have a 20% to 35% risk of developing problems later; normal outcome is possible if the neurologic findings have normalized within 1 week after birth. Abnormalities consistent with

Sarnat and Sarnat stage III may last hours to weeks, and are infrequently accompanied by seizures. The risk of mortality is about 75%, and impairment occurs in nearly all survivors.

Neonatal electroencephalography (EEG) is complicated because of maturational effects superimposed on the normally complex waveforms from different sites on the brain surface. Amplitude-integrated EEG (aEEG) is a two-lead waveform that displays fluctuations in the high and low voltages produced by the brain. aEEG may be helpful in assessing the severity of brain injury, but is user dependent. Furthermore, the sensitivity and specificity for predicting long-term outcome with aEEG is debated. The poor negative predictive value of aEEG limits its value. Confusing segments are best evaluated by examining the conventional EEG pattern obtained at the same time. Newer aEEG devices are capable of storing waveforms for this analysis. Several waveform patterns have been described and related to central nervous system status (Figure).

Figure: The classification of primary aEEG background patterns, as well as the three degrees of sleep-wake cycling (SWC). a) Continuous background (C) with SWC in healthy term infant (two channels, EEG upper panel, aEEG lower panel). b) C and discontinuous (DC) aEEG background with immature SWC in an infant who has Dandy Walker malformation at 35 weeks' gestation (one channel, aEEG upper panel, EEG lower panel). c) DC background that gradually becomes more continuous, as seen by the rise in the minimum amplitude, in a term infant after cardiac surgery. d) DC background in normal very preterm infant, in whom the maximum amplitude is often higher and the variability in the minimum amplitude is larger than in term infants who have DC patterns. e) Burst-suppression with age;100 bursts/h (BS+) in a moderately sedated preterm infant. f) Burst-suppression with <100 bursts/h (BS-) in a severely asphyxiated term infant. g) Low voltage (LV) in a severely asphyxiated infant. h) Flat (FT) aEEG and EEG in a term infant who has severe asphyxia





- **A “continuous” pattern denotes one that has a regular bandwidth and is considered the normal status at term gestation. In this waveform, the baseline value is higher than 5 µV and the peaks range from 20 to 40 µV. This pattern may be demonstrated in infants delivered before 30 weeks' gestation, but generally it is not the prevalent pattern until after 30 weeks' gestation. Often, the lower limit may show a scalloped or sine-wave appearance with occasional dips below 5 µV, but not down to the baseline. These variations are called “sleep-wake cycles” and may be seen in infants born as early as 25 weeks' gestation. If this pattern is noted, severe brain injury is less likely.**
- **A “discontinuous” pattern denotes variability in the pattern bandwidth. Its low-voltage variant has peak amplitude ranging from15 to 30 µV and the lower limit of the pattern is less than 3 µV. The discontinuous high-voltage pattern has lower limits of 3 to 5 µV with peaks in the 20 to 40 µV range. Among infants born before 30 weeks' gestation, the discontinuous pattern is the most prevalent pattern and gradually is replaced by the continuous pattern described before. A “discontinuous” pattern is a more ominous pattern among term or late preterm infants. Sleep-wake cycles may be present with a mildly discontinuous pattern, and their presence within the first 36 hours after an ischemic insult is associated with a more favorable prognosis.**
- **A “low-voltage” pattern has peak amplitudes lower than 5 µV with the lower limit nearing zero. This is an ominous pattern.**
- **A “burst suppression” pattern results from periods of isoelectricity interspersed by episodes of electrical activity generally exceeding 100 µV. Presence of burst suppression is of considerable concern, however, in some cases it may be a transient pattern and revert to normal with time. Outcomes are guarded with a burst-suppression aEEG.**
- **A profoundly suppressed pattern with voltages nearing zero is associated with an isoelectric (flat line) EEG pattern and reflects profound brain injury and poor outcome.**
- **“Seizures” are represented by symmetric elevations of the lower margin of the tracing with high peak amplitude. Regardless of the baseline pattern, the presence of seizures is considered evidence of encephalopathy because of the relationship of seizures to adverse outcomes.**

Assessment of aEEG patterns was integrated in the inclusion criteria for brain cooling (neuroprotection) in the “cool cap” study; it was not an inclusion requirement in the whole body cooling study done by the National Insitute of Child Health and Human Development. An analysis of the outcome-related factors in the studies on brain cooling showed clinical grading of encephalopathy to have the best correlation, followed by the aEEG background pattern, and then by seizures on aEEG.

Apgar scoring has been a mainstay of delivery room care for over 50 years and it remains a simple method to record the infant's heart rate, presence and vigor of breathing, responsiveness to stimulation, tone, and color. Many analyses of the relationship of the Apgar score with outcome have shown that Apgar scores are not sufficiently predictive of outcome to make accurate prognostic statements in all but the most extreme circumstances. Many nonasphyxial causes for low Apgar scores have been identified. When combined with grading of the stage of encephalopathy, especially if aEEG is incorporated, the Apgar score fails to be a predictive independent variable..

Computed tomography (CT) is most useful to detect central nervous system hemorrhagic lesions, which have been documented in 10% to 25% of patients with hypoxic-ischemic

encephalopathy. Because of the time required for parenchymal changes to develop after an asphyxial injury, CT is not the test of choice to make decisions about brain cooling in this vignette.

Magnetic resonance (MR) imaging, the most useful of the imaging techniques in neonatal encephalopathy, can be very sensitive in detecting ischemic lesions, both focal and multifocal. Although the use of diffusion-weighted imaging can sometimes detect ischemia-related changes within 6 to 8 hours after birth, generally the evolution of ischemic changes is slower in neonates than in adults. Reliable changes generally require more than 24 hours. If the infant is being considered for neuroprotection with hypothermia (which currently needs to be initiated within 6 hours after birth), MR will not likely add to the current assessment because of physiologic and practical considerations. Later in the course, MR is the imaging mode of choice to evaluate the brain parenchyma.

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American Board of Pediatrics Content Specification(s):

Know the indications for and limitations of various neurodiagnostic tests, including electroencephalography (EEG), brainstem auditory-evoked response (BAER), visual-evoked response (VER), and somatosensory evoked potential (SEP)

Understand the indications for, contraindications, and interpretation of spinal fluid analysis

Understand the indications for and limitations of various neuroimaging studies (including ultrasonography, magnetic resonance imaging study, positron emission tomography, and near-infrared spectroscopy), and be able to recognize normal and abnormal structures

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11 November 08

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October: Question 6

A 10-day-old infant presents with eyelid edema and moderate mucopurulent discharge from both eyes. A gram-stained smear of the exudate is negative. Giemsa-staining of a conjunctival scraping demonstrates blue-stained intracytoplasmic inclusions within epithelial cells, and enzyme immunoassay confirms a diagnosis of *Chlamydia trachomatis*.

Of the following, the ocular prophylaxis agent MOST likely to prevent conjunctivitis caused by *C trachomatis* is:

1	erythromycin ophthalmic ointment (0.5%)
2	povidone-iodine solution (2.5%)
3	silver nitrate solution (1%)
4	tetracycline ophthalmic ointment (1%)
5	topical colostrum

You selected 3, the correct answer is 2.

Ophthalmia neonatorum is defined as conjunctivitis occurring within 28 days after birth. The causes of ophthalmia neonatorum include bacteria such as *Neisseria gonorrhea*, *Chlamydia trachomatis*, and *Staphylococcus aureus*; viruses, such as herpes simplex virus and adenovirus; and chemical irritation from ocular agents, particularly silver nitrate solution. Infection is caused by mucosal exposure to contaminated maternal discharge during vaginal birth, however, ascending infection in infants born by cesarean section occurs as well.

Before the availability of ocular prophylaxis and antimicrobial agents, ophthalmia neonatorum was the leading cause of blindness in children. Without prophylaxis, ophthalmia neonatorum develops in up to 42% of infants exposed to *N gonorrhea* and up to 30% of infants exposed to *C trachomatis*. Untreated gonococcal ophthalmia leads to corneal scarring and blindness in up to 90% of cases. *Chlamydia* conjunctivitis tends to be self-limited and rarely results in vision loss, but without systemic treatment, is associated with the development of pneumonia in 5% to 20% of cases. The prevalence of infection with *N gonorrhea* and *C trachomatis* relates directly to the prevalence of infection among pregnant women, screening and treatment of pregnant women, and ocular prophylaxis of the newborn. In the United States, neonatal conjunctivitis occurs in 0.5% to 6% of live births, with *C trachomatis* being the most common pathogen.

In the late 19th century, Crede reported a reduction in the incidence of gonococcal ophthalmia with ocular instillation of silver nitrate solution. Subsequent widespread use of silver nitrate ocular prophylaxis reduced the prevalence of gonococcal ophthalmia neonatorum from 10% to

0.2% of live births in Europe. Silver nitrate solution is also effective against penicillinase-producing gonococcus. However, silver nitrate solution has limited antimicrobial activity against *C trachomatis*, and is associated with a marked, but self-limiting, chemical conjunctivitis in up to 50% of recipients. Despite these limitations, silver nitrate solution is widely used in resource-poor regions, and is a preferred agent in areas with a high incidence of penicillinase-producing *N gonorrhea*.

In the United States, erythromycin ophthalmic ointment is the most commonly used antimicrobial for neonatal ocular prophylaxis. As with silver nitrate solution, erythromycin ointment is not adequate treatment for conjunctivitis caused by *C trachomatis*, likely because topical treatment fails to eradicate the organism from the nasopharynx.

Povidone-iodine solution is an inexpensive, nontoxic, and potentially widely available agent with broad antibacterial and antiviral activity, including against *N gonorrhea, C trachomatis,* human immunodeficiency virus, and herpes simplex virus. Compared with silver nitrate and erythromycin, 2.5% povidone-iodine opthalmologic solution demonstrates greater efficacy against *C trachomatis*, and at least equivalent efficacy against *N gonorrhea* and *S aureus*. In addition, povidone-iodine currently lacks microbial resistance, and results in a mild chemical conjunctivitis in fewer than 20% of recipients. Furthermore, instillation of povidone-iodine transiently turns the surface of the eye brown, which confirms proper application. Presently in the United States, povidone-iodine is not approved for ocular prophylaxis, but has great potential for use in areas with a high prevalence of antimicrobial resistance and limited resources.

Increasing microbial resistance has reduced the efficacy of tetracycline ophthalmic ointment, which is no longer recommended as first-line treatment for gonococcal infections. Furthermore, lack of effectiveness against *C trachomatis* makes tetracycline ointment a suboptimal agent for ophthalmia neonatorum prophylaxis.

Topical instillation of colostrum or human milk is a traditional remedy for ophthalmia neonatorum in some countries. In vitro inhibition of growth of *N gonorrhea*, *S aureus,* and various coliform organisms has been demonstrated with colostrum. Currently data are unavailable to support widespread use of colostrum for ophthalmia neonatorum prophylaxis.

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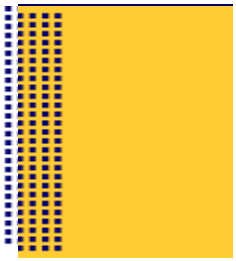
American Board of Pediatrics Content Specification(s):

Understand the benefits and complications of eye prophylaxis with antibiotics or silver nitrate (eg, obstructed nasolacrimal duct)



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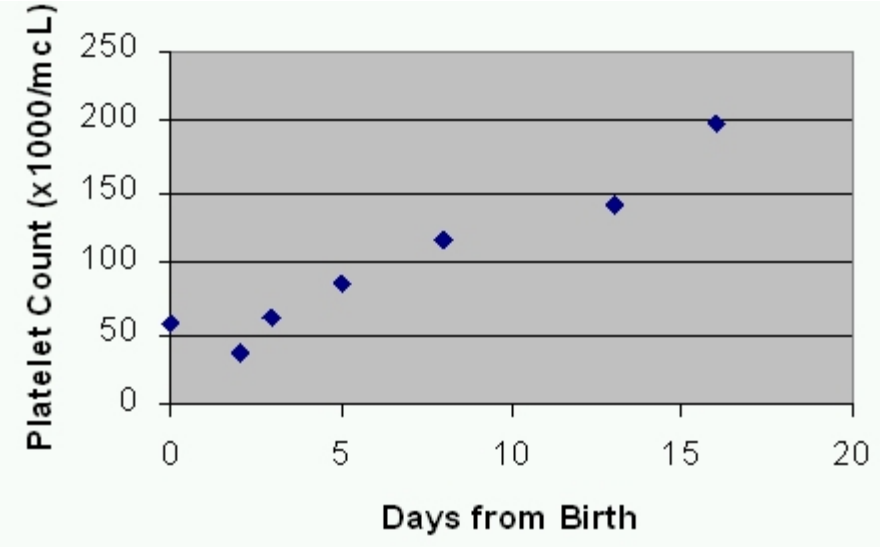
October: Question 7

A 34-week-gestation male infant was born by induced vaginal delivery to a 24-year-old primiparous woman who had preeclampsia with progressive hypertension, headache, and proteinuria. The infant had Apgar scores of 5 and 8 at 1 and 5 minutes, respectively. Physical examination findings were consistent with maternal dates and he was vigorous shortly after birth. He had no respiratory problems but developed moderate hyperbilirubinemia which was treated with phototherapy. His platelet count at birth was 58×10^3/μL (58×10^9/L). Other hematologic values were normal. Subsequent platelet counts are shown (Figure 1).

Figure 1



Of the following, the MOST accurate statement about platelet production or destruction is that:

1	Normal platelet counts are lower in the premature infant than in older individuals
2	Platelets are produced by large multinucleated cells called megakaryocytes
3	Platelet life span averages 3 to 5 days
4	Thrombopoietin is produced in the lungs of premature infants and adults
5	Thrombopoietin stimulates hematopoietic progenitor cells to become megakaryocytes

You selected 5, the correct answer is 5.

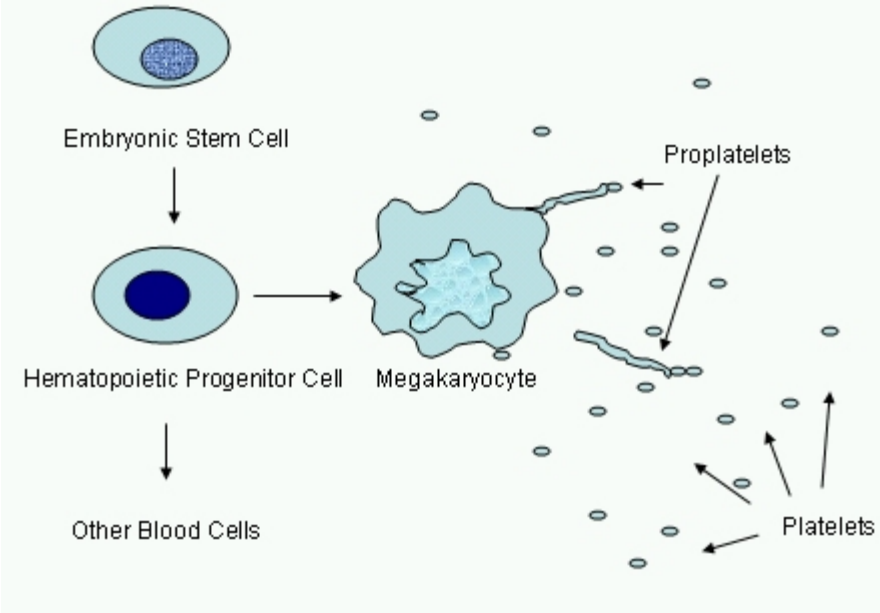
Thrombocytopenia affects about one in four infants admitted to neonatal intensive care units. The smaller and more ill the infant, the higher the risk of thrombocytopenia. However, the

normal platelet count (150-400×10^3/μL [0.15-0.4×10^9/L]) is constant from mid-gestation to adulthood. The circulating pool represents about two-thirds of all the platelets in the body. The rest reside in the spleen. The average life span of a platelet is 7 to 10 days. Low counts are attributed to a lack of production and/or increased consumption. In the case of preeclampsia, recovery generally begins shortly after delivery because the inciting cause (not defined) has been removed.

In the newborn period, a platelet count of less than 50×10^3/μL (0.05×10^9/L) defines severe thrombocytopenia and calls for an investigation of the cause as well as consideration for treatment (however, many clinicians treat healthy-appearing infants only if their low platelet counts are persistent). Although the bleeding caused by thrombocytopenia generally occurs from mucocutaneous surfaces (mouth, gastrointestinal tract), it can occur elsewhere, especially when there is already a predisposing coagulation disturbance (eg, intraventricular hemorrhage).

Platelets are shed from megakaryocytes. Megakaryocytes, in turn come from megakaryocyte progenitor cells which are derived from undifferentiated (pleuripotential) hematopoietic stem cells (Figure 2).

Figure 2



This maturation process, including the maturation of immature megakaryocytes to more mature forms, is regulated by thrombopoietin. Mature megakaryocytes develop long cytoplasmic protrusions that shear off as proplatelets that then become platelets. This latter event is likely to occur across pulmonary capillary membranes. A less popular theory proposes that the shearing events occur in the bone marrow.

Thrombopoietin appears to be produced at a steady rate. Megakaryocytes and platelets have surface receptors (called *Mpl receptors*) for thrombopoietin. These receptors bind thrombopoietin, internalize it, and subsequently catabolize it. Thus a negative feedback mechanism is produced in which thrombopoietin concentrations correlate inversely with the combined body mass of megakaryocytes and platelets.

Thrombopoietin is a 353 amino-acid protein that is made in the liver and kidney. Smaller amounts of messenger RNA for thrombopoietin have been detected in spleen and bone marrow, but not in lung tissue. Part of the amino-acid sequence of thrombopoietin is homologous with erythropoietin. The gene for thrombopoietin is mapped to the long arm of chromosome 3.

Other factors that can stimulate platelet production include interleukin (IL)-3, IL-6, IL-11, IL-7, and erythropoietin. None of these agents is as specific and important to the process as thrombopoietin.

The nucleus of the megakaryocyte is a single, large, lumpy appearing organelle that contains more than one copy of the genome. Neonatal megakaryocytes are smaller than adult megakaryocytes and have fewer (usually two) copies of the genome in their nuclei. Neonatal megakaryocytes tend to divide in response to thrombopoietin stimulation. Adult megakaryocytes, on the other hand, respond to thrombopoietin by increasing their size and continuing with endomitosis (mitosis short of anaphase/telophase) longer than neonatal cells and can contain 8 to 64 copies of the genome (known as *polyploidy*). Neonatal megakaryocytes also produce fewer platelets than adult megakaryocytes perhaps because of their reduced surface area.

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Wong W, Glader B. Approach to the newborn who has thrombocytopenia. *NeoReviews.* 2004;5:c444-c450

American Board of Pediatrics Content Specification(s):

Understand the normal pattern of platelet production and maturation

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11 November 08

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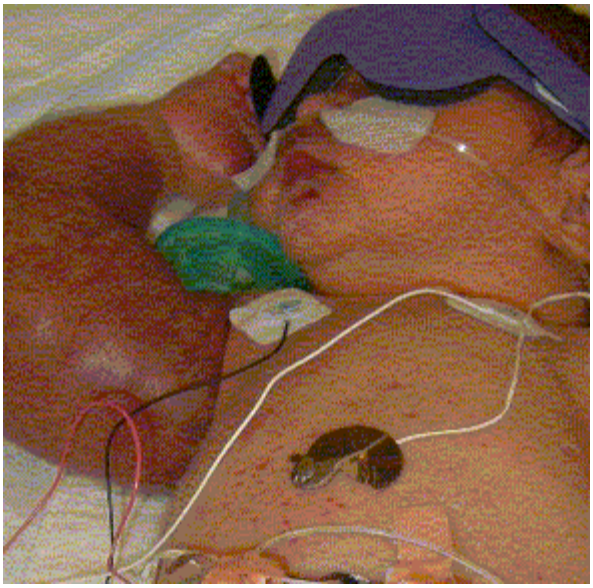
October: Question 8

A male infant is born at 35 weeks' gestation. Maternal history was significant for severe preeclampsia that led to induction of labor and vaginal delivery. The infant has a diffuse petechial rash and a large swelling in his right arm (Figure).

Figure



Laboratory data reveal the following:

Laboratory Findings	Patient Results (SI Units)
Hematocrit, %	33 (0.33)
Peripheral blood smear	Multiple schistocytes
Platelet count, $\times 10^3/\mu L$ ($\times 10^9/L$)	23 (23)
Fibrinogen, mg/dL (μmol/L)	80 (2.4)

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

1	classic infantile hemangioma
2	congenital leukemia
3	kaposiform hemangioendothelioma
4	neuroblastoma
5	preeclampsia

You selected 3, the correct answer is 3.

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Kaposiform hemangioendothelioma, as seen in the infant in this vignette, is an aggressive form of giant hemangioma. Such a vascular tumor is often associated with severe thrombocytopenia from platelet trapping (Kasabach-Merritt phenomenon), hypofibrinogenemia and elevated fibrin degradation products from consumption coagulopathy, and anemia from fragmentation of red blood cells.

Although children with classic infantile hemangiomas were once thought to be at risk for these complications, the Kasabach-Merritt phenomenon is now known to be associated mostly with two types of vascular tumors: tufted angioma and kaposiform hemangioendothelioma. The Kasabach-Merritt phenomenon is not associated with classic infantile hemangiomas. The lesions in kaposiform hemangioendothelioma are noted at birth in approximately 50% of patients. The male-to-female ratio is close to 1:1. When complicated by Kasabach-Merritt syndrome, the mortality rate approaches 30% to 40%.

Classic infantile hemangiomas evolve in two phases: an initial growth phase and a subsequent involutional phase. Females are three times more likely to have hemangiomas, and the incidence is increased in preterm infants. Fifty-five percent of hemangiomas are present at birth, whereas the remainder develop in the first few weeks after birth. Most cutaneous hemangiomas are benign; ulceration is the most common complication. These hemangiomas do not cause thrombocytopenia or hemolytic anemia.

Bone marrow infiltrative disorders such as neonatal leukemia and neuroblastoma can cause decreased platelet production, disseminated intravascular coagulopathy, and anemia. The infant in this vignette has evidence of hemolytic anemia, as suggested by the presence of schistocytes on peripheral smear, which would be unlikely in either of these disorders.

Thrombocytopenia is common in infants of mothers with preeclampsia and is often associated with neutropenia. The incidence of thrombocytopenia has been estimated at 1 per 100 live births, and it is more likely to occur in preterm infants. In affected infants, thrombocytopenia typically is seen at birth, the nadir is reached at 2 to 4 days of age, and it resolves by day 7 to 10. The infant in this vignette has evidence of disseminated intravascular coagulopathy, which is not a common complication of maternal preeclampsia.

