An extremely low-birthweight (ELBW) infant is admitted to the neonatal intensive care unit and will require parenteral nutritional supplementation. At this gestational age, infants' growth rates in utero and metabolic needs are high.

Of the following, a TRUE statement regarding protein metabolism of the ELBW infant is that

1. intravenous amino acids administered at 1 g/kg per day at low caloric intakes are insufficient to avert protein loss
2. intravenous amino acids administered at 3 g/kg per day at low caloric intake results in positive nitrogen balance
3. loss of protein in early life is directly proportional to gestational age at birth
4. metabolic acidosis is more common among ELBW infants receiving intravenous amino acids
5. without protein (amino acid) intake, the protein loss in ELBW infants is about 0.3 g/kg per day

You selected 5, the correct answer is 5.

Even at low caloric intake, protein balance in the extremely low-birthweight (ELBW) infant can be improved with an amino acid intake of 3 g/kg per day. When given glucose-only intravenous supplementation from birth, ELBW infants immediately begin to lose protein at rates that can exceed 1 g/kg per day. Intravenous amino acid supplementation of 1 g/kg per day can avert body protein losses, but it is insufficient to restore positive protein balance. An intake of 3 g/kg per day allows the achievement of a positive protein balance of greater than 1.5 g/kg per day. These data support the early introduction of amino acids for the ELBW infant.

The loss of protein in early life is inversely proportional to gestational age at birth. At lower gestational age, protein loss (per kg) among infants receiving glucose-only intravenous fluids is greater. This loss is estimated at 0.6 g/kg per day at term, 1 g/kg per day at 32 weeks' gestation, and 1.5 g/kg per day at 26 weeks' gestation.

Several studies have addressed the metabolic consequences of increasing protein intakes. At the rate of 3 g/kg per day, randomized studies have shown no increase in blood urea nitrogen levels, base deficit, or ammonia levels.

References:


Content Specification:

Understand the protein requirements of preterm and full-term infants
You are discussing with a medical student the benefits of breastfeeding in terms of preventing infectious diseases during infancy.

Of the following pathogens, it is MOST likely that breastfeeding provides protection against infection caused by

- cytomegalovirus
- Escherichia coli
- herpes simplex virus
- human immunodeficiency virus
- Mycobacterium tuberculosis

You selected 5, the correct answer is 2.

Human milk is protective against enteropathogenic Escherichia coli and other gastrointestinal pathogens. This protection is greatest during an infant's first 3 months of life and declines with increasing age. During the weaning period, partial breastfeeding continues to confer some protection. The mechanisms of protection are at least threefold. Breastfeeding confers protection through active components of human milk, which include cells, antibodies, carrier proteins, enzymes, and hormones. The process of breastfeeding itself may decrease exposure to enteropathogenic E coli that could be present in contaminated bottles, milk, or water. Finally, administration of human milk initiates and maintains the growth of Lactobacillus bifidus in the gut; this decreases luminal pH, which inhibits the growth of E coli. For these and other reasons, breastfeeding should be encouraged.

Breastfeeding is contraindicated in women who have human immunodeficiency virus (HIV) infection because human milk is a well-known source of transmission of this virus. HIV virions have been observed by electron microscopy within histiocytes and in the cell-free fraction of human milk. Colostrum contains a higher concentration of lymphocytes and macrophages than mature milk and, therefore, is more likely to harbor cell-associated viruses such as HIV. The risk of transmission of HIV through breastfeeding is increased when infection is recent or illness is more advanced in the mother. Both of these clinical situations are associated with a high viral load in body fluids, including human milk.

Human milk does not confer protection against herpes simplex virus (HSV). Perinatal HSV infection can occur by transplacental, intrapartum, or postnatal transmission. The latter is most likely to occur following contact with orolabial herpes. Postnatal transmission of HSV also can occur if breast lesions are present.

Human milk does not confer protection against Mycobacterium tuberculosis. Neonatal tuberculosis is acquired in four ways: by inhalation of infected droplets (via the lung), by ingestion of infected droplets (via the gut), by contamination of traumatized skin or mucous membranes, or by ingestion of infected milk. Among these routes of acquisition, the lung is by far the most common portal of entry in the neonate.

Human milk also is a source of transmission of cytomegalovirus (CMV). CMV infection is an endemic, often subclinical infection among women of low
socioeconomic status. Prolonged viral shedding of CMV is common, primarily through the genital tract and milk. The fetus can be infected by the transplacental route. However, the newborn is infected more frequently by contamination from the genital tract during birth or by ingestion of infected milk.

References


Ruff AJ. Breastmilk, breastfeeding, and transmission of viruses to the neonate. Semin Perinatol. 1994;18:510-516


Content Specification(s)
Understand the immunologic constituents in human milk and their physiologic effects
A 1,300-g male infant was born at an estimated gestational age of 32 weeks with a small omphalocele, which was closed surgically shortly after birth. The infant received parenteral nutrition with glucose/amino acid solution and lipid emulsion for the first 10 days after birth, at which time the administration of lipid was stopped because of concerns about hyperbilirubinemia. Several attempts to establish enteral feedings failed, and the infant was sustained exclusively with intravenous glucose/amino acid solution. Parenteral antibiotics were started on day 14 after the peripherally placed central venous catheter site became erythematous. At 3 weeks of age, a generalized scaly dermatitis is observed.

Of the following, the treatment that is MOST likely to ameliorate the skin condition in this infant is

- antifungal cream
- emollient lotion
- intravenous lipid
- reduced light exposure
- vitamin A

You selected 2, the correct answer is 3.

The history and clinical finding of scaly dermatitis described for the infant in the vignette are consistent with the diagnosis of essential fatty acid deficiency. The cause of essential fatty acid deficiency in this infant is the lack of exogenous lipid supplement. Therefore, administration of intravenous lipid is the appropriate treatment. The appropriateness of the practice of withholding lipids in the face of hyperbilirubinemia, as described for the infant in the vignette, remains unconfirmed. Lipid administration at a dose of 0.5 to 1.0 g/kg per day is sufficient to avoid essential fatty acid deficiency and not to interfere with bilirubin-albumin binding.

Linoleic and linolenic acids are required for normal growth, cell membrane integrity, lipid metabolism, and prostaglandin synthesis. Both are required in the diets of infants and, therefore, are classified as essential fatty acids. Essential fatty acid deficiency can occur rapidly once fatty acids are not available by dietary or parenteral means. Among infants receiving only glucose/amino acid solutions, essential fatty acid deficiency has been detected as early as the second day after birth. Essential fatty acid deficiency can be confirmed in the laboratory by measurement of the triene-to-tetraene ratio. If sufficient linoleic acid is present, enzymatic conversion to arachidonic acid (a tetraene) proceeds rapidly; with insufficient linoleic acid, the product of enzymatic conversion is eicosatrienoic acid (a triene). A triene/tetraene ratio in excess of 0.4 is associated with essential fatty acid deficiency. In a cohort of 63 preterm infants who received no fat intake in the first postnatal week, approximately 67% were reported to have low plasma linoleic acid concentrations, and 44% had elevated triene/tetraene ratios. The clinical manifestations of essential fatty acid deficiency include failure to thrive, scaly dermatitis (Figure), sparse hair growth, thrombocytopenia, susceptibility to infection, and delayed wound healing. Essential fatty acid deficiency can be prevented with the provision of 2% to 4% of nonprotein parenteral calories as linoleic acid. Most intravenous lipid emulsions contain approximately 50% linoleic acid, which provides 4% to 8% of nonprotein parenteral calories.
Fungal skin infections can produce a scaly, seborrheic rash, mostly in the areas of skinfolds or moisture (diaper area). A systemic infection may be accompanied by a generalized skin rash, usually in association with other signs of sepsis. The fungus, mostly Candida sp, can be identified with microscopic examination of a skin scraping using a potassium hydroxide preparation and confirmed with standard culture techniques. Topical antifungal medications can be used to treat skin rash localized to skinfolds or the diaper area. If fungemia is suspected as the cause for generalized skin rash and systemic disease, intravenous antimicrobial treatment with amphotericin or an imidazole derivative is warranted. The location of the rash on the infant in the vignette suggests a cause other than fungal infection.

Emollient lotions have been suggested as a means to decrease transepidermal water loss and reduce skin breakdown and cracking early in life. The use of emollient lotions for the generalized skin rash of later onset in the infant in the vignette probably only would cover the affected area without eliminating the underlying cause of the skin rash and may place the child at risk for infection. White petrolatum-containing products have been used among extremely preterm infants in the first week after birth to maintain skin integrity and decrease transepidermal fluid loss. Prolonged use of such skin preparations may be associated with the risk of infection.

Exposure to ambient light in the nursery is unlikely to cause a scaly dermatitis. Infants placed directly under fluorescent phototherapy lights with no intervening plastic barrier receive significant exposure to ultraviolet light and may develop a generalized erythematous rash similar to sunburn in the exposed areas.

Vitamin A deficiency is associated with dry skin. Vitamin A is provided in the intravenous vitamins used in parenteral nutrition, making its deficiency an unlikely cause of the skin rash for the infant in the vignette.

References:


Content specifications:

Identify the clinical and laboratory features of essential fatty acid deficiency and how to prevent it

Distinguish between essential and nonessential fatty acids
You are examining a newborn in the nursery and palpate a large mass in the abdomen.

Of the following, the MOST likely diagnosis is:

- autosomal dominant polycystic kidney disease
- horseshoe kidney
- multicystic kidney dysplasia
- renal vein thrombosis
- Wilms tumor

You selected 4, the correct answer is 3.

A palpable abdominal mass in a newborn constitutes a medical emergency. The most common cause of an abdominal mass in the neonatal period is hydronephrosis. One common cause of hydronephrosis is multicystic kidney dysplasia (MKD). This congenital malformation is caused by obstruction to urine flow during in utero development, which results in abnormal parenchymal development. Renal ultrasonography reveals multiple cysts scattered throughout the renal parenchyma, with marked echogenicity of the parenchyma, indicating nonspecific renal dysplasia. The cysts are of varying size, often replacing normal renal tissue. Because the anomaly usually is unilateral, most children who have MKD have normal renal function. However, because at least 50% of patients have an abnormality of the contralateral kidney, voiding cystourethrography (VCUG) to evaluate for vesicoureteral reflux is essential. Other anomalies of the contralateral kidney include ureteropelvic junction obstruction (with hydronephrosis), duplicated ureters, renal dysplasia, and hydronephrosis. If MKD is bilateral, renal failure is assured.

MKD is associated with other malformations, including CHARGE syndrome; Jeune syndrome; fetal alcohol syndrome; Marfan syndrome; Noonan syndrome; prune belly (Eagle-Barrett) syndrome; rubella syndrome; trisomies 8, 9, 13, 18, 21, and 22; tuberous sclerosis; and Zellweger syndrome. Additionally, MKD occurs in infants of diabetic mothers. Serum electrolyte concentrations must be obtained in any newborn who has MKD.

In most instances, it is difficult to distinguish between hydronephrosis and MKD. Therefore, a renal scan (eg, DMSA scan) should be performed. If the patient has hydronephrosis, evidence of renal function will be apparent on the scan. However, function may not be demonstrated with MKD. If the contralateral kidney is large and the serum creatinine level is normal, the contralateral kidney probably is normal, but follow-up renal ultrasonography is required to demonstrate progressive function of the contralateral kidney and further atrophy of the affected kidney. Repeat ultrasonography and measurement of serum creatinine levels annually are appropriate follow-up.

