# GASTROENTEROLOGY AND NUTRITION

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DEVELOPMENT OF THE GASTROINTESTINAL SYSTEM

1. **How does the primitive gut develop in the fetus, and what are its three divisions?**

   Folding occurs along the embryo in a cephalocaudal progression that leads to the incorporation of some of the endodermal-lined yolk sac into the embryo, which in turn results in the creation of the primitive gut. The primitive gut is composed of the foregut, midgut, and hindgut. The foregut is most cephalic and will become the esophagus and stomach. The midgut becomes the small intestines, and the hindgut becomes the colon (Fig. 10-1).
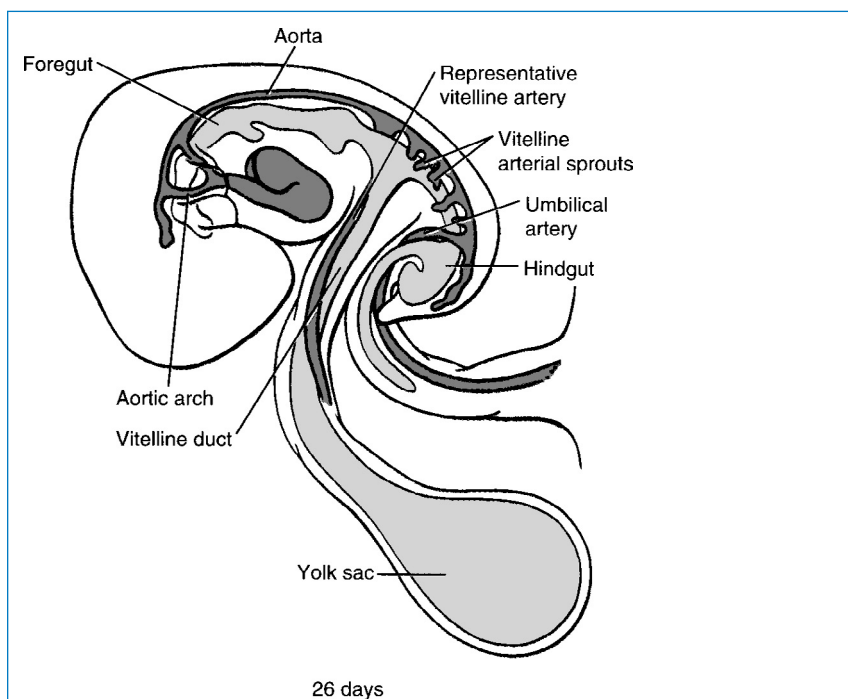
Figure 10-1. The foregut, midgut, and hindgut of the primitive gut tube are formed by the combined action of differential growth and lateral and cephalocaudal folding. The foregut and hindgut are blind-ending tubes that terminate at the buccopharyngeal and cloacal membranes, respectively. The midgut is at first completely open to the cavity of the yolk sac. (From Larsen WJ, Sherman LS, Potter SS, Scott WJ, editors. Human embryology. 3rd ed. New York: Churchill Livingstone; 2001. p. 237.)

2. When does the lung bud separate from the esophagus?

At approximately 4 weeks of gestation, the lung buds appear on the ventral surface of the foregut. This outpocketing from the esophagus will eventually separate completely, forming separate walls known as the esophagotracheal septum. This separation is critical, and any remnant in connection leads to esophageal atresia, a tracheoesophageal fistula, or both. The most common type of developmental abnormality that can occur as a result of this splitting is proximal esophageal atresia with a distal esophagotracheal fistula, which accounts for about 85% of all esophageal atresias.

3. When does the liver develop?

The liver forms at about the third week of gestation as an outgrowth, known as the hepatic diverticulum or liver bud, of the endodermal epithelium of the foregut. This connection grows and narrows to form the bile duct to connect the developing liver to the foregut. A small ventral outgrowth forms that will develop into the gallbladder and connecting cystic duct. The intrauterine failure to develop a complete biliary tree can lead to extrahepatic biliary atresia of embryonic or fetal form, which occurs in 10% to 35% of all cases.

Petersen C. Biliary atresia: the animal models. Semin Pediatr Surg 2012;21(3):185–91.

4. How does the pancreas develop?

The pancreas develops in two separate locations as a bud from the endodermal-lined foregut. The dorsal pancreas develops from a bud on the dorsal surface opposite the developing biliary tree. The dorsal pancreatic bud is located within the dorsal mesentery and grows with a central dorsal pancreatic duct draining to the foregut through the minor papilla. The ventral pancreatic bud develops close to the developing bile duct. When the duodenum rotates to become C-shaped, the bud is rotated onto the dorsal surface along the dorsal pancreas in a position immediately below and behind it. The two developing pancreas parts grow together, and the dorsal pancreatic duct fuses with the ventral pancreas to form the main pancreatic duct (of Wirsung) draining through the major papilla into the duodenum (Fig. 10-2).

5. What is the clinical significance of the embryologic development of the pancreas?

If the connection from the dorsal pancreas continues to drain directly into the duodenum by way of this secondary drainage system (the accessory pancreatic duct of Santorini), the condition is known as pancreas divisum. This connection drains through the minor papilla at a separate location and is the most common anomaly of pancreatic development. Any variation in this process can lead to completely separated drainage to a duplicate drainage of the pancreas. The clinical significance of this condition is the higher risk of pancreatitis in patients with pancreatic duct anomalies.

6. What is the significance of the rotation of the midgut?

During the sixth week of gestation the small intestines and the colon herniate into the umbilical cord as a result of the rapid growth of the liver. The intestine then rotates around a central axis formed by the superior mesenteric artery. This counterclockwise rotation is completed, and the intestine migrates back into the abdominal cavity to be fixed in position. This rotation results in the colon being located anterior to the small intestines, with the cecum being located in the right lower quadrant. An interruption during this physiologic herniation and rotation will result in abnormalities. When the gut fails to return to the abdominal cavity, an omphalocele is formed. This abnormality occurs in approximately 2.5 in 10,000 births. There is a high rate of associated developmental defects, such as cardiac abnormalities, spinal defects, and chromosomal abnormalities. Malrotation is another abnormality that occurs when the midgut fails to rotate completely. Malrotation can cause the inappropriately positioned small bowel to twist on the superior mesenteric artery and lead to vascular insufficiency and volvulus. The gold standard for diagnosis of malrotation remains the upper gastrointestinal tract series that shows the duodenal C-loop crossing to the left of midline at a level equal to or greater than the pylorus.

Martin V, Shaw-Smith C. Review of genetic factors in intestinal malrotation. Pediatr Surg Int 2010;26(8):769–81.
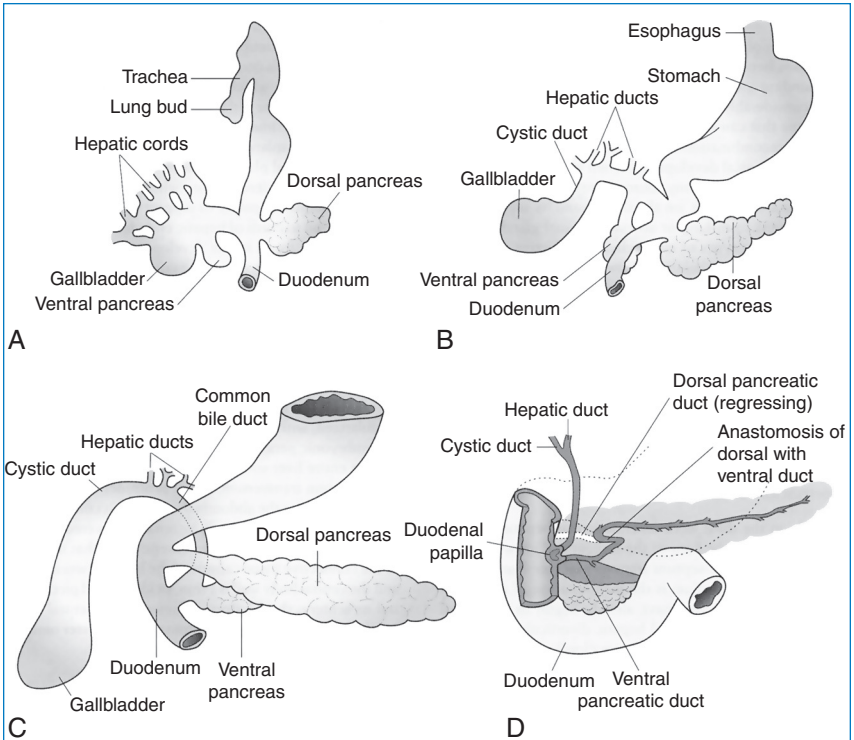
Figure 10-2. Development of the primordial pancreas from the ventral aspect. **A,** Fifth week of development. **B,** Sixth week of development. **C,** Seventh week of development. **D,** The late fetus, showing fusion of the dorsal and ventral pancreatic ducts and regression of the distal portion of the dorsal duct. (From Carlson BM. Human embryology and developmental biology. 2nd ed. St Louis: Mosby; 1999. p. 338.)

7. How does the hindgut develop?

The hindgut forms the most distal part of the primitive gut. It develops into the distal third of the transverse colon and the upper part of the rectal canal. Initially the urogenital system and the hindgut join together in the cloaca. The two systems separate from each other, and the rectal canal fuses with the surface to form an open pathway that will form the anus and rectum. Any abnormalities with this development can result in a continued connection, or urorectal fistula, between the urologic and gastrointestinal tracts. When the anorectal canal fails to fuse with the surface, a rectoanal atresia occurs with resulting imperforate anus. Imperforate anus occurs in 1 in 50,000 live births and has a high incidence of other associated birth defects.

Juang D, Snyder CL. Neonatal bowel obstruction. Surg Clin North Am 2012;92(3):685–711.

8. What is the enteric nervous system (ENS)?

The ENS is the nervous system that regulates intestinal smooth muscle to control gastrointestinal motility. The ENS is composed of a complex network of ganglia that function independently from the central nervous system. Although independent, the ENS can be influenced by vagal and pelvic nerves of the parasympathetic nervous system and spinal nerves. Within the ENS the interstitial cells of Cajal are the pacemaker cells and are responsible for the coordinated smooth muscle contractions within the gut.

✓ KEY POINTS: GASTROINTESTINAL DEVELOPMENT

1. The most common form of transesophageal fistula is proximal esophageal atresia with a distal tracheoesophageal fistula.

2. Although most cases of biliary atresia are caused by a destructive, perinatal inflammatory process, a subset appears to be caused by a prenatal developmental abnormality of the extrahepatic biliary tree that is associated with other congenital anomalies, such as polysplenia.

3. Rotational abnormalities of pancreas development can be observed either as an annular pancreas presenting with obstruction or as ductal abnormalities presenting with pancreatitis later in childhood.

4. Delayed passage of meconium should raise consideration of both anatomic abnormalities (e.g., variants of imperforate anus) and motility disorders (e.g., Hirschsprung disease).

MECONIUM

9. What is meconium?

Meconium is the material and secretions created by or swallowed by the fetus in the gastrointestinal tract while *in utero*. It contains ingested amniotic fluid, lanugo, intestinal cells, bile salts and pigments, and pancreatic enzymes.

10. When is meconium normally passed in a term infant?

Normally, the initial passage of meconium occurs within the first 12 hours after birth. Meconium passage will occur in 99% of term infants and 95% of premature infants within 48 hours of birth.

11. What is the significance of the lack of passage of meconium at the normal time?

When meconium is not passed by 48 hours of life, the possibility of an anatomic or neuromuscular abnormality must be considered, such as Hirschsprung disease.

Kenny SE, Tam PK, Garcia-Barcelo M. Hirschsprung's disease. Semin Pediatr Surg 2010;19(3):194–200.

FETAL GROWTH AND ASSESSMENT

12. Why is it important to routinely monitor fetal growth during pregnancy?

Intrauterine growth is one of the most important signs of fetal well-being and one of the most reliable indicators of the pathologic conditions that affect the mother and fetus during pregnancy. Early identification of alterations in fetal growth can allow for early intervention to prevent long-term complications for the fetus and newborn infant.

13. What do the terms low birth weight (LBW), very low birth weight (VLBW), and extremely low birth weight (ELBW) indicate?

- LBW: less than 2500 g
- VLBW: less than 1500 g
- ELBW: less than 1000 g

This classification is clinically relevant because neonatal morbidity and mortality are strongly correlated with the infant's gestational age and birth weight.

14. What are the most common causes of intrauterine growth restriction (IUGR)?

Intrinsic (fetal causes):

- Constitutional
- Genetic

- Toxic
- Infectious
- Teratogenic
- Behavioral
- Intrauterine constraint

Extrinsic (maternal/placental) causes:

- Maternal age younger than 16 years or older than 35 years
- Maternal illness
- Placental dysfunction
- Multiple gestation
- Demographic

15. What causes neonates to be large for gestational age?

Infants with birth weight above the 90th percentile on the intrauterine growth chart are classified as large for gestational age. Maternal diabetes is the most common cause of fetal growth acceleration owing to the induction of fetal hyperinsulinism during gestation. Other causes include fetal hydrops (edema), Beckwith–Wiedemann syndrome, transposition of the great vessels, and maternal obesity.

16. Why is it clinically useful to classify small-for-gestational-age infants as symmetric or asymmetric?

Infants who are symmetrically growth retarded have proportionally reduced size in weight, length, and head circumference. This type of growth retardation starts early in pregnancy, and it is often secondary to congenital infection, chromosomal abnormalities, and dysmorphic syndromes. Most babies with IUGR, however, are asymmetrically growth retarded, with the most severe growth reduction in weight, less severe length reduction, and relative head sparing. Asymmetric IUGR is caused by extrinsic factors that occur late in gestation, such as pregnancy-induced hypertension. Distinguishing between symmetric and asymmetric IUGR is important because infants with asymmetric IUGR have a better long-term growth and developmental outcome.

MEDICAL PROBLEMS OF THE GROWTH–RESTRICTED INFANT

17. What are the long-term risks of IUGR?

- Development: Because this group is heterogeneous, the outcome depends on perinatal events, the etiology of growth retardation, and the postnatal socioeconomic environment. In general, the asymmetric growth-retarded baby does not show significant differences in intelligence or neurologic sequelae but does demonstrate differences in school performance related to abnormalities in behavior and learning.
- Health effects: An increased risk of hypertension is found in adolescents and young adults. Growth-retarded infants with a low ponderal index (measurement of leanness calculated by body mass divided by height cubed) are at increased risk for syndrome X (non–insulin-dependent diabetes mellitus, hypertension, and hyperlipidemia) and death resulting from cardiovascular disease by the age of 65 years (Barker hypothesis).
- Growth: Fetuses that experienced growth failure after 26 weeks' gestation (asymmetric growth retardation) exhibit a period of catch-up growth during the first 6 months of life. However, their ultimate stature is frequently less than an appropriate-for-gestational-age (AGA) baby.

CALORIC REQUIREMENTS

18. What is the significance of energy balance?

Energy, being neither created nor destroyed, conforms to classic balance relationships. Energy balance is a state of equilibrium when energy intake equals expenditure plus losses. If energy intake

exceeds expenditure plus losses, the infant is in positive balance, and excess calories are stored. If energy intake is less than expenditure plus losses, the infant is in negative balance, and calories are mobilized from existing body stores. Maintenance, or basal, energy requirements are the energy needs required to cover basal metabolic rate or resting energy expenditure; total energy expenditure in infants is the sum of the energy required for basal metabolic rate, activity, thermoregulation, diet-induced thermogenesis, and growth. The energy balance equation may be stated as follows:

$$\text{Gross energy intake} = \text{energy excreted} + \text{energy expended} + \text{energy stored or}$$
$$\text{Metabolizable energy} = \text{energy expended} + \text{energy stored}$$

19. What are the caloric requirements for LBW infants?

LBW infants require at least 120 cal/kg/day, partitioned to approximately 75 cal/kg/day for resting expenditure and the remainder for specific dynamic action (10 cal/kg/day), replacement of inevitable stool losses (10 cal/kg/day), and growth (25 cal/kg/day) (Table 10-1).

20. What is the respiratory quotient (RQ), and what is its significance?

The RQ is the ratio of the volume of carbon dioxide (CO_2) produced to the volume of oxygen (O_2) consumed per unit of time (V_{CO_2}/VO_2). This ratio varies with the type of nutrient oxidized. In addition, the energy produced varies with the type of substrate burned. Thus various substrates have different RQs, and varying proportions of different nutrients result in different energy production per liter of O_2 consumption or CO_2 production. The RQs and caloric equivalents of O_2 and CO_2 for carbohydrate, fat, and protein are shown in Table 10-2.