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References:

Drolet BA, Esterly NB, Frieden IJ. Hemangiomas in children. *N Engl J Med*. 1999;341:173-181

Dubois J, Hershon L, Carmant L, Belanger S, Leclerc JM, David M. Toxicity profile of interferon alfa-2b in children: a prospective evaluation. *J Pediatr.* 1999;135:782-785

Sarkar M, Mulliken JB, Kozakewich HP, Robertson RL, Burrows PE. Thrombocytopenic coagulopathy (Kasabach-Merritt phenomenon) is associated with Kaposiform hemangioendothelioma and not with common infantile hemangioma. *Plast Reconstr Surg.* 1997;100(6):1377-1386

Wong W, Glader B. Approach to the newborn who has thrombocytopenia. *NeoReviews.* 2004;5:e444-e450

American Board of Pediatrics Content Specification(s):

Know how to diagnose capillary and cavernous hemangioma

Know how to diagnose Kasabach-Merritt syndrome

Understand the clinical and laboratory findings of hemolytic anemia

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11 November 08

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October: Question 9

A 4-month-old infant, born at 25 weeks' gestation, has had a complicated postnatal course, including chronic lung disease, laser surgery for retinopathy of prematurity (ROP), partial intestinal resection for necrotizing enterocolitis, and hydrocephalus following intraventricular hemorrhage. All these complications of prematurity are believed to be manifestations of "oxygen radical disease of prematurity" which results from an imbalance between pro-oxidant insults and antioxidant defenses.

Of the following, the antioxidant enzyme MOST likely to convert hydrogen peroxide to water is:

1	alpha-1-proteinase inhibitor
2	catalase
3	glutathione reductase
4	superoxide dismutase
5	xanthine oxidase

You selected 5, the correct answer is 2.

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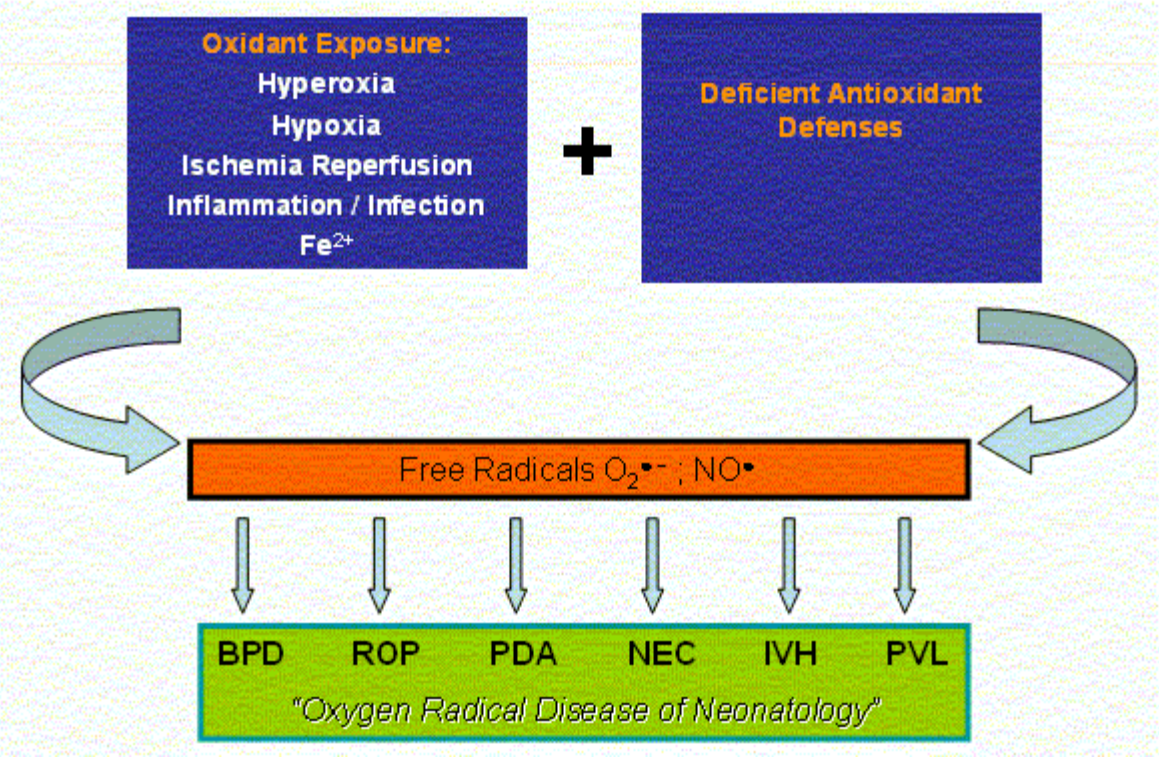
The term "oxygen radical disease of neonatology" was coined by Saugstad as a unifying hypothesis for the role of reactive oxygen species (ROS) in a wide range of neonatal morbidities, including bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, intraventricular hemorrhage, and periventricular leukomalacia. These morbidities in preterm infants, as seen in the infant in this vignette, are implied to be different manifestations of free radical injury (Figure 1).

Figure 1



Reactive oxygen species is a collective term that includes not only the oxygen free radicals (eg, superoxide $O_2^{\bullet -}$ and hydroxyl radical OH•), but some nonradical derivatives of oxygen (eg, hydrogen peroxide H_2O_2). Free radicals are atoms or molecules that contain one or more unpaired electrons. Because these free radicals are unstable, they easily combine with other molecules, trying to capture electrons to become stable and creating a chain reaction that stops when the free radical pairs up with an electron. Once started, this process can produce a cascade of events and disrupt the living cell by damaging proteins, DNA, and lipids.

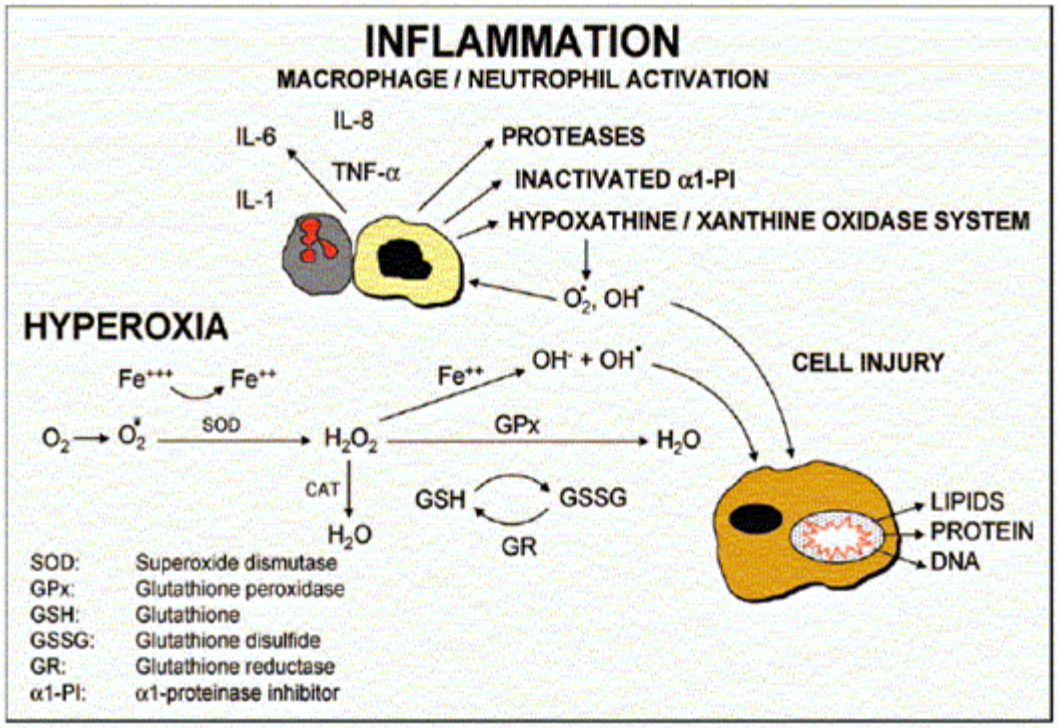
Free radicals are frequently referred to as ROS because the most biologically important free radicals are predominantly derived from oxygen (oxygen free radicals). More recently, reactive nitrogen species (RNS) derived from reactions involving nitric oxide (NO), have been recognized as free radicals; the best characterized being the peroxynitrite anion, formed by the reaction of $O_2^{\bullet -}$ with NO.

Free radicals have important functions in normal growth and regulation as second messengers and signal transducers. They modulate transcription factors such as activator protein-1 (AP-1), which controls the expression of cell growth mediators, and nuclear factor NF ?B, which regulates several genes important in immune and stress responses, inflammation, and apoptosis.

Small amounts of free radicals are generated continuously in living organisms and are necessary for normal cell reactions and cell growth. Normally, the body's antioxidant defenses handle free radicals. However, excessive production of ROS associated with deficient antioxidant defenses produces tissue injury and probably morbidities associated with prematurity (Figure 1).

Reactive oxygen species may be generated by the following different mechanisms (Figures 1 and 2):

Figure 2



- **mitochondrial electron transport fatty acid and prostaglandin metabolism**
- **ischemia-reperfusion**
- **hypoxia**
- **hyperoxia**
- **neutrophil and macrophage activation (inflammation)**
- **endothelial cell hypoxanthine-xanthine oxidase system (adenosine triphosphate degradation)**
- **increased free circulating transition metals**
- **Fenton reaction (ferrous to ferric iron)**

Increased formation of ROS is also caused by some drugs and chemicals such as paraquat or acetaminophen.

Oxidative stress results in activation of matrix collagenases, proinflammatory gene products, and vascular proteins such as vascular endothelial growth factor, resulting in aberrant development and maturation. Prolonged exposure to supraphysiologic levels of oxygen is also characterized by rapid neutrophil and macrophage infiltration of the lung. Activated neutrophils and macrophages release potent proteases, other enzymes, and toxic oxygen radicals. These toxic oxygen radicals, generated by the tissue-bound xanthine oxidase system, inactivate protease inhibitors (alpha-1-proteinase inhibitor). The net result is an imbalance between proteases and their inhibitors (Figure 2). Oxidative stress also increases matrix metalloproteins and their inhibitors, causing disruption of the extracellular matrix and contributing to fibrosis.

Oxygen free radical damage is usually prevented by a series of enzymatic and nonenzymatic antioxidant defenses (Table).

Table. Major Antioxidants in Human Blood and Tissues*	
Class	Antioxidant
Enzymes	Superoxide dismutase Catalase Glutathione peroxidase Glutathione reductase
Vitamins	Vitamin A Vitamin C Coenzyme Q β carotene
Reducing agents	Glutathione Cysteine Thioreduxin
Binding proteins	Albumin Ceruloplasmin Lactoferrin Transferrin
Constituent of enzymes	Copper Zinc Selenium
Others	Uric acid Bilirubin Erythropoietin

* Adapted from Shoji (2007).

The most important antioxidant enzymes are copper-zinc superoxide dismutase (SOD), found in cytoplasm and peroxisomes, and manganese SOD in mitochondria. SOD catalyzes the dismutation of superoxide anion to H_2O_2 (Figure 2). Glutathione peroxidase (GPx) in mitochondria and catalase in peroxisomes catalyze the reaction of H_2O_2 to molecular oxygen and water. In addition, there are extracellular types of SOD and GPx.

Nonenzymatic antioxidants include nutrients such as selenium, copper, and zinc that function as components of antioxidant enzymes, vitamins E and C, ceruloplasmin, transferrin, glutathione (GSH), and bilirubin. Selenium takes part in many selenoenzymes, with GPx being the most important. Vitamin E blocks natural peroxidation of polyunsaturated fatty acids found in the lipid layers of cellular membranes, substituting oxygen in the reaction and stabilizing lipid free radical hydrogen. Vitamin C (ascorbic acid) is an important antioxidant that directly scavenges superoxide and hydroxyl radicals to form dehydroascorbate. Conversely, vitamin C can act as a pro-oxidant in the presence of free iron, reducing ferric iron to a ferrous state, which in the presence of H_2O_2, stimulates the formation of toxic hydroxyl radicals. Bilirubin has been demonstrated as a potent antioxidant scavenger of peroxyl radicals, with an action similar to that of vitamin E. Glutathione (GSH) is the most abundant low-molecular-weight peptide present in cells and is a major antioxidant. In a reaction catalyzed by GPx, GSH reduces H_2O_2 and lipid peroxides, producing the oxidized glutathione (GSSG). Reduced GSH is then regenerated via glutathione reductase.

Transition metals like iron, copper, chromium, molybdenum, cobalt, manganese, nickel, and vanadium contain unpaired electrons and therefore fulfill the criteria of being free radicals. Iron is the most abundant transition metal in humans; it catalyzes the reaction between the superoxide anion and hydrogen peroxide, leading to the formation of the toxic hydroxyl radical. Iron is normally sequestered by iron-binding protein; therefore iron can be transported to and used in the cells. Non–protein-bound iron is normally absent in plasma, because any free ferrous ion present is oxidized to ferric ion by the ferroxidase activity of ceruloplasmin and is tightly bound to transferrin. In newborns, and especially in preterm infants, low transferrin concentrations decreases transferrin iron binding, and low levels of ceruloplasmin and ferroxidase activity may contribute to the detection of non–protein-bound iron in plasma. Ferrous iron, (Fe_2^+), can participate in the Fenton reaction and generate the hydroxyl radical in

addition to a hydroxide ion:

$$H_2O_2 + Fe^{2+} \rightarrow OH\cdot + OH^- + Fe^{3+}$$

The hydroxyl free radical is the primary oxidizing species and can oxidize and break apart organic molecules. Thus, there is a concern that large intakes of enteral or parenteral iron may overwhelm the iron-binding capacity of preterm infant serum, resulting in cell membrane oxidative stress.

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American Board of Pediatrics Content Specification(s):

Understand the role of extracellular matrix proteins in inflammation

Understand the role of reactive oxygen intermediates (SOD, H_2O_2) in inflammation

Understand the role of enzymes in inflammation

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October: Question 10

You are observing the activity pattern of a 26-week-gestation infant and note periods of eye movement and muscle twitching while at rest. You wonder if she is asleep, leading you to review the evolution of sleep and sleep states in the preterm infant.

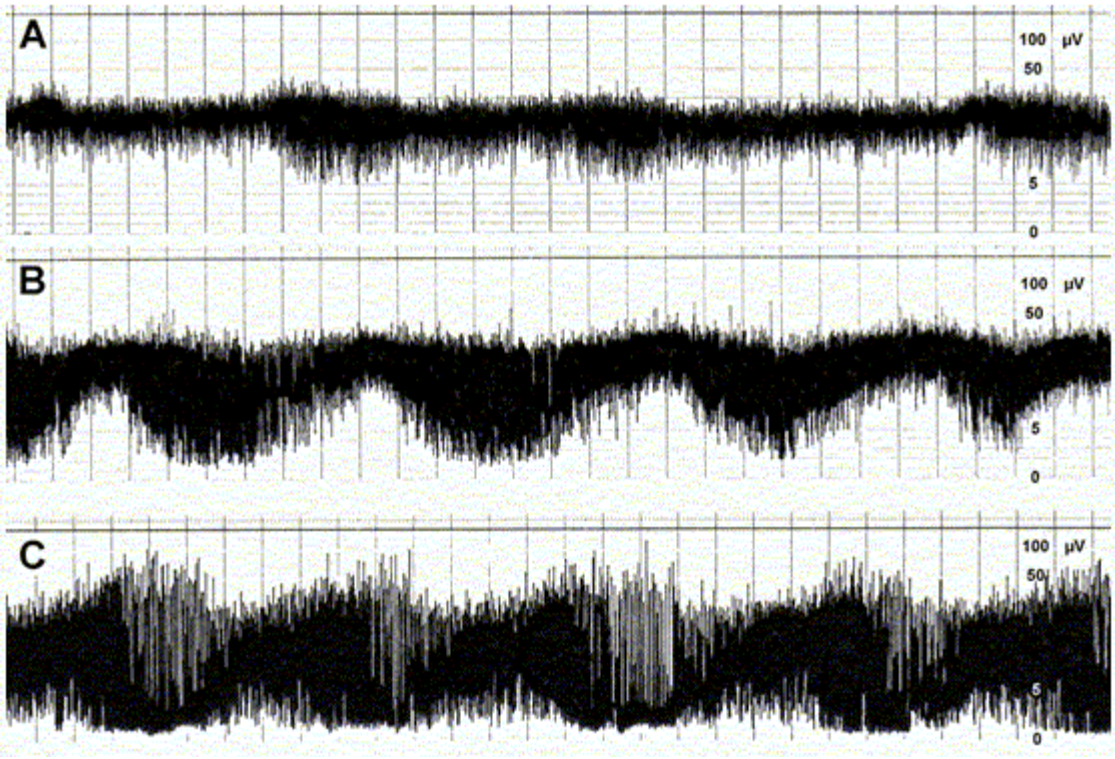
Of the following, the MOST accurate statement regarding sleep in the preterm infant is that rapid-eye-movement (REM) sleep:

1	begins at 28 weeks' gestation
2	can be detected by its association with truncal atonia
3	indicates a period of relative brain inactivity
4	precedes non-REM sleep by 2 to 4 weeks
5	reflects upregulation of aminergic cell groups of the brain stem

You selected 4, the correct answer is 1.

Neurodevelopmental processes that normally occur in the fetus must occur in the extrauterine environment in the infant in the vignette. Sleep is an important component of human daily life, and disruption of sleep cycles or deprivation of sleep overall has been shown to be detrimental to both humans and animals. Continuous amplitude-integrated electroencephalography (EEG) demonstrates a pattern of gradual rise and fall in the lower voltage in normal preterm infants as early as 24 to 25 weeks' gestation. These fluctuations have been attributed to sleep and are called sleep cycles, but at that gestation, none of the distinguishing characteristics of rapid-eye-movement (REM) or non-REM sleep are discernable on conventional EEG. Sleep cycling may be superimposed on different background patterns: the predominantly discontinuous pattern seen in infants of less than 30 weeks' gestation (Figure, panel B), the continuous pattern seen in older infants (Figure, panel A), or the more ominous pattern with a diminished lower baseline voltage (Figure, panel C) seen in infants with hypoxic-ischemic injury.

Figure: Sleep-wake cycles: superimposed on continuous (A), higher-voltage discontinuous (B), and low-baseline discontinuous (C) baseline tracings.



Beginning at 28 weeks' gestation, individual, but immature, sleep patterns are distinguishable for both REM and non-REM sleep. Initially, REM sleep predominates. When it first emerges, REM sleep manifestations include eye movements, muscle twitches, and body movements, but as the infant matures, atonia of the postural muscles is regularly evident by 2 to 3 months after term. As the fetus approaches term, the two stages of sleep each occupy about one-half of sleep time. At 8 months' beyond term, non-REM sleep occupies 80% of sleep.

Rapid eye movement sleep is associated with high brain activity, often exceeding the brain activity during wakefulness. In the interval from 20 to 28 weeks' gestation, the human fetus is believed to have indeterminate or "presleep" activity. Nevertheless, endogenous firings of ganglion cells of the various neurosensory systems and central processing centers of the brain are active, and through axon targeting, lead to precise and specific connections between sensory organs and their central processing components.

As the fetus matures past 28 weeks' gestation, endogenous stimulation patterns only occur during REM sleep. This developmental sequence has been well described in the visual system, in which frequent random firings of retinal ganglion cells are essential for the development of the lateral geniculate nucleus, visual cortex, and superior colliculus; the latter is essential for eye muscle coordination. Endogenous stimulation during REM sleep is essential for normal developmental progression of the somatesthetic, auditory, and olfactory senses. Similar progression is noted in the limbic system (emotional experience), hippocampal connections (learning and memory), and connections involving the components of the brain stem.

Interference with REM sleep has been shown to be associated with loss of the normal architecture of sensory nuclei; this loss leads to discernable abnormalities in topographic alignment in vision and touch systems and tonographic disorganization in the auditory system. Exogenous stimulation contributes to the ongoing development of all the neurosensory systems in the fetal period except the visual, for which exogenous stimulation only contributes after full-term gestation. For exogenous stimuli to be integrated optimally into sensory neurodevelopment, their intensities need to be distinguished and determined to be meaningful by the infant; the optimal inputs of sound, smell, touch, or position for developing preterm infants need further examination.

Sleep has an essential role in memory development. Stimuli occurring during wakefulness are

stored in a system of short-term circuits scattered throughout the brain. During non-REM sleep, strong or salient stimuli are sorted from weaker signals in the background, and these stronger stimuli are integrated and stored in areas of the hippocampus, parahippocampus, and amygdala (limbic lobe) of the brain. Thereafter, during REM sleep, characteristic pontine activity stimulates hippocampal communications with the long-term memory circuits of the neocortex, allowing for memory patterns to develop. A similar process underlies brain plasticity—the adaptability of the nervous system to modify its structure and function in response to environmental changes.

Rapid-eye-movement sleep is essential for normal neurodevelopment, learning, and adaptability. Preservation of sleep promotes the normal sequencing of neurodevelopment and the ability to convert short-term experience into learning and memory. Many of the treatments and environmental stimuli of the neonatal intensive care unit have the potential to either preserve or disrupt patterns of sleep, and thereby our care may facilitate or disrupt neurodevelopment and long-term outcomes.

Wakefulness is stimulated and maintained by aminergic cell groups in the brain stem and thalamus, whereas REM sleep is actively stimulated by cholinergic activity. The process of falling asleep consists of waning aminergic stimulation, a period of non-REM sleep, followed by REM sleep as the cholinergic phase increases. These stimuli alternate, producing cycles of wakefulness, non-REM, and REM sleep. This activity is not controlled by a single site, and different aspects of REM sleep are regulated by different cell groups in the brain stem, pons, and neocortex.

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References:

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Osredkar D, Toet MC, van Rooij LGM, van Huffelen AC, Groenendaaal F, deVries LS. Sleep-wake cycling on amplitude-integrated electroencephalography in term newborns with hypoxic-ischemic encephalopathy. *Pediatrics.* 2005;115:327-332

American Board of Pediatrics Content Specification(s):

Understand how states of alertness, sleep states, activity level, and visual attention change with increasing gestational age in the preterm infant, term infant, and through infancy

Understand how visual acuity changes with age in the preterm and full-term infant

Understand the evolution of auditory abilities in the preterm and full-term infant

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11 November 08

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November: Question 1

A woman who is 35 weeks' pregnant requests a cesarean section delivery in 3 weeks. She has a history of irregular menstrual periods and is not certain of her last menstrual period. The women's obstetrician has performed a number of clinical and ultrasonographic assessments to determine the gestational age of the fetus.

Of the following, the assessment or finding that MOST accurately indicates the gestational age of this fetus is:

1	embryonic crown-rump length
2	fetal heart tones
3	fundal height
4	gestational sac diameter
5	Naegle's rule

You selected 1, the correct answer is 1.

Knowledge of gestational age is vital for obstetric and neonatal decision-making. Precise determination of the gestational age of the pregnancy would require detection of the date of implantation of the conceptus into the uterus. Currently, no tools are available to provide such accurate information. During the initial stages of a pregnancy, minor inaccuracies (4-6 days) exist in determining the gestational age and estimated date of delivery even when a mother is confident about the dates of her last menstrual period. The inaccuracies occur because of inherent biological variation in time to fertilization of the egg and time to blastocyst implantation. Assisted reproductive techniques may define the time of fertilization but timing of implantation of the blastocyst will vary.

Ultrasonography is an essential tool for dating pregnancies, especially when a mother has irregular menstrual periods, early pregnancy bleeding, poor recall, or has been taking oral contraceptive medications. The crown-rump length is the standard measurement of the embryo during the first trimester (Table).