Treatment neither is required nor available for unilateral MKD. Most affected kidneys eventually atrophy; hence, prior recommendations to perform nephrectomy in anticipation of possible malignant transformation no longer are advocated. However, annual renal ultrasonography should be performed to assess the size of the affected kidney.
Autosomal dominant polycystic kidney disease (ADPKD) is a very common cause of renal failure in adults. However, because it is a very slowly progressive disease, it rarely is seen in newborns. ADPKD typically presents with hematuria, urinary tract infection, and hypertension. Although horseshoe kidneys are infrequently observed in newborns, they may present with urinary tract infections, hematuria, or abdominal mass.

Nephroblastoma is a general term used to describe a tumor of the kidney. The most common cause in early childhood is Wilms tumor, which presents as an abdominal or flank mass and may be heralded by hematuria and rarely, hypertension. It can be associated with other congenital anomalies, including genitourinary anomalies, hemihypertrophy, aniridia, gastrointestinal anomalies, polydactyly, and hydrocephalus. Although this is the most common solid tumor in childhood, it rarely presents during the newborn period.

The typical presentation of renal vein thrombosis in a child is gross hematuria and an abdominal mass. Although rare, it often results in complete loss of function of the affected kidney.

References:

Content Specification(s):
Recognize the clinical and laboratory features of common neonatal malignancies, including teratomas, hemangiomas, neuroblastoma, Wilms tumor, retinoblastoma.
A newborn male has excess abdominal skin, deficiency of the abdominal musculature, and cryptorchidism.

Of the following, the MOST likely etiology of these findings is:

1. chronic amniotic fluid leakage during pregnancy
2. early urethral obstruction
3. extrophy of the bladder
4. polycystic kidneys
5. renal agenesis

You selected 5, the correct answer is 2.

Early urethral obstruction sequence results most commonly from urethral valve formation, but it can be due to urethral atresia or more distal urethral obstructions. It causes accumulation of urine in the fetal bladder and urinary system beginning at about 8 weeks of gestation, when urine formation begins. Because the most common etiology of the disorder is malformed development of the penile urethra, it is most common in males, who also typically have cryptorchidism due to failure of the testes to descend because of pressure from the enlarged bladder. The bladder distension also causes hydronephrosis and renal dysplasia. In some cases, compression of the abdominal contents by the bladder can lead to malrotation of the colon, and rarely compression of the iliac vessels can disrupt blood flow to the lower extremities, leading to limb deficiency. The abdominal distension results in an excess of abdominal skin and a deficiency of abdominal musculature, as described for the infant in the vignette. This condition has been called prune belly syndrome because of the flaccid, wrinkled appearance of the abdominal skin. Affected infants also display the features of oligohydramnios deformity complex, including hypoplastic lungs, breech presentation, altered facial features, and abnormal positioning of the hands and feet.

Severe obstruction is fatal in fetal life unless the urinary bladder is decompressed. This can occur in utero though rupture. In some centers, prenatal decompression of the bladder by vesicoamniotic shunt placement, which also increases amniotic fluid volume to promote lung development, has been attempted. Infants who are born alive frequently have renal damage, although the abdominal musculature usually develops postnatally. The disorder occurs most commonly as a sporadic event and is associated with a low recurrence risk for future pregnancies.

Chronic amniotic fluid leakage and renal agenesis result in the oligohydramnios sequence, which causes pulmonary hypoplasia and fetal compression. However, prune belly is not an associated feature because the bladder is not distended. Extrophy of the bladder refers to exposure of the bladder due to failure of the intraumbilical mesoderm to invade the cloacal membrane. Polycystic kidneys do not cause an obstructive uropathy, although in some cases they are associated with oligohydramnios.

References:

Content Specification(s):
Recognize the etiology, clinical manifestations, laboratory features, and approach to therapy of infants with anatomic abnormalities of the urinary tract
You are examining a newborn in the nursery and palpate a large mass in the abdomen.

Of the following, the MOST likely diagnosis is:

- [ ] autosomal dominant polycystic kidney disease
- [ ] horseshoe kidney
- [x] multicystic kidney dysplasia
- [ ] renal vein thrombosis
- [ ] Wilms tumor

You selected [x], the correct answer is [x].

A palpable abdominal mass in a newborn constitutes a medical emergency. The most common cause of an abdominal mass in the neonatal period is hydronephrosis. One common cause of hydronephrosis is **multicystic kidney dysplasia** (MKD). This congenital malformation is caused by obstruction to urine flow during in utero development, which results in abnormal parenchymal development. Renal ultrasonography reveals multiple cysts scattered throughout the renal parenchyma, with marked echogenicity of the parenchyma, indicating nonspecific renal dysplasia. The cysts are of varying size, often replacing normal renal tissue. Because the anomaly usually is unilateral, most children who have MKD have normal renal function. However, because at least 50% of patients have an abnormality of the contralateral kidney, voiding cystourethrography (VCUG) to evaluate for vesicoureteral reflux is essential. Other anomalies of the contralateral kidney include ureteropelvic junction obstruction (with hydronephrosis), duplicated ureters, renal dysplasia, and hydronephrosis. If MKD is bilateral, renal failure is assured.

MKD is associated with other malformations, including CHARGE syndrome; Jeune syndrome; fetal alcohol syndrome; Marfan syndrome; Noonan syndrome; prune belly (Eagle-Barrett) syndrome; rubella syndrome; trisomies 8, 9, 13, 18, 21, and 22; tuberous sclerosis; and Zellweger syndrome. Additionally, MKD occurs in infants of diabetic mothers. Serum electrolyte concentrations must be obtained in any newborn who has MKD.

In most instances, it is difficult to distinguish between hydronephrosis and MKD. Therefore, a renal scan (eg, DMSA scan) should be performed. If the patient has hydronephrosis, evidence of renal function will be apparent on the scan. However, function may not be demonstrated with MKD. If the contralateral kidney is large and the serum creatinine level is normal, the contralateral kidney probably is normal, but follow-up renal ultrasonography is required to demonstrate progressive function of the contralateral kidney and further atrophy of the affected kidney. Repeat ultrasonography and measurement of serum creatinine levels annually are appropriate follow-up.

Treatment neither is required nor available for unilateral MKD. Most affected kidneys eventually atrophy; hence, prior recommendations to perform nephrectomy in anticipation of possible malignant transformation no longer are advocated. However, annual renal ultrasonography should be performed to assess the size of the affected kidney.
Autosomal dominant polycystic kidney disease (ADPKD) is a very common cause of renal failure in adults. However, because it is a very slowly progressive disease, it rarely is seen in newborns. ADPKD typically presents with hematuria, urinary tract infection, and hypertension. Although horseshoe kidneys are infrequently observed in newborns, they may present with urinary tract infections, hematuria, or abdominal mass.

Nephroblastoma is a general term used to describe a tumor of the kidney. The most common cause in early childhood is Wilms tumor, which presents as an abdominal or flank mass and may be heralded by hematuria and rarely, hypertension. It can be associated with other congenital anomalies, including genitourinary anomalies, hemihypertrophy, aniridia, gastrointestinal anomalies, polydactyly, and hydrocephalus. Although this is the most common solid tumor in childhood, it rarely presents during the newborn period.

The typical presentation of renal vein thrombosis in a child is gross hematuria and an abdominal mass. Although rare, it often results in complete loss of function of the affected kidney.

References:

Content Specification(s):
Recognize the clinical and laboratory features of common neonatal malignancies, including teratomas, hemangiomas, neuroblastoma, Wilms tumor, retinoblastoma.
You are called to the delivery room to evaluate a male infant because of an abnormality of the lower abdomen. You see the following on physical examination:

![Image of a male infant's lower abdomen]

Otherwise, he looks normal.

Of the following, the MOST likely associated anomaly in this infant is:

1. anal atresia
2. congenital heart disease
3. cryptorchidism
4. inguinal hernia
5. ureteropelvic junction obstruction

You selected 4, the correct answer is 1.

The infant in this vignette has extrophy of the bladder, which is seen more often in boys than in girls (male to female ratio, 2.5 to 1). Clinical features include an open bladder area, inferiorly displaced umbilicus, and diastasis of the pubis. Presence of an omphalocele, intestinal opening into the exposed bladder mucosa, and absence of an anal opening are characteristic of cloacal extrophy, a more extensive and severe condition. The defects in extrophy occur due to failure of migration of infraumbilical mesenchyme about the 6th to 7th week of development, resulting in continued contact between the bladder portion of the cloaca and the overlying ectoderm. More extensive mesodermal deficiency results in cloacal extrophy. Infraumbilical mesenchyme gives rise to the lower abdominal wall, genital tubercles, and pubic rami. Its lack results in breakdown of the cloacal membrane as in other areas where mesoderm does not separate ectoderm from endoderm, such as the mouth, anus, and urogenital areas. Extrophy of the bladder is more common among first-born children, and it is rarely seen among African Americans. Parents having an infant with bladder extrophy have a 1 in 275 chance for extrophy or epispadias in a future infant. Children of affected individuals experience a 1 in 70 risk.

The anomaly most associated with extrophy of the bladder in male infants is inguinal hernia. The prevalence of inguinal hernia is estimated at 80% in male infants, and only 10% in female infants.

Anal atresia is not commonly seen with the extrophy/epispadias combination as seen in the vignette. Children with the more extensive mesenchymal deficiency associated with cloacal extrophy have anal atresia and often have a prolapsed segment of ileum coming from the cecal...
portion of the exposed cloacal membrane. Fecal and urinary continence should be expected with bladder exstrophy after reconstructive surgery. In contrast, patients with cloacal exstrophy rarely achieve either urinary or fecal continence.

Congenital heart disease is not prevalent among infants with bladder exstrophy.

Cryptorchidism usually is not seen with bladder exstrophy. The lesion often results in lateral displacement of the scrotum due to the widened pubic tubercles, but the testes are usually retractile and will not require orchidopexy.

Ureteropelvic junction abnormalities are not seen often with exstrophy. Vesicoureteral reflux is common due to the short course of the ureter through the bladder wall in exstrophy. Renal agenesis is rare. In contrast, exstrophy of the cloaca is associated frequently with upper urinary tract anomalies, such as agenesis, multicystic kidney, pelvic kidney, and ureteral duplication. Females have bifid uterine horns and duplicated, short or atretic vaginas.

References:


Content Specifications:

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

Know how to diagnose specific anatomic abnormalities of the urinary tract in infants

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

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

1. end-stage renal disease
2. hydronephrosis
3. posterior urethral valves
4. prostatic hypoplasia
5. vesicoureteral reflux

You selected 2, the correct answer is 1.

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

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

References:


**Content specifications:**

Recognize the clinical manifestations of anatomic abnormalities of the urinary tract in infants
Know how to diagnose specific anatomic abnormalities of the urinary tract in infants
Know the recommended supportive and corrective treatment of anatomic abnormalities of the urinary tract in infants
Prenatal ultrasonography of a male fetus reveals bilateral hydronephrosis. Postnatal abdominal ultrasonography confirms bilateral hydronephrosis, with markedly reduced renal parenchyma. A voiding cystourethrogram reveals posterior urethral valves and bilateral grade IV vesicoureteral reflux (VUR). A urologist performs ablation of the valves and bilateral ureterostomies. The infant’s serum creatinine at 2 weeks after birth is 2.1 mg/dL (185.6 mcmol/L). The remainder of the serum electrolyte concentrations are normal, and the urine output is 5.2 mL/kg per hour. The patient has no sign of volume depletion or overload.

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

1. is unlikely to progress to end-stage renal disease (ESRD)
2. is unlikely to reach ESRD until adulthood
3. likely will develop ESRD within 5 years
4. needs to start peritoneal dialysis immediately
5. should progress slowly to ESRD by adolescence

You selected 3, the correct answer is 3.