21. What is the energy cost of growth?

The energy cost of growth includes the energy used for synthesis of new tissues (e.g., absorption, metabolism, and assimilation of fat and protein) and the energy stored in these new tissues. The energy cost of growth varies with the type of tissue added during growth. The precise caloric requirements for growth are unknown. A wide range of values for energy cost of growth in neonates has been

TABLE 10-1. CALORIC REQUIREMENTS OF LOW–BIRTH–WEIGHT INFANTS	
	REQUIREMENTS (kcal/kg/day)
Resting*	50 to 75
Specific dynamic action	5% to 8% of total intake
Stool losses	10% of total intake
Growth	25 to 45
Total†	85 to 142

*Estimate includes caloric expenditure for maintenance of basal metabolism plus activity and response to cold stress.
†Includes sum of resting and growth requirements for specific dynamic action and replacement of stool losses plus an increment of 15% to 18%.

TABLE 10-2. RESPIRATORY QUOTIENTS AND CALORIC EQUIVALENTS			
	RESPIRATORY QUOTIENT	**ENERGY PRODUCED/L OF O_2 (kcal)**	**ENERGY PRODUCED/L OF CO_2**
Carbohydrate	1	5	5
Fat	0.71	4.7	6.6
Protein	0.80	4.5	5.6

determined (1.2 to 6 kcal/g of weight gain). Separate evaluations of energy expenditure requirement for fat and protein deposition in premature newborns estimate that 1 g of protein deposition requires 7.8 kcal, and 1 g of fat requires 1.6 kcal.

CARBOHYDRATE REQUIREMENTS

22. How can carbohydrate requirements be estimated in newborn infants?
Strict carbohydrate requirements are difficult to estimate because glucose, a preferred metabolic fuel for many organs (including the brain), is synthesized endogenously from other compounds. Several methods have been used to assess carbohydrate requirements in neonates:
- Breast milk intake of lactose (assuming breast milk provides optimal intakes of all nutrients)
- Constant infusion of labeled glucose to determine the rates of glucose production and oxidation (as a reflection of overall carbohydrate metabolism)
- Altering the amount of the carbohydrate intake in the diet and determining its effect on energy metabolism and nitrogen retention

23. The rate of endogenous glucose production in neonates has been estimated to range from 4 to 6 mg/kg/min. Do these values represent the ideal carbohydrate intake in neonates?
No. The rates of endogenous glucose production should be regarded as only the minimal carbohydrate requirement because of the methods and conditions in which these measurements were performed. These studies were done in neonates under basal or resting metabolic conditions and during fasting periods. In addition, these studies did not take into account the energy cost of physical activity, growth, and thermal effect of feeding. Higher values ranging from 5.8 to 6.8 mg/kg/min have been used as guidelines for the initiation of glucose infusion in neonates receiving parenteral nutrition with the ability to increase toward 13 mg/kg/min, depending on the infant.

24. What problems can be associated with excessive carbohydrate intake?
Excessive intake of carbohydrate in infant feedings may lead to delayed gastric emptying, emesis, diarrhea, and abdominal distention caused by excessive gas formation as colonic bacteria digest the extra carbohydrates. The excessive administration of intravenous glucose, at rates exceeding 13.8 mg/kg/min, may be associated with metabolic complications such as hyperglycemia, glycosuria, and osmotic diuresis. In addition, the excessive glucose metabolized is stored mainly as fat. Early overfeeding may be an important factor in later childhood and adult obesity, though more recent work suggests that genetic factors may be as important.

Zhao J, Grant SF. Genetics of childhood obesity. J Obes 2011;2011:845148.

25. Why do infant formulas contain comparable amounts of lactose and glucose polymers?
- Premature infants have a limited ability to digest lactose because intestinal lactase does not reach maximal activity until near term.
- Glucose polymers are well digested and absorbed by premature infants.
- The use of glucose polymers allows the osmolarity of the formula to remain low, even at high caloric density of 24 kcal/30 mL (<300 mOsm/L), thereby providing premature infants with adequate caloric intake and preventing such consequences as osmotic diarrhea.

26. What is the metabolic fate of the lactose malabsorbed by the small intestine?
The malabsorbed lactose is fermented in the colon, forming various gases such as CO_2, methane, and hydrogen and short-chain fatty acids such as acetate, propionate, and butyrate. These short-chain fatty acids are absorbed in the colon, reducing energy losses in the stools and maintaining the nutrition and function of the colon. Despite these putative benefits of lactose fermentation, metabolic

concerns that result from the reduced digestion and absorption of lactose in the small intestine include the following:

- Decreased insulin secretion and a reduced effect on protein synthesis
- Lower adenosine triphosphate formation when lactose is fermented to acetate instead of following the glucose metabolic pathways
- Possible increased risk of necrotizing enterocolitis

PROTEIN REQUIREMENTS

27. What are the essential amino acids?
The amino acids that cannot be synthesized in the body are regarded as essential amino acids:

- Leucine
- Threonine
- Phenylalanine
- Isoleucine
- Methionine
- Tryptophan
- Valine
- Lysine
- Histidine

28. Which of the amino acids are considered conditionally essential for the preterm infant?
Cysteine, tyrosine, and taurine are essential because of immaturity of the enzymes (decreased activity) involved in their synthesis.

29. What is the whey-to-casein ratio of cow's milk and human milk protein?
The whey-to-casein ratio of cow's milk protein is 18:82 and that of human milk protein is 60:40. In total, most formulas contain up to 1.5 times more protein than human milk in order to approximate the protein quality of human milk.

Martinez JA, Ballew MP. Infant formulas. Pediatr Rev 2011;32:179–89.

30. How does the whey-to-casein ratio change during lactation?
The ratio of whey to casein is about 90:10 at the beginning of lactation and rapidly decreases to 60:40 (or even 50:50) in mature milk.

31. What is the predominant whey protein in human milk and cow's milk?
The predominant whey protein in cow's milk is beta-lactoglobulin, and the predominant whey protein in human milk is alpha-lactalbumin.

32. What are the non-nutritive roles of protein in human milk?
- Whey proteins are known to be involved in the immune response (immunoglobulins), lactose synthesis (alpha-lactalbumin), and other host defenses (lactoferrin).
- Casein phosphopeptides are believed to enhance the absorption of minerals.
- Casein fragments are thought to increase intestinal motility.
- Glycoproteins may promote the growth of certain beneficial bacteria.

33. Name the methods used for determining protein requirements.
- Factorial method (based on reference data of infant body composition)
- Balance method (protein intake = protein retention − inevitable protein losses)
- Indices of protein nutritional status (e.g., plasma albumin and transthyretin concentrations; protein intake required to maintain these indices within an acceptable range)

■ Stable isotope tracer techniques (insight into the way metabolism changes with clinical state or nutritional status and thus an assessment of protein requirement)

34.   What is a lactobezoar?
Lactobezoars are intragastric masses composed of partially digested milk curd (i.e., casein, fat, and calcium). Rarely seen now, lactobezoars were reported in LBW infants (<2000 g) fed casein-predominant formulas because casein can form large curds when exposed to gastric acid that are difficult for the LBW infant to digest. Whey protein, however, is less likely to precipitate and is emptied more rapidly from the stomach.

35.   What is the protein requirement of term and preterm infants?
The recommended protein intake for term infants is approximately 2 to 2.5 g/kg/day; for preterm infants it is 3 to 4 g/kg/day.

36.   What factors may affect protein use in the neonate?
■ Energy intake
■ Quality of protein intake
■ Intake of other nutrients
■ Infections and stress

37.   What is the protein content of currently available formulas?
Term formulas:
■ Milk-based formulas (e.g., Similac Advance, Enfamil LIPIL, Good Start Supreme): 2.1 to 2.8 g/100 kcal or about 1.5 to 1.8 g/100 mL
■ Soy-based formulas (e.g., Similac Isomil Advance, Enfamil Prosobee LIPIL, Good Start Supreme Soy): 2.3 to 2.5 g/100 kcal or about 1.4 to 1.6 g/100 mL
Preterm formulas (e.g., Similac Special Care, Enfamil Premature LIPIL):
■ 2.5 to 2.9 g/100 cal, 1.6 to 2 g/100 mL
Follow-up formulas for LBW weight infants (e.g., Similac NeoSure Advance, EnfaCare LIPIL):
■ 2.6 to 2.8 g/100 kcal, 1.6 to 1.8 g/ 100 mL

38.   What is the rate of protein loss in premature infants who receive only 10% dextrose and water in the immediate newborn period?
ELBW infants (<1000 g) who receive only glucose lose approximately 1.2 g/kg/day. More mature infants lose protein at a slower rate (0.9 g/kg/day at 28 weeks and 0.7 g/kg/day at 31 weeks). Any protein deficits that are accrued must be replaced.

39.   How can the protein losses be minimized?
Early provision of protein (1 to 1.5 g/kg/day) along with minimal calories (30 cal/kg/day) can minimize the protein losses in ELBW infants. Even with good early protein administration, however, rates of intrauterine growth are virtually never achieved and some degree of extrauterine growth failure is the norm.

40.   How do protein requirements differ when protein is delivered parenterally versus enterally?
Protein requirements are higher parenterally because preterm infants retain only 50% of amino acids administered intravenously but 70% to 75% of formula or human milk protein.

41.   What is the ideal calorie-to-protein ratio to ensure complete assimilation of protein?
■ Enteral feedings: approximately 30 cal/g of protein
■ Parenteral feedings: 20 to 30 cal/g of protein (based on limited data)

LIPID REQUIREMENTS

42. What are the beneficial effects of lipid emulsions in a premature infant?
- Provision of calories (in a calorically dense form)
- Prevention of essential fatty acid deficiency

43. What is the percentage of calories provided by fat in human milk?
The percentage of fat calories in human milk is between 40% and 55%.

44. What is the source of fat in breast milk?
Most of the fat in breast milk is formed from circulating lipids derived from the mother's diet. A small amount of fat is synthesized by the breast itself, with that percentage increasing in women receiving a low-fat, high-carbohydrate diet.

45. What structural features of fatty acids improve enteral absorption?
- Shorter-chain-length to medium-chain triglycerides are absorbed more efficiently than long-chain triglycerides.
- Fatty acids with double bonds are absorbed more efficiently.

46. What are the energy contents of long-and medium-chain triglycerides?
- Long-chain triglycerides: 9 cal/g
- Medium-chain triglycerides: approximately 7.5 cal/g

47. What is the energy cost of synthesizing fat from carbohydrate?
Synthesis of fat from glucose requires about 25% of the glucose energy invested in synthesis. In comparison, synthesis of fat from fat requires only 1% to 4% of the energy invested.

48. What fatty acids are essential for fetuses and premature infants?
All humans have a requirement for linoleic and linolenic acid. These are 18-carbon, omega-6 and omega-3 fatty acids, respectively. Linoleic and linolenic acid serve as precursors for long-chain polyunsaturated fatty acids (LCPUFAs) such as arachidonic (a 20-carbon omega-6 fatty acid), eicosapentaenoic (a 20-carbon omega-3 fatty acid), and docosahexaenoic acid (a 22-carbon omega-3 fatty acid). LCPUFAs are essential components of membranes and are particularly important in membrane-rich tissues such as the brain and retina, thereby affecting visual and neurodevelopmental outcomes in children. In addition, eicosapentaenoic and arachidonic acids are precursors for prostaglandins, leukotrienes, and other lipid mediators. The fetus receives essential fatty acids (including LCPUFAs) transplacentally, and breastfed babies receive them in breast milk. Vegetable oil–based formulas do not contain LCPUFAs, and the ability of preterm infants to synthesize LCPUFAs from linoleic and linolenic acid may be limited.

49. What are the current recommendations for LCPUFA supplementation?
Currently all formulas contain the addition of LCPUFAs, particularly docohexaenoic acid (range of 0.15% to 0.32% total fatty acids) and arachidonic acid (range of 0.4% to 0.64% total fatty acids), because studies have consistently found significant benefit with such supplementation.

50. What are the side effects of LCPUFA depletion?
- Omega-6 LCPUFA: reduced growth
- Omega-3 LCPUFA: alterations in electroretinogram responses, reduced visual acuity, and possible cognitive abnormalities

51. What is the advantage of supplying calories as lipid rather than carbohydrate in infants with chronic lung disease?
The RQ of lipids is lower than that of carbohydrate. Therefore the use of lipid infusions should theoretically decrease CO_2 production in infants with bronchopulmonary dysplasia, one of the cardinal problems of infants with chronic lung disease in the neonatal period.

52. What is the advantage of using a 20% lipid emulsion versus a 10% lipid emulsion in newborn infants?

Twenty-percent lipid emulsions are cleared from the circulation more rapidly than 10% emulsions. Ten-percent lipid emulsions contain proportionately more emulsifier (egg yolk phospholipid). In 10% emulsions the phospholipid-to-triglyceride ratio is 0.12, and in 20% emulsions the ratio is 0.06. The excess phospholipid forms bilayer vesicles that extract free cholesterol from peripheral cell membranes to form lipoprotein X. Lipoprotein X is cleared very slowly from the circulation (half-life, 2 days).

53. What is the maximum acceptable triglyceride level in infants receiving lipid emulsions, and how often should they be checked?

The maximum level is 150 mg/dL. Routine monitoring of serum triglycerides is necessary as they are being advanced.

TOTAL PARENTERAL NUTRITION: MONITORING AND COMPLICATIONS

54. What is the usual distribution of nutrients in total parenteral nutrition (TPN) solutions used for neonates?

TPN is written with a calorie distribution of 8% to 10% from amino acids, 30% to 40% from lipid emulsions, and 50% to 60% from dextrose.

55. What are the metabolic advantages of using different regimens containing high carbohydrate (67%) and low fat (5%) or low carbohydrate (34%) and high fat (58%)?

There are none. The administration of TPN solutions containing a moderate carbohydrate (60%) to fat (32%) ratio has been shown to result in a higher nitrogen retention rate than that of the unbalanced regimens.

Nose O, Tipton JR, Ament ME, et al. Effect of energy source on changes in energy expenditure, respiratory quotient and nitrogen balance during total parenteral nutrition in children. Pediatr Res 1987;21:538–41.

56. Hyperglycemia is a common complication observed in ELBW infants receiving parenteral nutrition. Should insulin infusions be provided routinely to these infants?

In most infants hyperglycemia is a transient problem and resolves when the rate of glucose or lipid administration is reduced. Insulin infusions have been used for infants weighing less than 1000 g who develop hyperglycemia (serum glucose level in excess of 150 mg/dL) and glycosuria during the course of parenteral nutrition, providing low glucose infusion rates (<12 mg/kg/min). In these infants insulin infusions at rates of 0.04 to 0.1 U/kg/h have been shown to improve glucose tolerance and promote weight gain, compared with infants in a control group.

Sinclair JC, Bottino M, Cowett RM. Interventions for prevention of neonatal hyperglycemia in very low birth weight infants. Cochrane Database Syst Rev. 2011 Oct 5;10:CD007615.

Bottino M, Cowett RM, Sinclair JC. Interventions for treatment of neonatal hyperglycemia in very low birth weight infants. Cochrane Database Syst Rev. 2011 Oct 5;10:CD007453 [Review].

57. The clearance of intravenous fat emulsions in neonates is improved by all the following measures except for which of the following? (A) Increasing the period of infusion from 8 to 24 hours; (B) adding a low dose of heparin to the TPN solutions (1 U/mL); (C) exposing the fat emulsions to ambient light or to phototherapy lights; (D) using 20% instead of 10% lipid emulsions.

The answer is (C). Exposure of lipid emulsions to ambient or phototherapy lights increases the formation of triglyceride hydroperoxide radicals but does not enhance lipid clearance. Lipid clearance in neonates is improved by prolonging the infusion period; by adding heparin to TPN solutions (which

releases lipoprotein lipase from capillary endothelial cells); and by using 20% lipid emulsions, which contain a lower phospholipid content than 10% lipid emulsions.

58. Why do premature infants who receive prolonged courses of parenteral nutrition develop osteopenia resulting in pathologic bone fractures?

The development of osteopenia during the course of TPN in premature infants is believed to result from the inability to provide the calcium and phosphorus required for proper bone mineralization. The solubility of calcium and phosphorus in TPN solutions can be improved by providing a high amino acid intake and by the supplementation of cysteine hydrochloride. These measures allow for a greater, though still inadequate, intake of calcium and phosphorus. The administration of calciuric diuretics such as furosemide, the use of postnatal steroids, and the development of cholestatic liver disease further aggravate calcium homeostasis in these patients. The intravenous administration of vitamin D does not prevent the occurrence of TPN-induced osteopenia.

59. Which of the trace elements in TPN solutions can be potentially toxic for patients with cholestatic liver disease?

Copper and manganese are potentially toxic for these patients. Both of these trace elements are metabolized in the liver and primarily excreted in bile. Therefore the chronic administration of trace elements in patients with cholestasis may result in toxic states. Manganese and copper supplements should be withheld from TPN solutions when hepatic cholestasis is present. Monitoring of serum levels of copper and manganese is indicated in patients with cholestasis who require a prolonged course of TPN.

60. What is the most common complication of TPN administered by peripheral vein catheters?

The most common complication is the accidental infiltration of TPN solution into the subcutaneous fat tissue that results in skin necrosis. This complication can be minimized by lowering the osmolality of TPN solution through the administration of dextrose concentrations that do not exceed 10% and by the concomitant administration of lipid emulsions.