Table

Table. Antenatal Gestational Age Assessment		
	Accuracy	Comment
Clinical		
Last menstrual period	±2 wks	Depends on cycle length and recall
Uterine size-1st trimester	±2 wks	Depends on operator skill
Fetal heart tones-auscultation	±2 wks	~ 20 wks (fetoscopy)
		~ 12 wks (Doppler scope)
Fundal height measurement	±3 wks	Varies with maternal body habitus
Ultrasonography		
Gestational sac diameter	±5 days	Variable shape affects measurement; performed 4.5-5.5 wks
Embryonic crown-rump length	±3 days	Performed 5-12 wks
Biparietal diameter, femur length, cerebellar transverse diameter	±10 days	Performed 15-22 wks
	±14 days	Performed >22 wks

The greatest length of the embryo from the outer edge of the cephalic pole to the rump determines the crown-rump length (http://www.emedicine.com/med/topic3236.htm). Although the gestational age can be projected based on the crown-rump length using tables, the gestational age in days can be estimated for embryos smaller than 25 mm by adding 42 to the crown-rump length. Ultrasonographic measurement of the crown-rump length is accurate to ±3 days when the gestation is between 7 and 10 weeks. This is the most accurate indicator of the gestational age of the fetus. The accuracy of crown-rump length decreases to approximately 5 days at a gestation of 10 to 14 weeks' and thereafter is no longer predictive.

Cardiac activity can be detected with ultrasonography beginning at about 6 weeks' gestation in the embryo that is too small to measure a crown-rump length. Fetal heart activity can be detected using Doppler technology beginning at about 12 weeks' gestation. Fetal heart tones can be auscultated with a fetoscope at approximately 20 weeks' gestation. Both measurements are accurate to ±2 weeks.

Fundal height, or uterine size, is a physical finding that increases as gestation proceeds and is accurate to ±3 weeks. The uterus is normally a pelvic organ until 12 weeks' gestation. The size of the uterus during the early weeks of gestation has been compared to the size of different fruits:

- **6 to 8 weeks' gestation: Small pear**
- **8 to 10 weeks' gestation: Orange**
- **10 to 12 weeks' gestation: Grapefruit**

After 12 weeks' gestation, the uterus enters the abdomen where the fundus can be palpated:

- **16 weeks' gestation: Midway between symphysis pubis and umbilicus**
- **20 weeks' gestation: Umbilicus**

The gestational sac initially lies in the endometrium and is the first ultrasonographic sign of an intrauterine pregnancy. The gestational sac is composed of the chorionic cavity, implanting chorionic villi, and decidua tissue. No distinct structures are seen in the sac when it first presents. When the gestational sac is detectable, usually when 2 to 3 mm in size, the correlating gestational age is about 4 weeks + 1 to 3 days. There are tables that correlate gestational sac diameter and mean

sac diameter with gestational age in days. Accuracy of gestational sac measurements is ±5 days because the sac may not remain spherical. In addition, the yolk sac is the first structure to be ultrasonographically detected in the gestational sac (about 5 weeks' gestation) and is used to confirm an intrauterine pregnancy. On ultrasonography, the embryonic disk then appears in the gestational sac at about 5 to 6 weeks' gestation.

Naegle's rule is the most common method of dating a pregnancy and estimating the date of delivery (EDD). The rule depends on knowledge of the first date of the last menstrual period (LMP):

LMP [plus 1 year] – 3 months + 7 days = EDD

This rule is accurate to ±2 weeks and assumes a 28-day menstrual cycle, fertilization on day 14 after the first date of the LMP, and implantation of the blastocyst by 21 days. Inaccuracies occur because of irregular menstrual periods, vaginal bleeding early in pregnancy, and use of oral contraceptive medications.

References:

Engle WA; American Academy of Pediatrics Committee on Fetus and Newborn. Age terminology during the perinatal period. *Pediatrics.* 2004;114:1362-1364

Filley RA, Hadlock FP. Sonographic determination of gestational age. In: Callen PW, ed. *Ultrasonography in Obstetrics and Gynecology.* 4th ed. Philadelphia, Pa: WB Saunders; 2000:146-170

MacKenzie AP, Stephenson CD, Funai EF. Prenatal assessment of gestational age. UpToDate.com Web site. Accessed January 24, 2008, at: www.uptodate.com (subscription required)

Mongelli M. Evaluation of gestation. emedicine.com Web site. Accessed February 17, 2008, at: www.emedicine.com/med/topic3236.htm

American Board of Pediatrics Content Specification(s):

Know the ultrasound findings and their limitations in determining gestational age

November: Question 2

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11 November 08

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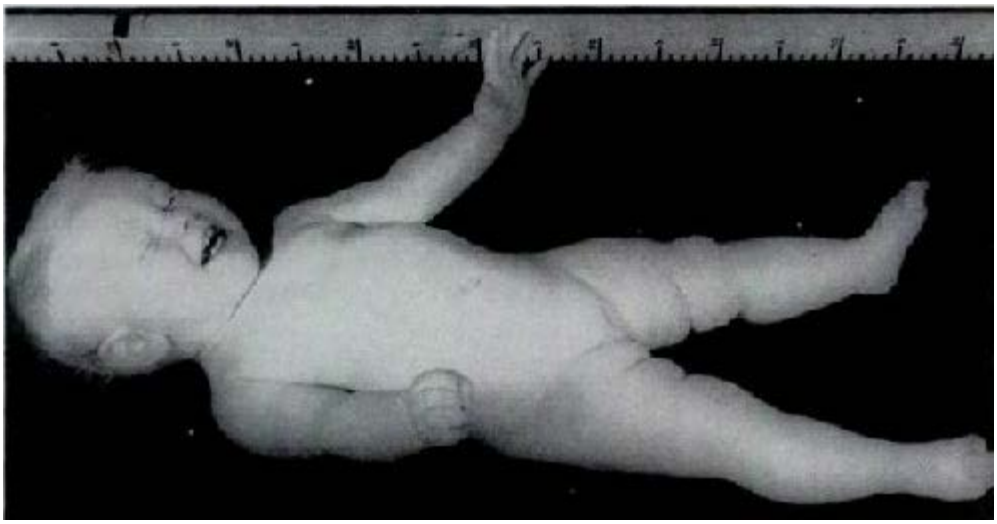
You are asked by a pediatrician to see a newborn with white skin (Figure 1). As you examine the infant in the mother's room, you see that both parents are black. You plan how you will tell the parents about the various hypopigmentation disorders and associated medical conditions.

Figure 1: An infant with a hypopigmentation disorder (from Kretchmer and Etzwiler [1958])



Of the following, the hypopigmentation disorder MOST associated with abnormal leukocyte function is:

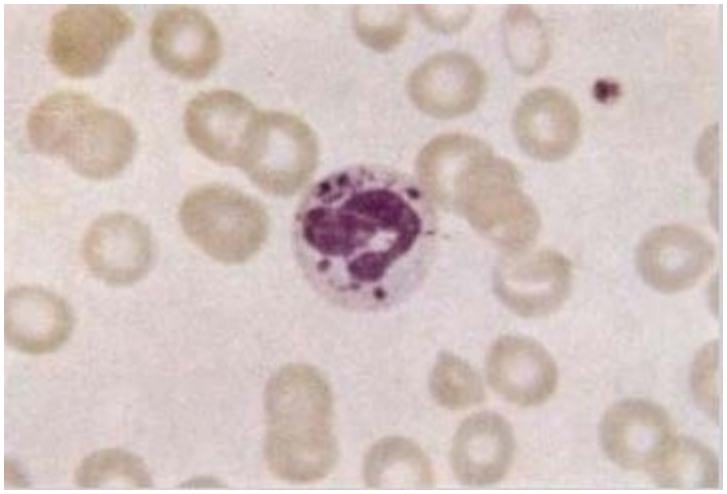
1	albinism
2	Chediak-Higashi syndrome
3	phenylketonuria
4	tuberous sclerosis
5	Waardenburg syndrome

You selected 2, the correct answer is 2.

Hypopigmentation in the neonate can be a clue to extracutaneous problems. Albinism is associated with eye abnormalities. Phenylketonuria is associated with central nervous system dysfunction. Tuberous sclerosis may present at birth with cardiac rhabdomyomas. Waardenburg syndrome includes hearing loss. The disorder most associated with abnormal leukocyte function is Chediak-Higashi syndrome.

Chediak-Higashi syndrome is an autosomal recessive disorder with an estimated incidence of 1 in 1,000,000 live births. In this disorder, a mutation in the *LYST* gene on chromosome 1q42 results in a defective or absent lysosomal transport protein, which produces large lysosomal granules in myeloid cells (Figure 2).

Figure 2: Large lysosomal granules in a leukocyte of a child with Chediak-Higashi syndrome (from Donohue and Bain [1957])



Melanocytes are unable to release melanin to keratinocytes. Lysosomes are unable to supply enzymes to phagosomes, which result in decreased killing of microbes and an increased susceptibility to infections of the skin and the respiratory tract. Treatment of the infections is the mainstay of therapy. Most patients die in childhood. Successful bone marrow transplantation has been reported in a few cases.

Albinism comprises a group of mainly autosomal recessive disorders affecting the production of melanin. The incidence is 1 in 20,000 live births. A previous classification was based on the absence of tyrosinase ("complete albinism") or its presence ("partial albinism"). Tyrosinase-present albinism is thought to involve other proteins that transport tyrosinase or melanin. Specific genetic markers are now used to identify at least 10 different types of albinism, including a temperature-sensitive type.

Clinical features of complete albinism include white hair and skin, pink or red irides, photophobia, nystagmus, strabismus, and decreased visual acuity. There is a significant risk for cutaneous malignancies. Management is based on photoprotection such as sunscreen and protective clothing. Close follow-up by an ophthalmologist and a dermatologist is indicated.

Phenylketonuria is an autosomal recessive disorder with an incidence of 1 in 10,000 live births. Absence of phenylalanine hydroxylase (or its dysfunction because of an absent cofactor) results in high serum phenylalanine and low tyrosine concentrations. Low tyrosine production results in low or absent melanin production, and gives the infants light hair, blue eyes, and hypopigmented skin. Low concentration of tyrosine, as a precursor to dopamine and norepinephrine, is associated with hyperreflexia, seizures, and mental retardation. Management of phenylketonuria depends on life-long dietary control of phenylalanine intake, monitored with frequent serum phenylalanine measurements.

Tuberous sclerosis is an autosomal dominant disorder with variable penetrance caused by a defect in chromosome 9q34.3 coding for hamartin, or a defect in chromosome 16p13.3 coding for tuberin. Tuberous sclerosis has an estimated incidence of 1 in 10,000 to 1 in 100,000 live births, depending on how stringently it is defined. Case definitions are based on major and minor criteria and may include skin and nervous system abnormalities as well as hamartomas almost anywhere in the body. Newborns may show hypopigmented macules, from one to several centimeters in diameter, with regular or irregular margins. Having four or more macules is highly

suggestive of tuberous sclerosis; having fewer macules may be a variation of normal. Newborns may also show poliosis (a patch of hypopigmented hair). Shagreen patches, adenoma sebaceum, and ungual fibromas are not usually seen until later in childhood.

Noncutaneous manifestations of tuberous sclerosis may include cardiac rhabdomyomas, renal cysts or hamartomas, subependymal nodules or astrocytomas, and lymphangiomyomatosis. Management of tuberous sclerosis is largely centered on correction or control of any renal or central nervous system dysfunction. Intractable seizures and infantile spasms may require neurosurgical intervention.

Waardenburg syndrome is an autosomal dominant disorder with an incidence of 1 in 15,000 live births. It is seen in 1% to 2% of congenitally deaf children. Several types are described, but the most common are caused by mutations in the *PAX* gene at 2q35 or the *MITF* gene at 3p12.3-14.1. Characteristics of the syndrome may include dystopia canthorum (telecanthus), heterochromic or hypochromic irides, synophrys, poliosis, vitiligo (piebaldism), and a variable sensorineural hearing loss. The areas of local hypopigmentation are caused by defects in melanocyte proliferation and migration. Management focuses on early recognition of the hearing loss.

References:

Donohue WL, Bain HW. Chediak-Higashi syndrome: a lethal familial disease with anomalous inclusions in the leukocytes and constitutional stigmata. *Pediatrics.* 1957;20:416-430

Ellis SS, Mallory SB. Hypopigmentation disorders. In: Eichenfield LF, Frieden IJ, Esterly NB, eds. *Textbook of Neonatal Dermatology*. Philadelphia, Pa: WB Saunders; 2001:353-369

Kretchmer N, Etzwiler DD. Disorders associated with the metabolism of phenylalanine and tyrosine. *Pediatrics.* 1958;21:445-475

Levy HL. Phenylketonuria. *Pediatr Rev.* 1986;7:269-275

American Board of Pediatrics Content Specification(s):

Know how to manage hypopigmentation, including albinism, phenylketonuria, Chediak-Higashi syndrome, tuberous sclerosis, partial albinism, and Waardenburg syndrome

Recognize the clinical features of the Waardenburg syndrome

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November: Question 3

A 4.5-kg term male newborn was delivered by emergency cesarean for a nonreassuring fetal heart rate pattern. Apnea, hypotonia, and acrocyanosis were present at birth; the heart rate was greater than 100 beats per minute. Apgar scores were 6 and 7 at 1 and 5 minutes, respectively. Manual ventilation was provided and the infant was placed on positive pressure ventilation with a fraction of inspired oxygen (FiO_2) of 0.6, peak inspiratory pressure (PIP) of 18 cm H_2O, positive end-expiratory pressure of 4 cm H_2O, and ventilator rate of 30 breaths per minute. His blood pressure was 75/54 mm Hg and oxygen saturation 100%. Initial studies were as follows.

Laboratory Findings	Patient Results (SI Values)
Total WBC count, $\times 10^3/\mu L$ ($\times 10^9/L$)	8.2 (8.2)
WBC differential	
Segmented cells, %	65
Lymphocytes, %	30
Platelet count, $\times 10^3/\mu L$ ($\times 10^9/L$)	150(150)
Hemoglobin, g/dL (g/L)	10 g/dL (100)

Chest radiograph shows clear lung fields, lung expansion to 8 ribs, normal cardiac silhouette. Echocardiogram shoes normal cardiac anatomy, left to right shunting across the foramen ovale and ductus arteriosus. Arterial blood gases were as follow: pH 7.30, $PaCO_2$ 44 mm Hg, PaO_2 100 mm Hg, bicarbonate 21 mEq/dL (22 mmol/L).

Of the following, the intervention MOST likely to increase oxygen delivery in this infant is:

1	dopamine infusion
2	increase in FiO_2
3	increase in PIP
4	inhaled nitric oxide
5	RBC transfusion

You selected 5, the correct answer is 5.

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The amount of oxygen (O_2) that can be delivered to the tissues (DO_2) depends on two major factors: cardiac output (CO) and the O_2 content of the blood (CaO_2). This can be expressed as follows:

$$O_2 \text{ delivery } (DO_2) = (CO) \times (CaO_2)$$

The O_2 content of arterial blood (CaO_2) depends on the amounts of O_2 bound to hemoglobin (HbO) and dissolved in the plasma (dissolved O). Hemoglobin-bound O is quantitatively the

most important contributor to CaO_2 because the amount of O_2 dissolved in blood is very small at normal PaO_2. The CaO_2 of blood is expressed as follows:

$$CaO_2 = (HbO_2) + (\text{dissolved } O_2)$$

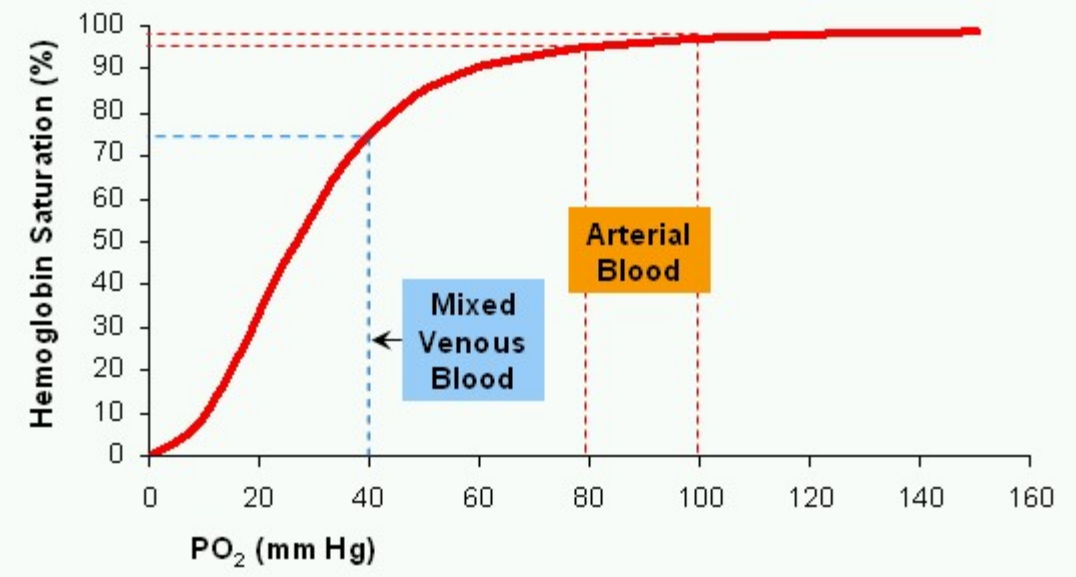
The amount of O_2 carried in the blood by hemoglobin depends on the concentration of hemoglobin (g % Hb), percentage of hemoglobin saturation (% saturation) and O_2 capacity of hemoglobin. Mathematically, this is expressed as follows:

$$HbO_2 = (\text{g\% Hb}) \times (O_2 \text{ capacity}) \times (\text{\% saturation})$$

O_2 capacity is a constant that represents the maximum amount of O_2 that can be carried by a gram of hemoglobin. This value is 1.34 mL/g of hemoglobin.

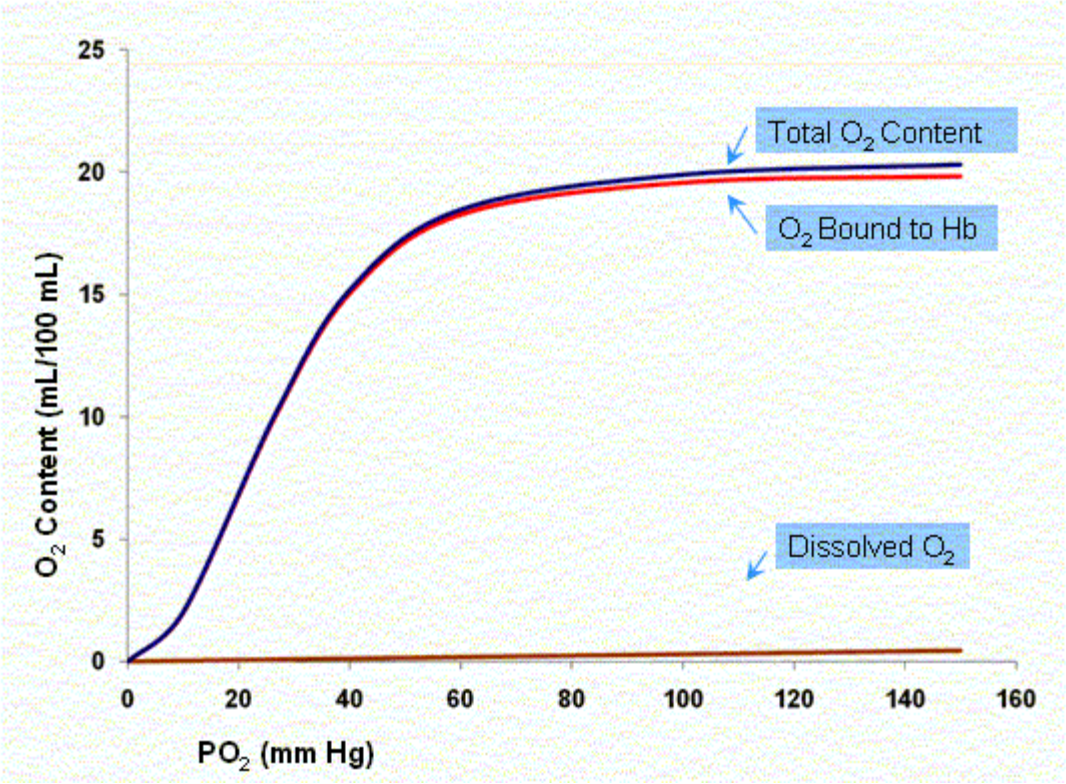
The relationship between arterial oxygen tension (PO_2) and amount of O_2 combined with hemoglobin, or hemoglobin saturation, is sigmoidal over the physiologic range (oxyhemoglobin dissociation curve). Hemoglobin is almost fully saturated at PO_2 of 80 to 100 mm Hg (Figure 1).

Figure 1: The relationship between arterial oxygen tension (PO_2) and hemoglobin saturation



A small amount of O_2 is dissolved in the plasma (Figure 2).

Figure 2: The O_2 content of arterial blood (Cao_2) depends on several factors, the most important being the O_2 bound to hemoglobin. In addition, some O_2 is carried in dissolved form in plasma



This amount is directly proportional to PO_2 from 0 to 600 mm Hg. At 38°C, 0.003 mL of O_2 is dissolved in 100 mL of plasma per mm Hg of O_2.

$$\text{Dissolved } O_2 = (0.003 \times PO_2) \text{ mL/100 mL of plasma}$$

Assuming that a normal term newborn infant has a hemoglobin concentration of 15 g/100 mL of blood, and that arterial blood is normally 100% saturated, the CaO_2 is:

$$CaO_2 = (HbO_2) + (\text{Dissolved } O_2)$$

$$=[(\text{g \% Hb}) \times (O_2 \text{ capacity}) \times (\text{\% saturation})] + \text{Dissolved } O_2$$

$$CaO_2 = (15) \times (1.34) \times (1.0) + (0.003 \times 100)$$

$$= 20.10 + 0.3$$

$$= 20.4 \text{ mL per 100 mL of arterial blood}$$

Assuming that the normal newborn cardiac output is approximately 120 mL/kg per minute, the amount of O_2 that can be delivered by the systemic circulation is calculated as follows:

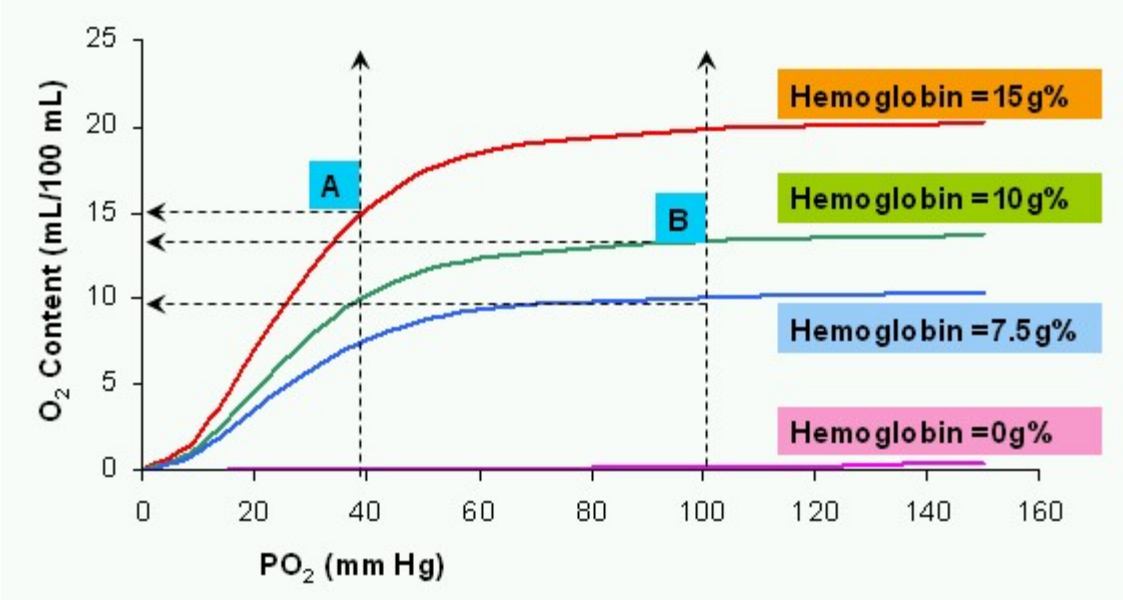
$$O_2 \text{ delivered} = (CO) \times (CaO_2)$$

$$= (120 \text{ mL/kg per minute}) \times (0.204 \text{ mL } O_2/\text{mL blood})$$

$$= 24.48 \text{ mL } O_2/\text{kg per minute}$$

The infant in this vignette has a lower than normal concentration of hemoglobin (10 g/dL [100 g/L]). An increase in hemoglobin concentration to 15 g/dL (150 g/L) after an RBC transfusion will increase the CaO_2 from 13.7 mL/100 mL of arterial blood to 20.4 mL/100 mL of arterial blood; the delivered O_2 will be 24.48 mL/kg per minute (Figure 3). Of note, the CaO_2 of blood with a hemoglobin concentration of 15 g/dL at a PO_2 of 40 mm Hg is higher than that of anemic blood at PO_2 of 100 mm Hg.