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

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

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

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

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

Content Specifications:
Recognize the clinical manifestations of anatomic abnormalities of the urinary tract in infants
Know the recommended supportive and corrective treatment of anatomic abnormalities of the urinary tract in infants
A 7-day-old female who was born at an estimated gestational age of 24 weeks, has experienced weight loss that exceeds 15% of birthweight. Although her skin appears well keratinized, it has poor turgor. She is breathing spontaneously in room air with ambient humidity of 70% and is receiving intravenous nutrition along with trophic enteral feeds. She has received neither indomethacin nor diuretics. Her serum electrolytes are: sodium 158 mEq/L (158 mmol/L), potassium 4.6 Eq/L (4.6 mmol/L), and chloride 116 mEq/L (116 mmol/L). Her serum osmolality is 328 mOsm/kg (328 mmol/kg H2O). Her urine output is 5.8 mL/kg per hour and urine osmolality 70 mOsm/kg. A lack of effect of the hormone arginine vasopressin (AVP) is suspected.

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

1. inadequate secretion of AVP from posterior pituitary
2. lack of AVP receptors in distal nephron and collecting duct
3. lack of production of cyclic AMP after AVP binding to its receptor
4. lack of water channel proteins, aquaporins, in the kidney
5. metabolic degradation of AVP by cysteine aminopeptidase

You selected 4, the correct answer is 3.

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

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

The effects of AVP are mediated by two major classes of receptors, V1 and V2. The V1 receptor is distributed widely in tissues including vascular smooth muscle, liver, platelets, and cerebrum. The V2 receptor, more specific for the antidiuretic response, is found principally in the kidney; the specific sites include the medullary thick ascending limb of the loop of Henle and the collecting duct. In sheep, the fetal kidney is replete with V2 receptors with binding
characteristics similar to those in the adult kidney. Likewise, the fetal kidney in humans is replete with V2 receptors. Thus, the lack of AVP receptors in the distal nephron and the collecting duct is not the limiting factor for the lack of effect of AVP in preterm infants.

Located on the basolateral membranes of the cells of the collecting duct, the V2 receptors, when occupied by AVP, initiate a cascade of intracellular events. These events begin with activation of adenylate cyclase for generation of cyclic AMP from adenosine triphosphate (ATP), which is followed by phosphorylation of protein kinases. The stimulation of protein kinases results in the translocation of cytoplasmic water channels (aquaporins) to the apical membrane of the cells of the collecting duct. The net result is an increase in water permeability of the collecting duct. The other renal site of AVP action is the medullary thick ascending limb of the loop of Henle, which possesses the AVP-sensitive adenylate cyclase. Upon activation of adenylate cyclase, sodium is transported actively into the renal interstitium, which generates a hypertonic interstitial renal medulla and increases the osmotic water gradient across the collecting duct, resulting in augmentation of its antiuretic action. In newborn rats, the adenylate cyclase response to AVP is low (approximately 25% of adult response) and does not reach maturity until about 30 days after birth. The adenylate cyclase response to AVP is immature in human neonates, particularly preterm infants. Thus, the lack of production of cyclic AMP after AVP binding to its receptor from immaturity of the adenylate cyclase is the limiting factor that accounts for the lack of effect of AVP in preterm infants.

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

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

**References:**


**Content Specifications:**

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

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

Understand the impact on water requirements of renal and metabolic fluid disorders that arise because of endocrine dysfunction in infants
Soon after birth, a term infant develops severe respiratory distress requiring assisted mechanical ventilation. Prenatal ultrasonography at 20 weeks’ gestation revealed markedly enlarged kidneys, oligohydramnios, and minimal bladder fluid. Postnatal ultrasonography reveals bilaterally enlarged kidneys with diffusely increased echogenicity, but no visible cysts. You suspect the child has autosomal recessive polycystic kidney disease (ARPKD).

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

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

You selected 5, the correct answer is 1.

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

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

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

References:

Roy S, Dillon MJ, Trompeter RS, Barratt TM. Autosomal recessive polycystic kidney disease:


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


Content Specifications:

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

Know the recommended supportive and corrective treatment of anatomic abnormalities of the urinary tract in infants
A 21-day-old male, whose birthweight was 820 g and estimated gestational age at birth was 26 weeks, has the following serum electrolytes: sodium 125 mEq/L (125 mmol/L), potassium 5.4 mEq/L (5.4 mmol/L), chloride 95 mEq/L (95 mmol/L), and bicarbonate 20 mEq/L (20 mmol/L). During the last week, he has averaged caloric intake of 90 kcal/kg per day, sodium intake of 2.8 mEq/kg per day, and weight gain of 15 g/kg per day. He is breathing spontaneously in room air and has received neither indomethacin nor diuretics. His serum creatinine is 0.4 mg/dL (30.5 mmol/L). His urine measurements are: output 86 mL/kg per day, sodium 72 mEq/L, and creatinine 6 mg/dL.

Of the following, the hormone/vasoactive peptide whose dysfunction is MOST likely to account for the serum electrolyte abnormalities in this infant is

1. aldosterone
2. arginine vasopressin
3. atrial natriuretic peptide
4. catecholamine
5. cortisol

You selected 3, the correct answer is 1.

The preterm infant in this vignette has evidence of late hyponatremia. Typically, the serum sodium concentration in this disorder is less than 130 mEq/L (130 mmol/L) and the postnatal age at the time of manifestation is 2 weeks to 6 weeks. The hyponatremia is attributed to a negative sodium balance in which the sodium output, largely through urine, exceeds sodium intake. A rapid weight gain associated with growth, not water retention, may be accompanied by increased accretion of sodium in the tissues and may exaggerate hyponatremia.

The urine sodium output can be estimated from the urine output and urine sodium concentration, assuming that the sodium excretion in the urine is uniform throughout the day. Using the equation:

\[
\text{Urine sodium output (mEq/kg per day)} = \frac{[\text{Urine sodium concentration (mEq/L)} \times \text{urine output (mL/kg per day)}]}{1000},
\]

and assuming zero losses of sodium in the stool and sweat, the total sodium output in the infant in this vignette is estimated at 6.2 mEq/kg per day. With a sodium intake of 2.8 mEq/kg per day, the sodium balance is negative, with a calculated deficit of 3.4 mEq/kg per day. Additionally, the weight gain in this infant, assuming no water retention, suggests that that sodium accretion in the tissues may be contributing to hyponatremia.

The high urine sodium output is reflected in the elevated renal fractional excretion of sodium (FE_{Na}), which is calculated using the equation:

\[
\text{FE}_{Na} (%) = \frac{[\text{urine Na (mEq/L)} \times \text{serum creatinine (mg/dL)}]}{[\text{serum Na (mEq/L)} \times \text{urine Na (mEq/L)}]} - 100.
\]
The FE\textsubscript{Na} varies inversely with gestational age, ranging in the first 2 days after birth from >5% in neonates of gestational age 27 weeks or younger to 1% in those born at term. The FE\textsubscript{Na} also varies inversely with postmenstrual age, ranging at 2 weeks after birth from approximately 1% in infants 27 weeks or younger by gestational age to 0.2% in those born at term. The FE\textsubscript{Na} in the infant in this vignette is calculated at approximately 3.8%.

A review of renal absorption of sodium may facilitate our understanding of late hyponatremia in preterm infants. In the kidney, the proximal tubule receives an ultrafiltrate of plasma from the glomerulus and reabsorbs all of the filtered glucose and amino acids along with most of the chloride and bicarbonate. Much of the reabsorption of sodium is mediated by an energy-consuming transporter, Na/K-ATPase, located on the basolateral membrane of the tubular cell, and by specific ion transporters, located on the apical membrane. Of the net reabsorption of sodium in the nephron, approximately 70% occurs in the distal half of the proximal tubule, mediated by an Na/H\textsubscript{x} exchanger and a Cl/OH\textsubscript{x} exchanger; 25% in the thick ascending limb of the loop of Henle, mediated by an Na/K/2Cl cotransporter; 5% in the distal tubule, mediated by an Na/Cl cotransporter; and 1% in the collecting duct, mediated by a Na channel. The factor that limits the reabsorption of sodium in the nephron and promotes its excretion in the urine is not any structural or functional deficiency of Na/K-ATPase or other ion transporters, but the lack of their abundance in the neonatal kidney, particularly in preterm infants.

The most likely cause of late hyponatremia from excessive urine loss of sodium in preterm infants is the lack of renal tubular response to aldosterone. Aldosterone is produced by zona glomerulosa of the adrenal cortex. Angiotensin II, a product of the renin-angiotensin system, is the major secretotogule involved in regulating aldosterone secretion in response to changes in sodium intake or fluid volume. Aldosterone induces reabsorption of sodium and excretion of potassium largely by regulating the permeability of sodium in the distal tubule and collecting duct. In the fetus, angiotensin II is a poor stimulus for aldosterone secretion. In contrast, birth causes a marked increase in renin, angiotensin II, and aldosterone concentrations in both term and preterm neonates. However, the immaturity of proximal tubular function in the preterm infant limits the responsiveness of the proximal tubule to reabsorption of sodium, thereby increasing the load of sodium presented to the distal tubule and collecting duct. The lack of abundance of Na/K-ATPase and other ion transporters limits the responsiveness of the distal nephron to aldosterone, particularly in the presence of increased load of sodium from the proximal tubule. The net result is natriuresis.

Arginine vasopressin (AVP), the antidiuretic hormone, is the major determinant of renal water excretion. AVP is synthesized in its precursor form in the hypothalamic neurons of the supraoptic and paraventricular nuclei. AVP, produced by cleavage of its precursor, is stored in the posterior pituitary, and its release is regulated by the osmolality of plasma. AVP induces reabsorption of water largely by regulating the water permeability of the collecting duct. Excess of AVP results in retention of water and dilutional hyponatremia. In the fetus, AVP production is active as indicated by high concentrations of AVP in cord arterial blood. After birth, AVP production in both term and preterm neonates can be increased in response to hypoxia, acidemia, hemorrhage, infection, central nervous system disease, pulmonary complications, and cardiac conditions. The absence of such factors in the infant in this vignette makes it unlikely that high AVP concentrations were the cause of late hyponatremia.

Atrial natriuretic peptide (ANP) is produced in the cardiac atria. The major stimulus for ANP secretion is increased cardiac atrial wall tension, resulting from acute or chronic fluid volume expansion, congestive heart failure, and other conditions associated with increased intra-atrial pressure. ANP induces diuresis and natriuresis by at least two mechanisms. The afferent arteriolar dilatation and efferent arteriolar constriction in the glomerulus induced by ANP increases glomerular filtration of fluid and electrolytes, including sodium. The tubular contribution to natriuresis by ANP involves the collecting duct and may be mediated by
inhibition of the action of angiotensin II. In the human fetus, ANP is detected as early as 10 weeks’ gestational age. The circulating concentrations of ANP increase throughout gestation and during the first 7 to 10 days after birth. Although high ANP concentrations are seen in preterm neonates, particularly those with lung disease, the renal diuretic and natriuretic response to ANP in these infants is blunted. Possible reasons for this include low renal perfusion pressure in the neonatal kidney, and inhibition of ANP effect by high circulating concentrations of angiotensin II and aldosterone. Thus, the late hyponatremia of prematurity is unlikely to be caused by ANP abnormalities.