61. What is the most common cause of bacterial infection in neonates receiving TPN by central vein catheter?

Staphylococcus epidermidis remains the most common cause of bacterial sepsis during the course of TPN. Other organisms include *Staphylococcus aureus, Escherichia coli, Pseudomonas* species, *Klebsiella* species, and *Candida albicans.* TPN-related infections are more common in the smallest and sickest infants who receive prolonged courses of TPN through a central catheter. The rate of these infections can be reduced by aseptic preparation of TPN solutions and by avoiding the use of the TPN catheter for blood transfusions, administration of medications, and blood sampling. Most important, TPN should be discontinued (and central lines removed) when "full" enteral volume feedings have been achieved (approximately 100 mL/kg/day).

In recent years many NICUs have demonstrated that the rates of catheter-related infections can be substantially reduced through careful aseptic technique and thoughtful, conscientious management of indwelling lines. A number of NICUs have been able to go beyond 1 year without a single catheter-related infection. It is evident that this complication is far more preventable than was once thought possible.

ENTERAL NUTRITION

62. What is the carbohydrate source in human milk and in term and preterm formulas?

Lactose is the major source of carbohydrate in human milk and in formulas for term infants. The preterm formulas contain a mixture of lactose and glucose polymers to compensate for the

developmental lag and lower concentration of lactase in the intestinal mucosa. Lactose, however, remains important both in calcium absorption and as a prebiotic. Glycosidase enzymes involved in the digestion of glucose polymers are active in preterm infants.

63. Why is the fat absorption of preterm infants lower than that of term infants?
The lower fat absorption reported in preterm infants is attributed to their relative deficiency of pancreatic lipase and bile salts.

64. Why is the fat of human milk well absorbed by preterm infants?
The human milk triglyceride molecule has palmitic acid in the beta position and is more easily absorbed compared with triglyceride molecules of cow's milk, vegetable fats, and animal fats that have palmitic acid in the alpha position. The presence of human milk lipase also improves fat absorption.

65. When should soy protein–based formulas be used for feeding infants?
Soy formulas are recommended for the following:
- Infants with congenital lactase deficiency and galactosemia (soy formulas are lactose free)
- Infants with an immunoglobulin E–mediated allergy to cow's milk protein (8% to 14% of these infants will also react to soy)
- Infants of parents requesting a vegetarian-based diet

66. What essential amino acid is added to soy-based infant formulas?
Because soy protein has low concentrations of methionine, this amino acid is added to all soy-based formulas.

67. When can preterm infants successfully use the nipple to feed?
The success of feeding a preterm infant by nipple depends on the ability of the infant to coordinate sucking and swallowing, which develops at approximately 33 to 34 weeks of gestational age.

68. Why may transpyloric feedings result in fat malabsorption?
Transpyloric feedings may result in fat malabsorption as a result of bypassing the lipolytic effect of gastric lipase.

69. Why are early minimal enteral feedings recommended for preterm infants receiving parenteral nutrition?
Gastrointestinal hormones such as gastrin, enteroglucagon, and pancreatic polypeptide may have a trophic effect on the gut. Postnatal surges of these hormones occur in preterm infants receiving minimal enteral feedings. Minimal enteral feeding has also been reported to produce more mature small intestinal motor activity patterns in preterm infants. Thus early minimal enteral feedings given along with parenteral nutrition may improve subsequent enteral feeding tolerance and may shorten the time to achieve full enteral intake. Furthermore, enteral feedings stimulate the enterohepatic circulation and are known to lessen parenteral nutrition–associated liver disease. The most recent Cochrane Review, however, suggests that the evidence for this effect is unclear, at best.

Bombell S, McGuire W. Early trophic feeding for very low birth weight infants. Cochrane Database Syst Rev 2009;3:CD000504.

70. What are the reported advantages of feeding human milk to preterm infants over the commercially available infant formulas?
- A lower incidence of necrotizing enterocolitis in preterm infants fed human milk
- Faster gastric emptying in preterm infants fed human milk compared with those fed bovine milk–derived formulas
- Improved long-term cognitive development, which has been correlated with human milk feedings in preterm infants

71. Does human milk completely meet the nutritional requirements of VLBW preterm infants (birth weight below 1500 g)?

Growth rates of preterm infants fed banked human milk or their own mother's milk are lower than those of infants fed preterm formulas. In addition, the calcium and phosphorus content of human milk is insufficient to fully support adequate skeletal mineralization. Supplementation of human milk with available human milk fortifiers that provide protein, calcium, phosphorus, sodium, zinc, and up to 23 vitamins helps overcome these nutritional inadequacies. Newly designed preparations of pooled human breast milk (Prolacta) do contain adequate calories and minerals for growth.

BREASTFEEDING

72. What are the determinants of milk volume (milk production)?

Initially, hormonal factors (prolactin and oxytocin) affect the synthesis and secretion of milk. Once mother's milk "comes in," tight junctions close, and lactation shifts from endocrine control to auto-crine control, or control driven by milk removal. The frequency of breastfeeding then becomes the most important factor affecting the continuation of adequate milk production. The term infant should receive between 8 and 12 feedings per day in the first week and more than 5 daily thereafter. To minimize the volume of residual milk, mothers should alternate the breast they start with at the next feeding. When breastfeeding is first initiated, mothers should switch the infant from one side to the other approximately every 5 to 10 minutes. Maternal diet and fluid intake rarely affect milk volume; however, in the setting of severe malnutrition there may be diminished milk production.

73. How can milk production be increased?

There are no magic potions or medications that increase milk production, though increasing maternal fluid intake may be of modest help. The administration of metoclopramide will occasionally increase serum prolactin and increase milk production. Unfortunately, this medication has side effects, including sedation and extrapyramidal neurologic signs. Oxytocin will not increase milk production, but it may help milk ejection (once milk already has been synthesized). Herbal remedies have been advocated, but no data are available that determine their efficacy or associated risks. Fatigue and stress also affect milk production adversely. A small percentage of women (2% to 5%) have lactation insufficiency and cannot produce adequate quantities of milk.

74. What are the contraindications for breastfeeding?

- Galactosemia
- Use of controlled substances such as cocaine, narcotics, and stimulants.
- Miliary tuberculosis: Breastfeeding should not take place until adequate therapy has been received for approximately 2 weeks.
- Human immunodeficiency virus (HIV): This contraindication has far-reaching global concerns. In the United States women who test positive for HIV should not breastfeed. The risk-to-benefit ratio must be determined for particular populations outside the United States. Efforts are under way to determine the risk-to-benefit ratio and cost-to-benefit ratio for the use of antiretroviral therapy along with breastfeeding or the use of infant formula in high-risk populations.

Only a few medications are incompatible with breastfeeding, although most medications do enter breast milk in low concentrations. The following are some of the contraindicated drugs:

- Bromocriptine (suppresses lactation)
- Amiodarone
- Ergotamine
- Thiouracils
- Chemotherapeutic agents
- Metronidazole
- Radiopharmaceuticals
- Klonapin

- Phenindione
- Salts containing bromide and gold
- Amantadine

75. Does energy expenditure differ between breastfed and formula-fed infants?
In studies of AGA gavage-fed infants, there was significantly lower energy expenditure in the infants fed human milk compared with those fed formula.

Lubetzky R, Vaisman N, Mimouni F, et al. Energy expenditure in human milk– versus formula-fed preterm infants. J Pediatr 2003;143:750–3.

76. A mother has breastfed her 5-week-old infant exclusively. She now calls with the concern that she has recently noticed a burning pain in her nipple during breastfeeding. You examine the mother and note some erythema of her areola. You diagnose a fissure and advise her to use dry heat and a few drops of milk on her areola after breastfeeding. She calls back in a few days to report that the pain is increasing. What other diagnosis should you consider?
This is not an uncommon presentation for a Candida infection of the nipple. You should examine the infant for evidence of perioral thrush. If thrush is evident, the baby should be treated with an oral medication and the mother with an antifungal.

77. A mother calls you and explains that she is worried because her 4-day-old baby is not receiving enough breast milk. How do you assess whether a newborn is receiving sufficient amounts of breast milk during the first week after birth?
Understand why the mother is concerned. Some of the following factors should influence your decision either to see the mother and baby or to reassure the mother over the phone: frequency of feeding (8 to 12 times in 24 hours, no interval longer than 4 hours), urine output (light yellow–stained diapers), and stool output (no more meconium stools after day 3). Some practitioners use the following rough guide for urine and stool output in the first week: minimum of one urine output in the first 24 hours, two to three in the next 24 hours, about four to six on day 3, and six to eight on day 5; stools should be one per day on days 1 and 2, two per day on day 3, and four or more afterward, although this can vary substantially among infants. The mother should sense that her milk has "come in" between the second and fourth days postpartum. The baby should have established feeding activities, such as lip smacking and rooting. You should hear swallows, and the baby should be satisfied after a feeding. Feeding activities, however, vary widely. Some adequately hydrated infants are sleepy and need coaching with feedings. If a mother experiences leaking from one breast while the child is nursing at the other, her milk supply is usually quite adequate. Weighing an infant before and after feeding can provide an accurate assessment of milk intake. The technique requires an electronic scale and strict attention to details such as not unwrapping the infant or changing diapers before the reweighing is done.

78. You see a 5-day-old male infant in the office for a routine check after early hospital discharge. The mother reports no particular problems; he is much easier to manage than she thought a newborn would be. She is breastfeeding every 3 hours but lets him sleep at night (last night he slept for 6 hours). About once a day she notes that he has dark yellow urine in his diaper. He had a dark-green, tarry stool yesterday. The mother thinks her milk has "come in," but she acknowledges no signs of engorgement. You examine the infant and note jaundice to the level of the umbilicus and dry skin but moist mucous membranes. He is responsive and alert. You examine the mother and note that her breasts are moderately engorged. The infant's body weight is 11 ounces below his birth weight of 7 pounds, 8 ounces. You check his serum bilirubin

concentration, which is 11 mg/dL. There is no blood group incompatibility. How would you manage this case, and what would you advise the mother?

You should observe a breastfeeding to ensure that the baby has a good latch-on to the breast and is able to suck and swallow. You advise the mother to breastfeed every 2 hours. You do not advise water supplements because the baby needs calories. His bilirubin level should decline with this strategy. If the mother had not been making milk, you might suggest that she mechanically express her milk after every feeding to increase stimulation. You must schedule a return visit in 24 hours to reassess the infant.

79. **What is the most variable nutrient in human milk?**

Fat is the most variable content of all nutrients in human milk. The fat content rises slightly during lactation, increases from the beginning (foremilk) to the end (hindmilk) of the feeding, varies among women (probably a direct effect of body fat stores), and varies over the course of the day. If the mother does not completely empty her breast after feeding, the baby will not receive all the calories (fat). Mothers using mechanical methods to express their milk may not completely empty the breast.

80. **Breastfeeding a premature infant can be a challenge. How do you advance from tube-feeding to breastfeeding in a premature infant?**

Note the sucking and swallowing ability of the infant. Parental skills, infant feeding cues, and timing of feedings should also be considered. Begin one breastfeeding in place of a tube feeding or in addition to the tube feeding. If the latch-on is good and clinical signs of sucking, swallowing, and some drooling of milk are noted, then continue the process each day. Withdrawing milk from an indwelling feeding tube to assess milk intake from breastfeeding will not yield accurate results because gastric emptying from the stomach occurs rapidly after a human milk feeding. Furthermore, clinical signs of feeding activity and maternal assessment of breast emptying are inexact measures of milk intake and may not reflect small amounts consumed. Weighing the infant before and after breastfeeding is the most accurate way to assess milk intake.

Funkquist EL, Tuvemo T, Jonsson B, et al. Influence of test weighing before/after nursing on breastfeeding in preterm infants. Adv Neonatal Care 2010;10(1):33–9.

81. **Do mothers benefit from breastfeeding?**

Postpartum weight loss and uterine involution may be more rapid with breastfeeding. The postpartum amenorrhea during lactation is an acknowledged method of child spacing, especially for 4 to 6 months. This technique is most reliable if breastfeeding is practiced around the clock. Several reports now suggest that women who breastfed their infants had a decreased incidence of premenopausal breast cancer and ovarian cancer. Women who breastfed their infants also may have a decreased incidence of osteoporosis.

Labbok MH: Health sequelae of breastfeeding for the mother. Clin Perinatol 1999;26:491–503.

VITAMINS AND TRACE NUTRIENTS

82. **A 2-month-old preterm infant (with an estimated gestational age of 26 weeks) develops osteopenia of prematurity and fractures of both humeri. The infant is receiving 400 units of vitamin D daily. Should the dose of vitamin D be increased?**

No. Contrary to an earlier theory, osteopenia of prematurity results primarily from inadequate intake of mineral substrate (calcium and phosphorus) and not vitamin D. High doses of vitamin D do not appear to aid in the prevention or treatment of osteopenia of prematurity. Infants born prematurely are at risk for developing osteopenia because of limited accretion of bone mass *in utero* (fetal accretion rates for calcium and phosphorous range from 92 to 119 mg/kg/day and 59 to 74 mg/kg/day, respectively). Preterm infants often cannot receive the ideal amount of calcium by way of parenteral

nutrition and thus do not receive the daily goal of calcium until full enteral feedings are established. Diuretics, steroids, and physical inactivity have a negative effect on bone mineralization. To mimic fetal accretion, an enteral intake of 120 to 230 mg/kg/day of calcium and 60 to 140 mg/kg/day of phosphorus is recommended for preterm infants. This amount is provided by 150 cc/kg/day of premature infant formula or fortified breast milk.

83. A 6-week-old infant is recovering from necrotizing enterocolitis that necessitated resection of two thirds of the jejunum and placement of an ileostomy. When enteral feedings are restarted, the drainage from the ileostomy becomes excessive. The infant is growing poorly (despite an adequate caloric intake) and develops vesiculobullous and eczematous lesions around the eyes, mouth, and genitals. What mineral deficiency should be considered?

Infants with abnormal gastrointestinal losses (persistent diarrhea, excessive ileostomy drainage) may be at risk for zinc deficiency because fecal loss is the major excretory route. Signs of zinc deficiency include poor wound healing, poor linear growth, decreased appetite, hair loss, depressed immune function, and skin lesions that commonly mimic a diaper rash but are also perioral in location.

84. What are the causes of zinc deficiency in LBW infants?
- Poor zinc stores
- Increased requirement for growth
- Prolonged intravenous nutrition containing inadequate zinc
- Abnormally low zinc content of mother's milk
- Supplements of iron or copper that compete with zinc for absorption

Adapted from Atkinson SA, Zlotkin S. Recognizing deficiencies and excesses of zinc, copper, and other trace elements. In: Tsang RC, Zlotkin SH, Nichols BL, Hansen JW, editors. Nutrition during infancy. 2nd ed. Cincinnati: Digital Educational Publishing; 1997.

Shah MD, Shah SR. Nutrient deficiencies in the premature infant. Pediatr Clin North Am 2009;56(5):1069–83.

85. The requirements for what nutrient are increased under phototherapy?

Riboflavin is a photosensitive vitamin, and requirements may be increased in infants receiving phototherapy.

86. Is fluoride an essential nutrient for a newborn infant?

Although fluoride has been considered "beneficial for humans," whether it is essential remains unknown. Fluoride supplementation is not recommended from birth because of questions concerning whether the benefit of fluoride warrants the risk of dental fluorosis. Commercial infant formulas do not contain fluoride.

✓ KEY POINTS: GROWTH AND NUTRITION

1. The parents of IUGR infants should be aware that significant catch-up growth will occur in the first year of life but that ultimate stature may be less than that of an AGA infant.

2. Lactose malabsorption is extremely uncommon in infants unless they have had a significant insult to the intestinal mucosa (e.g., infection, short gut syndrome) or have the very rare disorder of congenital lactase deficiency.

3. The infant with an ostomy should be carefully monitored for excessive sodium losses and zinc deficiency, both of which can impair growth.

4. A critical nutritional goal for the infant with short gut syndrome is to advance enteral feeds as clinically tolerated to enable intestinal adaptation and ultimate discontinuation of TPN.

TABLE 10–3.	WATER–SOLUBLE VITAMINS IN MATURE HUMAN MILK	

Adapted from Schanler RJ. Who needs water soluble vitamins? In: Tsang RC, Zlotkin SH, Nichols BL, Hansen JW, editors. Nutrition during infancy. 2nd ed. Cincinnati: Digital Educational Publishing; 1997.

	HUMAN MILK (RANGE)	AAP, CON* (UNITS/100 kcal)
Thiamin (μg)	31 (21-26)	40
Riboflavin (μg)	56 (42-85)	60
Niacin (mg)	0.29 (0.27-0.34)	0.25 (0.8)
Vitamin B_6 (μg)	20 (15-30)	35
Pantothenic acid (mg)	0.6 (0.3-1.0)	0.3
Biotin (μg)	0.7 (0.6-1.1)	1.5
Folate (μg)	7 (6-12)	4
Vitamin B_{12} (μg)	0.10 (0.07-0.16)	0.15
Vitamin C (mg)	8 (5-13)	8

*Committee on Nutrition of the American Academy of Pediatrics.