Figure 3: Effect of hemoglobin concentration and oxygen tension on oxygen content (CaO_2) of blood



The infant in the vignette is normotensive, and has normal perfusion. Cardiac activity appears normal on echocardiography. The normal neonatal heart functions at near capacity with stroke volume and heart rate maximized. Cardiac output (stroke volume × heart rate), therefore, is normally maximized. Administration of dopamine will increase systemic vascular resistance and, to a lesser degree, cardiac contractility but is unlikely to substantially increase cardiac output in this case.

The PaO_2 in the infant in the vignette is 100 mm Hg and oxygen saturation (Sao_2) is 100%. Increasing PaO_2 by increasing either FiO_2 or peak inspiratory pressure will not significantly affect the hemoglobin bound O_2 because the oxyhemoglobin dissociation curve is flat above a PaO_2 of 90 mm Hg.

Because O_2 is poorly soluble in blood, increasing the PaO_2 will not significantly increase the amount of dissolved O_2; therefore CaO_2 does not change appreciably. Even if the PaO_2 is increased to 400 mm Hg, only 0.9 mL of O_2/100 mL of blood is added to the CaO_2.

Inhaled nitric oxide functions to lower pulmonary vascular resistance when it is elevated, thereby increasing PaO_2 and SaO_2. Inhaled nitric oxide does not affect pulmonary vascular resistance when it is normal. Therefore, treatment with inhaled nitric oxide is unlikely to raise the PaO_2 and oxygen delivery in the infant in the vignette.

References:

Duc G. Assessment of hypoxia in the newborn: suggestions for a practical approach. *Pediatrics.* 1971;48(3):469-481

Durand DJ, Phillips B, Boloker J. Blood gases: technical aspects and interpretation. In: Goldsmith JP, Karotkin E, eds. *Assisted Ventilation of the Neonate*. 4th ed: Philadelphia, Pa: WB Saunders; 2003:279-292

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Simon BA, Moody EJ, Johns RA. Therapeutic Gases: Oxygen, Carbon Dioxide, Nitric Oxide, and Helium. In: Brunton LL, ed. *Goodman and Gilman's The Pharmacologic Basis of Therapeutics*. 11th ed. USA: McGraw-Hill; 2006

American Board of Pediatrics Content Specification(s):

Know the causes of arterial hypoxemia in a patient with a structurally normal heart and how to differentiate among them using measurements of arterial blood gas tensions

Understand the basic gas laws and how they apply to the clinical setting

Understand the various factors affecting oxygen uptake, transport, and delivery, including the blood and circulation

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November: Question 4

A 24-year-old primiparous woman is undergoing prenatal assessment at an estimated gestational age of 30 weeks. The amniotic fluid index, measured ultrasonographically, is estimated at 3.0 cm, suggestive of oligohydramnios. There is no history of preterm rupture of membranes and prolonged leakage of amniotic fluid. You are discussing with medical students the factors that contribute to amniotic fluid volume during pregnancy.

Of the following, the LARGEST contributor to amniotic fluid volume at 30 weeks' gestational age is fetal:

1	lung liquid synthesis
2	membrane fluid flux
3	oral/nasal secretion
4	swallowing
5	urine production

You selected 5, the correct answer is 5.

During the course of normal gestation, the amniotic fluid volume increases steadily from an estimated average of 65 mL at 12 weeks, reaches a peak average of 835 mL at 32 weeks, and decreases thereafter to an average of 500 mL at 42 weeks (Table).

Table. Amniotic Fluid Volume as a Function of Gestational Age*

Gestational Age, wk	50th Percentile, mL	5th Percentile, mL	95th Percentile, mL
12	65	20	125
16	170	85	420
20	375	170	750
24	585	250	1290
28	750	335	1670
32	835	420	1880
36	790	375	1750
40	625	290	1420
42	500	250	1130

*Adapted from Brace and Wolf (1989).

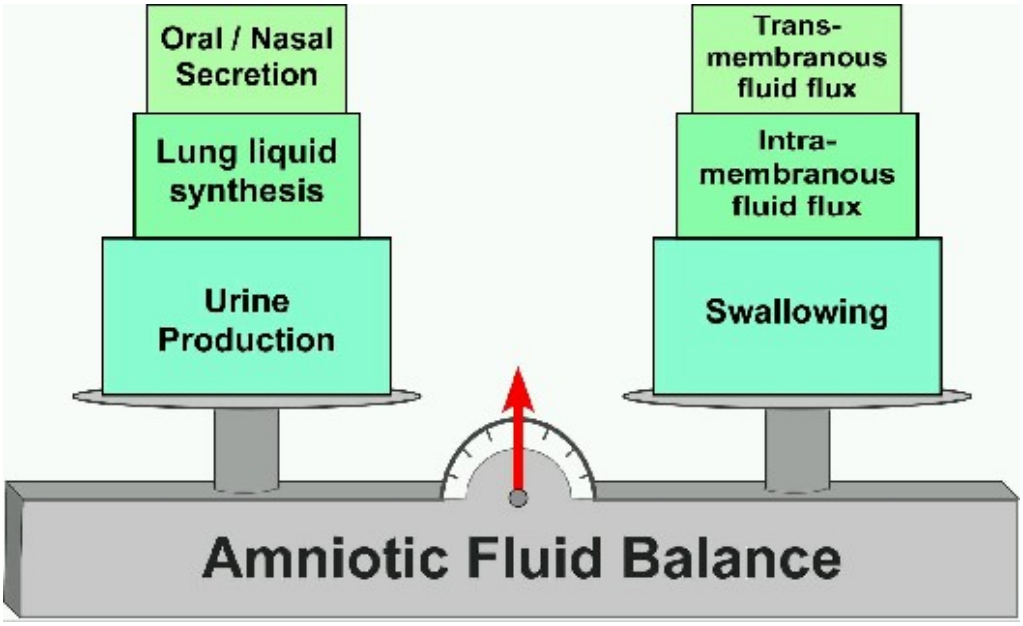
Oligohydramnios is diagnosed when the amniotic fluid volume is less than 45% of the mean volume for any given gestational age. Similarly, polyhydramnios is diagnosed when the amniotic fluid volume is greater than 220% of the mean volume for any given gestational age. Alternatively, oligohydramnios and polyhydramnios may be diagnosed using absolute cutoff limits for the amniotic fluid volume independent of the gestational age; oligohydramnios is defined as an amniotic fluid volume less than 300 mL, and polyhydramnios is defined as an amniotic fluid volume in excess of 2,000 mL.

Clinically both oligohydramnios and polyhydramnios can be diagnosed using

an ultrasonographic measurement of the amniotic fluid index, a summation of the maximal vertical fluid dimension visualized in the four quadrants of the uterus. The amniotic fluid index is stable at approximately 14 cm throughout the second and the third trimesters of pregnancy. An amniotic fluid index less than 5.0 cm, as in this vignette, indicates oligohydramnios, whereas an index greater than 25 cm indicates polyhydramnios.

During the latter half of gestation, fluid movement into and out of the amniotic sac uses six potential pathways (Figure).

Figure: Amniotic fluid balance



The entry of fluid into the amniotic sac is influenced largely by fetal urine production, to a lesser extent by fetal lung liquid synthesis, and only partly by fetal oral/nasal secretion. The exit of fluid from the amniotic sac is influenced largely by fetal swallowing and partly by fetal membrane fluid flux. The latter has two components: (1) intramembranous fluid flux which represents movement of water and solutes between amniotic fluid and fetal blood (in the placenta as well as in the umbilical cord), and (2) transmembranous fluid flux which represents movement of water and solutes between amniotic fluid and maternal blood within the wall of the uterus.

The largest contributor to amniotic fluid volume in the latter half of pregnancy is fetal urine production. Based on ultrasonographic measurements of fetal urinary bladder volume, the fetal urine production is estimated at 200 mL/kg of body weight per day. Any fetal condition that precludes the formation of urine (for example, renal agenesis or dysplasia) or prevents its release into the amniotic sac (for example, obstructive uropathy) often results in oligohydramnios. Whereas low fetal urine production and oligohydramnios are known to be associated, no such association has been shown between excess fetal urine production and polyhydramnios. The latter is most often the result of reduced amniotic fluid clearance.

The second major contributor to amniotic fluid volume in the latter half of pregnancy is fetal lung liquid synthesis. To date, the precise rate of lung liquid synthesis has not been determined in the human fetus. Based on ovine studies that mimic the human condition, the fetal lung liquid synthesis during the latter third of gestation is estimated at 100 mL/kg of body weight per day. Fetal lung liquid secretion is mediated by an active chloride transport in the pulmonary epithelium. Only approximately 50% of the fetal lung liquid is believed to enter the amniotic sac, whereas the remainder is swallowed by the fetus upon its exit via the trachea.

A minor contributor to amniotic fluid volume in the latter half of pregnancy is fetal oral/nasal secretion. Based on ovine studies, the fetal oral/nasal secretion rate during late gestation is estimated at 8.0 mL/kg of body weight per day.

Fetal swallowing represents the major route of amniotic fluid resorption. Limited human studies have shown that fetal swallowing increases steadily throughout gestation from an estimated average of 50 mL/kg of body weight per day at 18 weeks to a peak average of 155 mL/kg of body weight per day (range, 70-260 mL/kg of body weight per day) at term. Swallowing occurs primarily during episodes of fetal breathing, and it decreases to near zero just before the onset of labor and delivery. Any fetal condition that precludes swallowing (for example, anencephaly) or that impairs swallowing (for example, high gastrointestinal obstruction such as esophageal atresia) often results in polyhydramnios.

A minor contributor to amniotic fluid resorption in the latter half of pregnancy is fetal membrane fluid flux. Based on ovine studies, the intramembranous fluid flux between amniotic fluid and fetal blood is estimated at 60 mL/kg of body weight per day, whereas the transmembranous fluid flux between amniotic fluid and maternal blood is estimated at 3.0 mL/kg of body weight per day.

In this vignette, in the absence of a history of prolonged leakage of amniotic fluid, it is prudent to examine the fetus for abnormalities of renal structure and function as a cause of oligohydramnios.

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American Board of Pediatrics Content Specification(s):

Know how to diagnose oligohydramnios, its significance and the management of pregnancy when it is diagnosed

Know how to diagnose polyhydramnios, its significance and the management of pregnancy when it is diagnosed

PREVIOUS NEXT

November: Question 5

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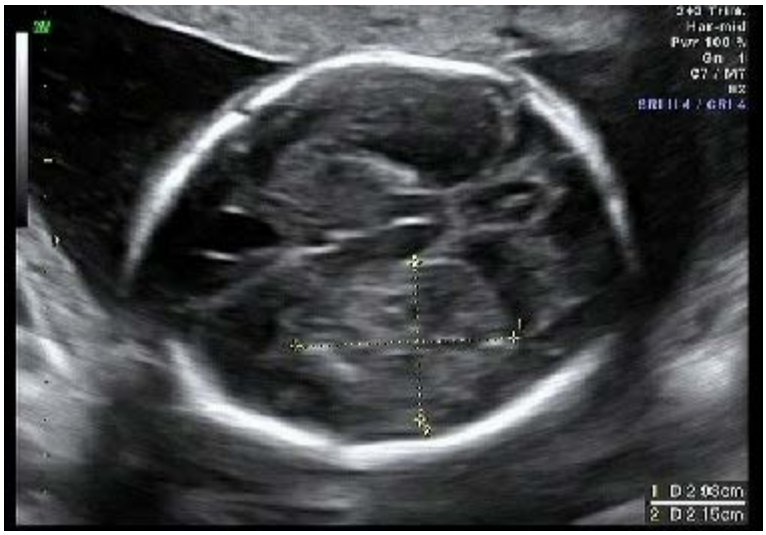
At 21 weeks' gestation, a large intracranial mass is detected on fetal ultrasonography (Figure). The mass measures 29 mm × 22 mm × 27 mm, is of mixed echogenicity, and consumes approximately one-third of the left cerebral hemisphere. Midline structures are shifted to the opposite side, and bilateral ventriculomegaly is noted. The differential diagnosis includes congenital cerebral neoplasm.

Figure: Ultrasonography of fetal head demonstrating large intracranial mass



Of the following, the PREDOMINANT intracranial tumor presenting in the fetus is:

1	astrocytoma
2	choroid plexus papilloma
3	ependymoma
4	medulloblastoma
5	teratoma

You selected 5, the correct answer is 5.

With an incidence of 0.34 per million live births, intracranial tumors presenting at birth or within the first 2 months are rare, and only comprise 1% to 3% of all pediatric brain tumors. Teratomas predominate, and account for 48% of brain tumors presenting in the fetus or at birth. Among intracranial tumors that present in the first 2 months after birth, neuroepithelial tumors predominate; however, teratomas still comprise 26% of this group. Medulloblastomas are the most common neuroepithelial brain tumors (18% of all nonteratomatous lesions), but

astrocytomas (15%), choroid plexus papillomas (13%), and ependymomas (11%) occur with similar frequency. Mesenchymal lesions, such as craniopharyngiomas, comprise less than 20% of the nonteratomatous neonatal brain tumors.

The fetus in this vignette has an intracranial mass consistent with a congenital teratoma. Teratomas are tumors that contain representative elements of the three germinal layers: ectoderm, mesoderm, and endoderm. Immature teratomas occur most frequently, and are characterized by the presence of cellular populations that retain embryological features and may include primitive neural tissue. Congenital intracranial teratomas may be quite large, greater than 5 cm in diameter, and may fill the cranial cavity completely. Congenital intracranial teratomas commonly originate from the region of the lateral ventricle (20%), in contrast to teratomas presenting after birth, which typically originate from the pineal region.

Congenital intracranial teratomas characteristically present with macrocrania, cranial-pelvic disproportion, dystocia, stillbirth, or preterm labor. Spontaneous rupture of the skull during delivery has been reported. Other features related to the displacement of intracranial tissue by the tumor may include local skull swelling, proptosis, and epignathus. Hydrocephalus also may be present, particularly with smaller intracranial lesions. Seizures, hemiparesis or quadriparesis, and cranial nerve abnormalities are more characteristic of tumors presenting after birth. Intracranial hemorrhage occurs with nearly 20% of neonatal brain tumors, but is more often associated with neuroepithelial or vascular lesions, than with teratomas.

Ultrasonography remains a good initial choice for the diagnosis of neonatal brain tumors. Fetal neoplasms have been demonstrated as early as 22 weeks'gestation, but only biopsy can determine the precise histologic type. The presence of calcifications and cystic components suggest a teratomatous lesion. Ultimately, computed tomography and magnetic resonance imaging are the mainstays of the diagnostic evaluation.

The clinical management of neonatal intracranial tumors is variable. When feasible, these brain tumors are managed definitively by surgical excision. As adjunctive treatment, chemotherapy and radiation are used infrequently.

The prognosis for neonatal brain tumors relates to the time of diagnosis and the histologic type of the neoplasm. Because the tumors are usually extensive at presentation, teratomas are associated with the poorest outcome and mortality rates exceeding 90%. The prognosis for nonteratomatous neonatal brain tumors is more variable. Medulloblastomas have an associated mortality rate exceeding 80%, and astrocytomas and ependymomas are potentially curable. Choroid plexus papillomas have the best prognosis, with minimal mortality rates and minimal associated neurodevelopmental impairment.

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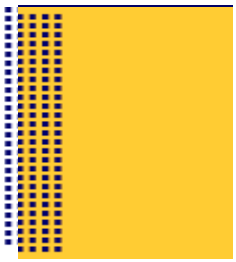
Washburne JF, Magann EF, Chauhan SP, et al. Massive congenital intracranial teratoma with skull rupture at delivery. *Am J Obstet Gynecol*. 1995; 173:226-228

American Board of Pediatrics Content Specification(s):

Understand the clinical features, diagnosis, management, and outcomes of congenital cerebral neoplasms



November: Question 6

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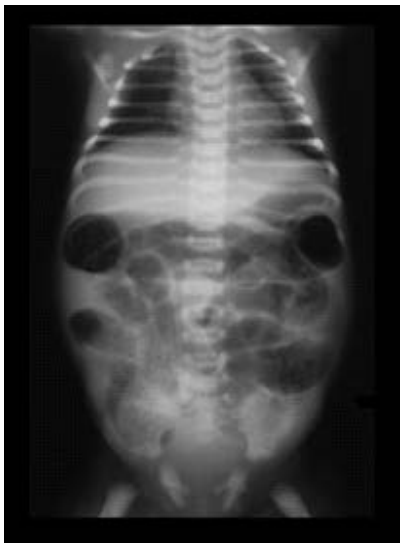
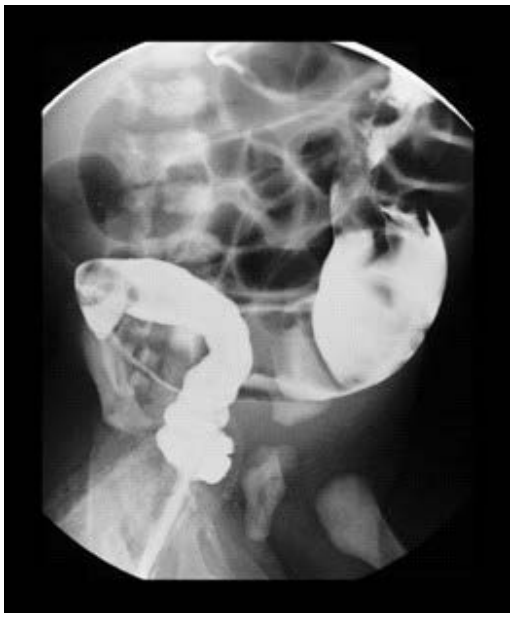
A term male infant passes no meconium during the first 24 hours after birth, develops abdominal distention, and has emesis after oral feedings. A nasogastric tube is placed, feedings are discontinued, and intravenous fluids are started. A complete blood cell count is normal. An abdominal radiograph shows multiple dilated loops of bowel (Figure 1).

Figure 1: Abdominal radiograph showing multiple dilated loops of bowel (courtesy of Robert G. Wells, MD, Milwaukee Wis)



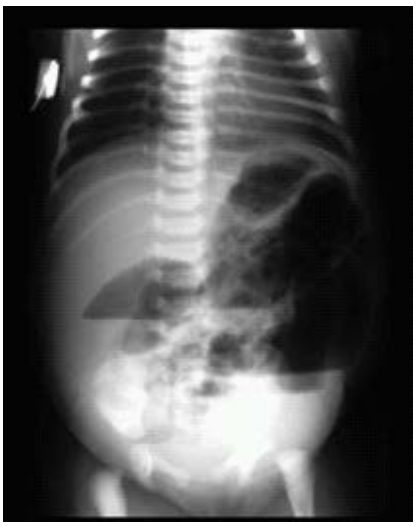
A water-soluble contrast enema (Figure 2) reveals a dilated proximal colon and a less dilated rectosigmoid colon. A suction rectal biopsy demonstrates aganglionosis and hypertrophy of the nerve trunks, confirming the diagnosis of Hirschsprung disease.

Figure 2: Water-soluble contrast enema showing a dilated proximal colon and a less dilated rectosigmoid colon



Twenty-four-hours after the rectal biopsy he becomes lethargic, develops a tympanic, tender, distended abdomen and passes a very large watery foul smelling stool. His temperature is 38.9°C, his respiratory rate is 45 breaths per minute, and his heart rate is 130 beats per minute. Blood pressure is 70/45 mm Hg. An abdominal radiograph is shown in Figure 3.

Figure 3: Abdominal radiograph



Multiple distended loops of bowel with air-fluid levels are identified. No evidence of perforation is observed.

A complete blood cell count with differential and an arterial blood gas are shown. You discuss the infant's immediate treatment with the surgical team.

Laboratory Test	Patient Result
White blood cell count, /μL (×10⁹/L)	21,000 (14)
Differential	
Bands	15
Segmented neutrophils,	64
Lymphocytes	16
Monocytes	5
Platelet count /μL (x×0⁹/L)	95,000 (95)
Arterial blood gas	
pH	7.27
PCO_2, mm Hg	45
PO_2, mm Hg	76
Bicarbonate, mEq/L (mmol/L)	20
Base deficit, mEq/L (mmol/L)	−2

Of the following the MOST likely next step in treatment is a(n):

1	exploratory laparotomy
2	leveling colostomy
3	rectal irrigation
4	sodium cromoglycate treatment
5	Swenson procedure

You selected 1, the correct answer is 3.

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Hirschsprung disease (HD), a common cause of distal intestinal obstruction in the newborn, is characterized by an absence of ganglion cells in the myenteric and submucosal plexus of the distal bowel. Approximately 50% to 90% of children with HD present during the neonatal period with a functional bowel obstruction.

The infant in the vignette develops Hirschsprung enterocolitis (HEC), the most serious and potentially life-threatening complication of HD. In published reports the incidence of HEC among cases of HD varies from 17% to 52%. Presenting signs and symptoms vary (Table).

Table. Presenting Features of Hirschsprung Enterocolitis	
Signs or Symptoms	% of Cases
Diarrhea (foul smelling, explosive, and watery	80-100
Abdominal distention	30-83
Vomiting	10-77
Explosive expulsion of flatus and liquid stool during rectal examination	30-69
Abdominal pain	20-30
Pyrexia	11-50
Hematochezia	2-10
Bowel perforation	2-5

Abdominal radiographs show distended loops of colon and small bowel dilation with multiple air fluid levels. Pneumotosis intestinalis may be present along with a pneumoperitoneum in cases of intestinal perforation.

Approximately 11% of neonates diagnosed with HD during the first week after birth will present with HEC. It can occur not only before the diagnosis of HD is established, but also after definitive surgical repair. Factors associated with HEC among infants who have not undergone a repair include: long segment aganglionosis, a family history of HD, and the presence of a major anomaly.