Catecholamines, both neuronally derived and locally produced in the renal parenchyma, are increased markedly in concentration in the first few hours after birth and under stressful conditions thereafter. The renal sympathetic nerve activity, mimicked by catecholamines, reduces renal sodium excretion by limiting the increase in the glomerular filtration rate that occurs in the early neonatal period and by promoting the reabsorption of sodium in the tubules. Likewise, cortisol, a glucocorticosteroid hormone, enhances tubular reabsorption of sodium by promoting the maturation of ion transporters, specifically Na/H exchanger in the distal segment of the proximal tubule. Thus, neither catecholamines nor cortisol has been linked to the pathogenesis of late hyponatremia of prematurity.

References:


Content Specifications:

Understand the production sites and actions of various types of vasoactive peptides that affect renal function

Understand the etiology of electrolyte abnormalities in the neonate
| Recognize the clinical and laboratory manifestations of electrolyte abnormalities in the neonate |
| Know how to calculate renal clearance |
A male infant is born at term with a birthweight of 2,120 g. The pregnancy was complicated by fetal bilateral hydronephrosis and a dilated, thickened bladder. A vesicoamniotic shunt was placed at 17 weeks' gestation due to severe oligohydramnios. At delivery, the infant required endotracheal intubation for respiratory distress. Physical examination of the infant reveals a severely wrinkled and lax abdominal wall (Figure 1).

Figure 1

Voiding cystourethrography demonstrates a markedly dilated urinary tract (Figure 2).

Figure 2: Dilated urinary bladder, ureters, and pelvic caliceal system

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

- abnormal karyotype
- bilateral cryptorchidism
- diaphragm hypoplasia
- hypospadias
- multicystic-dysplastic kidneys

You selected 5, the correct answer is 2.
The infant in this vignette has laxity of the abdominal wall and hydroureteronephrosis, characteristic of the Eagle-Barrett syndrome. This condition has also been called the prune belly syndrome and the Triad syndrome, and is defined by three specific anomalies in a male infant: deficient abdominal wall musculature, a dilated urinary tract, and bilateral cryptorchidism. Infants with the wrinkled and lax abdominal wall, without bilateral undescended testes or a dilated urinary tract, are considered to have partial or pseudo prune belly. Female infants can only have pseudo prune belly.

The incidence of Eagle-Barrett syndrome is 1 in 40,000 live births, and the pathological spectrum is wide. The kidneys may be near-normal to severely dysplastic or small and cystic to enlarged and hydronephrotic. High-grade obstruction is associated with severe dysplasia in most, but not all, cases. Typically, the ureters are dilated, elongated, tortuous, and thick walled, and may be obstructed at the uretero-pelvic junction, within the ureter, or at the ureterovesical junction. Vesico-ureteric reflux occurs in 75% of cases. The bladder is often enlarged, thickened, and nontrabeculated. A patent urachus or urachal cyst occurs in 25% to 50% of cases. Although posterior urethral valves, atresias, stenoses, and functional obstructions are described, urethral obstruction is not always present. Patients without urethral obstruction are able to void, but evacuation of the bladder may be incomplete.

The pathogenesis of Eagle-Barrett syndrome continues to be debated and likely involves either hyperextension injury or faulty embryogenesis or both. While most cases are sporadic, familial occurrences have been described. A consistent chromosomal abnormality has not been identified; however, this syndrome has been reported with the trisomies 13, 18, and 21. One pathogenic theory proposes that early urethral obstruction produces back pressure on the fetal urinary tract, leading to ectasia and renal dysplasia. The resultant massive abdominal distention leads to degeneration of the abdominal wall musculature, particularly in the lower abdomen. Because abdominal distention from other causes, such as fetal ascites, may result in deficient abdominal wall muscles, the timing of urinary obstruction (before 15 weeks’ gestation) and the magnitude of the distention are likely key pathogenic elements. The lack of postnatal evidence of intrinsic urinary tract obstruction in many cases supports a potentially transient nature of the obstruction.

The current most plausible theory proposes that an insult to the embryonic mesoderm, between the 3rd and 10th weeks of gestation, simultaneously affects the muscles of the developing abdominal wall and urinary tract, resulting in replacement of musculature with fibrous tissue. Ineffective bladder emptying and ureteral ectasia ensues. Microscopy supports this theory, with findings of disorganized muscle fibers and large glycogen aggregates in the muscle. Supporters of this theory point out that abdominal muscle pathology occurs infrequently in other obstructive uropathies. In addition, the occasional lack of correlation between the urinary tract and abdominal wall pathology and the frequent asymmetry of the muscular defect is poorly explained on the basis of distention alone.

In addition to the triad of findings defining Eagle-Barrett syndrome, up to 75% of patients have associated anomalies or complications, generally attributable to the deficient abdominal wall musculature or oligohydramnios. Intrauterine compression may lead to chest wall and limb deformities, including talipes equinovarus, congenital hip dislocation, and scoliosis. Oligohydramnios may result in mild to severe pulmonary hypoplasia. In 10% to 17% of cases, cardiac anomalies are found, which include atrial and ventricular septal defects, patent ductus arteriosus, and valvular defects. Imperforate anus is reported, and intestinal malrotation occurs in up to 30% of cases. Hydropsplasias and diaphragm hypoplasia are rarely described.

The prognosis for patients with Eagle-Barrett syndrome varies as well, with the degree of pulmonary hypoplasia or renal dysplasia having the greatest impact on mortality. A near-normal life expectancy may be possible. Management aims to preserve functioning renal tissue and may include diversion of the urinary tract. Most patients will have a low pressure collecting system that drains adequately despite dilatation, and drainage tends to improve with age. Reconstructive surgery of the urinary tract should be selective and targeted at definite obstructive lesions. Although these children remain unable to sit up from the supine position, the abdominal wall deformity improves cosmetically with age, as subcutaneous fat is deposited. Improved management of renal dysfunction, including dialysis and renal transplant, has led to long-term survival rates as high as 90%.

References:


American Board of Pediatrics Content Specification(s):

Know the causes, laboratory, and clinical signs of congenital nephrosis

Recognize the clinical manifestations of anatomic abnormalities of the urinary tract in infants
Know how to diagnose specific anatomic abnormalities of the urinary tract in infants
A 38-year-old primiparous woman is in her 24th week of pregnancy. Fetal ultrasonography reveals generalized skin edema, bilateral pleural effusions, and mild ascites. Mother's blood type is O Rh-positive. You discuss with medical students the pathophysiology of interstitial fluid accumulation characteristic of hydrops in this fetus.

Of the following, the factor MOST protective against interstitial fluid accumulation is high:

1. capillary filtration coefficient
2. capillary hydrostatic pressure
3. central venous pressure
4. interstitial oncotic pressure
5. osmotic reflection coefficient

You selected 4, the correct answer is 5.

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

Hydrops fetalis is defined as excessive accumulation of interstitial fluid in the fetus. With the successful implementation of strategies for prevention and treatment of Rh blood group isoimmunization, approximately 90% of the cases of hydrops fetalis currently are of the nonimmune type, as in the fetus in this vignette. A review of the regulation of fluid movement between vascular and interstitial spaces may facilitate our understanding of the pathophysiology of hydrops fetalis.

**Interstitial fluid balance (Figure 1)**
is determined by the rate of formation of the interstitial fluid from the vascular compartment and the rate of its drainage through the lymphatic system. Let us examine first the interstitial fluid formation and then we will return to review the interstitial fluid drainage.

The driving forces for fluid extravasation from the vascular space to the interstitial space are the hydrostatic pressure within the capillary (PC) and the colloid oncotic pressure within the interstitial fluid (pi). Conversely, the driving forces for fluid return from the interstitial space to the vascular space are the hydrostatic pressure within the interstitial fluid (Pi) and the colloid oncotic pressure within the capillary (pC).

Thus, the higher the hydrostatic pressure gradient (?P = PC - Pi), the greater is the rate of interstitial fluid formation. Conversely, the lower the colloid oncotic pressure gradient (?p = pC - pi), the greater is the rate of interstitial fluid formation.

Two characteristics of the capillary influence the fluid flux: capillary filtration coefficient (CFC) and osmotic reflection coefficient (s). The former, CFC, is a product of capillary surface area and capillary hydraulic conductivity; whereas the latter, s, is a measure of capillary endothelial permeability. The higher the capillary surface area and the capillary hydraulic conductivity (ie, the higher the capillary filtration coefficient), the greater is the rate of interstitial fluid formation. On the other hand, the higher the osmotic reflection coefficient (s) (ie, lesser capillary endothelial permeability), the lower is the rate of interstitial fluid formation.

The colloid oncotic pressure in the vascular and interstitial spaces depends on the concentration of osmotically active particles in each compartment and the permeability of the intervening capillary endothelium. The less permeable the endothelium, meaning high s, the greater is the separation of osmotic particles and the greater is the efficacy of colloid oncotic pressure difference in preventing fluid flux toward the interstitial space. Conversely, the more permeable the endothelium, meaning low s, the greater is the equilibration of osmotic particles and the lesser is the efficacy of colloid oncotic pressure difference in preventing fluid flux toward the interstitial space.

The fluid movement between the vascular space and the interstitial space is summarized by the following equation:

\[ Jv = CFC \ (\ ?P - s\ ?p) \]
in which $J_v$ is the fluid flux across the capillary, $CFC$ is the capillary filtration coefficient, $\Delta P$ is the hydrostatic pressure gradient ($P_C - P_i$), $s$ is the osmotic reflection coefficient, and $\Delta p$ is the colloid oncotic pressure gradient ($p_C - p_i$).

The fetus, in contrast to the adult, is much more susceptible to interstitial fluid accumulation for the following reasons:

- **First**, the capillary filtration coefficient is about fivefold higher in the fetus than in the adult.
- **Second**, the interstitium of the fetus is much more compliant than that of the adult, that is, the interstitial space is capable of accumulating a large amount of fluid with only a small increase in the interstitial hydrostatic pressure. This low $P_i$ accounts for a higher $\Delta P$ in the fetus.
- **Third**, the fetal capillary is more permeable to plasma proteins. The effect of this enhanced solute permeability is that for any given solute concentration difference across the capillary endothelium, the colloid oncotic pressure difference drives fluid less effectively from the interstitium to the vascular space.
- **Fourth**, the plasma protein concentration is lower in the fetus than in the adult, which results in a reduced plasma colloid oncotic pressure.

Pathologically, any condition that increases the hydrostatic pressure gradient, increases the capillary permeability, or decreases the colloid oncotic pressure gradient is conducive to excessive interstitial fluid accumulation and resultant hydrops.

Finally, let us examine the interstitial fluid drainage through the lymphatic system, the second component of the interstitial fluid balance. The lymph flow depends on the anatomic development of the lymphatic system and the pressure gradient between the interstitial fluid space and the venous compartment. In conditions associated with anomalous development of lymphatics (eg, lymphangiectasia) or lymphatic obstruction (eg, thoracic duct occlusion), the interstitial fluid drainage is impaired. Also, a high central venous pressure relative to interstitial hydrostatic pressure impairs lymph flow. In the fetus, lymph flow ceases when the central venous pressure exceeds 10 mm Hg in contrast to approximately 25 mm Hg in the adult. Pathologically, any condition that alters the lymphatic system, or that increases the central venous pressure is conducive to impaired interstitial fluid drainage and resultant hydrops.

In this vignette, among all the factors that determine the interstitial fluid balance, the factor most protective against interstitial fluid accumulation and resultant hydrops is high osmotic reflection coefficient.