87. **What is the scientific rationale for administering vitamin A to prevent bronchopulmonary dysplasia?**
    - Lung differentiation is regulated in part by vitamin A.
    - Vitamin A deficiency causes replacement of mucus-secreting epithelium by stratified squamous keratinizing epithelium in the trachea and bronchi.
    - Bronchopulmonary dysplasia has been associated with vitamin A deficiency in VLBW preterm infants.
    - Premature birth deprives the newborn infant of the supply of retinol (vitamin A).
    - The histopathology of bronchopulmonary dysplasia includes findings commonly seen with vitamin A deficiency (e.g., loss of ciliated cells and keratinizing metaplasia).

88. **What are the concentrations of water-soluble vitamins in mature human milk, and how do they compare with the recommended dietary allowances for healthy term infants?**
    See Table 10-3.

IRON REQUIREMENTS

89. **How long can iron stores meet the needs of term, LBW, and preterm infants before supplementation is necessary?**
    The quantity of iron stored is proportional to the birth weight of the infant. On average, the iron stores in a term infant can meet the infant's iron requirement until 4 to 6 months of age and that of LBW and preterm infants until 2 to 3 months of age. Transfused infants, however, likely have greater iron stores.

90. **What are the daily dietary iron requirements for term, LBW, and preterm infants?**
    The estimated daily requirement is 1 mg/kg/day for term infants and 2 to 4 mg/kg/day for LBW and preterm infants.

91. **Do breastfed infants require iron supplementation?**
    Although the bioavailability of iron in breast milk is high (because of the presence of lactoferrin, which enhances iron absorption), the content is relatively low. Additional sources of iron are recommended for breastfed infants after 4 to 6 months of age.

92.   What is the iron content of hemoglobin?

Each gram of hemoglobin contains 3.4 mg of iron.

93.   Where is iron absorbed, and what factors can influence iron absorption?

Dietary iron is absorbed in the duodenum and the proximal jejunum. Absorption is influenced by the body's demand and also by the dietary source. The majority of the dietary iron (in plant foods and fortified food products) is nonheme iron. Ascorbic acid enhances the absorption of nonheme iron, whereas calcium, phytates, manganese, and polyphenols decrease it.

94.   Do premature infants need more or less iron than term infants?

Overall, premature infants need more iron than term infants during their first postnatal year. The reason for this increased need stems from two factors. First, iron is accreted primarily during the last trimester. The fetus maintains a fairly steady level (75 mg of elemental iron per kilogram of body weight) during this period. At 24 weeks' gestation the fetus has 37.5 mg of total body iron, whereas at term the newborn has 225 mg. Therefore premature birth results in significantly reduced total body iron. Second, premature infants exhibit a more rapid rate of growth per kilogram of body weight than the term infant. Iron intake must increase to support the increase in hemoglobin mass. Whereas the term newborn needs approximately 1 mg/kg of iron per day, the preterm infant needs between 2 and 4 mg/kg/day. The more premature the infant, the greater the need.

95.   What groups of term neonates are at increased risk of low iron stores at birth?

Growth-retarded infants and infants of diabetic mothers are at risk for reduced iron stores. Approximately 50% of IUGR infants and 65% of infants of diabetics have cord serum ferritin concentrations below the fifth percentile (60 ng/L). In growth-restricted infants the etiology is probably related to impaired placental transport of nutrients. The pathophysiology of low iron stores in infants of diabetic mothers is more complex. Chronic maternal hyperglycemia results in chronic fetal hyperglycemia and hyperinsulinemia, both of which increase the oxygen consumption of the fetus by approximately 30%. Chronic fetal hypoxia leads to increased erythropoietin secretion and secondary polycythemia, which in turn requires increased iron delivery. Each extra gram of hemoglobin synthesized by the fetus requires an additional 3.49 mg of elemental iron delivered by the placenta. The human placenta is not capable of upregulating placental transport to that extent, leaving the fetus of a diabetic mother dependent on its accreted iron stores to support its expanding fetal blood volume. The result is that iron is redistributed away from storage and nonstorage tissues and into the red cell mass. It does not appear that either group needs additional dietary iron postnatally, supporting the principle that the neonatal intestine avidly absorbs iron.

Verner AM, Manderson J, Lappin TR, et al. Influence of maternal diabetes mellitus on fetal iron status. Arch Dis Child Fetal Neonatal Ed. 2007;92(5):F399–401.

Siddappa AM, Rao R, Long JD, et al. The assessment of newborn iron stores at birth: a review of the literature and standards for ferritin concentrations. Neonatology. 2007;92(2):73–82.

96.   What is the effect of recombinant human erythropoietin (rhEPO) on the iron needs of the premature infant?

Erythropoietin increases the need for iron by up to threefold to 6 mg/kg/day. A recent study suggested that once weekly dosing at 1200 units/Kg/dose was adequate to maintain hematocrit levels in premature neonates. Studies of erythropoietin given to sheep with varying degrees of iron sufficiency demonstrated that the degree of hemoglobin response is directly related to the iron sufficiency of the animal. In addition, some recent evidence suggests that EPO may have neuroprotective effects, including reduction of risk of retinopathy of prematurity.

Ohls RK, Roohi M, Peceny HM, et al. A randomized, masked study of weekly erythropoietin dosing in preterm infants. J Pediatr 2012;160(5):790–5.

Romagnoli C, Tesfagabir MG, Giannantonio C, et al. Erythropoietin and retinopathy of prematurity. Early Hum Dev 2011;87(Suppl 1):S39–42.

97. True or false: premature infants are iron overloaded at hospital discharge.
This is a trick question. In fact, preterm infants could be iron deficient, iron neutral, or iron over-loaded. Preterm AGA infants start with approximately 75 mg of iron per kilogram of body weight. This amount of iron is considered sufficient for the neonatal period, and iron supplementation probably should not begin until the preterm infant is at least 2 weeks of age. Preterm infants are born with very immature antioxidant systems, and there is a concern that large doses of iron could overwhelm the system and lead to disease related to oxidant stress (e.g., retinopathy of prematurity, broncho-pulmonary dysplasia). On the other hand, the rapid growth rate of preterm infants results in a rapid expansion of the blood volume, and iron is required to support this growth. Those who are born at low gestational ages, who have a benign neonatal course, and who are fed a low-iron diet (e.g., breast milk without iron supplementation) are at high risk of using up all the available stores soon after discharge. These infants should have their iron and hemoglobin status checked earlier than the usual 9 months of age recommended for term infants. In contrast, a sick preterm infant who requires multiple transfusions to maintain cardiovascular stability may be at high risk for iron overload. Preterm infants can have ferritin concentrations of 500 ng/dL at discharge, suggesting significant iron loading of the liver.

98. Does placental iron transport depend on maternal iron status, fetal iron status, or both?
Both. Early studies clearly establish a relationship between maternal iron stores, as indexed by the mother's ferritin concentration and the infant's cord serum ferritin concentration. This relation-ship appears to be particularly strong when the mother is suffering from profound iron deficiency. However, lesser degrees of iron deficiency do not seem to influence fetal iron status. In fact, the fetus manages to maintain iron sufficiency in the face of maternal iron deficiency. Conversely, certain fetuses can become iron deficient in spite of maternal iron sufficiency. This occurs when placental iron transport is disturbed by uteroplacental vascular insufficiency (resulting in IUGR) and when fetal iron demand exceeds placental iron transport ability. The latter occurs in pregnancies complicated by diabetes mellitus and chronic fetal hypoxia with augmented secondary fetal erythropoiesis.

99. How can the fetus increase placental transport of iron?
In pregnancies complicated by fetal iron deficiency, as indexed by a low cord serum ferritin con-centration or decreased placental iron content, the expression of iron transport proteins such as the transferrin receptor is increased on the apical (maternal-facing) membrane of the syncytiotropho-blast. Studies have shown that this upregulation is most likely in response to the iron status of the syncytiotrophoblast. This upregulation is achieved by intracellular iron regulatory proteins that bind transferrin receptor mRNA, stabilizing it to produce more copies of the receptor and leading to greater iron transport. Thus the fetus appears to regulate its own iron accretion. A similar system has been described for the transport of certain amino acids by the placenta.

Georgieff MK, Berry SA, Wobken JA, et al. Increased placental iron regulatory protein-1 expression in diabetic pregnancies complicated by fetal iron deficiency. Placenta 1999;20:87–93.

   Petry CD, Wobken JD, McKay H, et al. Placental transferrin receptor in diabetic pregnancies with increased fetal iron demand. Am J Physiol 1994;267:E507–E514.

GASTROESOPHAGEAL REFLUX

100. How common is gastroesophageal reflux (GER)?
Gastroesophageal reflux is seen in up to 50% of infants with recurrent emesis.

101. What is the course of GER in a healthy infant?
During infancy GER is very common because of the immaturity of the lower esophageal sphincter. Recurrent vomiting is the most common manifestation of reflux in this age group and is usually effortless. It is clinically evident in 50% of infants in the first 3 months of life. Only 5% to 10% of

children have reflux at the age of 1 year. There is gradual resolution of vomiting by the age of 1 to 2 years. If regurgitation has not resolved by 24 months of age, further evaluation is recommended.

102. What does the term "happy spitter" signify?

These infants have uncomplicated GER. They have no concerning signs or symptoms and have effortless, painless vomiting. Weight gain is normal, and the children develop normally. Reassurance, education, and anticipatory guidance are generally the only interventions required.

### 103. What are the red flags of GER disease (GERD) in infants?

- Bilious or forceful vomiting
- Hematemesis
- Failure to thrive

Any of these findings should suggest severe GERD, or an alternative diagnosis to GERD should be sought.

104. What is the differential diagnosis for GERD in infants and children?

A key point is differentiating GERD from the causes of recurrent or persistent vomiting:

- Gastrointestinal obstruction
- Pyloric stenosis
- Malrotation with intermittent volvulus (Fig. 10-3)
- Intermittent intussusception
- Intestinal duplication
- Hirschsprung disease
- Antroduodenal web
- Incarcerated hernia
- Gastrointestinal disorders
- Gastroparesis
- Gastroenteritis
- Eosinophilic esophagitis or gastroenteritis
- Food allergy or intolerance
- Achalasia
- Peptic ulcer disease
- Neurologic problems: Increased intracranial pressure
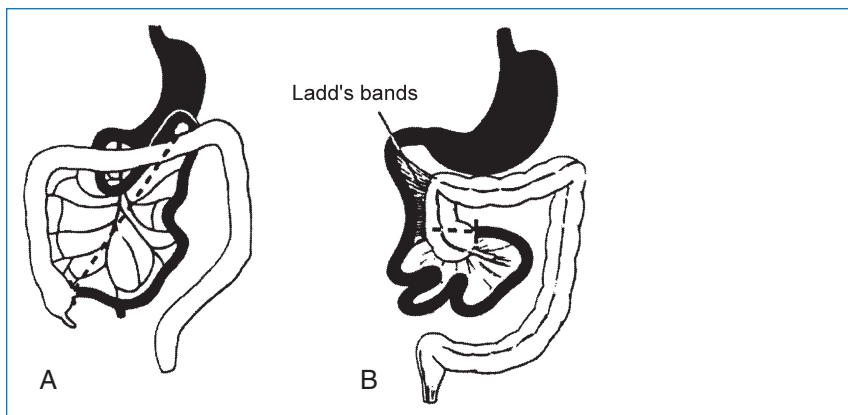
Figure 10-3. A, The cecum descends into the right lower quadrant. Note the normal broadness of the small bowel mesentery *(dashed line).* **B,** In malrotation the duodenal loop lacks 90 degrees of its normal 270-degree rotation such that the duodenojejunal flexure does not cross midline, and the cecocolic loop lacks 180 degrees of its normal rotation.

- Infectious disorders
  - Sepsis
  - Meningitis
  - Urinary tract infection
  - Hepatitis
  - Pneumonia
- Metabolic/endocrine disorders
  - Galactosemia
  - Urea cycle defects
  - Hereditary fructose intolerance
  - Amino and organic acidemias
  - Congenital adrenal hyperplasia
  - Maple syrup urine disease
- Renal disorders
  - Obstructive uropathy
  - Renal insufficiency
- Environmental causes
  - Ingestion of or exposure to toxins
  - Munchausen syndrome by proxy
- Cardiac disorder: congestive heart failure

105. What diagnostic tests are available to evaluate GER?
See Table 10-4.

106. What are nonmedical treatment options for GER?
- Smaller-volume feeds given more frequently
- Thickened formula
- Avoidance of seated or supine positions after feeding
- Elevation of the head of the crib
- Elimination of second-hand smoke (which causes relaxation of the lower esophageal sphincter)
- Trial of cow's milk protein–free formula

Infants with GER may be placed in an upright position for at least 30 minutes after meals, and the head of the crib may be elevated to 30 to 45 degrees. Placing the child in a car seat in the home is not recommended. Thickening of the formula with rice cereal or commercial thickening agents may help decrease the amount of regurgitation and lessen irritability. The recommended starting amount is 1 teaspoon per ounce of formula; this may be increased to 1 tablespoon per ounce as needed. Modification of the feeding schedule to offer smaller feeds at more frequent intervals can help decrease gastric distention and regurgitation of less frequent larger feeds.

107. What are the medical treatments for GER?
Pharmacologic:
- Antacids
- Prokinetic agents (e.g., metoclopramide, bethanechol, erythromycin)
- H_2-receptor antagonists (e.g., ranitidine, cimetidine, famotidine, nizatidine)
- Proton-pump inhibitors (e.g., omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole)
- Surface agents (sucralfate gel)

Surgical:
- Transpyloric feeding tubes
- Fundoplication
- Pyloroplasty

TABLE 10–4.	DIAGNOSTIC TESTS FOR THE EVALUATION OF GASTROESOPHAGEAL REFLUX	
TEST	**ADVANTAGES**	**DISADVANTAGES**
Upper gastrointestinal tract series (UGIS)	Evaluates for structural abdnormalities	Short duration (<1 h) that may miss a reflux episode Manipulation during study can produce a reflux event in an otherwise healthy infant Low sensitivity and specificity for GER
Gastroesophageal scintigraphy	Evaluates for gastric emptying time, reflux, and aspiration in lungs Longer study period than UGIS (1 to 2 h) to better assess frequency and degree of aspiration	Study limited to time period of feeding bolus May underestimate frequency of daily events if volume or composition of feed is altered for the study Lacks standardized technique and age-specific normative data.
24-hour pH probe monitoring	Evaluates pH changes over extended period of time, ideally 24 h, to better assess frequency of reflux Can correlate with symptom scales No activity restriction during testing	Must be on bolus feeds and off acid suppression medications for 72 h for an accurate study Invasive Does not evaluate for alkaline reflux
Impedance probe	Evaluates for pH changes as well as impedance Extended study, ideally 24 h, as with pH probe Can detect non–acid reflux episodes Can correlate with symptom scales No activity restriction during testing	Must be on bolus feeds and off acid suppression medications for 72 h for an accurate study. Invasive
Esophago-gastroduodenoscopy	Evaluates gross and histologic mucosal changes of the esophagus, stomach, and duodenum	Most invasive test; often requires anesthesia
GER, Gastroesophageal reflux.		

EOSINOPHILIC GASTROINTESTINAL DISORDERS

108. What are eosinophilic enteropathies?

Eosinophilic enteropathies are eosinophilic inflammatory conditions that can be present throughout the entire gastrointestinal tract. The inflammatory process is characterized by the selective infiltration of large numbers of eosinophils into the bowel mucosa, smooth muscle, or both. The initial trigger for this process is unknown, but antigens in food are believed to contribute to ongoing disease.

109. What is the differential diagnosis for eosinophils in the gastrointestinal lining in newborns?

The differential diagnosis includes idiopathic eosinophilic gastroenteritis, formula protein intolerance, GERD, and normal variation.

110. How does this process present in neonates?

This disease process can present as failure to thrive, diarrhea, malabsorption, regurgitation and irritability (identical to GER), and colitis. In neonates the protein found in cow's milk or soy protein may

be the offending antigen for the inflammatory process. When this occurs, the process is called dietary protein–induced colitis, milk protein colitis, enteritis, and so forth. A common presentation is an infant who has a history of irritability, diarrhea with mucus and blood, poor weight gain or failure to thrive, and some degree of anemia. It is the most common cause of bloody stools in the first year of life. The second common presentation in neonates is that of reflux that does not respond to therapeutic management. In this clinical picture the neonate has symptoms of GER and irritability that do not improve as expected despite appropriate medical and nonmedical therapeutic interventions.

111. What is the prognosis of eosinophilic colitis in the neonate?

Eosinophilic colitis in infants has a very good prognosis. The vast majority of patients are able to tolerate milk protein by the age of 1 to 3 years. Some studies associate eosinophilic colitis with the later development of inflammatory bowel disease, but this association is under debate.