Although recent series show HD mortality (0%-39% of cases) to be decreasing, presumably because of earlier recognition and improved supportive care, most deaths that do occur usually are related to HEC.

Microscopically, HEC is characterized by infiltration of the intestinal crypts with white cells leading to the formation of crypt abscesses. With ongoing crypt abscess formation, there is progressive ulceration of the mucosa and possible transmural necrosis with perforation.

The causes of HEC are still unknown. Obstruction of the intestine and resultant stasis predisposes children to enterocolitis. Infectious agents such as *Clostridium difficile* or rotavirus have been associated with HEC, but few data support a specific pathogen. Inherent abnormalities of the mucosal immune system and mucosal mucin production may play roles in the development of HEC in certain patients with HD.

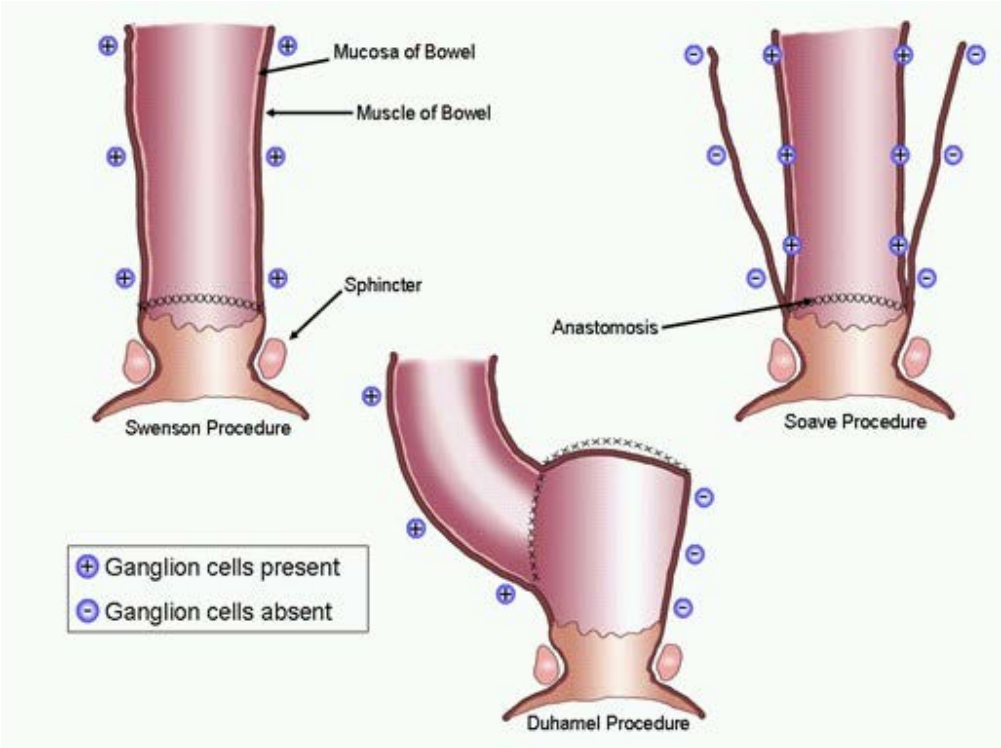
Treatment of HEC is largely supportive and includes fluid resuscitation, broad-spectrum antibiotics, and prompt decompression of the bowel from above using a nasogastric tube and from below with rectal irrigations. A large rectal catheter is inserted to aspirate gas and stool and to irrigate the colon. Warm saline irrigations are done through the catheter two to three times per day until the bowel is decompressed.

A leveling colostomy is required only if initial bowel decompression, fluid resuscitation, and antibiotic treatment fail to adequately decompress the bowel. Leveling refers to intraoperative determination of the site at which ganglion cells first appear. Frozen seromuscular biopsy specimens are reviewed by a pathologist during surgery and the ostomy is placed proximal to the site in which ganglion cells are present. In severe cases of HEC, the colon may become necrotic and an exploratory laporatomy will be necessary to resect the gangrenous colon. The infant in the vignette does not have clinical signs of severe HEC and an exploratory laporatomy is not indicated before beginning a trial of conservative management.

Definitive surgical repair of HD includes one of three surgical procedures (Figure 4).

- **The Swenson procedure involves a low anterior resection of the aganglionic bowel and anastomosis of the proximal ganglionic bowel to the rectum just above the dentate line.**
- **The Soave procedure requires removal of the distal mucosa of the bowel just above the dentate line to the peritoneal reflection. The remaining aganglionic bowel is resected. The ganglionic bowel is brought down into the sleeve of the bowel left behind and then anastomosed to the rectum above the dentate line.**
- **The Duhamel procedure leaves the last segment of aganglionic bowel in place and brings the ganglionic segment down behind it. The segments are sewn together to create a common channel above the dentate line.**

Figure 4: Three surgical procedures used in the repair of Hirschsprung disease



There are no prospective trials comparing the three surgical treatments, and the outcomes are similar. Each of the procedures can be done laparoscopically. Even though there has been a move to a one-stage procedure without a colostomy, surgeons may still need to place a stoma before performing a definitive repair procedure in neonates with severe HEC, bowel perforation, or a massively dilated proximal bowel. A definitive surgical procedure such as a Swenson procedure would be done after the neonate's HEC was successfully treated, and quite possibly after a colostomy had been placed to provide a period of bowel rest.

Sodium cromoglycate has been used in at least one case series of patients with HD with recurrent HEC. This experimental treatment has not been subjected to the rigors of a randomized trial and is not used in the initial treatment of neonates with HEC.

Do you want to add anything to your Learning Plan?
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Vieten D, Spicer R. Enterocolitis complicating Hirschsprung's disease. *Semin Pediatr Surg.* 2004;13:263-272

American Board of Pediatrics Content Specification(s):

Know the clinical manifestations of Hirschsprung disease

Know the pathological features and approach to diagnosis of Hirschsprung disease

Know the treatment and complications of Hirschsprung disease

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November: Question 7

A 14-day-old male neonate, whose birthweight was 952 g and estimated gestational age at birth was 27 weeks, has sudden onset of apnea and bradycardia, temperature instability, lethargy, and poor skin perfusion. He requires mechanical ventilation, a high fraction of inspired oxygen, vasopressor support, and intravenous nutrition. He also is receiving broad-spectrum antibiotics for suspected sepsis. Thyroid function tests, performed as a part of a research study, reveal the following plasma concentrations.

Thyroid Function Tests	Patient Results (SI Values)	Normal Values
Total thyroxine, µg/dL (nmol/L)	8.0 (104)	8.0-16.0 (104-208)
Total triiodothyronine, ng/dL (nmol/L)	39 (0.6)	80-200 (1.2-3.1)
Total reverse triiodothyronine, ng/dL (nmol/L)	98 (1.5)	15-65 (0.2-1.0)
Free thyroxine, ng/dL (pmol/L)	4.3 (56)	2.0-4.0 (26-52)
Thyroid-stimulating hormone, mIU/L	0.4	0.5-10.0 (0.5-10.0)
Thyroxine-binding globulin, mg/dL (nmol/L)	1.2 (192)	1.5-3.0 (240-480)

Of the following, the abnormal thyroid function in this infant MOST likely involves:

1	coupling enzyme
2	5'-deiodinase
3	thyroid peroxidase
4	thyroid-stimulating hormone
5	thyroxine-binding globulin

You selected 2, the correct answer is 2.

The clinical features and thyroid function tests in the infant in this vignette are consistent with the diagnosis of euthyroid sick syndrome (ESS), also called nonthyroidal illness or low T_3 syndrome. In ESS, thyroid function is altered by a systemic illness in the absence of an intrinsic thyroid glandular disease.

To understand thyroid function in ESS, it is important to examine the synthesis of the thyroid hormones. Thyroid hormone synthesis involves three critical steps: uptake of iodide, iodination of tyrosine, and deiodination of thyronines.

In ESS, the iodide uptake by the thyroid gland under the influence of TSH is usually normal. Likewise, the iodination of tyrosine and the formation of iodothyronines under the influence of thyroid peroxidase and coupling enzyme are usually normal. Also although the synthesis of TBG is usually normal, the binding of the thyroid hormone to TBG is decreased. The problem in ESS

relates to deiodination of thyronines.

Removal of iodine (deiodination) from specific positions within the tyrosyl and phenolic rings of T_4, under the influence of deiodinase, is required for the formation of functional thyroid hormones. Triiodothyronine (3,3', 5-triiodothyronine) (T_3) is derived by 5'-deiodination; it is the most biologically active form of thyroid hormone. Reverse triiodothyronine (3,3',5'-triiodothyronine) (rT_3) is derived by 5-deiodination; it is biologically inactive. Further deiodination results in the formation of diiodothyronines and monoiodothyronines, which have no biologic activity. The process of deiodination of thyronines is critical for balancing thyroid function; 5'-deiodination is predominant when active thyroid hormone is needed, whereas 5-deiodination prevails when thyroid function needs to be suppressed.

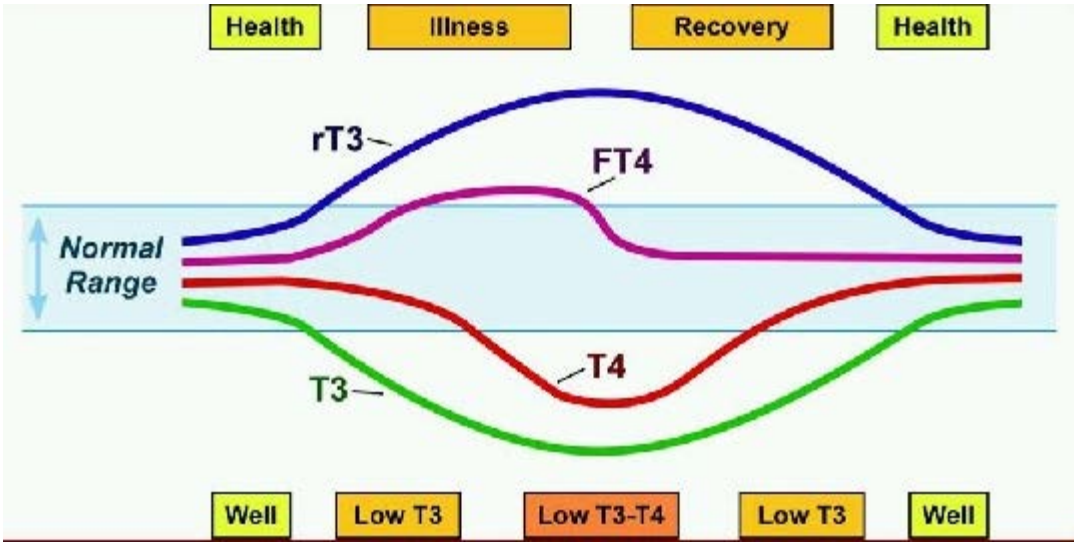
The cardinal feature of ESS is the markedly depressed plasma concentration of total T_3, resulting from a decrease in the conversion of T_4 to T_3 in the peripheral tissues, mediated by inhibition of 5'-deiodinase. The plasma concentration of total rT_3 is increased reciprocally. The plasma concentration of total T_4 is normal or low, whereas that of fT_4 may be increased modestly from a defect in the binding of the thyroid hormone to its carrier proteins (TBG, transthyretin, and albumin). The plasma concentration of TSH may be low, reflecting immaturity of the hypothalamic-pituitary-thyroid axis.

Euthyroid sick syndrome has many causes, which include:

- systemic infection
- systemic illness resulting in hypoxemia, hypercapnea, and hypotension
- metabolic derangements such as hypoglycemia and hypocalcemia
- organ dysfunction including liver and kidney disease
- injury from trauma, surgery, and burns
- catabolic conditions such as malnutrition
- medications such as glucocorticosteroids and dopamine

The changes in thyroid function resulting from these factors probably are triggered by cytokines released from macrophages and monocytes as a part of a systemic immune response. The earliest evidence of thyroid dysfunction in systemic illness is the depletion of circulating T_3—hence the term *low T_3 syndrome*—and a reciprocal increase in circulating rT_3 (Figure).

Figure: Sequential changes in thyroid function in euthyroid sick syndrome



Worsening of the systemic illness is characterized by an additional depletion of circulating T_4, often referred to as low T_3-T_4 syndrome. Recovery from the systemic illness is characterized by reversal of these changes in thyroid function.

The preterm infant in this vignette has many of the factors that can contribute to ESS. Further research is needed to delineate the specific changes in thyroid function associated with ESS in preterm infants. This research may help determine whether thyroid hormone treatment is safe and efficacious in such cases.

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References:

Nicoloff JT, LoPresti JS. Nonthyroidal illness. In: DeGroot LJ, ed. *Endocrinology.* 3rd ed. Philadelphia, Pa: WB Saunders; 1995:665-675

Polk DH, Fisher DA. Fetal and neonatal thyroid physiology. In: Polin RA, Fox WW, Abman SH, eds. *Fetal and Neonatal Physiology.* 3rd ed. Philadelphia, Pa: WB Saunders; 2004:1926-1933

American Board of Pediatrics Content Specification(s):

Understand the proper use of laboratory tests (including screening tests) in the diagnosis of thyroid dysfunction

Understand the causes of transient hypothyroidism in the neonate

Understand the embryology and normal physiological function of the normal thyroid gland

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November: Question 8

A pregnant woman who initially presented at 8 weeks' gestation had her pregnancy dates confirmed by crown-rump length measurement. Genetic screening results were normal and maternal weight gain and overall health were good. Currently, at 33 weeks' gestation, the uterine fundal height is 29 cm. Repeat ultrasonography reveals an estimated fetal weight of 1,200 g and a relatively small, low-lying placenta, leading you to consider the placental role in fetal growth.

Of the following, the MOST important placental hormone involved in regulating the growth of the fetus is:

1	corticotropin-releasing hormone
2	estrogen
3	human chorionic gonadotropin
4	human placental lactogen
5	progesterone

You selected 3, the correct answer is 4.

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The human placenta plays a pivotal role in fetal growth. It must integrate fetal demand with maternal substrate supply. In addition to transferring nutrients and waste products, the placenta has metabolic and endocrine functions that assist with fetal growth. In its role as an endocrine organ, it produces peptide hormones, such as human chorionic gonadotropin (hCG), human growth hormone variant (hGHv), human placental lactogen (hPL), insulinlike growth factors (IGFs), and corticotropin-releasing hormone (CRH), as well as steroid hormones, such as estrogens, progesterone, and glucocorticoids. Depending on the compound, hormones are released into the fetal and/or maternal circulations.

The placental hormone important for fetal growth regulation required in this vignette is hPL. hPL is secreted into both the maternal and fetal circulations after 6 weeks' gestation. In the pregnant woman, hPL stimulates production of IGF, ultimately resulting in an increase in glucose and amino acid availability to the fetus. In the fetus, hPL modulates embryonic development and influences fetal growth by stimulating production of other hormones, such as IGFs and insulin, which are important in cellular proliferation and growth.

CONTENT SPECIFICATIONS ADDRESSED ABP American Board of Pediatrics

Corticotropin-releasing hormone is produced by the placenta and secreted into the fetal circulation, increasing fetal cortisol production and assisting with fetal lung maturation. CRH is also secreted into the maternal circulation. Because peak CRH concentrations are observed at the time of labor, it is postulated that CRH is an important trigger for the onset of labor.

Although the placenta secretes estrogen in increasing amounts throughout pregnancy, estrogen is not directly involved in fetal growth. It has many functions, including regulation of progesterone, maturation of fetal organs, proliferation of the uterine endometrium, and stimulation of fetal adrenocorticotropic hormone secretion.

During early pregnancy, hCG enters the maternal circulation and stimulates progesterone production in the corpus luteum. It does not play a role in fetal growth. Maximal concentrations of hCG are reached at week 8 of gestation and by week 13, the placental production of progesterone supports the continuing pregnancy.

Placental production of progesterone begins approximately 35 to 47 days after ovulation. Although some studies have shown correlations between maternal progesterone concentrations and birthweight, progesterone has minimal direct effect on fetal growth. Instead, progesterone is necessary for maintaining a quiescent uterus. It also has antiinflammatory and immunosuppressive abilities, protecting the fetus from immunologic rejection by the mother.

Human GHv is another hormone produced by the placenta that plays an indirect role in fetal growth. However, unlike hPL, it is only secreted into the maternal circulation. During pregnancy, maternal pituitary GH production is suppressed and hGHv becomes the dominant GH in the maternal circulation. Human GHv can stimulate IGF production in the pregnant woman and influence fetal growth by increasing the nutrient availability to the fetus. Interestingly, maternal serum concentrations of hGHv are reduced in growth-restricted fetuses.

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(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:

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Handwerger S, Freemark M. The roles of placental growth hormone and placental lactogen in the regulation of human fetal growth and development. *J Pediatr Endocrinol Metabol* 2000;13:343-356

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American Board of Pediatrics Content Specification(s):

Understand the hormonal factors that affect intrauterine growth

Understand the fetal factors that affect intrauterine growth

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11 November 08

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November: Question 9

A 15-day-old, 890-g male infant is receiving mechanical ventilation, supplemental oxygen, and parenteral nutrition through a central venous catheter. He is not being fed enterally. The infant has required an increase in mechanical ventilation and oxygen support during the last day. Tracheal secretions have increased and are cloudy. A new right lower lobe infiltrate is noted on chest radiography. His blood culture yields *Escherichia coli*. The hospital infection control nurse reports that the same K1 strain caused bacteremia and meningitis in two nonventilated low-birthweight infants several weeks ago.

Of the following, the mode of transmission MOST likely associated with the infant's infection is:

1	airborne nucleus
2	common vehicle
3	droplet
4	intermediary
5	vector

You selected 2, the correct answer is 4.

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The infant in the vignette has acquired an infection caused by *Escherichia coli*, a gram-negative coliform. Although there is wide genetic diversity of human commensal isolates, strains of *E coli* that cause neonatal illness are few in number.

One of the capsular antigens of *E coli*, K1, is uniquely associated with meningitis. Neonates with meningitis caused by the K1 strains have significantly higher mortality and morbidity rates than infants with meningitis caused by non-K1 strains. The K1 strain of *E coli* can colonize the maternal birth canal, and subsequently the infant, during labor or delivery. In addition, nursery personnel have high carriage rates of the K1 strain; such colonization poses a risk for postnatal transmission to infants.

Late-onset (>3 days after birth) hospital-acquired infections caused by gram-negative bacilli account for approximately 19% of bloodstream infections and 30% of pneumonias in neonatal intensive care units. Outbreaks of hospital-acquired infections usually occur in clusters, as seen in the vignette. Recognition of such an outbreak depends on rigorous surveillance and application of criteria to differentiate endemic, or isolated, cases from epidemic cases of infection. Evaluating real-time trends of data is imperative for outbreak recognition. Once a cluster of patients with a common microbial cause for infection is identified, an epidemiologic investigation is warranted. Such an investigation should include genotyping of the causative organism and identification of potential reservoirs, risk factors, and mode(s) of transmission.

Microorganisms can spread among patients through several routes. Contact is the dominant mode of transmission. *Direct contact* involves direct transfer from an infected or colonized person to a patient. Spread of organisms through an intermediary, such as a person's hands or an inanimate object (fomite), is referred to as *indirect contact* transmission. Transmission occurs more frequently from the hands of caregivers than by contaminated fomites. Because the newborn gastrointestinal tract is a major reservoir for gram-negative pathogens, with concentrations of microorganisms exceeding billions per gram of stool, it is not surprising that the hands of caregivers can be contaminated even with casual contact with colonized neonates. This transient hand flora, which survives brief periods in the superficial layers of skin, is responsible for most hospital-acquired infections. Inadequate hand hygiene was likely responsible for the indirect transmission of gram-negative organisms among neonates in the vignette. Effective hand cleansing by caregivers decreases colonization rates of resident flora (organisms that attach to deeper layers of the skin and inhabit the skin at all times) as well as transient flora, and reduces indirect transmission among patients. Use of gloves when handling body liquids in concert with diligent hand hygiene may further reduce risk of indirect contact transmission of microbes.

Common vehicle, or common source, infection occurs when a medication, solution, or equipment becomes contaminated and transfers the infection to infants. Outbreaks caused by a common vehicle are rare in neonatal intensive care units; however, they can occur, particularly when new devices or technologies are introduced into the nursery. The list of published common source outbreaks is extensive and includes contaminated intravenous fluids, lipid emulsions, multidose vials, breast milk, formula, suction machines, and laryngoscopes. A common vehicle would be a less likely mode of transmission for the *E coli* infections in the vignette because they occurred several weeks apart, and cases did not share common treatments (such as intravenous fluids, respiratory equipment, or formulas).

Vector transmission refers to the spread of infections by insects. This is unlikely for the infections in the infants in the vignette because vector transmission is exceedingly rare in a well-maintained hospital. Still, it should be remembered that ants, roaches, and flies can transmit microbes on their legs.

Airborne transmission of organisms occurs via three distinct methods of dispersal: droplet nucleus transmission, shedding, and dispersion of fungal spores. Droplet nuclei, which are just a few microns in diameter, can be aerosolized from the respiratory tract. Such nuclei can float on currents of air over long distances and remain suspended in the air for more than an hour. Their size allows them to penetrate the upper airway defenses and enter the lung. Pathogens transmitted in such a fashion include measles, tuberculosis, Legionella, influenza ,and varicella. Information about droplet nucleus transmission in neonates is sparse and gram-negative bacilli are not spread as droplet nuclei.

Droplet transmission involves transfer of the microorganism by large respiratory droplets generated during coughing, sneezing , or exhuberant speech, especially when pronouncing the letters "t" and "p." Transmission of droplets is easily interrupted by a mask or by maintaining a distance of at least 3 or 4 feet from the infected patient because the droplets travel only a few feet in the air. Pathogens spread by droplet transmission include *Bordetella pertussis*, *Neisseria meningitides*, and group A streptococci. Hospital-acquired spread of these pathogens in a neonatal intensive care unit is rare, and gram-negative bacilli are not transmitted by droplet transmission.

Strategies for preventing hospital-acquired infections include a combination of "better practices" rather than any single intervention. Principles for prevention of such infections are summarized in the Table.

Table. Best Practice Recommendations to Prevent Nosocomial Infection in the Neonatal Intensive Care Unit
Observe recommendations for universal precautions with all patient contact
Gowns, mask and isolation as indicated
Nursery design/engineering
Appropriate nurse-to-patient ratio
Avoid overcrowding and excessive workload
Readily accessible sinks, antiseptic solutions, soaps, and paper towels
Handwashing
Improve handwashing compliance
Wash hands before and after each patient encounter
Appropriate use of soap, alcohol-based preparations, or antiseptic solutions
Alcohol-based antiseptic solution at each bedside
Provide emollients for nursery staff
Education and feedback for nursery staff
Minimizing risk of central venous catheter (CVC) contamination
Maximal sterile barrier precautions during CVC insertion
Minimize entry into the line for laboratory tests or medications
Aseptic technique when entering the line
Minimize CVC days
Sterile preparation of all fluids to be administered via a CVC
Respiratory care
Decrease duration of mechanical ventilation
Minimize interruptions of airway circuit
Use sterile techniques for suctioning
Elevate head of bed
Meticulous skin care
Encourage early and appropriate advancement of enteral feedings
Education and feedback for nursery personnel
Continuous monitoring and surveillance of nosocomial infection rates in the nursery

* Adapted from Adams-Chapman and Stoll [2002].