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

**References:**


**American Board of Pediatrics Content Specification(s):**
Know the differential diagnosis and the plan of management of a fetus with nonimmune hydrops
March: Question 5

A 2-day-old male newborn, whose birthweight was 640 g and estimated gestational age was 23 weeks, is being managed in a radiant warmer. His skin is covered with an emollient. Around the infant, a microenvironment is created with a transparent plastic barrier, so that ambient humidity around the infant is 80%, and his abdominal skin temperature is being maintained at 36.5°C. He has no ultrasonographic or biochemical evidence of intrinsic renal disease, and he has received neither indomethacin nor diuretics. He is receiving exclusively intravenous fluids containing glucose, amino acids, and electrolytes, and he is being assisted with a conventional mechanical ventilator.

You wish to monitor the state of hydration of the infant to guide fluid-electrolyte management. Of the following, the MOST useful guide for monitoring hydration in this infant is:

1. bioelectrical impedance
2. hematocrit
3. indicator dilution
4. skin turgor
5. urine osmolality

You selected 5, the correct answer is 5.

Do you want to add anything to your Learning Plan?

(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

The extremely-low-birthweight infant in this vignette is at risk for developing fluid-electrolyte abnormalities, and his hydration status warrants monitoring to maintain an optimal water balance and promote optimal body water distribution within its different compartments. Water balance is determined as water intake minus water output. The goal in fluid management is to maintain zero water balance (water intake equals water output), if the body water content is normal (state of optimal hydration); positive water balance (water intake greater than water output), if the body water content is lower than normal (state of dehydration); or negative water balance (water intake less than water output), if the body water content is higher than normal (state of overhydration).

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

Monitoring hydration includes assessment of clinical variables, measurement of blood indices, evaluation of urine parameters, and body water measurements.
Clinical variables include body weight, skin turgor, oral mucosal moisture capillary refill, heart rate, blood pressure, and feel of the fontanel. Blood indices include hemoglobin and hematocrit, serum electrolytes, serum osmolality, and blood urea nitrogen. Urine parameters include urine volume, urine osmolality, and urine electrolytes. Body water measurements can be performed using such investigational methods as indicator dilution, bioelectrical impedance, and stable isotope tracers.

Among the options presented, the most useful and practical guide for monitoring a neonate's hydration status is urine osmolality. Assuming no intrinsic renal disease and no postnatal alteration of renal function by medications, such as indomethacin or diuretics, as in the infant in this vignette, a urine osmolality between 75 and 300 mOsm/kg is optimal, as it indicates that neither renal concentrating mechanisms nor renal diluting mechanisms are being stressed unduly. Urine osmolality is influenced by renal solute load and the volume of water required to excrete that load. Within the typical range of renal solute excretion of 7.5 to 15 mOsm/kg per day and within the optimal range of urine osmolality (75 to 300 mOsm/kg), the required water loss in the urine amounts to 50 to 100 mL/kg per day, or approximately 2 to 4 mL/kg per hour. If there is no endocrine disorder, such as dysfunction of arginine-vasopressin, and if there is no spillage of glucose, protein, or heme in the urine, a urine osmolality in excess of 300 mOsm/kg with a urine volume less than 2 mL/kg per hour represents dehydration, whereas a urine osmolality less than 75 mOsm/kg with a urine volume more than 4 mL/kg per hour represents overhydration. Urine osmolality measured by freezing point depression correlates well with urine specific gravity as measured by refractometry. The range of urine specific gravity corresponding with the optimal range of urine osmolality (75 to 300 mOsm/kg) is between 1.003 and 1.012. Considering the caveats mentioned above, the urine specific gravity can be used in place of urine osmolality to monitor hydration.

Bioelectrical impedance is a technique that allows estimation of total body water. The technique is based on the assumptions that only water can conduct electricity within the body, and that the body is a homogeneous, perfect cylinder with a uniform cross-sectional area. Bioelectrical impedance is determined by measuring the voltage change that occurs in relation to a reference standard when a small electrical current (800 micro amperes) is applied across the skin of the subject at a frequency capable of penetrating cell membranes (50 kHz). Total body water is estimated from the resistance component of the bioelectrical impedance using a regression equation for the population. The advantages of this technique are that it is noninvasive, safe, and rapid, and the equipment is portable and inexpensive. However, its use in neonates is limited. The considerable variations in the regression equation, confounded by factors such as gestational age, birthweight, postnatal age, and growth variations, make bioelectrical impedance less predictable in neonates.

Hematocrit measurement is at best a rough guide for monitoring neonatal hydration because several factors independent of hydration status can influence this measurement. These factors include blood loss clinically apparent blood loss as in gastrointestinal bleeding, occult blood loss as in intracranial hemorrhage, and iatrogenic blood loss related to blood sampling, hemolysis from blood group incompatibility and other causes, and transfusion of blood products. In the absence of these hematological factors, hemoconcentration may indicate dehydration, whereas hemodilution may indicate overhydration.

Indicator dilution is a technique that allows estimation of extracellular fluid volume. The commonly used indicators are inulin, sucrose, thiosulfate, and bromide. The technique is based on the assumption that the indicator, administered systemically, is distributed uniformly throughout the extracellular fluid (both plasma fluid and interstitial fluid) and that it is limited to the extracellular compartment with no leakage into the intracellular fluid. Limited diffusion of the indicator into the interstitial fluid and excessive diffusion of the
indicator into the intracellular fluid hamper the accuracy of these measurements in neonates. At best, indicator dilution provides a measure of only the extracellular fluid volume; to measure total body water, some other technique is necessary. For these reasons, indicator dilution is reserved mostly for investigational purposes.

Skin turgor is an extremely rough guide for monitoring hydration status in a neonate, particularly in the preterm infant. Wide variations in skin integrity, skin elasticity, and subcutaneous fat influence skin turgor interpretation. Severe dehydration, however, may be detectable by skin turgor. Conversely, skin edema may be a sign of overhydration. At best, skin turgor reflects late and severe manifestations of a change in hydration, or may be misleading in hypernatremic dehydration, making it less than ideal for monitoring neonatal hydration. A better clinical variable is the sequential measurement of body weight. Excessive weight loss may indicate dehydration. Conversely, excessive weight gain, more than 20g/kg per day, particularly in the absence of adequate energy intake, may indicate overhydration.

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

References:


Content Specification(s):

Know how to evaluate a neonate's state of hydration
Know how to recognize inadequate or excessive water intake by analyzing water intake, urine output, weight change, and serum sodium concentration
A 3,140-g male infant is delivered by vaginal route at 38 weeks of estimated gestational age. The maternal history is significant for oligohydramnios and fetal diagnosis of bilateral hydronephrosis. Abdominal ultrasonography of the infant reveals ascites, hydronephrosis, and perinephric urinoma (Figure 1).

**Figure 1: Abdominal ultrasonogram showing hydronephrosis (arrowhead), perinephric urinoma (short arrow), and ascites (long arrow). (Courtesy of Marta Hernanz-Schulman)**

Of the following, the MOST common cause of congenital hydronephrosis is:

1. posterior urethral valves
2. ureterocele
3. ureteropelvic junction obstruction
4. ureterovesical junction obstruction
5. urethral atresia

You selected 4, the correct answer is 3.

The infant in this vignette has congenital obstructive uropathy. Developmental anomalies of the kidney and urinary tract occur in approximately 5 per 1,000 live births; the incidence of congenital obstructive uropathy is estimated at 1 per 1,000 live births. The impairment of urinary flow characteristic of congenital...
obstructive uropathy can occur at any level (Figure 2)

**Figure 2: Sites of obstruction in congenital obstructive uropathy. (Courtesy of Terry Johnson)**

![Sites of Obstruction](image)

and may affect one or both sides. The hydronephrosis and resultant impairment of renal function are influenced by the site of obstruction (unilateral or bilateral) as well as its degree (partial or complete), nature (intermittent or persistent), and duration (late-onset or early-onset during pregnancy).

Ureteropelvic junction (UPJ) obstruction is the most common cause of congenital hydronephrosis, accounting for approximately 44% of cases. It occurs unilaterally in 60% to 90% of affected neonates; involves the left side in 60% of cases when unilateral; and is twice as common in males as in females. UPJ obstruction is classified as intrinsic, extrinsic, or secondary. Intrinsic UPJ obstruction may be the result of incomplete recanalization of the proximal ureter, abnormal structure or function of ureteral musculature, or intraluminal ureteral polyps or valves. Extrinsic UPJ obstruction results from compression of the proximal ureter by accessory or aberrant renal blood vessels. UPJ obstruction is considered secondary when a dilated and tortuous ureter resulting from vesicoureteral reflux occludes by kinking the proximal ureter. UPJ obstruction may be associated with other congenital anomalies (such as anorectal anomalies or congenital heart disease), syndromes (such as VACTERL syndrome), or other genitourinary malformations (such as duplex collecting system or horse-shoe kidney).

Although UPJ obstruction is sporadic in occurrence, familial cases have been reported, suggesting an autosomal dominant gene with variable penetrance. The diagnosis of UPJ obstruction can be suspected on abdominal ultrasonography. The characteristic findings include pelvic and caliceal dilatation with varying degrees of renal parenchymal involvement. The important negative findings include the absence of dilatation of the ureter and absence of bladder wall thickening as well as abnormal bladder emptying. The diagnosis of UPJ obstruction can be demonstrated with intravenous contrast urography and/or radionuclide scanning with or without diuretic enhancement.

Ureterovesical junction (UVJ) obstruction is the second most common cause of congenital hydronephrosis, accounting for approximately 21% of cases. It is
classified as primary or secondary. Primary UVJ obstruction may be the result of an intrinsic structural defect of the distal ureter or abnormal function of ureteral musculature that produces an aperistaltic segment. Primary UVJ obstruction occurs unilaterally in 75% to 85% of affected neonates and is fourfold more common in males than in females. Secondary UVJ obstruction is caused by extrinsic compression of the distal ureter by a thickened bladder wall resulting from other diseases such as posterior urethral valves (PUVs) or neurogenic bladder dysfunction. Secondary UVJ obstruction occurs mostly bilaterally and in males. UVJ obstruction is rarely associated with other congenital anomalies, syndromes, or other genitourinary malformations. The diagnosis of UVJ obstruction can be suspected on abdominal ultrasonography. The characteristic findings include dilatation and/or tortuosity of the ureter(s) with varying degrees of renal parenchymal involvement. The diagnosis of UVJ obstruction can be demonstrated with radionuclide scanning, intravenous contrast urography and/or voiding cystourethrography. In difficult cases, contrast antegrade pyelography may be necessary to differentiate between UVJ obstruction and other causes of urinary obstruction.

Posterior urethral valves are the third most common cause of congenital hydronephrosis, accounting for approximately 9% of cases. PUVs are obstructive membranous folds within the lumen of the prostatic urethra, believed to result from abnormal integration of wolffian ducts into the prostatic urethra during development of the urogenital sinus (Figure 3).