112. What treatment options are available?

Multiple medications have been tried and used depending on the location of the involved portion of the gastrointestinal tract. These medications, which mostly work by attempting to modify the immune response, include systemic steroids, protein pump inhibitors, histamine receptor-2 blockers, topical steroids, antacids, cromolyn, leukotriene antagonists, sucralfate, and prokinetics if there is secondary dysmotility. Elimination from the diet of the offending milk or soy protein allergen is accomplished in neonates by changing to a protein-hydrolyzed or amino acid formula or, on occasion, by eliminating dairy from the maternal diet for breastfed infants.

✓ KEY POINTS: INFLAMMATORY GASTROINTESTINAL DISORDERS

1. Features of gastroesophageal reflux and allergic esophagitis may be clinically similar; the latter should be considered when standard antireflux therapy is ineffective.

2. Allergic colitis is a relatively common cause of rectal bleeding and bloody stools in the otherwise healthy-appearing infant.

3. The presence of *Clostridium difficile* toxin in stools is a common finding in healthy infants.

4. Hirschsprung disease can be associated with an inflammatory enterocolitis that can be quite severe and life-threatening.

MALABSORPTION

113. What is an easy method of differentiating between osmotic and secretory diarrhea?

Patients with secretory diarrhea continue to have diarrhea even after they are not fed enterally. The laboratory method of differentiating between osmotic and secretory diarrhea is the measurement of the osmotic gap in the stool, which is achieved by measuring the stool osmolarity, sodium (Na), and potassium (K) concentrations in a random stool sample. Normal fecal osmolality is 290 mOsm/kg water, and the normal osmotic gap is less than 40 mEq/L.

$$\text{Osmotic gap} = \text{fecal osmolality} - 2 \times ([\text{Na}] \ [\text{K}])$$

Osmotic gap and sodium and potassium concentrations are expressed as mEq/L and fecal osmolality as mOsm/kg H_2O.

114. What are the most common causes of lactose malabsorption?

Almost any process damaging the mucosa of the small intestine can result in malabsorption of lactose owing to secondary lactase deficiency. The most common cause of secondary lactase deficiency is mucosal damage resulting from infection (e.g., postviral damage). Lactase enzyme has the lowest

activity of any brush border disaccharidases and is localized at the tip of the villus, thus making it most vulnerable to brush border injury at the time of infection. It is the first enzyme to be affected and the last one to recover after mucosal damage.

115. What are the stool characteristics of carbohydrate malabsorption? Why does diarrhea occur?

Stools in carbohydrate malabsorption are acidic, with a pH of less than 5.5 (owing to fermentation), and are positive for reducing substances (sugar). Reducing substances will be negative in the stool in the face of carbohydrate malabsorption if the sugar is not a reducing sugar (e.g., sucrose). In that situation the stool sample should be hydrolyzed with 0.1 N hydrogen chloride and boiled briefly to break up the sucrose before being tested to yield a positive result for reducing substances.

The malabsorbed carbohydrate induces an osmotic fluid shift in the small intestine, resulting in an increase in fluid delivery to the colon. There the carbohydrate is fermented by colonic bacterial flora to organic acids such as lactic acid, yielding an increase in the osmolality beyond the colon's salvage capacity, thereby leading to diarrhea. Colonic bacteria ferment the carbohydrate in a process known as colonic scavenging. The main by-products of fermentation are short-chain fatty acids, which can be used as a source of energy by the epithelial cells of the colon.

116. Is a 72-hour fecal fat collection useful for detecting fat malabsorption in the neonate?

The 72-hour fecal fat collection is useful only if patients are receiving a diet containing long-chain triglycerides as the only source of fat in the diet. The standard method used for quantitation of fat does not detect medium-chain triglycerides. A 72-hour dietary record must be obtained simultaneously so that the coefficient of fat absorption can be obtained.

117. What is the coefficient of fat absorption in infants younger than 6 months of age?

The coefficient is 85%.

118. How common is primary lactase deficiency in neonates?

Contrary to common belief, primary or congenital lactase deficiency is a very rare disease, with only a few dozen cases reported in the literature. The disease is manifested by severe diarrhea while the infant is receiving a lactose-containing formula or breastfeeding, and it starts within the first few hours or days of life. The diarrhea resolves after the infant is switched to a lactose-free formula.

119. What is microvillus inclusion disease?

This very rare congenital disease is often quoted as a cause of severe neonatal diarrhea. The major manifestation is severe secretory diarrhea unresponsive to the withdrawal of oral diet. Diagnosis is based on a small bowel biopsy in which shortened enterocyte microvilli with microvillus inclusions are seen on electron microscopy. The etiology is unknown, and prognosis is poor. Patients often become dependent on TPN and have a shortened life expectancy.

Other uncommon causes of congenital diarrhea include autoimmune enteropathy, enterocolitis associated with Hirschsprung disease, primary lactase deficiency, congenital chloride diarrhea, congenital sodium diarrhea, primary bile acid malabsorption, and enterokinase deficiency.

120. What is the cause of diarrhea in a neonate fed exclusively Pedialyte?

If other causes of diarrhea, such as that resulting from an infectious source, are excluded, congenital glucose-galactose malabsorption is high on the differential diagnosis because the carbohydrate in Pedialyte is dextrose (a form of glucose monohydrate). Glucose or galactose malabsorption is an autosomal recessive disease caused by a missense mutation in the *SGLT1* gene resulting in a complete loss of the Na-dependent glucose transporter, which mediates glucose absorption in the brush border of the intestine. The treatment is elimination of glucose and galactose from the diet with resolution of the diarrhea.

121. Is there a test to assess the absorptive integrity of the small intestine?

The delta-xylose absorption test is a useful tool frequently used for the evaluation of small intestine integrity and to screen for carbohydrate malabsorption. Delta-xylose is a five-carbon sugar handled similarly to natural six-carbon sugars by way of high-efficiency proximal small bowel uptake. It is not metabolized and is rapidly excreted in the urine. Thus it is ideally suited to test the most basic of carbohydrate pathways. The test is performed in a fasting patient who is given 14.5 g/m² of delta-xylose orally as a 10-g% solution. A serum level of the delta-xylose is measured 1 hour later. Small intestinal biopsies can be used to confirm anatomic disruption of the mucosal surface or reduced disaccharidase levels to complement the functional absorptive results obtained from a delta-xylose test.

122. A 21-year-old pregnant woman was diagnosed with polyhydramnios. A prenatal ultrasound study demonstrated distended loops of small intestine. The baby was delivered at 33 weeks' gestation by cesarean section, and at the time of delivery the amniotic fluid was noted to contain yellow-green stool. On day 2 of life the infant developed a hypochloremic metabolic alkalosis and loose stools. A stool sample contained high concentrations of chloride. What is the most likely diagnosis in this case?

The following features of this case suggest a diagnosis of congenital chloride diarrhea:
- High concentrations of fecal chloride (exceeding the sum of sodium and potassium)
- Polyhydramnios
- Distended loops of bowel on a prenatal ultrasound
- Prematurity

This is an autosomal recessive disease caused by a defect in the chloride-bicarbonate exchange transport system in the ileum and colon resulting in lifelong secretory diarrhea. The diagnosis is made by the high concentration of fecal chloride. Treatment consists of fluid and electrolyte replacement—initially intravenously and then orally. If the condition is diagnosed and treated early, the prognosis is excellent.

**123. What are the anatomic causes of gastric outlet obstruction in neonates and infants?**

- Hypertrophic pyloric stenosis
- Antral and pyloric membranes or webs
- Eosinophilic gastroenteritis
- Aberrant pancreatic tissue
- Duplication of antrum or duodenum
- Pyloric channel ulcer
- Pyloric atresia

124. What type of surgery is typically performed in complicated cases of meconium ileus?

In 1957 Bishop and Koop described the technique of resection of the dilated ileal segment and proximal end-to-distal side ileal anastomosis with distal ostomy, also known as the Bishop–Koop ileostomy. This procedure minimizes contamination, allows for anastomosis between appropriately sized bowel segments, provides access to the distal bowel for decompression and irrigation, and allows for bedside closure of the stoma once the obstruction has resolved. Various irrigating solutions have been used, including normal saline, Gastrografin, hydrogen peroxide, and 2% to 4% solutions of *N*-acetylcysteine. Figures 10-4 and 10-5 illustrate the typical findings of meconium ileus with obstruction and the Bishop–Koop ileostomy technique.

125. What is the operative approach if the patient has meconium ileus with suspected intestinal perforation?

If the infant has had a perforation with peritonitis, the clinician must determine the degree of peritonitis. If perforation occurs just before delivery, meconium ascites without calcification is usually present, whereas if it occurs several weeks or months before delivery, calcification and dense adhesions
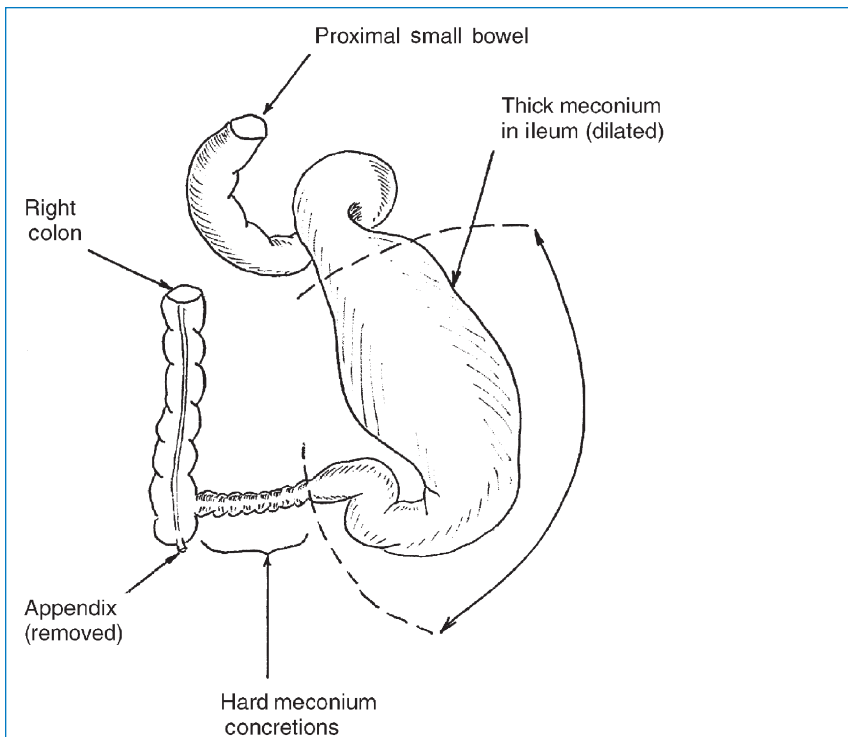
Figure 10-4. Typical appearance, at the time of operative exploration, of a neonate with meconium ileus that failed nonoperative management. Note the dilated ileum proximal to the point of obstruction. Thick, viscous meconium is found in the dilated segment, and hard meconium pellets are found in the segment of ileum that is causing the complete mechanical obstruction. For this degree of disease the massively dilated bowel must be resected.

will develop. Occasionally, a fibrous wall forms around the meconium, leading to a pseudocyst, often referred to as giant cystic meconium peritonitis. Operative repair of the obstruction can be difficult because the adhesions are usually quite vascular, carrying a high risk of intraoperative mortality. The goal is relief of the obstruction and, if possible, restoration of bowel continuity or creation of a temporary Bishop–Koop ileostomy. Ostomy closure is usually safe 6 to 8 weeks later. TPN may be necessary if inadequate bowel length is available for feeding.

✓ KEY POINTS: INHERITED DISORDERS OF ABSORPTION AND MOTILITY

1. An infant who continues to produce significant amounts of stool in the absence of oral intake should be evaluated for an inherited or acquired disease of secretory diarrhea.

2. Congenital disorders of carbohydrate malabsorption that cause significant diarrhea in the infant are extremely rare.

3. The diagnosis of cystic fibrosis should be considered in any infant with meconium ileus.

4. An abnormal stooling pattern in an infant with Down syndrome should raise the possibility of Hirschsprung disease.
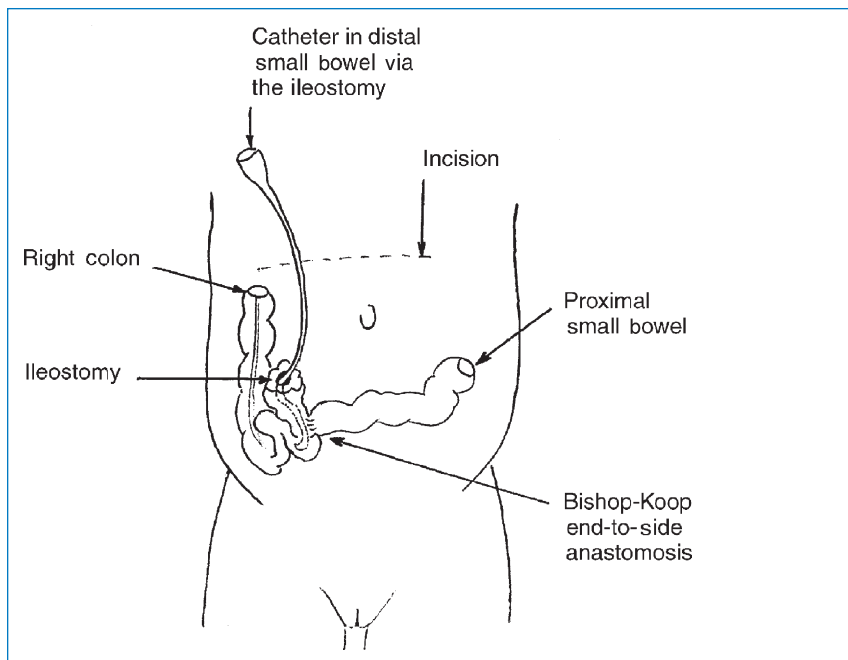
Figure 10-5. Creation of the Bishop–Koop ileostomy after segmental ileal resection for management of meconium ileus. Note that the distal loop of bowel forms the ostomy and the more proximal end forms the end-to-side anastamosis. A catheter can be placed in the ileostomy for postoperative irrigation of the distal ileum and colon to clear the remaining bowel of partially obstructing thick meconium.

126. In newborns what are the three most common gastrointestinal manifestations of cystic fibrosis?

- Meconium ileus is the earliest clinical manifestation of cystic fibrosis. Between 10% and 20% of patients with cystic fibrosis develop intestinal obstruction *in utero* during the last trimester of development. Abdominal distention is marked, with no passage of meconium. The obstruction is secondary to a mass of extremely thick, tenacious meconium, which adheres to the wall of the distal small bowel and impacts the lumen.
- The most common complication is volvulus of meconium-laden loops, frequently associated with ischemia, necrosis, perforation, and peritonitis. Twisted devitalized loops may become adherent, lose their continuity with the intestinal lumen, and form a gelatinous pseudocyst.
- Spillage of meconium into the peritoneal cavity after antenatal intestinal perforation results in the development of meconium peritonitis. Meconium peritonitis may be seen before birth on ultrasound, and if it occurred early in utero, it can present as calcifications of the abdomen during the newborn period.

SHORT GUT SYNDROME

127. What is short gut syndrome?

The healthy newborn intestine is approximately 200 to 300 cm in length. Traditionally, the definition of short gut was less then 75 cm of total small bowel, thus an approximate loss of about half of the small bowel. Short gut syndrome is presently defined on the basis of the constellation of symptoms,

signs, and metabolic and nutritional alterations associated with a physiologically significant loss of gut. The overall prognosis would depend on what specific sections were lost and the overall remaining bowel function, including the following:

- Amount of remaining small intestine
- Whether it is proximal (jejunal) or distal (ileal)
- Whether the ileocecal valve is resected
- Whether the colon is resected
- Degree of intestinal adaptation
- Presence of residual bowel disease

128. What are the mechanisms responsible for diarrhea in short gut syndrome?

- Decreased absorptive surface area
- Rapid transit time
- Bacterial overgrowth
- Hypersecretion and impaired regulation of gut motility
- Decreased absorption of bile salts, particularly with the loss of the terminal ileum: The unabsorbed bile salts are deconjugated by anaerobic bacteria, causing inhibition and even net secretion of water and electrolytes.
- Steatorrhea: secondary to decreased availability of bile salts necessary for fat absorption
- Loss of the ileocecal valve: This permits reflux of colonic bacteria into the small intestine, thereby contributing to bacterial overgrowth.
- Colonic resection: The colon is where most fluid reabsorption occurs.

129. What problems may be associated with enteral feeding in patients with short gut syndrome?

Enteral feeds should be initiated early and aggressively advanced as tolerated to promote intestinal adaptation and help diminish the complications associated with TPN. Formula is given through a feeding tube at a continuous rate initially to maximize absorption during advancement. No conclusive data prove that one type of formula or breast milk is ideal, and many different regimens have been used successfully. The major limiting factor in the formulas is the amount of carbohydrate, because unabsorbed sugars increase the osmotic load in the colon and cause an osmotic diarrhea that can lead to significant water loss and acidosis. The excessive malabsorption is accompanied by an increase in stool volume (stool outputs greater then 40 to 50 mL/kg/day), positive reducing substances, and a stool pH below 5.5.