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References:

Adams-Chapman I, Stoll B. Prevention of nosocomial infections in the neonatal intensive care unit. *Curr Opin Pediatr.* 2002;14:157-164

Harris JS, Goldmann DA. Infections acquired in the nursery: epidemiology and control. In: Remington JS, Klein JO, eds. *Infectious Diseases of the Fetus and Newborn Infant.* 5th ed. Philadelphia, Pa: WB Saunders Co; 2001;1371-1418

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Klein JO. Bacterial sepsis and meningitis. In: Remington JS, Klein JO, eds. *Infectious Diseases of the Fetus and Newborn Infant.* 5th ed. Philadelphia, Pa: WB Saunders Co; 2001;943-998

McCracken GH, Sarff LD, Glode MP, et al. Relation between *Escherichia coli* K1 capsular polysaccharide antigen and clinical outcome in neonatal meningitis. *Lancet.* 1974;2:246-250

Nissen MD. Congenital and neonatal pneumonia. *Paediatr Resp Rev.* 2007;8:195-203

Polin RA, Saiman L. Nosocomial infections in the neonatal intensive care unit. *NeoReviews.* 2003;4:e81-e89

American Board of Pediatrics Content Specification(s):

Understand the epidemiology, pathogenesis and prevention of neonatal infections with *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Proteus*, *Citrobacter*, *Salmonella*, and *Pseudomonas*

Understand the effective techniques for control of nosocomial infection in the nursery, neonatal intensive care unit, and obstetrical unit

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November: Question 10

A nurse in your neonatal intensive care unit comes to you with an urgent request. She has just had a routine 30-minute prenatal ultrasound study of her 26-week-gestation fetus, during which no fetal breathing movements were seen. She is scheduled to see her obstetrician on the next day for an interpretation of the ultrasound study, but she wants to know now if she could have done anything to inhibit the fetal breathing movements.

Of the following, the maternal factor MOST likely to inhibit fetal breathing movements is:

1	betamethasone
2	hyperglycemia
3	hyperoxia
4	indomethacin
5	labor

You selected 2, the correct answer is 5.

Fetal breathing movements (FBMs) are present from the 10th week of gestation. Their frequency increases with gestational age to 6% of the time by 19 weeks, 14% of the time by 26 weeks, and up to 50% of the time by the last 10 weeks of pregnancy. Some factors that lead to increased or decreased FBMs in the last 10 weeks of pregnancy are listed (Tables 1 and 2). Labor at any gestational age is the factor most likely to inhibit FBMs.

Table 1. Some Maternal Factors That Increase Fetal Breathing Movements
Hypoventilation or breathing 2%-4% CO_2
Hyperoxia, if intrauterine growth-restricted fetus
Fever
Glucose infusions after maternal fasting; maternal postprandial glucose rise
Smoking (faster breathing rate, but more time spent apneic)
Acute caffeine dose of 454 mg (not seen with 200 mg)
Betamethasone, terbutaline, or indomethacin

Table 2. Some Maternal Factors That Decrease Fetal Breathing Movements
Hyperventilation
Hypoxemia with acidemia, but not hypoxemia alone
Labor or approaching labor
Hypothermia
Alcohol, barbiturates, methadone, or prostaglandin E_2

Very little fluid is exchanged during FBMs, with volumes estimated as 0.5 mL or less per breath. During periods of breathing, the respiratory rate is usually 40 to 60 breaths per minute. These breathing periods are episodic: in normal third-trimester fetuses, no FBMs are seen in 8% of the observed 30-minute intervals, the typical observation interval during an ultrasound study used to determine a biophysical profile of the fetus.

The FBMs decrease within 3 days of preterm or term birth, mediated by increasing maternal serum concentrations of prostaglandin E_2 and blocked by prostacyclin inhibitors such as indomethacin. These changes have been described using pooled data comparing the mean values from groups of patients. Attempts to use a decrease in FBMs to predict imminent onset of labor for a specific individual have been unsuccessful. During active labor, FBMs are seen less than 10% of the time.

Other maternal medications affect FBMs. Stimulants, such as terbutaline or cocaine, cause increased FBMs. Depressants, such as alcohol or magnesium sulfate, decrease FBMs. The mechanism by which betamethasone increases FBMs may involve greater uterine blood flow and oxygen delivery to the fetus.

Hyperoxia in a normal pregnancy is not associated with any change in FBMs. Hyperoxia in a pregnancy with intrauterine growth restriction causes increased FBMs. Hypoxemia with acidemia is associated with decreased FBMs, but hypoxemia alone is not.

Hyperglycemia causes increased FBMs if the mother has fasted. This includes the daily fasting between meals: the second and third hours after a normal meal during pregnancy are associated with increased FBMs. Chronic hyperglycemia without fasting, as in a diabetic mother, causes no change in FBMs.

Maternal cigarette smoking may have several different effects on FBMs. Some reports find an increase in the breathing rate, but also an increase in the number of long periods of apnea that can confound the scoring of a biophysical profile. Other reports find that smoking abolishes FBMs, and still others observe no significant change.

The most important application of FBMs is with the biophysical profile. The biophysical profile involves detection of FBMs and four other items: muscle tone, body movement, heart-rate changes (the nonstress test), and amniotic fluid volume. No single item is very predictive. The five items are combined in a biophysical profile score of 0 to 10, assigning either a 0 or 2 to each item. A score of less than 6 has been associated with increased perinatal mortality and often leads to delivery.

References:

Harman CR. Assessment of fetal health. In: Polin RA, Fox WW, Abman SH. *Fetal and Neonatal Physiology.* 3rd ed. Philadelphia, Pa: WB Saunders; 2004:357-401

Miller MJ, Fanaroff AA, Martin RJ. Respiratory disorders in preterm and term infants. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal Perinatal Medicine Diseases of the Fetus and Infant.* 8th ed. Philadelphia, Pa: Mosby Elsevier; 2006:1122-1146

Richardson BS, Gagnon R. Fetal breathing and body movements. In: Polin RA, Fox WW, Abman SH. *Fetal and Neonatal Physiology.* 3rd ed. Philadelphia, Pa: WB Saunders; 2004:181-197

American Board of Pediatrics Content Specification(s):

Know the factors affecting control of fetal breathing movements

Understand the rationale, interpretation, and shortcomings of maternal detection of the biophysical profile as a means of assessing fetal well-being

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December: Question 1

A 28-year-old primiparous woman is about to deliver at an estimated gestational age of 34 weeks. Maternal history is significant for autoimmune thyrotoxicosis (Graves disease) diagnosed during the first trimester of pregnancy. Although propylthiouracil treatment was recommended, the mother's compliance with the medication has been poor. Evaluation of the thyroid status of the neonate is planned, specifically to determine the risk of neonatal thyrotoxicosis.

Of the following, the umbilical cord blood test MOST predictive of neonatal thyrotoxicosis is the measurement of:

1	thyroid-stimulating hormone
2	thyroxine-binding globulin
3	total reverse triiodothyronine
4	total tetraiodothyronine
5	total triiodothyronine

You selected 2, the correct answer is 1.

Hyperthyroidism in the pregnant woman is uncommon with an estimated incidence of 1 to 2 cases per 1,000 pregnancies. The most common cause of maternal hyperthyroidism is autoimmune thyrotoxicosis (Graves disease), accounting for approximately 90% of cases. Hyperthyroidism in the neonate is rare, occurring only in about 1 in 70 pregnancies complicated by maternal thyrotoxicosis. The neonatal disease is attributed to transplacental passage of maternal thyroid-stimulating immunoglobulin (TSI). The titer and the rate of clearance of TSI determines the duration of the neonatal disease. A maternal TSI titer exceeding 500% of control reference values is associated with fetal and/or neonatal thyrotoxicosis. The half-life of maternal TSI in the newborn is approximately 21 days, which accounts for the typical duration of neonatal disease that varies between 3 and 12 weeks after birth.

Most antithyroid drugs, including propylthiouracil, readily cross the placenta and potentially can suppress thyroid function in the fetus/neonate. However, when maternal thyrotoxicosis is controlled judiciously with appropriate dosage of antithyroid drugs and careful monitoring of maternal thyroid status, the risk of fetal/neonatal hypothyroidism is low. Because the mother in this vignette was not compliant with antithyroid medication, her fetus/neonate is not likely to manifest hypothyroidism. On the contrary, the mother's uncontrolled thyrotoxicosis raises the likelihood of thyrotoxicosis in her fetus/neonate.

The umbilical cord blood test most predictive of neonatal thyrotoxicosis is the measurement of thyroid-stimulating hormone (TSH). The normal TSH in cord blood ranges from 3.0 to 12.0 mIU/mL. A TSH value less than 0.05 mIU/mL, indicating suppression of anterior pituitary in response to the hyperthyroid state, is diagnostic of neonatal thyrotoxicosis. In neonatal thyrotoxicosis, the cord blood concentrations of total tetraiodothyronine (thyroxine, T_4), triiodothyronine (T_3), and reverse triiodothyronine (rT_3) are usually normal.

The most striking physiologic increase in plasma concentration of thyroxine-binding globulin (TBG)—the principal thyroid hormone–binding protein—occurs during pregnancy. This increase is attributed primarily to an increase in sialic acid content, which prolongs the biological half-life of TBG. The increase in maternal plasma TBG concentration may be observed as early as 3 weeks after implantation and reaches its peak around the end of the second trimester and the beginning of the third trimester of pregnancy. In the newborn, the plasma TBG concentration is approximately 1.5 times the normal adult concentration of 1.0 to 2.0 mg/dL (160-320 nmol/L). The cord blood concentration of TBG is not predictive of neonatal thyrotoxicosis.

The clinical manifestations of neonatal thyrotoxicosis include irritability and tremors, tachycardia and hypertension, and poor weight gain or excessive weight loss. Thyroid enlargement and exophthalmos are invariably present. Hepatosplenomegaly with jaundice, thrombocytopenia, and hypoprothrombinemia have been observed. The symptoms and signs of neonatal thyrotoxicosis may be delayed as long as 8 to 10 days after birth. This delay often is the result of maternal antithyroid treatment, which may suppress the thyroid function in the neonate initially. Untreated, neonatal thyrotoxicosis has a 25% risk of mortality, which may result from cardiac arrhythmia and failure.

References:

Becks GP, Burrow GN. Diagnosis and treatment of thyroid disease during pregnancy. In: DeGroot LJ, ed. *Endocrinology.* 3rd ed. Philadelphia, Pa: WB Saunders Co; 1995:799-820

Fisher DA, Polk DH. Thyroid disease in the fetus, neonate, and child. In: DeGroot LJ, ed. *Endocrinology.* 3rd ed. Philadelphia, Pa: WB Saunders Co; 1995:783-798

American Board of Pediatrics Content Specification(s):

Identify the etiology and clinical manifestations of congenital hyperthyroidism

Know the laboratory features and treatment of congenital hyperthyroidism

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December: Question 2

A 16-day-old breastfeeding infant with a normal medical history presents with persistent jaundice since the third day after birth. Bilirubin concentrations (total and conjugated) are 7.5 mg/dL (128 µmol/L) and 3 mg/dL (51 µmol/L).

Extrahepatic biliary atresia is a cause of persistent cholestatic jaundice in the newborn period. Early diagnosis is important because a portoenterostomy can delay or prevent liver destruction. History can help in diagnosis, but a complete investigation is called for to identify infants who might benefit from the surgical procedure.

Of the following, the clinical finding in addition to jaundice MOST associated with extrahepatic biliary atresia at this age is:

1	dark yellow diaper staining
2	gray stools in the first week
3	hepatosplenomegaly
4	male sex
5	vomiting and/or weight loss

You selected 4, the correct answer is 1.

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Extrahepatic biliary atresia occurs in 1 in 15,000 to 20,000 live births in North America. The incidence is higher in Asia (1 in 10,000). The female-to-male ratio is 1.4:1. The diagnosis should be suspected in any infant who continues to have jaundice beyond the second week and has more than 20% of the total bilirubin in the direct or conjugated fraction. Dark urine and clay-colored (acholic or gray) stools are also typical.

Isolated extrahepatic biliary atresia is considered an acquired disease partly because it has never been seen in a fetus, and rarely do acholic stools appear at birth or in the ensuing week. The meconium is usually dark and subsequent stools become green and then yellow before acholic stools are seen. Splenomegaly, firm or enlarged liver, and gastrointestinal symptoms including weight loss are seen later, usually after the fourth week.

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Early diagnosis of extrahepatic biliary atresia is important because the outcome of surgical management is improved when operative correction, the Kasai portoenterostomy, is performed before 8 weeks of age. Screening programs for this condition are being investigated in Asia. The incidence and severity of extrahepatic biliary atresia might also justify a screening program in North America.

Extrahepatic biliary atresia is one of many causes of conjugated hyperbilirubinemia at this age (Table).

Table. Relative Frequency of Various Forms of Neonatal Cholestasis*

Clinical Forms	Cases, %	Frequency†
Idiopathic neonatal hepatitis	30-35	1.25
Extrahepatic biliary atresia	25-30	0.70
Intrahepatic cholestasis syndromes (Alagille, Byler, etc)	5-6	0.14
Bacterial sepsis (*Escherichia coli, Listeria*, syphilis, etc)	2	<0.1
Hepatitis		
Cytomegalovirus	3-5	<0.1
Rubella, Herpes	1	<0.1
Endocrine (hypothyroidism, panhypopituitarism)	1	<0.1
Galactosemia	1	<0.1
Other inborn errors (tyrosinemia, α_1-antitrypsin deficiency, cystic fibrosis, etc)	2-3	<0.1
Inborn errors of bile acid biosynthesis	2-5	<0.1

* Modified from Zallen et al.
† Per 10,000 live births.

In general, infants with idiopathic neonatal hepatitis and extrahepatic biliary atresia are asymptomatic early on, and infants with infectious causes and inborn errors often appear ill.

Any infant with persistent jaundice beyond the second week after birth should undergo a serum bilirubin determination (total and conjugated or direct). Conjugated bilirubin, unlike unconjugated bilirubin, is bound to protein weakly, filtered into renal glomeruli, and appears in the urine. Conjugated bilirubin stains diapers a deep yellow-orange. A history of such staining should arouse suspicion for conjugated hyperbilirubinemia.

When the diagnosis of extrahepatic biliary atresia is suspected with the aforementioned findings, it must be confirmed as promptly as possible. After a complete history and physical examination to rule out Alagille syndrome, the following studies may be helpful:

- **liver enzymes, serum proteins, and hepatic clotting studies**
- **cultures and/or serologic studies for bacteria and viruses**
- **a_1-antitrypsin level and phenotype**
- **thyroxine and thyroid-stimulating hormone**
- **sweat chloride testing**
- **metabolic screening including amino acids and ferritin**
- **biliary tract ultrasonography**
- **nuclear medicine imaging of hepatobiliary tract**
- **operative cholangiography, exploration, and liver biopsy**

High liver enzymes, clotting abnormalities, and low albumin concentration point toward hepatitis, but are not diagnostic. Acholic stools can occur with severe hepatitis as well as with biliary atresia. Absence of a gall bladder points to extrahepatic biliary atresia as does absence of bile flow into the duodenum on nuclear medicine imaging. However, the diagnosis remains in doubt until a specific test for infection or inborn error is positive or until a surgeon performs an exploratory procedure, cholangiography, and liver biopsy.

If extrahepatic biliary atresia is the definitive diagnosis, the Kasai portoenterostomy is performed either through an abdominal incision or via laparoscopy. This operation results in bile flow in 30% to 50% of cases (ie, successes). By adolescence, more than half of the successes will require liver transplantation, as will all of the failures. The natural history of extrahepatic biliary atresia includes cirrhosis of the liver, liver failure, portal hypertension, and hepatic carcinoma.

feature.)

References:

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Mack CL. The pathogenesis of biliary atresia: evidence for a virus-induced autoimmune disease. *Semin Liv Dis.* 2007;27:233-242

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American Board of Pediatrics Content Specification(s):

Recognize the clinical manifestations of extrahepatic biliary atresia

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December: Question 3

A 33-year-old pregnant woman presents to the emergency department at 21 weeks' gestation with acute hypoxemia (oxygen saturation 84%) because of an asthma exacerbation. This is the second exacerbation during this pregnancy.

Of the following, the risk factor MOST associated with asthma exacerbations during pregnancy is:

1	atopy
2	Caucasian race
3	female fetus
4	severity of asthma
5	viral infection

You selected 3, the correct answer is 4.

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Asthma is one of the most common chronic pulmonary disorders that can complicate pregnancy. Between 3% and 12% of pregnant women have asthma, and the prevalence, morbidity, and mortality appear to be increasing. Complications found in pregnant women with severe asthma may include having a low-birthweight infant, preterm delivery, cesarean delivery, preeclampsia, asthma exacerbations, and rarely, death.

Approximately 20% of women with asthma experience exacerbations. One third of these episodes lead to hospitalization (5.8% of all women with asthma). Although likely an underestimate, one third of women with asthma experience a worsening of their condition during pregnancy, whereas one third remain unchanged and one third improve. The peak time for deterioration during pregnancy clusters around 20 weeks' gestation. Approximately 18% of women with asthma experience asthma symptoms during labor. Among women with severe asthma, 46% experience symptoms during labor.

The most important risk factor for exacerbation of asthma during pregnancy is severe asthma. Exacerbation rates generally increase with the severity of maternal asthma:

- **Mild asthma**
  - **Exacerbation rate: 12.6%**
  - **Hospitalization rate: 2.3%**
- **Moderate asthma**
  - **Exacerbation rate: 25.7%**
  - **Hospitalization rate: 6.8%**

- **Severe asthma**
  - **Exacerbation rate: 51.9%**
  - **Hospitalization rate: 26.9%**

A severity classification for asthma during pregnancy was developed by the Working Group on Asthma and Pregnancy sponsored by the National Institutes of Health (Table).

Table. Asthma Severity Classification

Classification	Criteria
Mild, intermittent	• Symptoms twice per week or less • Nocturnal symptoms twice per month or less • PEFR or FEV1 80% predicted or more, variability <20%
Mild, persistent	• Symptoms more than twice per week but not daily • Nocturnal symptoms more than twice per month • PEFR or FEV1 80% predicted or more, variability 20%-30%
Moderate, persistent	• Symptoms daily • Nocturnal symptoms more than once per week • PEFR or FEV1 60% to 80% predicted, variability >30%
Severe	• Continuous symptoms and frequent exacerbations • Frequent nocturnal symptoms • PEFR or FEV1 <60% predicted, variability >30% • Regular oral corticosteroids

PEFR, peak expiratory flow rate; FEV1, forced expiratory volume in 1 minute.

Failure to comply with medical treatment, especially inhaled corticosteroids, contributes to worsening of asthma. Pregnant women with asthma who regularly comply with use of inhaled corticosteroid treatment have a 75% reduction in frequency of asthma exacerbations.

Atopy is not a risk factor for exacerbation of asthma during pregnancy. Nonatopic asthma was associated with more episodes of acute asthma symptoms than atopic asthma in a single study.

Black race is a risk factor for worsening asthma. Being African American increases the incidence of asthma-associated hospitalizations, emergency department visits, and use of rescue oral corticosteroids for asthma during pregnancy. It is speculated that absent or limited prenatal care may confound this association.

In contrast to previous literature postulating an association between female fetus and maternal asthma exacerbation, current studies do not support this relationship.

Asthma symptoms often worsen during infectious illnesses. Approximately 35% of pregnant women with asthma experience viral upper respiratory illnesses or urinary tract infections compared with 5% of pregnant women without asthma. Furthermore, pregnant women with more severe disease are more susceptible to infections and exacerbation of asthma symptoms.

References:

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Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax.* 2006;61(2):169-176

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treatment implications. *Eur Respir J.* 2005;25:731-750

National Institutes of Health, National Heart, Lung, and Blood Institute. National Asthma Education Program: report of the Working Group on Asthma and Pregnancy—management of asthma during pregnancy. Washington, DC: Public Health Service, US Department of Health and Human Services; 1993. NIH Publication No. 93-3279. Accessed May 2, 2008, at: http://www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg.txt

American Board of Pediatrics Content Specification(s):

Know the effect of maternal acute and chronic pulmonary disease and their management on the fetus

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December: Question 4

A 4-day-old full-term infant presents with rapid onset of eyelid edema and profuse purulent discharge from both eyes. He appears otherwise healthy. The infant was born at a local hospital that uses erythromycin ointment for routine ocular prophylaxis. Examination of the conjunctival exudate reveals gram-negative bean-shaped diplococci.

Of the following, the MOST appropriate treatment plan for the infant in this vignette is:

1	intravenous cefotaxime, administered for 7 days
2	intravenous ceftriaxone, administered once
3	intravenous penicillin, administered for 10 days
4	oral erythromycin, administered for 10 days
5	tetracycline ophthalmic ointment, applied for 7 days

You selected 4, the correct answer is 2.

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Ophthalmia neonatorum is defined as conjunctivitis occurring within 28 days after birth. The causes of ophthalmia neonatorum include bacteria, such as *Neisseria gonorrhea*, *Chlamydia trachomatis*, and *Staphylococcus aureus*; viruses, such as herpes simplex virus and adenovirus; and chemical irritation from ocular agents, particularly silver nitrate solution. In the United States, ophthalmia neonatorum occurs in 0.5% to 6% of live births, and *C trachomatis* is the most common pathogen.

The infant in the vignette has ophthalmia neonatorum caused by the gram-negative diplococcus *N gonorrhea*. Neonatal infection results from exposure to contaminated maternal secretions during vaginal birth; however, ascending infection occurs as well. Conjunctivitis is the most common manifestation of neonatal gonococcal infection, occurring in up to 42% of exposed neonates. Concomitant pharyngeal colonization is found in 35% of cases. Systemic disease is rare, and includes sepsis, arthritis, and meningitis.

CONTENT SPECIFICATIONS ADDRESSED ABP American Board of Pediatrics

Gonococcal ophthalmia typically manifests as an acute purulent conjunctivitis 2 to 5 days after birth, but the presentation may be subacute or delayed. Initial tense edema of both lids is followed by a copious conjunctival exudate. Without treatment, the infection progresses to involve the subconjunctival connective tissue and corneas. Subsequent corneal ulcerations, scarring, and blindness occur in up to 90% of untreated cases. Panophthalmitis rarely occurs, but is associated with loss of the globe altogether.

Ocular prophylaxis, introduced in the late 19th century, with the instillation of silver nitrate solution into the eyes of newborns, markedly reduced the prevalence of gonococcal ophthalmia.

Present data support the use of the following agents for gonococcal ophthalmia prophylaxis: 1% silver nitrate solution, 0.5% erythromycin ointment, 1% tetracycline ointment, and 2.5% povidone-iodine solution. Additional preventive measures target a reduction in the prevalence of gonococcal disease among pregnant women through aggressive screening and treatment protocols. In North America, Western Europe, and other areas with access to prenatal care and sexually transmitted disease prevention programs, *N gonorrhea* causes fewer than 1% of cases of ophthalmia neonatorum.