Figure 3: Voiding cystourethrogram showing posterior urethral valves, dilated prostatic urethra, and dilated ureters. (Courtesy of Marta Hernanz-Schulman)

There is no known genetic or familial predisposition. PUVs occur only in male infants and are the most common congenital cause of bladder outlet obstruction. Elevated voiding pressures associated with PUVs cause the bladder to become thickened, trabeculated, and noncompliant. These pressures are transmitted to the kidneys, causing a wide spectrum of progressive renal failure depending on the severity of urethral obstruction and bladder dysfunction. Urinary extravasation may occur from a forniceal rupture resulting in retroperitoneal (perinephric) urinoma or urinary ascites, as in the infant in this vignette. Among infants with PUVs, many are identified with prenatal ultrasonography. The characteristic findings include bilateral hydronephrosis, dilated ureters, thickened trabeculated bladder, elongated bladder neck, dilated proximal urethra, and oligohydramnios. The last may be associated with pulmonary hypoplasia. The postnatal clinical presentation of PUVs may include a palpable, distended bladder; poor urinary stream; and symptoms and signs of renal and pulmonary insufficiency. The diagnosis of PUVs can be confirmed with voiding cystourethrography, which in addition to the findings on prenatal ultrasonography, may show associated vesicoureteral reflux in 30% of cases.
Ureterocele, a cystic dilatation of the intravesical portion of the ureter, is a rare cause of congenital hydronephrosis, accounting for less than 5% of cases. Ureterocele is often associated with duplication of the urinary system and mostly involves the ureter draining the upper pole of the duplex kidney. Ureterocele occurs unilaterally in approximately 85% of affected neonates and, in contrast to other causes of congenital obstructive uropathy, is fivefold more common in females than in males. The diagnosis of ureterocele can be suspected on prenatal ultrasonography. The characteristic findings include ureteral dilatation with a cystic structure within the bladder. The diagnosis of ureterocele can be demonstrated with voiding cystourethrography.

Urethral atresia is a rare cause of congenital hydronephrosis, accounting for less than 1% of cases. Its clinical manifestations and pathophysiologic consequences mimic those of PUVs in their most severe form.

References:

Becker A, Baum M. Obstructive uropathy. Early Hum Develop. 2006;82:15-22

Chevalier RL. Perinatal obstructive uropathy. Semin Perinatol. 2004;124-131


American Board of Pediatrics Content Specification(s):

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

Know how to diagnose specific anatomic abnormalities of the urinary tract in infants
An 840-g male infant was born at 25 weeks' gestation. He developed respiratory distress syndrome, for which he received surfactant, and assisted ventilation. Maximum weight loss was 10% of birth weight by the 4th day. Small volume enteric feedings using expressed breast milk were initiated on day 3 and advancements were begun on day 12. Apnea and bradycardia spells were first noted on the 13th day and he was treated with caffeine starting on the 15th day. Full enteric feedings (~120 kcal/kg per day) with expressed breast milk fortified with a human milk fortifier to 24 kcal/oz were given by the 18th day. On the 25th day, his caretakers noted that no net weight gain had occurred during the previous week. Serum electrolytes revealed the following: sodium, 133 mEq/L; potassium, 5.1 mEq/L; chloride, 105 mEq/L; and CO₂, 17 mEq/L. Blood urea nitrogen was 5 mg/dL (1.7 mmol/L) and creatinine 0.5 mg/dL (44.2 μmol/L). Creamatocrit concentration in a mixed sample of expressed milk was 5.7%.

Of the following, the nutritional supplement MOST likely to improve weight gain is:

1. additional human milk fortifier
2. polymerized glucose
3. medium-chain triglycerides
4. protein
5. sodium chloride

You selected 5, the correct answer is 5.

The infant in the vignette has mild hyponatremia. Hyponatremia is a common occurrence among infants born before 34 weeks' gestation. The incidence is highest among those fed human milk and those exposed to diuretics, including caffeine. The sodium requirement for neonates is estimated to be approximately 4 to 5 mEq/kg per day. The sodium content of human milk is around 1.7 to 2.0 mEq per 120 kcal, and human milk fortifier increases sodium content by about 0.8 mEq per 120 kcal. This adds up to 2.5 to 2.8 mEq/kg per day of sodium for a premature infant receiving full enteral feedings, which represents around 60% of the daily requirement. Al-Dahhan and associates have shown that sodium balance is negative for infants of less than 34* (NB: This should be 24*; see *note below) weeks' gestation in the first weeks after birth due to increased renal and gastrointestinal losses. They also showed that supplementing sodium to a total of 4 to 5 mEq/kg per day from the 4th to the 14th day leads to positive sodium balance, less weight loss, better weight gain, and less hyponatremia, without undesirable side effects. This is consistent with studies of sodium-deprived immature animals that demonstrate growth failure in the face of otherwise adequate nutrition.

All of the current human milk fortifiers available provide less than 1 mEq sodium chloride per 120 kcal of human milk when fortified to 24 kcal/oz (Table).

Table. Additional Nutrient Contribution from Human Milk Fortifiers (HMF)*

In the early lactation period, the milk of mothers of premature infants has been shown to have higher sodium and protein concentrations than that of term infants. However, with time, the two populations become similar in sodium and protein concentrations in their milk. The nitrogen content is adequate for the growth of the term infant, but the premature infant requires a higher nitrogen accretion rate and, therefore, supplementation. The added need for protein is generally provided by a human milk fortifier during initial hospitalization.

The fat content of human milk has been shown to be variable. This variation occurs in a single expressed sample depending on whether it comes from the milk first expressed, the later part of the expressed sample, or the last part. The fat content also varies from mother to mother. Because the major variable in the total caloric content of milk is the fat content, the caloric content can be estimated reasonably by measuring the fat concentration. This can be done simply and conveniently using the creamatocrit. Wang and associates have shown that the energy content of human milk can be calculated as follows:

- Fresh milk: Energy (kcal/dL) = 5.99 x creamatocrit (%) + 32.5
- Frozen milk: Energy (kcal/dL) = 6.20 x creamatocrit (%) + 35.1

The creamatocrit measurement described in the vignette is average for human milk and corresponds to a caloric density of 20 kcal/30 mL.

Medium-chain triglycerides (MCTs) would provide more calories, but the caloric content in the infant in this vignette should have been adequate to promote growth without any supplement. Furthermore, MCTs are indicated primarily for infants who have trouble processing fats with higher chain lengths, including those with malabsorption and liver disease.

Likewise, the added calories that polymerized glucose would provide would not have been necessary because we are satisfied with the caloric content of the feedings. In addition, the protein content of the fortified human milk would also have been adequate for growth.

*The statement that "Al-Dahhan and associates have shown that sodium balance is negative for infants of less than 24 weeks’ gestation ..." should have indicated 34 weeks’ gestation. The editors of NeoReviewsPlus thank an astute reader who pointed out this typographical error and made a rational argument for an alternative preferred response. The reader also suggested alternative answers to the preferred response to consider:

1. increase caloric intake with additional breastmilk volume (not an option in the responses).
2. increase caloric intake with a higher caloric density formula or supplement; additional human milk fortifier could be added to the breastmilk and provide additional calories, protein, and a small amount of sodium. However, the protein and calories provided are usually adequate to support growth in extremely preterm infants.
3. provide hindmilk (higher caloric density) rather than whole breastmilk feeds (not an option in the responses).

If you notice a typographical error or wish to make an argument for an alternative to the preferred response, please submit your thoughts to lzanzola@aap.org. After review by the editorial board, addenda to questions will be added in the archived course materials. Thank you in advance for your observations.
Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:


Schanler RJ, Oh W. Composition of breast milk obtained from mothers of premature infants as compared to breast milk obtained from donors. *J Pediatr.* 1980;96:679-681


American Board of Pediatrics Content Specification(s):

Understand the changing requirements of sodium, potassium, chloride, calcium, and phosphorous by the neonate at various gestational ages
A 1-day-old female infant, whose birthweight was 3,260 g and gestational age 39 weeks, has an abdominal mass in the left flank. Maternal history is negative for diabetes or for complications during pregnancy, labor, and vaginal delivery. Clinical examination reveals a well-appearing child with no respiratory or cardiac symptoms, enlarged liver or spleen, or ascites. Blood pressure is normal.

Laboratory blood tests reveal the following:

- Hemoglobin 15.8 g/dL (9.9 mmol/L)
- Erythrocyte count 4.5×10⁶/mm³ (4.5×10¹²/L)
- Platelet count 234×10⁹/mm³ (234×10⁹/L)
- Leukocyte count 8.2×10⁹/mm³ (8.2×10⁹/L)
- Differential normal
- Blood urea nitrogen 9.0 mg/dL (3.3 mmol/L)
- Creatinine 0.3 mg/dL (27 μmol/L)

Urinalysis findings are normal. An abdominal computed tomography scan is obtained (Figure).

Figure: Abdominal computed tomography scan shows localized solid mass (arrows) measuring 4.3 cm in diameter in the left kidney. The mass contains no calcification.

Of the following, the MOST likely diagnosis in this infant is:

1. Mesoblastic nephroma
2. Neuroblastoma
3. Renal angiomyolipoma
The infant in this vignette has clinical and radiographic findings consistent with the diagnosis of congenital mesoblastic nephroma (CMN). CMN is the most common solid renal tumor that is diagnosed at birth or within the first 3 months of age. Two histologic types of CMN, classic and cellular, have been described.

In classic CMN, the kidney is enlarged and distorted by the tumor, which ranges from 0.6 to 9.0 cm in diameter. The tumor has a whorled appearance, similar to that of a uterine leiomyoma. Histologically, the tumor is composed of spindle-shaped cells that resemble primitive mesenchymal tissue with few or no neoplastic cells. The spindle cells have eosinophilic cytoplasm and elongated nuclei, and their mitotic activity ranges from zero to one mitotic figure per 10 high-power fields. In cellular CMN, the tumor is softer than in the classic type and shows areas of hemorrhage, necrosis, and cystic degeneration. Histologically, the tumor is composed of sheets of closely packed cells with scanty cytoplasm, interspersed with thin-walled vascular spaces, and their mitotic activity ranges from 10 to 30 mitotic figures per 10 high-power fields.

Congenital mesoblastic nephroma usually presents as an asymptomatic abdominal mass in the newborn or infant. Most cases of classic CMN are diagnosed at birth, whereas most cases of cellular CMN are diagnosed at 3 months of age or later. Tumors are often unilateral, more common on the left side. The diagnosis can be confirmed with abdominal ultrasonography, computed tomography, or magnetic resonance imaging. The clinical course of classic CMN typically is benign, with complete resolution after radical nephrectomy. In contrast, cellular CMN has a potential for local invasion, recurrence, and metastasis, which warrants close monitoring of these infants.

Neuroblastoma is the most common malignant tumor in neonates. It originates from neural crest cells that normally give rise to the adrenal medulla and the sympathetic ganglia. Histologically, the tumor is composed of small round cells with scant cytoplasm arranged in rosettes. Approximately 60% of infants with neuroblastoma present with an abdominal mass from tumors arising in the adrenal medulla or retroperitoneal sympathetic ganglia. In others, the tumors may arise anywhere along the sympathetic nervous system, especially in the posterior mediastinum, neck, pelvis, and paravertebral sites. The mediastinal neuroblastoma can cause respiratory obstruction or obstruction of the superior vena cava. The cervical sympathetic ganglion involvement may result in Horner's syndrome (pupillary constriction, eyelid ptosis, and facial anhydrosis). The pelvic neuroblastoma may mimic presacral teratoma. The paravertebral tumors can grow through intervertebral foramina and cause spinal cord compression.

A unique feature of neuroblastoma is increased urinary excretion of catecholamine metabolites, vanillyl-mandelic acid, and/or homovanillic acid. These metabolites occasionally result in flushing, sweating, and irritability. Likewise, vasoactive intestinal polypeptides, also produced by the tumor, can cause secretory diarrhea. Metastatic lesions of neuroblastoma may occur in neonates and are characterized by hepatomegaly, bluish subcutaneous nodules, and bone marrow infiltration. The diagnosis of neuroblastoma can be confirmed with abdominal ultrasonography, computed tomography, or magnetic resonance imaging, which typically shows a solid, sometimes cystic, suprarenal tumor with calcification. The absence of many of the clinical features described herein makes neuroblastoma an unlikely cause of abdominal mass in the infant in this vignette.