130. What are the long-term complications of short gut syndrome?

- TPN-related liver disease
- Nutrient deficiencies
- Failure to thrive
- Small bowel bacterial overgrowth
- Catheter-related sepsis
- Motility disturbances
- Gastric acid hypersecretion
- Delta-lactic acidosis
- Renal stones and gallstones

IMPERFORATE ANUS

131. How is imperforate anus diagnosed?

Imperforate anus is often diagnosed in the nursery as the nursing staff attempts to obtain a rectal temperature from the neonate or during the newborn examination. Rectal atresia might be missed during the examination because the anal opening can appear normal. However, failure to pass meconium and increasing abdominal distention should warrant further evaluation.

132. How frequently is imperforate anus associated with other abnormalities?
Associated spinal and genitourinary anomalies are rather common, occurring in 20% to 50% of patients with imperforate anus. Imperforate anus may be seen as part of the vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia (VATER) or vertebral abnormalities, anal atresia, cardiac abnormalities, tracheoesophageal fistula and/or esophageal atresia, renal agenesis and dysplasia, and limb defects (VACTERL) association. The evaluation of an infant with imperforate anus includes looking for other associated anomalies.

133. What tests determine initial management of an infant with imperforate anus?
The initial testing should include a complete physical examination and a urine analysis. If the baby has a flat bottom without a well-developed gluteal fold or has meconium in the urine, a colostomy is indicated. Conversely, in the setting of a bucket-handle deformity or meconium staining in the perineal midline, a minimal anorectoplasty is indicated without colostomy. In girls a colostomy is warranted barring demonstration of a perineal fistula. These decisions are all made after 16 to 24 hours to permit increased luminal pressures to force meconium through a fistula so that it is noted on examination. In all cases an abdominal ultrasound should be obtained to rule out other anomalies.
- Colostomy not required: Perineal (cutaneous) fistula.
- Colostomy required: Rectourethral fistula (bulbar or prostatic), rectovesical fistula, imperforate anus without fistula, rectal atresia

HIRSCHSPRUNG DISEASE

134. When and by whom was Hirschsprung disease first classically described?
The classical description of Hirschsprung disease is attributed to Harald Hirschsprung, a pathologist, who described this condition in two children in 1888. This abnormality occurs in 1 in 5000 live births. Male children are four times more likely to be affected than female children.

135. Why does Hirschsprung disease occur?
The parasympathetic fibers that innervate the colonic bowel wall (to form the myenteric [Auerbach] and the submucosal [Meissner] nervous plexi) are derived from neural crest cells in the neural folds. During embryologic development the cells migrate along the bowel in a cranial to caudal migration, providing innervation. Hirschsprung disease results when the progression of such migration stops prematurely. Without this parasympathetic innervation, the intestine cannot relax when nitric oxide is released from the postganglionic nerve fibers. Approximately 80% of the time, the progression stops in the rectum, and only 20% of cases involve the total bowel or small bowel. Short-segment Hirschsprung disease does not extend beyond the rectosigmoid region, whereas long-segment Hirschsprung disease extends more proximally.

136. How is Hirschsprung disease diagnosed?
The diagnosis of Hirschsprung disease can be made with a barium enema, rectal suction or surgical full-thickness biopsy, or anorectal manometry. The initial test of choice is the unprepared barium enema. The test looks for the classic finding of a transition zone where the distal noninnervated section of bowel is smaller than the more proximal dilated bowel. The transition zone will occur in the location where the neurons stopped normal progression. The diagnosis by pathologic examination uses rectal biopsies to look for evidence of nerve cells directly. The biopsy will show absence of ganglion cells or presence of nerve cell hypertrophy or increased acetylcholinesterase with special staining. Anorectal manometry can be used to demonstrate the absence of the normal rectoanal inhibitory reflex that is present in the internal anal sphincter when innervated by the parasympathetic plexi.

137. Is there a genetic component to the disease?
Approximately 10% of children have a family history, especially with longer-segment Hirschsprung disease. A higher incidence occurs in children with Down syndrome and other genetic abnormalities.

Recent studies indicate the presence of mutations in the RET proto-oncogene in 17% to 38% of children with short-segment disease and in 70% to 80% of those with long-segment disease. Additional genes linked to the RET activation pathway and other mechanisms have now been identified.

Carter TC, Kay DM, Browne ML, et al. Hirschsprung's disease and variants in genes that regulate enteric neural crest cell proliferation, migration and differentiation. J Hum Genet 2012;57(8):485–93.

138. What are the complications after surgical repair of Hirschsprung disease?
- Obstruction
- Mechanical obstruction
- Incomplete resection of aganglionic bowel segments
- Motility disorder
- Functional megacolon
- Internal sphincter achalasia
- Enterocolitis
- Incontinence

GASTROINTESTINAL HEMORRHAGE

139. How does one determine whether swallowed maternal blood is the cause for gastrointestinal bleeding in the neonate?
This determination is made using the Apt–Downey test. For this test 1 part stool is mixed with 5 parts water and centrifuged for 2 minutes to separate out fecal material. The supernatant is removed, and 1 mL of 0.25 N (1%) sodium hydroxide is mixed with the 5 mL of supernatant. After 2 minutes there is a color change; if the hemoglobin is fetal, the color stays pink; if it is from the mother, it turns yellow-brown.

140. What are the sources of neonatal gastrointestinal bleeding?
See Table 10-5.

141. What are some of the risk factors and clinical features that help distinguish necrotizing enterocolitis (NEC) from other causes of gastrointestinal bleeding in the neonate?
NEC tends to be more common in premature infants and often occurs in those who have experienced some type of perinatal stress, such as hypoxia, need for mechanical ventilation, or sepsis. The

TABLE 10–5. SOURCES OF NEONATAL GASTROINTESTINAL BLEEDING	
HEMATEMESIS/MELENA	**HEMATOCHEZIA**
Swallowed maternal blood	Swallowed maternal blood
Gastritis or stress ulcers	Dietary protein intolerance
Duplication cyst	Duplication cyst
Coagulopathy: Vitamin K deficiency or DIC	Coagulopathy: Vitamin K deficiency or DIC
Maternal NSAID use	Maternal NSAID use
Maternal idiopathic thrombocytopenic purpura	Maternal idiopathic thrombocytopenic purpura
Vascular malformation	Colitis: infectious, NEC, Hirschsprung disease with enterocolitis
Hemophilia	Hemophilia
Esophagitis	Rectal fissure, tear, or hemorrhoids
DIC, Disseminated intravascular coagulopathy; NEC, necrotizing enterocolitis; NSAID, nonsteroidal antiinflammatory drug.	

addition of gross or occult blood in stools, feeding intolerance, abdominal distention or discoloration, bilious emesis, and lethargy should all lead to the consideration of NEC in the differential diagnosis.

142. What is the first step in the management of an acutely ill infant with significant gastrointestinal bleeding?

The key initial step is to obtain stable intravenous access for patient resuscitation. Particularly with hematemesis, the rapidity and severity of gastrointestinal bleeding can be significant, and the need for urgent intravenous access should not be underestimated. Once the ABCs of resuscitation have taken place, it is appropriate to focus on diagnosis and etiology.

NECROTIZING ENTEROCOLITIS

143. What is NEC?

NEC is a disease of unknown origin that primarily affects premature infants (80% of cases), typically after the onset of enteral alimentation during convalescence from the common cardiopulmonary disorders associated with prematurity. Manifestations cover a broad spectrum, from mild abdominal distention with hematochezia to a fulminant septic shock–like picture with transmural necrosis of the entire gastrointestinal tract (NEC totalis).

144. Which infants are at risk for developing NEC?

NEC typically occurs in infants with a corrected gestational age of 30 to 32 weeks and at a time when most premature infants are progressing on enteral feedings. Onset of NEC is unusual on the first day of life and highly uncommon among infants who have not received enteral feeds. NEC can occur sporadically, but often cases are clustered in place and time, which suggests an infectious etiology, although no consistent agent has been isolated from reported epidemics.

Many associated risk factors have been suggested but have not been shown to be directly associated with the pathogenesis of NEC. When investigated in carefully controlled studies, risk factors such as perinatal asphyxia, respiratory distress syndrome, umbilical catheters, patent ductus arteriosus, hypotension, and anemia have not been demonstrated to be more common among patients who developed NEC than among unaffected age-matched control subjects. The most dominant known risk factor for NEC is the degree of immaturity.

145. How are breast milk–fed infants thought to be protected from NEC?

Breast milk may reduce the risk of NEC. Breast milk offers many nutritive advantages in addition to protective immunologic substances. Milk macrophages and phagocytes, immunoglobulins A and G, and immunocompetent T and B lymphocytes may offer a protective advantage to the mucosa. These components potentiate the effect of the complement components C3 and C4, lysozyme, lactoferrin, and secretory immunoglobulin A. Furthermore, breast milk contains hormones (e.g., thyroid, thyroid-stimulating hormone, prolactin, steroid), enzymes (e.g., amylase, lipase), and growth factors (endothelial growth factor). Breast milk also favors the growth of *Lactobacillus bifidus* and promotes the development of a healthy gut microbiome.

Gephart SM, McGrath JM, Effken JA, et al. Necrotizing enterocolitis risk: state of the science. Adv Neonatal Care 2012;12(2):77–87.

146. What feeding risk factors have been associated with the development of NEC?

The absence of NEC *in utero* suggests an absolute requirement for gut colonization in its pathogenesis. Host luminal pH, proteases, oxygen tension, temperature, and osmolarity of enteral feedings have been implicated in the pathogenesis of NEC. The volume of milk fed to infants may also predispose them to NEC. Excessively rapid increments of milk feeding may overcome the infant's intestinal absorptive capability (especially in the presence of altered motility), resulting in malabsorption.

Large-volume milk feedings that are increased too rapidly during the feeding schedule may place undue stress on a previously injured or immature intestine. Two studies have shown that volume

increments in excess of 20 to 25 mL/kg/day have been associated with NEC, whereas another two studies have shown the safety of 30 to 35 mL/kg/day increments. The evidence therefore is unclear as to the role of rapid feeding advancement in the development of NEC. Volume increments probably should not be more than 20 to 35 mL/kg/day and should be advanced on the basis of the clinical examination, physiologic stability, and feeding tolerance.

Morgan J, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database Syst Rev 2011 Mar 16;3:CD001241.

147. Are probiotics useful in the prevention of NEC?

Recent prospective randomized trials have looked at the effects of probiotics and their ability to prevent NEC. Studies have shown that the use of probiotics decreases the incidence of NEC but not the mortality rates among those patients that do develop NEC. However, a higher incidence of sepsis was reported in those infants receiving probiotics. Thus probiotics can be considered but should be used with caution, based on current data. To date, no large-scale trial of probiotics has been successfully carried out, and there are currently many different bacterial components in available probiotics. No probiotic is currently approved by the Food and Drug Administration for neonatal use.

Neu J, Walker WA. Necrotizing entercolitis. N Engl J Med 2011;364:255–64.

148. What is the gas in pneumatosis intestinalis?

Malabsorbed carbohydrates are fermented by colonic bacteria and cause increased intestinal gas production, resulting in abdominal distention. This gas, which is 30% to 40% hydrogen gas, dissects into the submucosa and subserosa, producing pneumatosis intestinalis. High intraluminal pressure resulting from gaseous distention may reduce mucosal blood flow, producing secondary intestinal ischemia.

149. What infective agents are associated with NEC?

In many cases of NEC, no infective agent is identifiable. Bacteria identified by positive blood cultures are seen in only 20% to 30% of patients with NEC. *S. epidermidis* is the most common organism, followed by gram-negative bacilli such as *E. coli* and *Klebsiella* species. Epidemics have been associated with a single pathogen such as *E. coli, Klebsiella* species, *Salmonella* species, *S. epidermidis, Clostridium butyricum, Coronavirus* species, *Rotavirus* species, and enteroviruses. NEC has also been associated with fungal sepsis. NEC may also result from an enterotoxin-mediated illness, such as toxins from *Clostridium* species or *S. epidermidis*. It is important to emphasize that, unlike in adults, *Clostridium difficile* and associated toxins are found in the intestinal tracts of many neonates who are entirely asymptomatic. The asymptomatic carrier state in some infants may be due to differences in intestinal immaturity, local differences in the intestinal milieu, absence of toxin-related receptors, or other protective factors.

150. What are the criteria for considering the diagnosis of NEC?

NEC is a common cause of systemic inflammatory response syndrome in neonates. Based on systemic signs, intestinal signs, and radiologic signs, staging of NEC is performed as shown in Table 10-6.

151. A 1000-g infant, born at 28 weeks' gestation, had an initial course characterized by respiratory distress syndrome and suspected sepsis. He was initially treated with surfactant and mechanical ventilation. The antibiotics were stopped after 3 days because the blood culture results were negative. On day 5 he was placed on nasal continuous positive airway pressure until day 18. He began enteral gavage feeds on day 5, at 20-cc/kg/day increments, and finally achieved "full feeds" (150 cc/kg/day) by day 20. He then developed an increased frequency of apnea and bradycardia associated with temperature instability. The gavage feeds were held because of

TABLE 10–6. STAGING OF NECROTIZING ENTEROCOLITIS

STAGE	SYSTEMIC SIGNS	INTESTINAL SIGNS	RADIOGRAPHIC SIGNS	TREATMENT
IA (suspected NEC)	Temperature instability, apnea bradycardia, lethargy	Increased gastric residuals, mild abdominal distention, emesis, guaiac-positive stools	Normal or mild intestinal dilation, mild ileus	NPO with antibiotics × 3 days
IB	Same as IA	Bright red blood per rectum	Same as IA	Same as IA
IIA (definite, mild NEC)	Same as IA	Same as IA/IB plus decreased or absent bowel sounds ± abdominal tenderness	Intestinal dilation with pneumatosis intestinalis	NPO with antibiotics × 7 to 10 days
IIB (definite, moderate NEC)	Same as IIA plus mild metabolic acidosis and thrombocytopenia	Same as IIA plus definite abdominal tenderness, absent bowel sounds, possible abdominal cellultis or right lower quadrant mass	Same as IIA with definite ascites and possible portal vein gas	NPO with antibiotics × 14 days
IIIA (advanced, severe NEC)	Same as IIB plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, DIC, neutropenia, anuria	Same as IIB plus peritonitis; abdominal tenderness, distention, and erythema	Same as IIB	NPO with antibiotics × 14 days, fluid resuscitation, possible pressors or mechanical ventilation, paracentesis
IIIB (advanced, severe NEC with perforated bowel)	Same as IIIA	Sudden, severely increased abdominal distention with bowel perforation	Same as IIIA with pneumoperitoneum	Same as IIIA plus surgery

DIC, Disseminated intravascular coagulopathy; NEC, necrotizing enterocolitis; NPO, nothing by mouth.
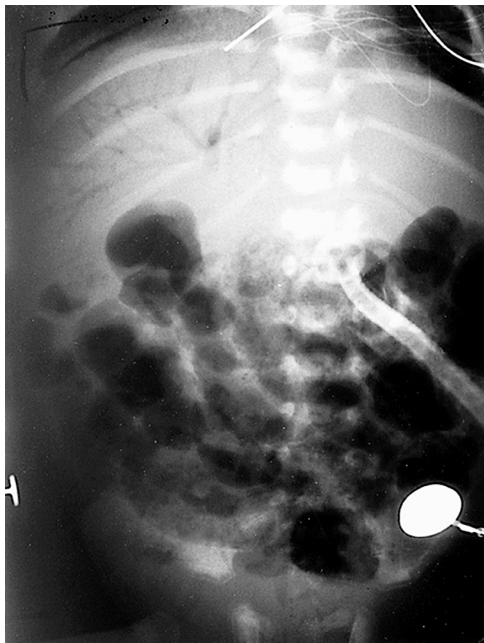
Figure 10-6. Abdominal radiograph 1 day after treatment for necrotizing enterocolitis stage IB. (Courtesy Dr. Jack Sty, Department of Pediatric Radiology, Children's Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee, Wisconsin.)

increasing gastric residuals, presence of blood in stools, and abdominal distention. What should be done next?

This infant falls into stage IB because of the temperature instability, apnea and bradycardia, increased gastric residuals, presence of blood in stools, and abdominal distention. An abdominal x-ray is recommended to view the bowel gas pattern. Dilated bowel loops are expected. Management includes the following: (1) consultation with a pediatric surgeon, (2) withdrawing all enteral feeds, (3) gastric decompression by placing an orogastric tube to low wall suction, and (4) beginning antibiotics after appropriate cultures are collected. Meanwhile, TPN is necessary for nutritional support. It is important to carefully follow up with this infant to monitor for progression to NEC and exclude other diagnostic possibilities that may mimic NEC at this age.

152. One day after beginning appropriate management, the same infant (see Question 151) develops persistent abdominal distention, right lower quadrant tenderness, and diminished bowel sounds. The abdominal radiographs are shown in Figures 10-6 and 10-7. How do you interpret these signs? What should be done next?