Gonococcal ophthalmia neonatorum may occur despite ocular prophylaxis. In cases in which mucosal disease is established before delivery, ocular prophylaxis will be ineffective. In addition, prophylaxis can fail as a result of antimicrobial resistance. Worldwide, a significant portion of gonococci is resistant to penicillin, either by decreased penicillin binding or by penicillinase production. Resistance to tetracycline, erythromycin, the quinolones, and spectinomycin has also been increasing. In 1991, 32% of all strains of gonococcus were resistant to at least one antimicrobial agent. Asymptomatic, but high-risk infants, such as those born to mothers with untreated gonococcal infection, should receive one dose of ceftriaxone, intravenously or intramuscularly, after delivery.

Neonates with gonococcal ophthalmia should be hospitalized and evaluated for signs of systemic infection. In the absence of disseminated disease, the recommended treatment for gonococcal ophthalmia is a single dose of ceftriaxone (25-50 mg/kg, intravenously or intramuscularly, not to exceed 125 mg). Oral and topical treatments are not adequate, and are unnecessary if systemic treatment is administered. Because of antimicrobial resistance, penicillin is no longer recommended for treatment of gonococcal disease. In addition, eye irrigations with saline solution should be performed at frequent intervals until the conjunctival discharge is eliminated. In the presence of disseminated infection, extended treatment with ceftriaxone or cefotaxime is recommended (7 days for sepsis and arthritis; 10-14 days for meningitis). Ceftriaxone displaces bilirubin from albumin-binding sites, and should be used with caution in jaundiced neonates. In addition, ceftriaxone cannot be coadministered with calcium-containing intravenous solutions because of the risk of precipitation of ceftriaxone calcium salt.

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References:

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Embree JE. Gonococcal infections. In: Remington JS, Klein JO, Wilson CB, Baker CJ, eds. *Infectious Diseases of the Fetus and Newborn Infant*. 6th ed. Philadelphia, Pa: Elsevier Saunders; 2006:393-399

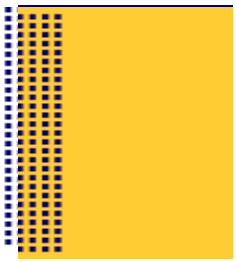
Institute for Safe Medication Practices. *Medication Safety Alert*. October 4, 2007. Accessed February 1, 2008, at: http://www.ismp.org/Newsletters/acutecare/articles/A4Q07Action.asp?ptr=y

American Board of Pediatrics Content Specification(s):

Understand the benefits and complications of eye prophylaxis with antibiotics or silver nitrate (eg, obstructed nasolacrimal duct)

Understand the causes of acute neonatal infection of the eyes, including ophthalmia neonatorum

Understand the treatment of acute neonatal infection of the eyes, including ophthalmia neonatorum



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11 November 08

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December: Question 5

A 72-hour-old female newborn, whose birthweight was 1,840 g at an estimated gestational age of 33 weeks, has a urine output of 0.8 mL/kg per hour. The maternal history was significant for spontaneous vaginal bleeding from acute placental abruption that led to an emergency caesarean delivery. The infant's Apgar scores were 7 and 8 at 1 and 5 minutes after birth, respectively, and the umbilical cord blood pH was 7.28. Initial physical examination of the infant revealed pallor, poor perfusion of the skin, and low blood pressure. The infant has no apparent anomalies or dysmorphic features. She is breathing spontaneously in room air, is receiving intravenous fluids, and has received no medications other than vitamin K and topical eye prophylaxis.

Laboratory data reveal the following:

Laboratory Studies	Patient Result (SI Units)
Plasma measurements	
Urea nitrogen, mg/dL (mmol/L)	38 (13.6)
Creatinine, mg/dL (µmol/L)	1.6 (141)
Sodium, mEq/L (mmol/L)	138 (138)
Potassium, mEq/L (mmol/L)	5.6 (5.6)
Urine measurements	
Creatinine, mg/dL (mmol/L)	8 (0.7)
Sodium, mEq/L (mmol/L)	10 (10)
Osmolality, mOsm/kg (mmol/kg)	310 (310)
Urinalysis	Microscopic hematuria
Renal ultrasonography	
Echogenecity	Increased
Corticomedullary differentiation	Normal
Urinary collecting system	Normal

Of the following, the laboratory finding MOST likely to distinguish prerenal from intrinsic renal failure in this infant is:

1	fractional excretion of sodium
2	plasma urea nitrogen–creatinine ratio
3	renal ultrasonography
4	urinalysis
5	urine osmolality

You selected 2, the correct answer is 1.

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The preterm neonate in this vignette has evidence of acute renal failure as characterized by oliguria, defined in infants as urine output less than 1.0 mL/kg per hour, and a plasma creatinine concentration

higher than 1.5 mg/dL (133 µmol/L). The incidence of acute renal failure is estimated at 6% to 8% among neonates hospitalized for intensive care. Acute renal failure in neonates has multiple causes that can be classified broadly into three categories: prerenal, renal (intrinsic), and postrenal (obstructive) (Table). Prerenal failure is the most common type of acute renal failure in the neonate, accounting for up to 85% of the cases.

Table. Causes of Acute Renal Failure in the Neonate

Prerenal	Renal (Intrinsic)	Postrenal (obstructive)
Hypovolemic causes	*Acute tubular necrosis*	*Obstructive causes*
Hemorrhage	Hypoxia-ischemia	Urethral obstruction
Dehydration	Drug-induced	Bilateral ureteral obstruction
Salt wasting	Toxin-mediated	Ureteropelvic junction obstruction
Diabetes insipidus	Malformations	Ureterovesical junction obstruction
Cardiovascular causes	*Renal dysplasia*	*Obstructive nephrolithiasis*
Congestive heart failure	Polycystic/multicystic kidney disease	Functional causes
Cardiac tamponade	Vascular lesions	Neurogenic bladder
Arrhythmia	Renal artery thrombosis	
Distributive causes	Renal vein thrombosis	
Sepsis	Cortical necrosis	
Hypoproteinemia	Infectious causes	
Tissue trauma	Sepsis	
Capillary leakage	Pyelonephritis	
Drug-induced causes		
Prostaglandin synthetase inhibitors		
Angiotensin-converting enzyme inhibitors		
Vasodilators		

The history and clinical course in the infant in this vignette are suggestive of prerenal failure resulting from hypovolemia secondary to perinatal blood loss. In prerenal failure, the renal function is decreased from impaired renal perfusion, but the kidney is intrinsically normal. When renal perfusion is decreased, at least two compensatory mechanisms are set in motion. First, the glomerular afferent arteriole relaxes to decrease renal vascular resistance and to maintain glomerular blood flow. This effect is mediated largely by vasodilatory prostaglandins, including prostacyclin. Second, the glomerular efferent arteriole constricts to increase the hydrostatic pressure in glomerular capillaries and to maintain glomerular filtration. This effect is mediated largely by vasoconstrictive angiotensin II. Prerenal failure occurs when these compensatory mechanisms fail to maintain perfusion of the renal microvasculature.

Prerenal failure results from either true blood volume contraction or decreased effective blood volume. The true blood volume contraction results from causes that include hemorrhage, dehydration from gastrointestinal loss, salt-wasting renal or adrenal disease, central or nephrogenic diabetes insipidus, increased transdermal fluid loss, and disease states associated with extravascular fluid loss such as sepsis, hypoproteinemia, tissue trauma, and capillary leakage. Prerenal failure may also occur in the face of normal or increased blood volume when renal perfusion is impaired from diseases such as congestive heart failure, cardiac tamponade, and hepatorenal syndrome. Postnatal administration of medications such as prostaglandin synthetase inhibitors and angiotensin-converting enzyme inhibitors can cause prerenal failure by impairing renal perfusion in the presence of normal blood volume. Whether prerenal failure is caused by true blood volume contraction or decreased effective blood volume, correction of the underlying disturbance and restoration of renal perfusion results in a prompt return of renal function to normal.

Several laboratory tests have been proposed to differentiate between prerenal failure and intrinsic renal failure. This differentiation is based on the concept that in prerenal failure, the renal tubules function normally and therefore are able to reabsorb salt and water appropriately, whereas in intrinsic

renal failure the renal tubules are injured and therefore are unable to conserve salt and water.

Among the laboratory tests in this vignette, the fractional excretion of sodium (FE_{Na}) is the test most likely to distinguish prerenal failure from intrinsic renal failure. The FE_{Na} is calculated by using the following equation:

$$FE_{Na}\,(\%) = \frac{UNa \times PCr}{PNa \times UCr} \times 100$$

where UNa is urine sodium (mEq/L), PCr is plasma creatinine (mg/dL), PNa is plasma sodium (mEq/L), and UCr is urine creatinine (mg/dL).

In prerenal failure, the FE_{Na} in neonates is often 2.5% or lower, indicative of renal tubular conservation of sodium, whereas in intrinsic renal failure, the FE_{Na} is often greater than or equal to 3.0%, indicative of failed renal tubular reabsorption of sodium. The FE_{Na} in the infant in this vignette is calculated at approximately 1.4%. This value is consistent with the diagnosis of prerenal failure.

The plasma urea nitrogen–creatinine ratio (mg/mg) has been proposed as a measure to distinguish prerenal failure from intrinsic renal failure. In prerenal failure, the renal tubules retain the capacity to reabsorb sodium and water, which promotes passive reabsorption of urea. The net effect is an increased plasma urea nitrogen–creatinine ratio (>30). Conversely, in intrinsic renal failure, the renal reabsorption of urea is decreased from impaired tubular reabsorption of sodium and water. Moreover, the plasma concentration of creatinine often is higher than in prerenal failure. The net effect is a decreased plasma urea nitrogen–creatinine ratio (<20). The plasma urea nitrogen–creatinine ratio in the infant in this vignette is calculated at approximately 24. This value is not helpful in discriminating between prerenal and intrinsic renal failure.

In prerenal failure, the renal tubules retain the capacity to reabsorb water, and therefore the urine osmolality tends to be high (>350 mOsm/kg [350 mmol/kg]). Conversely, in intrinsic renal failure, the renal osmolality is relatively low (<300 mOsm/kg [300 mmol/kg]). The urine osmolality in the infant in this vignette is 310 mOsm/kg (310 mmol/kg). This value is not helpful in discriminating between prerenal and intrinsic renal failure.

In prerenal failure, the urinalysis is usually normal or may show minor changes such as microscopic hematuria. In intrinsic renal failure, impaired sodium reabsorption by injured tubular epithelial cells increases sodium concentration in the tubular lumen. The increased intratubular sodium polymerizes Tamm-Horsfall protein, a protein normally secreted by the loop of Henle, which contributes to the formation of casts. Presence of such casts, in addition to sloughed epithelial cells and red blood cells, often suggests intrinsic renal failure. The finding of microscopic hematuria on urinalysis in the infant in this vignette is not helpful in differentiating prerenal from intrinsic renal failure.

Renal ultrasonography findings are usually normal in prerenal failure, and, may be normal or reveal increased echogenecity with loss of corticomedullary differentiation in intrinsic renal failure. The finding of increased echogenecity on renal ultrasonography in the infant in this vignette is subjective and not sensitive or specific for discriminating between prerenal and intrinsic renal failure.

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Vogt BA, Dell KM, Davis ID. The kidney and urinary tract. In: Martin RA, Fanaroff AA, Walsh MC, eds.

Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant. **8th ed. Philadelphia, Pa: Mosby Elsevier; 2006:1659-1683**

American Board of Pediatrics Content Specification(s):

Know the common causes of acute renal failure in the neonate

Know the clinical manifestations and laboratory features of acute renal failure in the neonate

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December: Question 6

A 24-year-old woman has had insulin-dependent diabetes mellitus for 12 years. She reports an occasional need to increase her insulin dose after admitted dietary transgressions, but fears hypoglycemia even more than hyperglycemia. She has experienced two hypoglycemic events in the past year. Her physical examination findings are normal; her body mass index is 22.5 kg/m^2; and her hemoglobin A1c is 7.0%. Her creatinine concentration is mildly elevated at 1.4 mg/dL(124 µmol/L) with creatinine clearance of 75 mL/min (1.25 mL/s). Her neurologic examination findings are normal, and retinal examination shows a few soft exudates. She wishes to become pregnant and to minimize the effect of her diabetes on her fetus and herself. She is being treated with a goal of achieving rigid glycemic control to lower the risk of fetal congenital anomalies and fetal macrosomia.

Of the following, strict glycemic control before and during early pregnancy in this woman is MOST associated with potential worsening of hypoglycemia and an increased maternal risk of:

1	gastroparesis
2	infertility
3	nephropathy
4	neuropathy
5	retinopathy

You selected 3, the correct answer is 5.

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Strict glycemic control is a mainstay in the management of the insulin-dependent diabetic woman. Because hyperglycemia is teratogenic, a tighter control of blood glucose concentrations in the preconceptional period and early pregnancy has been documented to reduce the risk of fetal congenital anomalies. To achieve this fetal benefit, however, the woman in this vignette risks exacerbations of hypoglycemia as well as progression of her retinopathy.

Maintenance of euglycemia is defined as keeping hemoglobin (Hb) A1c concentration within the normal range. The rates of miscarriage and fetal anomalies remain at the baseline (rates in nondiabetic pregnant women) when HbA1c concentration is no greater than 1% above normal. The recommendations of the American College of Obstetricians and Gynecologists for women with type 1 diabetes during pregnancy suggest glucose concentrations shown in the Table.

Table. Recommended Glucose Concentrations at Various Times of Measurement*	
Time of Measurement	**Glucose Concentrations (SI Values)**
Fasting, mg/dL (mmol/L)	<95 (5.3)
Preprandial, mg/dL (mmol/L)	≤100 (5.6)
1 hour postprandial, mg/dL (mmol/L)	≤140 (7.8)
2 hour postprandial, mg/dL	≤120
Resultant mean capillary glucose, mg/dL	100
Hemoglobin A1c, %	≤6

* Based on recommendations of the American College of Obstetricians and Gynecologists.

Maintaining blood glucose concentrations at euglycemic levels before or in early pregnancy has been demonstrated to reduce the risks of preterm delivery (≤34 weeks' gestation) and fetal death, especially late-pregnancy stillbirth. One half of all cases of late-pregnancy stillbirth have been associated with uncontrolled hyperglycemia. The earlier that euglycemia is established, the lower is the incidence of fetal macrosomia: women whose mean self-monitored blood glucose concentration is less than or equal to 86 mg/dL (4.8 mmol/L) have one fourth the risk of fetal macrosomia than those with mean blood glucose concentrations exceeding 106 mg/dL (5.9 mmol/L). Reduction in macrosomia is associated with fewer cesarean births, less shoulder dystocia, fewer birth-injured infants, and easier control of neonatal glucose concentrations.

Among women with demonstrated retinopathy, the potential for progression of retinopathy during pregnancy is high. It varies from 10% of cases if no retinopathy were seen before pregnancy, to 21% if mild changes had been present (as in the woman in this vignette), and up to 55% if severe retinal changes preceded pregnancy. These changes are more likely if restoration of euglycemia is associated with pregnancy because the decrease in mean blood glucose concentrations is postulated to precipitate closure of narrowed, but previously patent, small retinal blood vessels. Current recommendations are that blood glucose concentrations be normalized before pregnancy and the patient be followed up by the retinologist before and during pregnancy.

Strict glycemic control also presents increased risk of hypoglycemia, especially during early pregnancy and if nausea and vomiting accompany pregnancy. Pregnancy alters glucose metabolism: after eating, transient hyperglycemia is potentiated by pregnancy-related insulin resistance; the continuous maternal and fetal requirement of glucose can result in hypoglycemia, especially at night. Nocturnal hypoglycemia may produce rebound hyperglycemia reflected in higher early morning blood glucose concentrations. In a nonpregnant woman, the risk of hypoglycemia correlates with the history and severity of hypoglycemic episodes and with the patient's ability to detect hypoglycemia. These combined effects justify more frequent blood glucose testing and adjustments in insulin administration (both intervals and dose, and perhaps formulation of the insulin itself). Exceedingly strict control may result in lower incidence of macrosomia, but paradoxically also has been associated with greater prevalence of intrauterine growth restriction (not because of any anomaly). Of note, hypoglycemia has not been associated with fetal teratogenesis. Maintaining the glycemic balance requires management by an experienced team and a cooperative patient.

Although the diabetic complications of gastroparesis, nephropathy, and peripheral neuropathy may preexist in the pregnant woman, pregnancy itself is not an independent predictor of these diabetic complications. Among women with severe nephropathy, not suggested in this vignette, pregnancy may be associated with significant risks of fetal loss and maternal hypertension. Strict glycemic control has not been documented to reduce the incidence of preeclampsia among diabetic women. Infertility is not associated with a stricter control of diabetes.

References:

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Dudley DJ. Diabetic-associated stillbirth: incidence, pathophysiology, and prevention. *Clin Perinatol.* 2007;34:611-626

Jovanovic L. Glycemic control in women with type 1 and type 2 diabetes mellitus during pregnancy. UpToDate.com Web site. Accessed February 14, 2008, at: http://www.uptodate.com/ (subscription required)

Murphy HR, Temple RC, Roland JM. Improving outcomes of pregnancy for women with type 1 and type 2 diabetes. *Br J Diabetes Vasc Dis,* 2007;7(1):38-42

American Board of Pediatrics Content Specification(s):

Know the components of pre-pregnancy nutrition on individuals with disease states such as type 1 diabetes

Understand the hormonal factors that affect intrauterine growth

Understand the relationship of maternal blood glucose to fetal glucose uptake and metabolism

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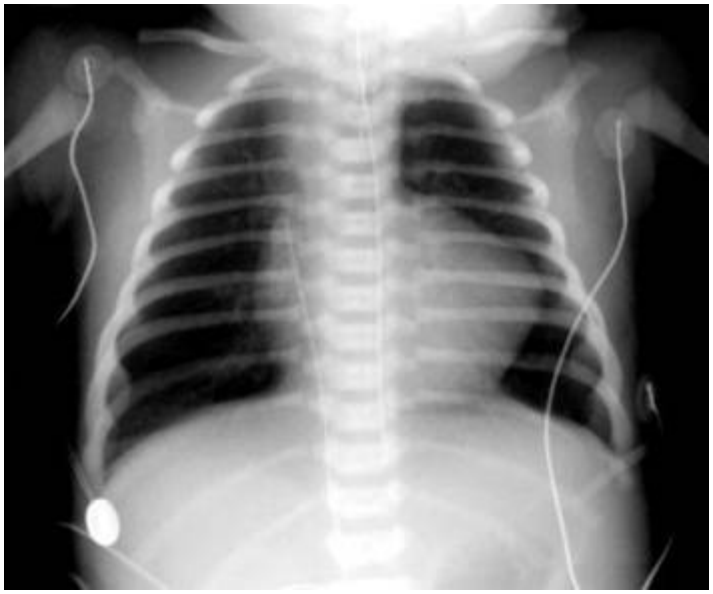
December: Question 7

You are asked to look at a radiograph sent electronically by a pediatrician from an outlying hospital. The 1-day-old infant is delivered at 37 weeks' gestation after an uncomplicated pregnancy. Today, the nurses called the pediatrician after the infant began receiving oxygen because of duskiness. The physician placed an umbilical arterial catheter, inserted an orogastric tube, and ordered the radiograph (Figure 1).



Of the following, this radiograph is MOST consistent with a cardiac diagnosis of:

1	Ebstein anomaly
2	hypoplastic left heart
3	tetralogy of Fallot
4	total anomalous pulmonary venous return
5	tricuspid atresia

You selected 5, the correct answer is 3.

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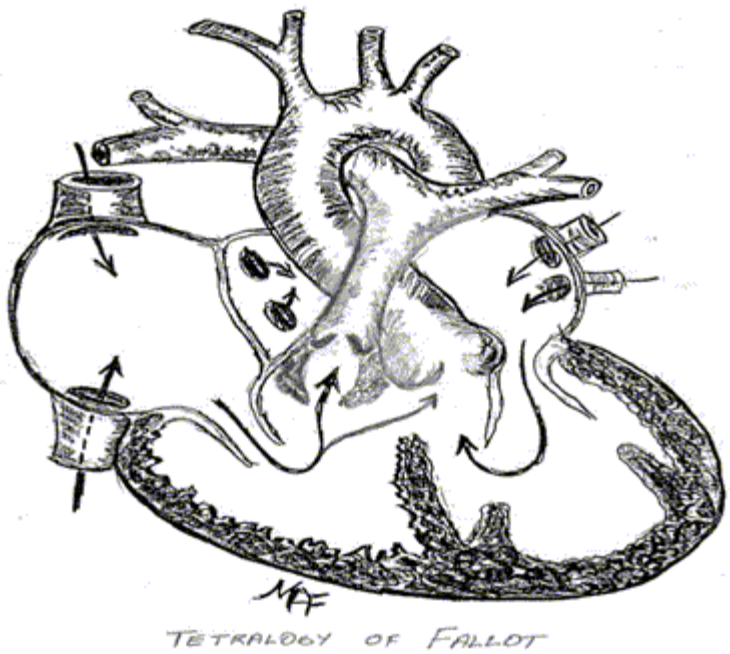
A number of cardiac conditions may result in cyanosis early in the newborn period. Pending consultation with a cardiologist and diagnostic echocardiography, review of the chest radiograph for heart size, pulmonary vascularity and lung fields, and position of the aortic arch may suggest a particular diagnosis and may guide early treatment (Table). The findings of a

normal-sized heart (with upturned apex), clear lung fields, and right aortic arch as noted by the position of the umbilical artery catheter (Figure 1) are most consistent with tetralogy of Fallot (TOF).

Table. Chest Radiography Findings

Lesion	Heart Size	Pulmonary Vascularity	Aortic Arch
Ebstein anomaly of tricuspid valve	Large to very large	Diminished	Usually normal
Hypoplastic left heart	Large	Increased vascular markings	Usually normal
Kartagener syndrome	Dextrocardia	Usually normal	Right arch, also with situs inversus
Tetralogy of Fallot	Normal, may have boot shape	Normal to decreased	25% have right arch
Total anomalous pulmonary venous return	Normal	Hazy lung fields, pulmonary edema	Usually normal
Transposition of the great arteries	Large	Increased vascular markings, congestion	Usually normal
Tricuspid atresia	Normal to enlarged	Diminished	Usually normal

Tetralogy of Fallot consists of a combination of ventricular septal defect (VSD), right ventricular outflow obstruction (infundibular and/or pulmonary valve stenosis), overriding of the aortic root above the VSD, and right ventricular hypertrophy. The aortic arch is right sided in 25% of infants having TOF, as seen in the radiograph, but not in the drawing (Figure 2).



In TOF, the heart shadow may have a characteristic "boot" shape: right ventricular hypertrophy displacing the apex upward and a right aortic arch, both easily seen in this example. The lung fields are underperfused. Not all infants having TOF manifest these "classic" radiographic findings, but cyanosis associated with absence of cardiomegaly and diminished pulmonary blood flow are important features in most cases. If the right ventricular outflow tract is severely obstructed or the pulmonary valve is atretic, pulmonary blood flow is dependent on the ductus arteriosus. With moderate to mild right-sided obstruction, ductal dependency may be present early after birth, while the pulmonary vascular resistance remains high. With TOF as the likely diagnosis and until cardiac anatomy can be ascertained with echocardiography, patency of the ductus arteriosus can be maintained with prostaglandin E infusion pending transfer to a facility

with full cardiology and cardiac surgery services. Knowing the position of the aortic arch is important because Blalock-Taussig shunts, if used, are best placed contralateral to the side of the aortic arch.