Renal angiomyolipoma manifests in late childhood, typically by the age of 10 years. It represents a mesenchymal tumor consisting of abnormal blood vessels with thickened walls and decreased elastic tissue, immature smooth muscle cells, and adipose tissue. Often multiple tumors of varying sizes are found in each kidney. Between 20% and 40% of angiomyolipomas occur in individuals with tuberous sclerosis complex, an autosomal dominant disorder with genetic locus heterogeneity and multisystem manifestations.
Renal vein thrombosis typically manifests with an abdominal flank mass from kidney enlargement, hematuria, albuminuria, and thrombocytopenia. Renal function impairment may be present in varying degrees, and the blood pressure may be elevated. Renal vein thrombosis is caused by venous stasis and decreased renal perfusion, and is therefore associated with asphyxia, dehydration, hypotension, cyanotic congenital heart disease, sepsis, and polycythemia-hyperviscosity. The latter is common among infants of diabetic mothers. Rarely, renal vein thrombosis may be caused by a heritable thrombotic disorder, such as factor V Leiden mutation, prothrombin G20210A mutation, hyperhomocysteinemia, and protein S deficiency. The diagnosis of renal vein thrombosis can be confirmed with Doppler ultrasonography, which shows renal enlargement and possibly visible thrombus in the renal vein and/or inferior vena cava. The absence of many of the clinical features, including hematuria, makes renal vein thrombosis an unlikely cause of abdominal mass in the infant in this vignette.

Wilms tumor is the most common renal malignancy in children, typically diagnosed between 1 and 5 years of age. The tumor arises from proliferation of nephrogenic rests—foci of abnormally persistent embryonic kidney cells—without normal differentiation into glomeruli and tubules. Wilms tumor frequently consists of an encapsulated solitary tumor occurring in any part of the kidney. Necrosis and hemorrhage within the tumor are common. Histologically, the tumor is composed of nephrogenic cells that demonstrate a glomerulotubular pattern; stromal cells that may differentiate into striated muscle, cartilage, fat, or bone; and epithelial cells that vary from primitive to well differentiated cells. Presence within the tumor of focal or diffuse anaplasia, which is characterized by marked variation in nuclear size with hyperchromatism and abnormal mitotic figures, represents a potentially invasive tumor.

Wilms tumor often involves both kidneys and is associated with renin-mediated hypertension. Approximately 10% of children with Wilms tumor have associated genetic syndromes and congenital anomalies. The genetic syndromes include WAGR syndrome (Wilms tumor, aniridia, genitourinary malformation, and mental retardation), Denys-Drash syndrome, and overgrowth syndromes such as hemihypertrophy and Beckwith-Wiedemann syndrome. The congenital anomalies include musculoskeletal abnormalities, skin lesions, and genitourinary anomalies. Wilms tumor frequently is associated with loss of heterozygosity at chromosome band 11p13 and/or 11p15, and resultant genetic mutations, specifically involving WT-1 gene, insulin-like growth factor II gene, and N-myc oncogene.

References:


American Board of Pediatrics Content Specification(s):
Know the etiology, clinical manifestations, laboratory features, and management of renal vein thrombosis

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

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Patient Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium, mEq/L (mmol/L)</td>
<td>125 (125)</td>
</tr>
<tr>
<td>Potassium, mEq/L (mmol/L)</td>
<td>7.8 (7.8)</td>
</tr>
<tr>
<td>Chloride, mEq/L (mmol/L)</td>
<td>110 (110)</td>
</tr>
<tr>
<td>Total calcium, mg/dL (mmol/L)</td>
<td>6.4 (1.6)</td>
</tr>
<tr>
<td>Ionized calcium, mg/dL (mmol/L)</td>
<td>2.6 (0.6)</td>
</tr>
</tbody>
</table>

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

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

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

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

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

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

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

In contrast to abnormal potassium concentrations, abnormal calcium concentrations rarely cause arrhythmias. Hypocalcemia is defined as a total serum calcium concentration lower than 7 mg/dL (1.75 mmol/L). Ionized calcium concentrations typically range from 4.4 to 5.4 mg/dL (1.10-1.36 mmol/L) but values of 3 mg/dL (>0.75 mmol/L) are often adequate. A prolonged QT interval is the most common EKG
finding in patients with hypocalcemia (Table). In contrast, infants with hypercalcemia, defined by ionized calcium concentration that exceeds 5.4 mg/dL (1.35 mmol/L), with or without an elevated total calcium concentration greater than 10.8 mg/dL (2.7 mmol/L), may display shortened QT intervals.

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

**Figure: Example of Possible Electrocardiogram in Infant in this Vignette**

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

**References:**


**American Board of Pediatrics Content Specification(s):**

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

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

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

You selected 1, the correct answer is 1.

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

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

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

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

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

**Figure 1A: Normal right kidney**

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

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

**Figure 2: Focal echogenic nodule in inferior vena cava consistent with thrombus**
Color-flow Doppler analysis demonstrates a decrease in the amplitude, or absence of venous signal, abnormal flow patterns in renal venous branches, or evidence of venous collateral development. Reverse diastolic blood flow is seen in the ipsilateral renal artery, owing to the increased vascular engorgement of the affected kidney (Figure 3).

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

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

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

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

References:

Chau AN, Sarwal MM. Acute renal failure management in the neonate. *NeoReviews*. 2005;6:e369-e376


http://emb.aap.org/courseprodv2/Index.asp[4/6/2012 3:00:05 PM]


**American Board of Pediatrics Content Specification(s):**

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

Understand the effects of various illness on renal function
A child is born at 28 weeks’ gestation and is now 7 days old, receiving mother's milk by gavage and parenteral nutrition. A capillary blood sample has a pH of 7.28, PCO₂ of 35 mm Hg, and a bicarbonate concentration of 16 mmol/L. Urine pH is 7.5 with an otherwise normal urinalysis. You suspect renal tubular acidosis of prematurity.

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

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

You selected 5, the correct answer is 5.

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

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

Neonates with renal tubular acidosis (RTA) of prematurity get better. Most premature infants can acidify their urine well by 6 weeks of age, but an adult level of control of acid-base status is not reached until 2 years.
Neonatal RTA can occur as any of a number of disorders unrelated to prematurity. These disorders are grouped into type 1 distal RTA, type 2 proximal RTA, and type 4 hyperkalemic RTA. A rare type 3 RTA has been described as a mixed proximal and distal disorder associated with osteopetrosis and abnormalities in carbonic anhydrase activity.

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

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

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

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

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

References:


American Board of Pediatrics Content Specification(s):

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

Be able to differentiate between proximal, distal, and transient renal tubular acidosis
A 34-year-old gravida 4 mother was in labor for 14 hours at term and noted to be getting tired. She was supported with an intravenous glucose infusion and, when the fetal heart tones demonstrated persistent variable decelerations, underwent cesarean section. A 2,450-g male infant was delivered with Apgar scores of 4 and 8 at 1 and 5 minutes, respectively. The physical examination findings were unremarkable and he was observed in a transition nursery until 6 hours of age when a blood glucose concentration obtained per nursery protocol was 27 mg/dL (1.5 mmol/L). The infant remained asymptomatic. He was given a nipple feeding and blood glucose concentration rose to 45 mg/dL (2.5 mmol/L) by 12 hours and above 50 mg/dL (2.8 mmol/L) after 24 hours. You conclude that the infant’s brain must have been metabolizing alternate fuels to maintain apparently normal neurologic function and consciousness.

Of the following, the source of MOST of the nonglucose energy used by the hypoglycemic brain is:

- acetoacetic acid
- beta-hydroxybutyric acid
- gamma-aminobutyric acid
- glutamic acid
- lactic acid

You selected 3, the correct answer is 5.

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

The infant in the vignette had asymptomatic transient hypoglycemia. He had at least three historical risk factors for transient hypoglycemia. These include suboptimal intrauterine growth, signs of perinatal distress, and a maternal glucose infusion around the time of birth. He was treated successfully with oral feedings. If he had any symptoms of hypoglycemia such as irritability, apnea, cyanosis, feeding problems, lethargy, or seizures, parenteral administration of glucose would have been preferred.

Glucose is the main source of energy for the brain in infants and in adults. When blood glucose concentrations are low, however, the brain makes several adaptations to compensate for the shortage of its primary source of energy. First, glucose transport into the brain and its cells is independent of insulin and is facilitated by specific protein transporters (especially GLUT1 and GLUT3). The rate of transport of glucose into brain cells depends on the concentration of the transporter proteins as well as the concentration of blood glucose. Hypoglycemia stimulates increased production of GLUT proteins.

Second, brain cells contain glycogen that can be hydrolyzed to glucose during systemic hypoglycemia, but these stores are limited.

Third, the brain at all ages can use alternative substrates for energy when glucose concentrations are low. The primary alternate substrate is lactic acid or lactate. In a neonatal animal model of systemic hypoglycemia, the brain switches from having 95% of its energy derived from glucose during normoglycemia to close to 60% of its energy from lactate during induced hypoglycemia. The brain can also derive energy from ketone bodies (especially acetoacetic acid and beta-hydroxybutyric acid), but ketone concentrations in brain and plasma remain low even during hypoglycemia and account for a small proportion of the energy produced. Blood lactate is elevated at birth in newborns whose mothers receive glucose infusions during labor (Figure).
Gamma-amino butyric acid (GABA) and glutamic acid (glutamate) are both neurotransmitters in the central nervous system. GABA is the main inhibitory neurotransmitter in term and near-term infants, but it may act as an excitatory neurotransmitter in extremely low-birthweight infants. Glutamic acid (glutamate) is the main excitatory neurotransmitter in the central nervous system. Both GABA and glutamate bind to ion channel receptors on the surface of neurons. They regulate the transmembrane passage of various ions and therefore cell functions. Neither neurotransmitter is used as a source of energy in the brain.

References:


American Board of Pediatrics Content Specification(s):

Know the fuels used for brain metabolism

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

Of the following, the substance with a HIGHER concentration in human milk than in cow milk is:

1. alpha-lactalbumin
2. beta-lactoglobulin
3. casein
4. fat
5. phosphate

You selected 4, the correct answer is 1.

Cow milk is great for newborn cows, but its differences from human milk make it unsuitable for newborn humans. Compared with human milk, cow milk has higher concentrations of protein, sodium, calcium, and phosphate, allowing for the more rapid growth in mass of the calf (Table). Most of the cow milk protein is in the form of casein. Beta-lactoglobulin is the main whey protein of cow milk, but is not found in human milk.

| Table. Composition of Human Milk and Cow Milk, per 100 mL |
|-----------------|-----------------|-----------------|
| **Constituent** | **Human Milk**  | **Cow Milk**    |
| Protein, g      | 0.9             | 3.3             |
| Fat, g          | 3.4             | 3.4             |
| Carbohydrate, g | 6.7             | 4.8             |
| Sodium, mEq     | 6               | 22              |
| Calcium, mEq    | 340             | 1,200           |
| Phosphate, mEq  | 150             | 930             |
| Osmolarity, mOsm/L | 260-300   | 280             |
| Casein:whey ratio | 40.60       | 80.20           |

Because of the relative immaturity of the human newborn in relation to other species, human milk has more immunoprotective mechanisms than cow milk. One example of this is the protein alpha-lactalbumin, in greater concentration in human milk than in cow milk. Alpha-lactalbumin, the major whey protein in human milk, has bactericidal, antiviral, and immunomodulatory activities. One of its modulating functions is to reduce release from monocytes of tumor necrosis factor alpha, and interleukins 1, 2, and 6. Another modulating function
is its ability to induce apoptosis in tumor cells. Human milk also has markedly more lactoferrin, lysozyme, and secretory immunoglobulin A, all with anti-infective functions, and all found only in trace amounts in cow milk.