At this stage the infant is showing definite signs of NEC (stage II), as demonstrated by the failure to recover from stage IB and worsening intestinal signs, such as diminished bowel sounds, guarding, and abdominal distention and tenderness. These clinical findings may herald the beginning of dilated viscus, submucosal or subserosal dissection of air, and peritonitis. Such an infant should be regarded
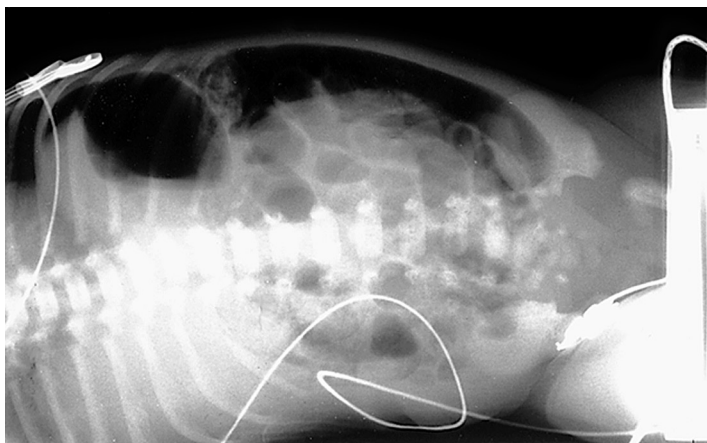
Figure 10-7. Abdominal radiograph of the infant shown in Figure 10-6 taken 8 hours later. (Courtesy Dr. Jack Sty, Department of Pediatric Radiology, Children's Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee, Wisconsin.)

as having NEC and is moderately ill. The radiograph in Figure 10-6 shows grossly dilated bowel loops and submucosal and subserosal pneumatosis intestinalis. Management based on this radiograph includes careful monitoring for worsening of clinical status (e.g., metabolic acidosis and thrombocy-topenia) and a course of antibiotics for a minimum of 7 to 10 days. However, the second radiograph in Figure 10-7 shows worsening disease, as manifested by portal vein gas (within the liver). At this stage it is imperative to anticipate the possibility of intestinal perforation. Management should now include correction of hypovolemia and metabolic acidosis using colloids and sodium bicarbonate, respectively. If NEC does not progress further, 2 weeks of appropriate antibiotics would suffice, with hopes to avoid surgical intervention.

153. The infant's condition suddenly deteriorates 24 hours later. He develops generalized abdominal tenderness and periumbilical erythema. An arterial blood gas determination shows a pH of 7.10, PCO_2 of 80 mmHg, PO_2 of 32 mmHg, HCO_3^- of 12 mEq/L, and a base deficit of 16. The blood count is remarkable for a platelet count of 22,000/μL. The abdominal radiography is shown in Figure 10-8. How do you interpret these signs? What should be the approach to the management of this infant?

The infant at this stage has advanced NEC and is severely ill. This condition is characterized by wors-ening hypotension, a combined respiratory and metabolic acidosis, thrombocytopenia, and anuria. Thrombocytopenia usually represents a consumptive thrombocytopenia with or without intestinal perforation. The sudden deterioration is ominous for a bowel perforation, and progressive abdominal distention with erythema signifies worsening peritonitis and pneumoperitoneum. The lateral decubi-tus abdominal radiograph is remarkable for worsening pneumatosis and free air (see Figure 10-8).

Figure 10-8. Abdominal radiograph of advanced necrotizing enterocolitis. (Courtesy Dr. Jack Sty, Department of Pediatric Radiology, Children's Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee, Wisconsin.)

This infant needs vigorous fluid resuscitation with colloids (i.e., fresh frozen plasma, albumin) and cellular products (i.e., packed red cells, platelets). Inotropic support using dopamine and epinephrine drips may be needed. Surgical exploration is indicated in this setting to facilitate abdominal decompression and salvage the viable bowel. If it is difficult to ventilate the infant at this stage, an abdominal paracentesis may be helpful.

154. When is surgery indicated for an infant with NEC? What are the complications of performing surgery on an infant with advanced NEC with bowel perforation?

Absolute indications for surgery include pneumoperitoneum and intestinal gangrene (as demonstrated by positive results of abdominal paracentesis testing). Relative indications include progressive clinical deterioration (metabolic acidosis, ventilatory failure, oliguria, thrombocytopenia), fixed abdominal mass, abdominal wall erythema, portal vein gas, and persistently dilated bowel loop.

The postoperative complications occurring immediately after surgery are usually related to the stoma (retraction, prolapse, or peristomal hernia) or wound (infection, dehiscence, enterocutaneous fistula). Rarely, intraabdominal abscesses, recurrence of NEC, and bowel obstruction can develop. Chronic complications result from the dysfunctional ostomies, strictures, or short gut syndrome depending on the amount of remaining healthy bowel.

In some extremely sick ELBW infants, the placement of an intraperitoneal drain may be an option as opposed to a laparotomy, which may be excessively stressful for the deteriorating infant. In the presence of obvious perforation, this approach is an extremely difficult one, but it may allow time for another therapy to exert an effect before the child is taken to the operating room.

155. A 30-week-gestation male infant had been diagnosed with stage IIA NEC and was appropriately managed medically for 10 days. He subsequently tolerated feeds poorly. The stooling pattern was reported as normal (small green stools). Different formulas and prokinetics were tried without any positive result. An abdominal x-ray revealed what was reported as a "gassy abdomen." Treatment with antibiotics was begun again, and feedings were held for 3 days. A sepsis work-up yielded negative results at 3 days. Feedings were then resumed with

an elemental formula. The same feeding-intolerance pattern prevailed. What are the diagnostic considerations in this infant?

Recovery after NEC occurs by second intention, with areas of patchy necrosis often healing by fibrosis and stricture formation. The repair process also involves the peritoneum, resulting in adhesions. Both of these processes can result in signs of functional or mechanical obstruction. An upper gastrointestinal contrast radiograph may show a prolonged transit time and gross dilation of jejunum consistent with more distal stricture formation. A lower gastrointestinal contrast x-ray may be necessary to identify strictures in the large bowel. At laparotomy this infant was found to have multiple strictures, which were resected and ultimately resulted in a short bowel syndrome.

156. **A 3500-g term female infant born after an uncomplicated pregnancy was discharged home from the newborn nursery after a normal transition. She was fed exclusively with breast milk. On her seventh day of life she presented acutely with bilious emesis. The clinical examination was remarkable for a pulse rate of 180 bpm, respiratory rate of 70/min, mean blood pressure of 30 mmHg, abdominal distention, and marked tenderness with diminished bowel sounds. She passed a dark, bloody stool. Laboratory study results were notable for an arterial blood gas of pH 7.15, PCO$_2$ level of 30 mmHg, PO$_2$ level of 120 mmHg, and HCO$_3^-$ level of 10 mEq/L. The complete blood count was remarkable for a hematocrit level of 24 and platelet count of 400,000/μL. What is the approach to management in this infant? How would you establish a diagnosis in this infant?**

The infant's examination is consistent with an acute abdomen. She also has signs of hypovolemia and shock. She needs immediate fluid resuscitation and correction of metabolic acidosis. Because sepsis is common in the neonatal period, antibiotics are indicated after blood cultures are obtained. A nasogastric tube should be placed and the stomach decompressed. An abdominal x-ray reveals gassy distended bowel loops with air-fluid levels. An upper gastrointestinal contrast radiograph is shown in Figure 10-9. The contrast fails to flow distally, suggesting intestinal obstruction. Furthermore, the pig-tail appearance of the contrast is classic for a diagnosis of volvulus, and surgical exploration should be considered.

157. **How do you differentiate NEC from volvulus? In what conditions is pneumatosis intestinalis seen?**

Table 10-7 summarizes the features that differentiate NEC from volvulus. Apart from NEC, pneumatosis intestinalis is also seen in midgut volvulus, acute or chronic diarrhea, postoperative gastrointestinal surgery, Hirschsprung disease, short gut syndrome, mesenteric thrombosis, postcardiac catheterization, structural disease of the hindgut (colonic atresias and stricture, imperforate anus), and intestinal malignancies.

NEONATAL HEPATITIS

158. **What are the common causes of neonatal liver failure, and what are the diagnostic tests for each?**

See Table 10-8.

159. **What are the components of neonatal biliary disease?**

Any disease process in the neonate with altered bile acid transport or biliary structure is a biliary disease. The clues to its presence include cholestasis (elevated serum bile acids), conjugated hyperbilirubinemia, and altered serum levels of enzymes resulting from biliary inflammation or obstruction (e.g., gamma-glutamyl transferase [GGT] and alkaline phosphatase).

160. **What is cholestatic jaundice?**

Conjugated bilirubin greater than 2 mg/dL or exceeding 15% of the total bilirubin is referred to as direct hyperbilirubinemia and is a clinical indicator of cholestatic jaundice. Unlike indirect
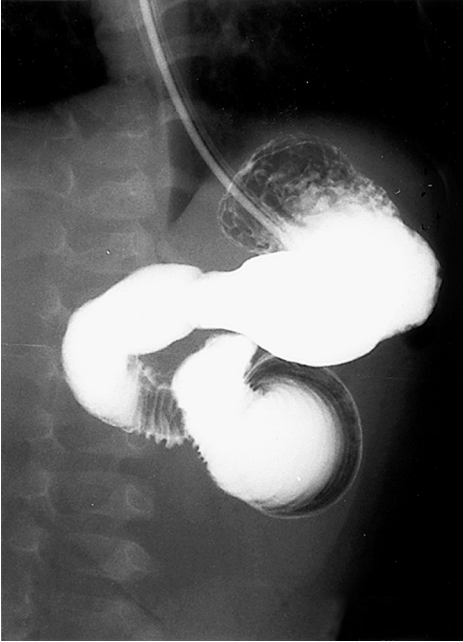
Figure 10-9. Upper gastrointestinal contrast radiograph. (Courtesy Dr. Jack Sty, Department of Pediatric Radiology, Children's Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee, Wisconsin.)

TABLE 10–7.   NECROTIZING ENTEROCOLITIS DIFFERENTIATED FROM VOLVULUS

Modified from Kliegman R. Necrotizing enterocolitis: differential diagnosis and management. In: Polin RA, Yoder MC, Burg FD, editors. Workbook in practical neonatology. 2nd ed. Philadelphia: Saunders; 1993. p. 449–70.

CHARACTERISTICS	NEC	VOLVULUS
Preterm	90%	30%
Onset by 2 weeks	90%	60%
Male:female ratio	1:1	2:1
Associated anomalies	Rare	25% to 40%
Bilious emesis	Unusual	75%
Grossly bloody stools	Common	Less common
Pneumatosis intestinalis	90%	2%
Marked proximal obstruction	Rare	Common
Thrombocytopenia without DIC	Common	Rare
DIC, Disseminated intravascular coagulopathy; NEC, necrotizing enterocolitis.		

TABLE 10-8. NEONATAL CAUSES OF ACUTE LIVER FAILURE AND DIAGNOSTIC TESTS	
DISEASE	**DIAGNOSTIC FINDINGS**
Galactosemia	Red cell galactose-1-phosphate uridyl transferase
Tyrosinemia	Urine succinyl acetone
Neonatal hemochromatosis	Elevated ferritin, extrahepatic iron deposition
Hemophagocytic lymphohistiocytosis and congenital leukemia	Bone marrow findings
Sepsis, shock	Positive blood cultures
Giant cell hepatitis with hemolytic anemia	Coombs-positive hemolytic anemia
HHV-6, Hepatitis b, adenovirus, parvovirus	Viral serology and polymerase chain reaction
Mitochondrial hepatopathy	Mitochondrial DNA, muscle and/or liver biopsy for quantitative respiratory chain enzymes
Vascular malformations and congenital heart disease	Echocardiography
Maternal overdose	History, toxicology screen
Hypocortisolism	Cortisol levels, ACTH stimulation test
ACTH, Adrenocorticotropic hormone; HHV-6, human herpesvirus 6.	

hyperbiloirubinemia, cholestatic jaundice is always physiologically abnormal and warrants a medical evaluation. Note that biliary disease can present with or without cholestatic jaundice.

161. What are the causes of direct hyperbilirubinemia?

The mechanisms include the following:

- Impaired bilirubin metabolism secondary to parenchymal disease of the liver
- Inherited disorders of bilirubin excretion
- Mechanical obstruction to biliary flow, either intrahepatic or extrahepatic
- Excessive bilirubin loads, such as may occur in massive hemolysis

162. When should an infant's fractionated bilirubin be obtained?

Evaluation of jaundice persisting beyond the normal physiologic period (2 weeks) in newborns must always include a fractionation of bilirubin.

163. How should the evaluation of cholestatic jaundice in infants be approached?

Neonatal cholestasis can be a manifestation of (1) extrahepatic biliary disease, (2) intrahepatic biliary disease, or (3) hepatocellular disease. All can present with similar symptoms. Therefore differentiation based on history and physical examination alone is usually not diagnostic.

The clinician should initiate further evaluation to promptly identify clinical conditions amenable to therapy (Table 10-9), particularly those in which any delay in treatment could be tragic (e.g., sepsis; urinary tract infection; hypothyroidism; biliary atresia; and congenital metabolic disorders requiring special diets such as galactosemia, hereditary fructose intolerance, and tyrosinemia).

164. What tests should be obtained during the initial evaluation of neonatal cholestasis?

See Table 10-10.

165. When should the infant be referred to a gastroenterologist?

As soon as cholestatic jaundice is diagnosed and sepsis ruled out, a gastroenterologist should be consulted. The tests mentioned in the previous question can be scheduled, but the clinician should not wait for the results before making the referral. In most cases a liver biopsy is needed to help make the final diagnosis. The hepatologist will also conduct a broad laboratory evaluation to make a diagnosis and initiate therapy. In addition to medical therapy, preventive therapy can be provided

TABLE 10–9. TREATABLE CAUSES OF NEONATAL CHOLESTASIS

Adapted from Dhawah A, Mieli-Vergani G. Acute liver failure in neonates. Early Hum Dev 2005;81:1005–10.

INFECTIOUS	SURGICAL	METABOLIC	OTHER
Urinary tract infection	Biliary atresia	Galactosemia	Hypothyroidism, panhypopituitarism
Sepsis	Choledochal cyst	Hereditary fructose intolerance	Bile acid synthetic anomalies
TORCH* infections	Cholelithiasis	Tyrosinemia	Histiocytosis X
Neonatal hepatitis	Biliary strictures	Iron storage disorders	Mass (neoplasia)
	Bile duct perforation		Alpha 1 antitrypsin deficiency
	Congenital duct anomalies		
	Intestinal obstruction		

*TORCH is an acronym for *T*oxoplasmosis, *O*ther infections, *R*ubella, *C*ytomegalovirus, and *H*erpes simplex virus 2.

TABLE 10–10. TESTS FOR THE INITIAL EVALUATION OF NEONATAL CHOLESTASIS

	INDICATION
Blood	
Fractionated bilirubin	Detect cholestatic jaundice
Complete blood count	Rule out sepsis
Blood cultures if clinically indicated	Rule out sepsis
Hepatic function panel	Detect hepatobiliary disease
Thyroid-stimulating hormone and free T_4	Rule out hypothyroidism
Coagulation studies	Assess liver synthetic function
Urine	
Urinalysis and culture	Detect urinary tract infection, sepsis
Reducing sugars	Detect galactosemia
Protein	Support galactosemia, hereditary fructose intolerance, or tyrosinemia
Imaging Studies	
Abdominal ultrasound	Detect choledochal cyst, stones, mass, or biliary stricture
Diisopropyl immodiacetic acid (DISIDA) scan	Differentiate between biliary atresia (non-excreting) and neonatal hepatitis (delayed uptake with excretion)

through genetic counseling. Time is of the essence to identify treatable causes of cholestasis and intervene early in such cases as biliary atresia for better outcomes.

166. What is spontaneous bile duct perforation?

Spontaneous perforation of the bile ducts is a rare occurrence but has been documented in infants between 4 and 12 weeks of age. The cause is currently unknown. It most often occurs at the point at which the cystic duct is joined to the common bile duct. Infants can present with lethargy, nonbilious vomiting, acholic stools, mild jaundice, dark urine, abdominal distention, and a mildly elevated conjugated hyperbilirubinemia. Definitive diagnosis can be made with a hepatoiminodiacetic acid scan or abdominal paracentesis.

TABLE 10–11. CHARACTERISTIC FEATURES IN PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS			
Adapted from Hori T, Nguyen JH, Uemoto S. Progressive familial intrahepatic cholestasis. Hepatobiliary Pancreat Dis Int 2010;9(6): 570–8.			
	PFIC1	*PFIC2*	*PFIC3*
Functional deficiency	*FIC1* gene	*BSEP* gene	*MDR3* gene
Age of onset	Neonates	Neonates	1 month to 20 years
Cholestasis	Chronic	Chronic	Chronic
Ductular proliferation	Absent	Absent	Absent
Progression to cirrhosis	Yes	Yes	Yes
Portal fibrosis	Present	Pronounced	Rare
Giant cell transformation	Present	Pronounced	Rare
Pruritis	Severe	Severe	Moderate
Serum GGT levels	Normal	Normal	High
Serum cholesterol levels	Normal	Normal	Normal
GGT, Gamma-glutamyl transferase.			