Ebstein anomaly of the tricuspid valve consists of variable degrees of displacement of the tricuspid valve into the right ventricle, resulting in dysfunction of the valve, asynchronous contraction of the atrial and ventricular portions proximal to the valve attachment, and variable degrees of right-sided ventricular hypoplasia resulting in right-to-left shunting at the atrial level. Most cases do not present in the neonatal period except those in which the predominance of the tricuspid regurgitation in utero led to massive enlargement of the right atrium. This type of enlargement is associated with life-threatening pulmonary hypoplasia in the early neonatal period. Ebstein anomaly is associated with enlargement of the cardiac shadow, mostly attributed to the right atrium (which can nearly fill the thoracic cavity) and diminished pulmonary markings. Right aortic arch is seldom associated with Ebstein anomaly. Some severely cyanotic infants benefit from a Blalock-Taussig shunt which allows greater pulmonary blood flow as the pulmonary vascular resistance drops after birth. Others, with less severe forms, may go undetected or improve as pulmonary blood flow through the right ventricle increases with decreased pulmonary vascular resistance.

Hypoplastic left heart, occurring in about 10% of infants who present with serious heart disease in the first week after birth, consists of a wide range of anomalies affecting the left side of the intracardiac and extracardiac circulations. Systemic circulation is dependent on patency of the ductus arteriosus. Radiographic findings usually include some degree of cardiomegaly and plethora of the lung fields. A right aortic arch is not commonly found.

Total anomalous pulmonary venous return (TAPVR) accounts for about 2% of neonatal congenital heart disease. Infants having TAPVR present in two forms: (1) unobstructed, in which the common pulmonary vein connects into the right atrium or systemic venous circulation without blockage to flow; and (2) obstructed, wherein the pulmonary veins enter a common channel that is obstructed on its path to the systemic venous circulation. Unobstructed TAPVR usually presents later as the pulmonary vascular resistance drops, resulting in large left-to-right shunting and congestive heart failure. The chest radiograph shows an enlarged heart and pulmonary congestion. Obstructed TAPVR may present shortly after birth with deep cyanosis in a critically ill child. The radiograph may show a normal-sized heart, but the lung fields will be affected, showing pulmonary edema (often confused with primary pulmonary disease, such as respiratory distress syndrome or pneumonia). Right aortic arch is not a common feature of TAPVR. Obstructed TAPVR may be associated with significant deterioration following the use of prostaglandin E_1 because of worsening pulmonary congestion.

Transposition of the great arteries (type D, or d-transposition) (d-TGA) is one of the more common cardiac lesions presenting in the newborn period. The transposed arteries result in pumping of systemic venous return into the aorta and the pulmonary venous return into the pulmonary artery. Survival depends on admixture of the two parallel circulations, which may occur at the atrial, ventricular, or vascular (patent ductus arteriosus) levels. Infants having d-TGA and no VSD present early with profound cyanosis which fails to improve with oxygen supplementation. The chest radiograph may appear normal, but more commonly cardiomegaly is associated with a narrow mediastinum and the lung markings are increased. Prostaglandin E_1 can help to sustain some circulatory admixture pending more definitive treatment using balloon septostomy. If a VSD contributes to admixture of the two circulations, symptoms are often delayed to the early newborn period when congestive heart failure follows massive increase in pulmonary blood flow. By this time, the radiograph will show cardiomegaly and pulmonary edema. Right aortic arch is not a regular feature of d-TGA.

Tricuspid atresia (TA) is an uncommon defect that would be better termed *tricuspid agenesis* based on the total absence of the tricuspid valve in most cases. Infants having TA may present early after birth, especially if there is no VSD, or if a VSD is present but right ventricular outflow is obstructed and pulmonary blood flow is totally dependent on the ductus arteriosus. The chest radiograph may show a normal to slightly enlarged cardiac shadow and diminished pulmonary markings; right aortic arch is not a regular feature of this relatively uncommon anomaly. Some

children having TA also have a large VSD and no obstruction to right ventricular outflow, resulting in later-onset symptoms associated with cardiomegaly and pulmonary congestion on the radiograph.

Definitive diagnosis in any of these instances follows arrival at facilities capable of echocardiography and consultation with a pediatric cardiologist. Of the conditions discussed, blood flow through the ductus arteriosus may be essential or variably helpful for patients with TOF, Ebstein anomaly, hypoplastic left heart, TGA, or TA. Prostaglandin E_1 may be included in pretransport stabilization. However, its use may precipitate the need for ventilatory support and caregivers should be ready to intervene if necessary. Infants having TAPVR, especially the obstructed form, may experience severe exacerbation of pulmonary edema if given prostaglandin E_1.

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Greenberg SB. Tetralogy of Fallot. eMedicine.com Web site. Accessed April 24, 2008, at http://www.emedicine.com/radio/TOPIC685.HTM#Multimediamedia1

American Board of Pediatrics Content Specification(s):

Recognize the clinical features of a cyanotic neonate

Recognize the laboratory and radiographic features of a cyanotic neonate

Formulate a differential diagnosis of a cyanotic neonate

Recognize the laboratory and radiographic features of a neonate with a right-sided cardiac lesion

Formulate a differential diagnosis of a neonate with a right-sided cardiac lesion

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December: Question 8

A 37-day-old, 1,000-g male infant is recovering from an episode of medically treated necrotizing enterocolitis. He is receiving parenteral nutrition through a central venous catheter. His nutritional intake includes:

- **enteral feeds of a 20 kcal/oz formula at 15 mL/kg per day**
- **parenteral fluids containing 13% dextrose and 2.4% amino acids at 135 mL/kg per day**
- **infusion of a 20% lipid emulsion at 0.45 mL/hour**

Recent laboratory data from the infant are shown. Because he has not gained weight over the past 5 days, you discuss with the residents how to increase his caloric intake to at least 110 kcal/kg per day.

Laboratory Data	Patient Result
Serum urea nitrogen, mg/dL (mmol/L)	5 (1.8)
Creatinine, mg/dL (µmol/L)	0.5 (38.1)
Albumin, g/dL (g/L)	2.6 (26)
Glucose, mg/dL (mmol/L)	95 (5.27)
Bilirubin	
Total, mg/dL (µmol/L)	2.3 (39.3)
Direct, mg/dL (µmol/L)	0.9 (15.4)
Electrolytes	
Sodium, mEq/L (mmol/L)	137 (137)
Potassium, mEq/L (mmol/L)	3.9 (3.9)
Triglyceride, mg/dL (mmol/L)	75 (0.85)

Of the following, the change MOST likely to increase the daily caloric intake in this infant to at least 110 kcal/kg per day would be to increase the:

1	enteral feeds to 20 mL/kg per day
2	lipid infusion to 0.65 mL/hour
3	parenteral amino acid concentration to 3%
4	parenteral dextrose concentration to 14%
5	parenteral fluids to 140 mL/kg per day

You selected 5, the correct answer is 2.

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Parenteral nutrition is often the primary source of nutritional support in critically ill neonates recovering from necrotizing enterocolitis. Although the neonate in this vignette may be receiving enough parenteral calories for a healthy low-birthweight neonate, a superimposed catabolic condition such as necrotizing enterocolitis may increase protein and nonprotein requirements and result in

weight gain and growth that are less than those seen in utero.

Carbohydrate and fat are the primary sources of nonprotein calories in parenteral nutrition; amino acids provide protein calories. Sufficient nonprotein energy is required to maximize protein accretion and limit breakdown of endogenous protein stores for energy. Approximately 60 kcal/kg per day of nonprotein calories are required to ensure protein accretion in a stable ventilated neonate receiving 3.0 g/kg per day of amino acids. To approximate intrauterine growth and nitrogen accretion, a stable neonate will require about 90 to 100 kcal/kg per day of parenteral calories: at least 80 kcal/kg per day of nonprotein calories and 3.0 g/kg per day of amino acids. Parenteral energy requirements are less than enteral requirements because no energy is lost in the stool or during digestion. Protein and energy requirements may be higher in neonates with prior malnutrition or who have disease processes with increased nitrogen turnover.

In the absence of protein intake, glucose is more effective than fat in preventing protein breakdown. In the presence of protein, calories from both glucose and lipid are known to be protein sparing. Studies in older children have shown a positive effect of both lipid and glucose on nitrogen retention. However, the optimal carbohydrate-to-fat ratio to maximize protein accretion in ill low-birthweight neonates is not known.

Providing 40% to 65% of parenteral calories as carbohydrate and 30% to 50% as fat may help to maximize protein accretion and minimize excess energy expenditure caused by a disproportionate amount of carbohydrate calories.

Caloric content of a parenteral solution can be determined assuming:

- **Dextrose = 3.4 kcal/g**
- **Lipids = 9.0 kcal/g**
- **Protein = 4.0 kcal/g**

The Table summarizes calculations used to determine the infant's parenteral caloric intake.

Table. Calculations of Calories for A 1-kg Infant

Nutrient	Nutrient Concentration, g/dL		Daily Volume, dL		Kcal/g of Nutrient		Total Kcal/kg/day	% of Total Parenteral Kcal
Carbohydrate	13	×	1.35	×	3.4	=	60	65
Protein	2.4	×	1.35	×	4	=	13	14
Fat	20	×	0.108	×	9	=	19	21

The infant in this vignette is receiving approximately 102 kcal/kg per day (92 kcal/kg per day from parenteral fluids and 10 kcal/kg per day [0.67 kcal/mL × 15 mL/kg] from enteral feeds). Glucose at 12 mg/kg per minute provides 65% of parenteral calories; lipid at 2.2 g/kg per day of a 20% lipid emulsion provides just 21% of parenteral calories. Although the infant is receiving 80 kcal/kg per day of nonprotein calories, 3.2 g/kg per day of amino acids by parenteral route, and 10 kcal/kg per day by enteral feeds, his weight gain is likely slowed by increased metabolic needs.

Because the infant is tolerating the current lipid infusion (triglyceride concentration: 75 mg/dL [0.85 mmol/L] [Laboratory Data]), increasing the infusion would increase caloric intake. Increasing the lipid infusion by 0.2 mL/hour to 0.65 mL/hour (3.1 g/kg per day) would provide an additional 8.6 kcal/kg per day:

$$0.20 \text{ mL/hour} \times 24 \text{ hour} \times 0.20 \text{ g/mL} \times 9 \text{ kcal/g} \div 1 \text{ kg} = 8.6 \text{ kcal/kg per day}$$

The infant's daily caloric intake would increase to at least 110 kcal/kg per day.

Increasing the enteral feeds by 5 mL/kg per day to 20 mL/kg per day would provide an additional 3.4 kcal/kg per day:

$$5 \text{ mL/kg per day} \times 0.67 \text{ kcal/mL} \div 1 \text{ kg} = 3.4 \text{ kcal/kg per day}$$

The infant's daily caloric intake would increase to just 105 kcal/kg per day.

The infant's serum glucose and blood urea nitrogen are in the normal range (see Laboratory Data), indicating that he is tolerating the current composition of parenteral fluids. Increasing the parenteral fluids by 5 mL/kg per day to 140 mL/kg per day would provide an additional 2.7 kcal/kg per day:

Dextrose: 13 g/dL × 0.05 dL/day × 3.4 kcal/g ¸ 1 kg = 2.2 kcal/kg per day

Protein: 2.4 g/dL × 0.05 dL/day × 4 kcal/g ¸ 1 kg = 0.5 kcal/kg per day

The infant's daily caloric intake would increase to just 105 kcal/kg per day.

Increasing the parenteral amino acid concentration by 0.6% to 3 % would provide an additional 3.2 kcal/kg per day:

0.6 g/dL × 1.35 dL/day × 4.0 kcal/g ¸ 1 kg = 3.2 kcal/kg per day

The infant's daily caloric intake would be approximately 105 kcal/kg per day.

Finally, increasing the parenteral dextrose concentration by 1.0% to 14% would provide an additional 4.2 kcal/kg per day:

1.0 g/dL × 1.35 dL/day × 3.4 kcal/g ¸ 1 kg = 4.6 kcal/kg per day

The infant's daily caloric intake would be approximately 107 kcal/kg per day.

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References:

Adamkin DH. Nutrition management of the very low-birthweight infant. I. Total parenteral nutrition and minimal enteral nutrition. *Neoreviews*. 2006;7:e602-606

Dusick AM, Poindexter BB, Ehrenkranz RA, Lemons JA. Growth failure in the preterm infant: can we catch up? *Semin Perinatol.* 2003;27:302-310

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Ziegler EE, Thureen PJ, Carlson SJ. Aggressive nutrition of the very low birthweight infant. *Clin Perinatol.* 2002;29:225-244

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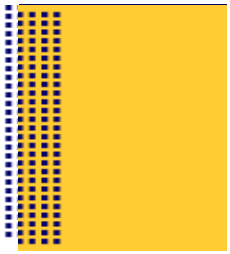
Zlotkin SH, Bryan MH, Anderson GH. Intravenous nitrogen and energy intakes required to duplicate in utero nitrogen accretion in prematurely born human infants. *J Pediatr.* 1981;99:115-120

American Board of Pediatrics Content Specification(s):

Understand the nutritional composition of parenteral solutions

Understand the importance of protein and nonprotein nutrients in achieving optimal utilization of energy and nitrogen

Know how to calculate the caloric content of parenteral nutrition solutions



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11 November 08

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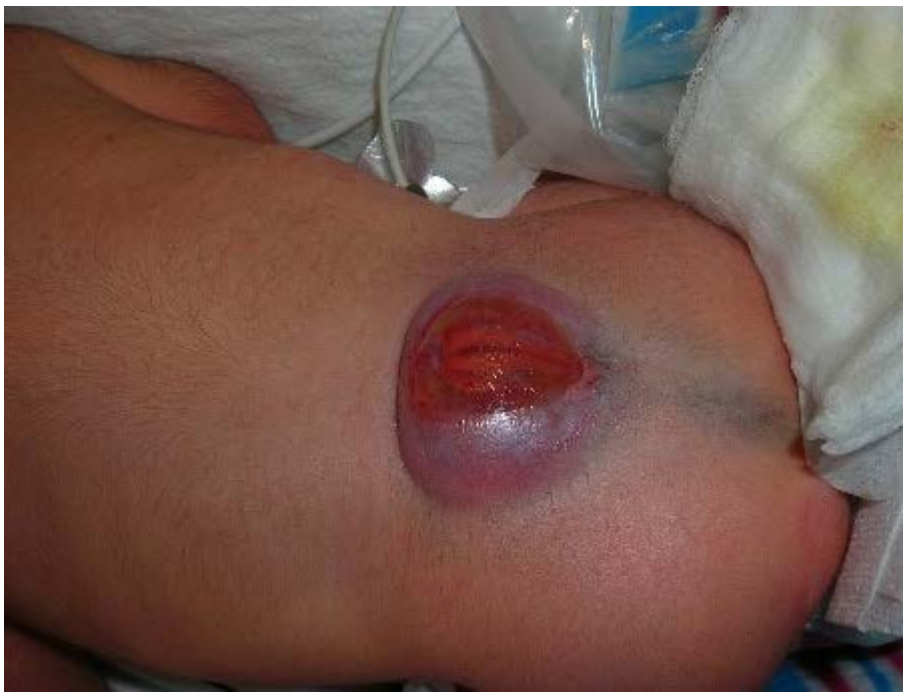
December: Question 9

A male infant is delivered at term gestation. Physical examination reveals the lesion shown in the Figure.



The infant spontaneously moves the lower extremities. The knee and ankle jerks are present, but the anal wink is absent. Intermittent postvoiding bladder catheterizations consistently drain 10 mL or more of urine. Mild hydrocephalus is revealed on magnetic resonance imaging of the head.

Of the following, the MOST likely long-term consequence of this infant's condition is:

1	deterioration of the urinary tract
2	mental retardation
3	moderate to severe scoliosis
4	seizures
5	wheelchair dependence

You selected 1, the correct answer is 1.

The infant in the vignette has a lumbosacral myelomeningocele (Figure). This primary neural tube defect results from a failure of posterior neural tube closure during the 3rd and 4th weeks of gestation. Dorsal bone and soft tissue defects permit a saccular outpouching of neural elements (neural placode), with an incomplete, although variable, dermal covering. The defect may occur at any point along the spine, however 80% of lesions involve the lumbar spinal region (thoracolumbar, lumbar, or lumbosacral). Eighty-four percent of patients with myelomeningocele develop hydrocephalus, with the incidence highest among lumbar lesions. Likewise, the Arnold-Chiari type II malformation (displacement of the medulla and crowding of the cerebellar tonsils into the foramen magnum) occurs in nearly every case of lumbar myelomeningocele, but is symptomatic in only one third of patients. Survival rates, although influenced by decisions regarding aggressiveness of early neonatal care, are approximately 90%. Mortality in the first year after birth is highest in the most severely affected patients, and is usually related to brainstem dysfunction.

The major long-term complications of myelomeningocele can be grouped into neurologic, orthopedic, and urinary tract problems. After the first year, the major cause of death and morbidity relates to urinary tract complications and renal damage. Abnormalities of bladder innervation and detrusor muscle dysfunction accompany lumbosacral lesions and lead to deterioration of the urinary tract in nearly 75% of patients. By adulthood, fewer than 40% of patients have a normal renal ultrasound and a normal serum creatinine concentration. Vesicoureteral reflux, chronic infection, and urolithiasis contribute to progressive loss of renal mass and subsequent chronic renal failure. More than 80% of young adults with myelomeningocele have social bladder incontinence. Tethering of the cord is nearly universal in older children, and likely contributes to this deterioration in urinary tract function.

About 15% to 20% of patients with myelomeningocele have mental retardation, which is usually attributable to central nervous system infection or subtle microscopic anomalies of neuronal migration and differentiation. High thoracic lesions, hydrocephalus, and ventriculoperitoneal shunts are associated with lower intellectual function. The mean intelligence quotient (IQ) for individuals with myelomeningocele and no hydrocephalus is 102. The addition of shunted hydrocephalus and infection reduces the mean IQ to 73. Up to 25% of patients develop seizures, which may contribute to impaired intellectual function.

Up to 50% of patients with myelomeningocele develop scoliosis, with the risk determined by the segmental level of the lesion. Significant scoliosis often is seen with lesions above L2, while this complication is unusual in lesions below S1.

Ambulation potential is reasonably predicted by the functional level of the lesion. Most patients with lesions below S1 ultimately walk unaided. In contrast, lesions above L2 usually result in wheelchair dependence for most activities. Intermediate lesions result in varying degrees of ambulation, with or without assistive devices, such as braces and crutches. During adolescence and young adulthood, weight gain, increased stature, and tethering of the cord lead to greater use of a wheelchair than orthotic devices.

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References:

Müller T, Arbeiter K, Aufricht C. Renal function in meningomyelocele: risk factors, chronic renal failure, renal replacement therapy and transplantation. *Curr Opinion Urol*. 2002;12:479-484

Volpe JJ. Neural tube formation and prosencephalic development. In: *Neurology of the Newborn.* 4th ed. Philadelphia, Pa: WB Saunders; 2001:3-44

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American Board of Pediatrics Content Specification(s):

Understand the long-term complications of myelomeningocele and encephalocele

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December: Question 10

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A full-term male infant presents at 2 weeks of age with multiple episodes of vomiting and a distended abdomen. Abdominal radiography and an upper gastrointestinal contrast series confirm an intestinal obstruction. During surgery, a gastrointestinal duplication is excised.

Of the following, the MOST likely location for this infant's gastrointestinal duplication is the:

1	colon
2	duodenum
3	gastrum
4	ileum
5	rectum

You selected 5, the correct answer is 4.

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Gastrointestinal duplications are rare congenital malformations observed in 1 of every 4,500 autopsies. These congenital anomalies are found more commonly in males and share three characteristics: a well-defined smooth muscle component, an epithelial lining containing part of the alimentary tract, and attachment to some portion of the gastrointestinal tract. Direct communication between the duplication and the native bowel occurs in 20% of patients. Duplications are thought to arise from abnormal recanalization of the bowel. Duplications can be found anywhere within the gastrointestinal tract; the small intestine is the most common location (44%) followed by the colon (15%), stomach (7%), and rectum (5%). Similar to the infant in this vignette, infants with ileal or colonic cystic duplications may present with a volvulus. Because duplications occur much more commonly in the ileum than in the colon, the ileum is the most likely location of this infant's duplication.

The clinical presentation of ileal duplications depends on the type of duplication (ie, cystic or tubular) and the absence or presence of gastric mucosa. Whereas small cystic duplications can be anchor points for a volvulus or intussusception, long tubular duplications often drain poorly, leading to retention of intestinal contents with obstruction of the adjacent intestine. If gastric mucosa is present within the duplication, ulceration with hemorrhage and/or perforation can occur. Ileal duplications are located on the mesenteric border, often sharing a muscular wall and blood supply with the intestine.

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Like ileal duplications, colonic duplications may be cystic or tubular. Similar to cystic ileal duplications, neonates with cystic colonic duplications may present with volvulus or an acute intestinal obstruction. These cystic lesions may be isolated or present with a fistula to the skin, urinary tract, or colon. In contrast to the cystic colonic type, infants with tubular colonic

duplications are usually asymptomatic.

Duodenal duplications account for approximately 5% of all gastrointestinal duplications. These duplications often contain ectopic gastric mucosa, increasing the risk of ulceration and bleeding. Duodenal duplications generally do not communicate with the intestinal lumen and can sometimes arise from the bile ducts or pancreas.

Gastric duplications are usually cystic and typically located on the greater curvature, without communication with the stomach. Patients with gastric duplications typically present at less than 1 year of age with vomiting, poor weight gain, and a palpable abdominal mass. Often, these infants are misdiagnosed as having pyloric stenosis. Patients also may have pancreatitis because of the potential connection between the duplication and the pancreatic duct.

Patients with rectal duplications may have constipation, rectal bleeding, rectal prolapse, perirectal abscess, or anal fistula. These duplications are present in the retrorectal space.

Most children (85%) with a gastrointestinal duplication are diagnosed before the age of 2 years and 60% are diagnosed by the age of 6 months. The diagnosis of these uncommon congenital abnormalities requires a high index of suspicion. Ultrasonography can be useful to diagnose a gastrointestinal duplication. Technetium scans also can be helpful to isolate heterotopic gastric linings within the duplication. However, in most infants, the diagnosis of gastrointestinal duplication is established at surgery after exploration of an abdominal mass, intestinal obstruction, or gastrointestinal bleeding. Once an abnormality is found, excision is generally the preferred treatment. Although surgical removal of the duplication is generally curative, patients must be followed up for pancreatitis or recurrent bleeding. If gastrointestinal duplications remain untreated into adulthood, neoplastic changes may occur.

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References:

Kuo HC, Lee HC, Shin CH, et al. Clinical spectrum of alimentary tract duplication in children. *Acta Pediatr* 2004;45:85-88

Saxena AK. Gastrointestinal duplications. eMedicine.com Web site. Accessed March 31, 2008, at: http://www.emedicine.com/ped/TOPIC2959.HTM

American Board of Pediatrics Content Specification(s):

Know the pathological features and locations of duplications of the GI tract

Know the clinical manifestations of duplication of the GI tract

Know the approach to diagnosis and treatment of the duplications of the GI tract

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