167. How do the bile salt transporter defects present?

This group of conditions is collectively known as progressive familial intrahepatic cholestasis. They typically present as neonatal cholestasis but individually have distinct clinical, laboratory, and histologic features that differentiate them (Table 10-11).

BILE DUCT AND BILIARY ATRESIA

168. A 6-week-old healthy term breast-fed infant was noted to be jaundiced at the routine well-baby visit. She was growing well. Examination of the abdomen revealed a palpable liver (1 cm below right costal margin) and spleen (2 cm below left costal margin). Her history revealed that she had pigmented stools since birth. Total and direct bilirubin levels were 6.9 and 4.3 mg/dL, respectively. Other findings include alanine aminotransferase (ALT), 138 U/L; aspartate aminotransferase (AST), 120 U/L; alkaline phosphatase (ALK), 205 U/L; GGT, 420 U/L; albumin, 3 g/dL; and prothrombin time (PT) 13.9 sec. Calcium, phosphate, and magnesium levels were normal; complete blood count, urinalysis, and culture had normal results. What do the laboratory results suggest, and which further tests need to be performed?

Apart from ruling out sepsis and urinary tract infection, the preceding tests are nondiagnostic. The liver enzymes, albumin level, and PT are useful for following the degree of hepatic injury and course of hepatic function. The following are some of the other tests that should be performed:

- Ultrasound: This is a quick, noninvasive test useful for detecting causes of extrahepatic cholestasis (e.g., choledochal cysts, biliary stones, tumors). Finding a gallbladder on ultrasound does not rule out biliary atresia, although the absence of a gallbladder would rasie the suspicion of biliary atresia.
- Radionuclide scans (diisopropyl iminodiacetic acid [DISIDA]): Good hepatic uptake of radionuclide with absence of excretion into the gut lumen suggests an obstructive process such as biliary atresia. Delayed excretion may also occur in hepatitis. If the hepatocytes are damaged to a degree that they cannot take up the tracer, there would also be no secretion on the scan, further complicating the test results.

169. In the infant described in the preceding question, the ultrasound revealed hepatosplenomegaly, and no gallbladder was seen. The DISIDA scan showed normal uptake but no excretion at 24 hours. A liver biopsy specimen was

TABLE 10–12. CAUSES OF PEDIATRIC ELEVATIONS OF GAMMA–GLUTAMYL TRANSFERASE	
DISEASE	**VARIATION OF GGT**
Extrahepatic biliary atresia	Increased up to 10 times upper limit
Alagille syndrome	Increased 3 to 20 times upper limit
Sclerosing cholangitis	Increased 50 to 100 times upper limit
PFIC types I and II	Normal or decreased
PFIC type III	Increased
Bile acid disorders	Normal
GGT, Gamma-glutamyl transferase; PFIC, progressive familial cholestasis.	

obtained, which showed intrahepatic cholestasis with proliferation of the bile ducts. Is the evaluation now complete for making a definitive diagnosis?
The evaluation is very suggestive of biliary atresia; however, the gold standard diagnostic test is an intraoperative cholangiogram. Other causes of neonatal cholestasis such as Alagille syndrome may clinically mimic biliary atresia and may be differentiated only by intraoperative cholangiogram.

170. What are the causes of extrahepatic neonatal cholestasis?
In general, these lesions lead to the extrahepatic obstruction of bile flow from the liver to the duodenum. These processes lead to bile buildup in the duct, causing inflammation and damage to the liver. The result is elevations of GGT and ALK consistent with biliary duct damage and varying degrees of elevation of liver enzymes and direct hyperbilirubinemia. Examples of extrahepatic bile duct disorders include the following:
- Biliary atresia
- Choledochal cyst and choledochocele
- Biliary hyperplasia
- Bile duct perforation
- Neonatal sclerosing cholangitis

171. What are the causes of pediatric elevations of GGT?
See Table 10-12.

172. Why is it critical to make an early diagnosis of biliary atresia?
The effectiveness of surgical therapy (Kasai procedure) for biliary atresia depends on the patient's age at surgery. Best outcomes are achieved when intervention occurs before 8 to 10 weeks of age. Biliary atresia is the leading indication for liver transplantation in children.

173. A 10-week-old, former 34-week premature, breastfed boy was referred for evaluation of jaundice and elevated liver enzymes. His test results indicated a conjugated bilirubin, 3.8 mg/dL; ALK 650 U/L; AST, 120 U/L; ALT, 138 U/L; and GGT, 1200 U/L. During the newborn period he had mild respiratory distress syndrome, was treated for sepsis, and received TPN for 7 days. He was discharged home on breast-milk feeds at the age of 3 weeks. How should the evaluation proceed?
The laboratory results show a disproportionately elevated serum GGT and ALK as well as a high conjugated bilirubin level, all of which suggest biliary disease. However, because the clinical manifestations of neonatal cholestasis are independent of the etiology, the initial basic evaluation should be broad, as previously described in Table 10-10.

174. A careful physical examination revealed that the patient in Question 173 had a prominent forehead, small chin, and a systolic heart murmur consistent with peripheral pulmonary stenosis. The ultrasound yielded normal results. The

DISIDA scan showed excretion at 24 hours. Is this sufficient for making the diagnosis of Alagille syndrome?

A liver biopsy is necessary to confirm the diagnosis and differentiate this syndrome from biliary atresia. Alagille syndrome is also referred to as syndromic bile duct paucity. During infancy the histologic studies may show bile duct proliferation. However, in later childhood and adulthood the liver histology commonly shows bile duct paucity. The genetic defect has been identified as jagged 1 *(JAG1)* located on chromosome 20p12. Inheritance occurs in an autosomal dominant pattern. Alagille syndrome is the most common form of familial intrahepatic cholestasis and consists of five characteristics:

- Chronic cholestasis: associated with hypercholesterolemia and paucity of intralobular bile ducts
- Congenital heart disease: most commonly peripheral pulmonic stenosis
- Bone defects: commonly butterfly vertebrae
- Eye findings: posterior embryotoxon
- Typical facies: frontal bossing, deep-set eyes, bulbous tip of nose, and pointed chin

Turnpenny PD, Ellard S. Alagille syndrome: pathogenesis, diagnosis and management. Eur J Hum Genet 2012;20(3):251–7.

✓ KEY POINTS: LIVER DISEASE

1. Direct hyperbilirubinemia is always abnormal.

2. The key to the evaluation of an infant with cholestatic jaundice requires early assessment for treatable causes and surgical intervention if biliary atresia is confirmed.

3. Significant hypoglycemia or coagulopathy in an infant with cholestatic jaundice may be an important sign of significant hepatocellular disease.

4. Do not forget silent urinary tract infection as an important, treatable cause of cholestatic jaundice in the infant.

175. What clinical conditions are associated with cholelithiasis?
- Hemolytic disease
- TPN
- Diuretic use
- Short gut syndrome
- Small bowel bacterial overgrowth
- Sepsis

176. What are common mistakes in the evaluation of an infant with neonatal cholestasis?
- Attributing all jaundice beyond the physiologic period in healthy infants to breast milk
- Not obtaining a fractionated bilirubin
- Not performing the basic evaluation in an expedited fashion
- Relying only on the clinical history and physical examination to make a diagnosis
- Delaying referral to a specialist

177. What is extrahepatic biliary atresia?
Extrahepatic biliary atresia is the term given to idiopathic progressive obliteration or discontinuity of the extrahepatic biliary tree in infancy. The process is a progressive destruction of the biliary tree. Two forms are recognized, depending on when the obliteration occurs.

The embryonic/fetal type of biliary atresia occurs in 10% to 35% of cases:
- Direct hyperbilirubinemia present at birth without any true jaundice-free period after physiologic jaundice
- More often associated with congenital malformations
- Bile duct remnants often not seen at time of surgery

The perinatal type of biliary atresia occurs in 65% to 90% of cases:

- Direct hyperbilirubinemia occurs at 4 to 8 weeks of age.
- There is a jaundice-free period after physiologic jaundice.
- Bile duct remnants are often seen at the time of surgery.

Hinds R, Davenport M, Mieli-Vergani G, et al. Antenatal presentation of biliary atresia. J Pediatr 2004;144:43–6.

178. What are the demographics of extrahepatic biliary atresia?

Extrahepatic biliary atresia occurs in 1 in 10,000 to 15,000 live births, with females affected 1.4 times more frequently than males. Approximately 10% to 20% of infants with biliary atresia will have associated anomalies (syndromic biliary atresia), including splenic abnormalities (polysplenia or asplenia), malrotation, and situs inversus.

179. What are the typical presenting clinical features of an infant with extrahepatic biliary atresia?

The usual presentation is that of an otherwise healthy infant who develops jaundice between 4 and 8 weeks of age. If an infant appears ill (e.g., vomiting, acidosis, failure to thrive), metabolic (nonobstructive) causes of jaundice should be considered promptly.

180. What are the typical radiographic findings in extrahepatic biliary atresia?

- Ultrasound: Hepatic parenchyma is often normal, and the gallbladder and common bile duct are generally not visualized. It is important to note that the gallbladder may not be visualized in healthy infants because of contraction; failure to visualize the gallbladder should not be considered evidence of biliary atresia. The main purpose of ultrasound in this setting is to rule out an obstructing choledochal cyst.
- DISIDA scan: There should be uptake of the radiotracer by the hepatic parenchyma, although uptake may be delayed secondary to associated hepatocyte injury. In biliary atresia absolutely no contrast will reach the bowel after 12 to 24 hours but instead will ultimately appear in the kidneys and urinary bladder as it is cleared through the urinary tract.

181. What are the typical histopathologic findings in extrahepatic biliary atresia?

Liver biopsy is the final step in preoperative diagnosis of biliary atresia. The biopsy will demonstrate proliferation of bile ducts and bile plugs in response to extrahepatic obstruction. The main purpose of the biopsy is to differentiate between obstructive and nonobstructive causes of cholestasis. A variable amount of fibrosis is also present, the degree of which depends on the age of the infant and the rapidity of disease progression.

182. How do the radiologic and histopathologic findings in biliary atresia compare with those of neonatal hepatitis?

See Table 10-13.

183. What is the natural history of untreated biliary atresia?

- Untreated biliary atresia is uniformly fatal within 2 years, with a median survival of 8 months. Untreated biliary atresia leads to biliary cirrhosis, portal hypertension, esophageal varices, failure to thrive, and liver failure with subsequent death from any of a number of complications.

184. What is appropriate surgical and medical therapy for biliary atresia, and how does therapy affect survival?

- Surgical: If the liver biopsy suggests biliary atresia, the infant undergoes exploratory laparotomy and an intraoperative cholangiogram. If biliary atresia is confirmed, an attempt to restore biliary drainage using the Kasai procedure (i.e., hepatic portoenterostomy) is made. During the Kasai procedure a loop of bowel is anastomosed directly to the hepatic capsule at the porta hepatis after resection of the fibrous biliary remnants. Bowel continuity is restored by formation of a Roux-en-Y intestinal anastomosis. The success of the procedure depends on the age of the infant at the time of the operation and the experience of the surgeon. Long-term survival rates may exceed 60% for infants younger

TABLE 10–13. BILIARY ATRESIA VERSUS NEONATAL HEPATITIS

IMAGING STUDY	BILIARY ATRESIA	NEONATAL HEPATITIS	OTHER DISORDERS OF INTEREST
Ultrasound	Nonvisualization of gallbladder, common bile duct	Normal gallbladder and common bile duct; echogenic liver	Choledochal cyst would show dilation of bile ducts.
DISIDA scan	Good or delayed uptake without excretion into the bowel	Delayed uptake of trace with some excretion into the bowel	Spontaneous rupture of biliary tree would show bile leak.
Liver biopsy	Proliferation of the bile ducts, bile plugs in the ducts, fibrosis of portal tracts or hepatocytes, cirrhosis	Inflammation of the hepatic parenchyma, cholestasis, possible giant cell transformation, hepatic acini (rosettes), variable inflammation	PFICs would show chronic cholestasis without ductular proliferation, cirrhosis, variable portal fibrosis and giant cell transformation

PFIC, Progressive Familial Intrahepatic Cholestasis

than 2 months of age at the time of portoenterostomy, compared with only 25% for those older than 2 months of age. The first sign of a successful portoenterostomy is the passage of green (bile-stained) stools rather than the acholic stools seen preoperatively. A retrospective study of 81 patients in the United States noted a success rate of approximately 38% with the Kasai procedure alone.

■ Medical: Any child with biliary atresia, regardless of the status of portoenterostomy, should be treated for chronic liver disease and its potential complications. Infants should receive fat-soluble vitamin supplementation (vitamins A, D, E, and K). Many infants require supplemental tube feedings, particularly if the portoenterostomy is unsuccessful. Good nutritional status will optimize the infant's survival if liver transplantation becomes necessary. Medical treatment with steroids after the Kasai procedure has been found to be beneficial in many studies and is implemented in practice at various institutions.

Wildhaber BE, Coran AG, Drongowski RA, et al. The Kasai portoenterostomy for biliary atresia: a review of a 27-year experience with 81 patients. J Pediatr Surg 2003;38:1480–5.

185. What are the potential complications of the Kasai portoenterostomy?
Specific complications include failure to achieve drainage, ascending cholangitis where drainage is achieved, and biliary cysts at the portoenterostomy site.

186. What are the therapeutic options for children who do not undergo portoenterostomy or in whom drainage is not achieved?
Liver transplantation is the only definitive therapy and has an approximately 80% expected 5-year survival rate.

187. Other than biliary atresia, what are the causes of obstructive jaundice in infancy?
Choledochal cysts and spontaneous perforation of the extrahepatic biliary tree are two causes of obstructive jaundice in infancy. Cholelithiasis is not a major cause of biliary obstruction in infancy, although gallstones may be seen as incidental findings on ultrasound of premature infants and occasionally even on prenatal ultrasound.

188. What are the demographics and presentation of choledochal cysts?
Choledochal cysts are much less common than biliary atresia, with estimates of incidence ranging from 1 in 13,000 to 1 in 2,000,000 live births. Girls are affected four times more frequently than boys. The classic triad of abdominal pain, mass, and jaundice occurs in fewer than 20% of cases. Choledochal cysts may present as jaundice, mass, vomiting, fever, and even pancreatitis. Fewer than half of choledochal cysts present in infancy.

TABLE 10–14. COMMON ABDOMINAL MASSES IN NEONATES		
MASS LOCATION	**EXAMPLES**	**CHARACTERISTICS**
Lateral	Renal cysts, hydronephrosis	Smooth, moderate mobility, transilluminates
	Renal tumor	Smooth, minimally mobile, does not transilluminate
	Neuroblastoma	Irregular contour, minimally mobile, frequently crosses midline
Midabdominal	Mesenteric cyst	Smooth, mobile, transilluminates
	Gastrointestinal duplication cyst	Smooth, mobile, does not transilluminate, associated with obstruction
	Ovarian cyst	Smooth, mobile, transilluminates
Upper abdominal	Hepatic tumors	Hard, immobile, do not transilluminate
	Choledochal cyst	Smooth, immobile, does not transilluminate, associated with jaundice
Lower abdominal	Hydrometrocolpos	Smooth, immobile, does not transilluminate, associated with imperforate hymen
	Urachal cyst	Smooth, fixed to abdominal wall, extends to umbilicus
	Sacrococcygeal teratoma	Hard, fixed, does not transilluminate, associated with external sacral component

189. What are the types of choledochal cysts?
- Type I: diffuse enlargement of the common bile duct (the majority fall in this category)
- Type II: diverticular cyst from the common bile duct
- Type III: choledochocele
- Type IV: multiple cysts of the intrahepatic and extrahepatic biliary tree
- Type V: caroli disease or cystic dilation of the intrahepatic biliary tree

ABDOMINAL MASSES

190. What is the origin of most neonatal abdominal masses?
More than half of all abdominal masses in the neonate arise from the urinary tract.

191. List the two most common causes of abdominal masses of urologic origin in the neonate.
- Hydronephrosis secondary to ureteropelvic junction obstruction
- Multicystic kidney disease

192. A pregnant woman has an antenatal ultrasound scan that reveals an intraabdominal mass in the fetus. Are any special arrangements necessary for the timing and mode of delivery?
No.

193. How do the location and other physical examination characteristics of the common abdominal masses in newborn infants provide clues for their identification?
Physical examination may significantly narrow the diagnostic possibilities, even if it does not provide an absolute answer (Table 10-14). Of note:
- Large masses may fill the entire abdomen, making it impossible to determine the site of origin on examination and therefore requiring further imaging studes.
- Hard, nodular masses are usually malignant tumors.
- A highly mobile mass is usually a mesenteric cyst, a duplication, or an ovarian cyst.