The protein concentration in breast milk correlates with the growth rate of each species, from human (0.9 g/100 mL in mature milk, 2.5 g/100 mL in colostrum) to cow (3.3 g/100 mL in mature milk) to blue whale (13 g/100 mL).

Cow milk protein is 80% casein versus 40% in human milk. Casein is harder to digest by the human neonate than whey, and may not be the best protein to support human brain development because of its abundance of phenylalanine, methionine, and tyrosine residues.

Beta-lactoglobulin is the main whey protein in cow milk. Mouse milk and human milk do not contain beta-lactoglobulin, so it is understandable that human allergy to cow milk is based mainly on reactions to this cow protein.

The total fat concentration in cow and human milk is similar (3.4%-4% by weight), but humans have more essential fatty acids and polyunsaturated fatty acids, such as linoleic acid, linolenic acid, arachidonic acid, and docosohexanoic acid, which are needed for the creation of the brain, retina, and red cell membranes.

Both cow and human milk suspend casein in aggregates called micelles. The negative electrical charge presented on the outside of each micelle helps separate it from other micelles and prevent clumping. In the absence of fat globules, as in skim milk, the proteins may impart some color to milk. The size of the casein micelle (0.1 μm) is just enough to scatter light, especially the shorter blue wavelengths, and causes the bluish tint of skim milk or human colostrum. Riboflavin may give a greenish tint.

The large concentrations of phosphate and calcium in cow milk help construct the rapidly growing calf skeletal mass. When fed to human neonates, however, the excess phosphate of cow milk may cause severe hypocalcemia, tetany, and rickets.

Why not feed cow milk to the human newborn? Because there is the risk of hypocalcemia, essential fatty acid deficiency, cow protein allergy, and gastrointestinal blood loss. The American Academy of Pediatrics recommends that cow milk not be given for the first 12 months after birth.

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

References:


American Board of Pediatrics Content Specification(s):
Understand the differences in the nutritional composition of human milk and cow milk
You are evaluating a 3,000-g birthweight male infant who was born at a local hotel after a 39-week gestation. He was intubated in the field with a 2.5-mm endotracheal tube because of cyanosis and poor respiratory effort. The infant's mother is 28 years old and had prenatal care from an out-of-state clinic. She has three children at home. In the emergency room the 1-hour-old neonate is pink and breathing spontaneously. Heart rate is 140 beats per minute, respiratory rate is 20 breaths per minute, and blood pressure is 65/35 mm Hg. Oxygen saturation is 94% while in room air. The rest of the physical examination findings are unremarkable. Arterial blood gas findings and serum electrolyte concentrations are as follows:

<table>
<thead>
<tr>
<th>Laboratory Values</th>
<th>Patient Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood gas</td>
<td>7.46</td>
</tr>
<tr>
<td>pH</td>
<td>55</td>
</tr>
<tr>
<td>PCO₂, mm Hg</td>
<td>76</td>
</tr>
<tr>
<td>PO₂, mm Hg</td>
<td>42 mEq/L</td>
</tr>
<tr>
<td>HCO₃, mEq/L (mmol/L)</td>
<td>18 (18)</td>
</tr>
<tr>
<td>Base excess, mEq/L (mmol/L)</td>
<td>3.8 (3.8)</td>
</tr>
<tr>
<td>Electrolytes</td>
<td></td>
</tr>
<tr>
<td>Sodium, mEq/L (mmol/L)</td>
<td>130 (130)</td>
</tr>
<tr>
<td>Potassium, mEq/L (mmol/L)</td>
<td>2.8 (2.8)</td>
</tr>
<tr>
<td>Chloride, mEq/L (mmol/L)</td>
<td>82 (82)</td>
</tr>
</tbody>
</table>

Of the following, the mother or rescue squad in this case is MOST likely to report:

1. administration of sodium bicarbonate during resuscitation
2. eating disorder during pregnancy
3. hypoventilation following resuscitation
4. polyhydramnios during pregnancy
5. siblings with cystic fibrosis

You selected 4, the correct answer is 2.

Newborns maintain extracellular pH within a narrow range. The primary systems that maintain pH include the body's buffer systems, the lungs, and the kidney. In utero the placenta is primarily responsible for maintaining extracellular pH.

The infant in this vignette has metabolic alkalosis characterized by elevations in blood pH (>7.45), bicarbonate ([HCO₃] >24 mEq/L [24 mmol/L]), and base excess (>6 mEq/L [6 mmol/L]). Metabolic alkalosis occurs by one of three mechanisms: loss of acid, such as hydrochloric acid from frequent emesis; ingestion of excess base, such as excessive HCO₃ administration during resuscitation; or
contraction of volume by loss of fluids containing more chloride than HCO₃. Metabolic alkalosis within hours of birth is uncommon. The most common causes of metabolic alkalosis in neonates are listed in the Table.

<table>
<thead>
<tr>
<th>Table. Common Causes of Metabolic Alkalosis in Neonates*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid loss</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Chloride deficiency</td>
</tr>
<tr>
<td>Administration of alkali</td>
</tr>
</tbody>
</table>

* Adapted from Martin and Fanaroff (2006).

The kidney excretes excess alkali efficiently; however, extracellular volume depletion with chloride or potassium loss can limit HCO₃ excretion and result in metabolic alkalosis. During volume depletion a decrease in glomerular filtration rate reduces the filtered load of HCO₃ and much of the HCO₃ that is filtered is reabsorbed in the proximal tubule in conjunction with avid sodium reabsorption. Volume depletion also increases aldosterone release through the renin-angiotensin system, which increases distal renal tubular absorption of sodium and excretion of both hydrogen ions and potassium. Potassium depletion maintains metabolic alkalosis by stimulating renal ammonia production and reducing movement of hydrogen ions out of the cell.

Maternal and fetal fluid and electrolyte homeostasis are intertwined. Maternal dehydration can result in a reduction in amniotic fluid, which returns to normal with maternal rehydration. Transplacental movement of chloride is bidirectional and almost symmetrical. Although a fetus can maintain normal or near-normal potassium concentrations, even in the face of maternal hypokalemia through the adenosine triphosphatase pump, significant maternal hypokalemia can cause fetal hypokalemia.

Eating disorders, such as anorexia nervosa with bulimia, are often associated with chronic vomiting that can lead to hypochloremic metabolic alkalosis with hypokalemia. Several authors have reported significant hypochloremic metabolic alkalosis, as seen in the infant in this vignette, in neonates born to mothers with chronic metabolic alkalosis from eating disorders. Replacement of fluid and chloride effectively corrects the metabolic alkalosis in the neonates.

A single dose of sodium bicarbonate administered during resuscitation has only a transient effect on the acid-base equilibrium because of the prompt renal response. The markedly elevated serum HCO₃ concentration seen in the infant in this vignette would have required a large dose of intravenous sodium bicarbonate to acutely raise the serum HCO₃ concentration from a normal serum concentration of approximately 20 mEq/L (20 mmol/L). A conservative method of determining the amount of sodium bicarbonate required to treat a base deficit is 0.3 × base deficit × weight (kilograms). In the infant in this vignette, to increase the base excess to 18 mEq/L (mmol/L) would have required at least 16 mEq of exogenous sodium bicarbonate during the resuscitation.

The infant in this vignette had hypochloremic, hypokalemic metabolic alkalosis that was partially compensated. Compensation of acidosis or alkalosis is either respiratory or renal. During metabolic alkalosis, an increase of 1 mEq/L (1 mmol/L) of HCO₃ should result in a 0.2 to 0.9 mm Hg increase in PCO₂. The infant in this vignette had at least a 20 mEq/L (20 mmol/L) increase in serum HCO₃ that resulted in an increase in the PCO₂ of approximately 15 mm Hg, assuming a normal PCO₂ of 40 mm Hg. This compensation is within the range of the expected respiratory compensation of an underlying metabolic alkalosis.

If the infant had acute respiratory acidosis, from pulmonary disease or hypoventilation during resuscitation, for each 1 mm Hg increase in PCO₂ serum HCO₃ should increase by 0.1 mEq/L (0.1 mmol/L). The infant’s serum HCO₃ would have risen by at the most 1.5 to 2 mEq/L (1.5-2 mmol/L) above normal. Acute hypoventilation and subsequent acute respiratory acidosis could not explain this
Polyhydramnios is seen in mothers of neonates with neonatal Bartter syndrome, which is rare. The primary abnormality in Bartter syndrome is defective chloride reabsorption in the thick ascending limb of the loop of Henle caused by inactivating mutations for genes responsible for regulating electrolyte movement in the ascending limb. A fall in sodium chloride reabsorption results in volume depletion, and enhanced secretion of renin and thus aldosterone. The combination of increased distal flow of sodium chloride and hyperaldosteronism promotes potassium and hydrogen secretion and the development of hypokalemic metabolic alkalosis. Neonatal Bartter syndrome is associated with severe hypercalciuria and nephrocalcinosis, which can be detected in utero. Polyhydramnios, the consequence of polyuria, often leads to premature delivery between 27 and 35 weeks' gestation. Prenatal diagnosis of neonatal Bartter syndrome is based on the striking features of polyhydramnios in a healthy mother and a morphologically normal fetus. The polyuria continues after birth, can last for 4 to 6 weeks, and can be associated with severe fluid and electrolyte abnormalities. The long-term clinical outcome is frequently complicated by nephrocalcinosis and renal failure. Neonatal Bartter syndrome is associated with a distinctive appearance that is characterized by a thin constitution and a triangular facies with a full forehead, large eyes, protruding pointed ears, and a pouting expression from drooping corners of the mouth. The infant in this vignette does not have these features.

Metabolic alkalosis can occur in cystic fibrosis beginning during infancy. Among infants with cystic fibrosis, loss of electrolytes in the sweat leads to volume contraction, hypokalemia, and hyper-reninemia. Because salt losses are limited during the neonatal period, cystic fibrosis does not present with metabolic alkalosis during the first week after birth.

References:

Stulc J. Placental transfer of inorganic ions and water. Physiol Rev. 1997;77:805-836

American Board of Pediatrics Content Specification(s):

Know the role of the placenta in the energy metabolism of the fetus, including transfer of glucose, electrolytes, and amino acids to the fetus
Recognize the clinical and laboratory manifestations of electrolyte abnormalities in the neonate
Understand the etiology of metabolic acidosis and metabolic alkalosis in infants
Recognize the clinical and laboratory manifestations of metabolic acidosis and metabolic alkalosis in infants
During routine prenatal ultrasonography at 22 weeks’ gestation, fetal ascites is identified. No other areas of fluid accumulation (i.e., no cutaneous edema, pericardial or pleural effusions) or structural abnormalities are found. The fetal echocardiogram is normal. Results of maternal serum and amniotic fluid testing for syphilis, toxoplasmosis, parvovirus, rubella, cytomegalovirus, coxsackievirus, and herpes simplex virus are negative. Maternal blood type is B positive with an antibody negative screen and the karyotype is normal.

Of the following, the MOST likely cause for the isolated ascites in this fetus is:

- arrhythmia
- laryngeal atresia
- meconium peritonitis
- metabolic storage disease
- posterior urethral valves

You selected 5, the correct answer is 5.

An infectious or urinary cause is found in approximately one third of fetuses with isolated ascites. Because findings on maternal and amniotic fluid testing for infections are negative, the fetus in this vignette most likely has urinary ascites induced by posterior urethral valves. As time progresses, the fetus in this vignette is at risk of developing a distended bladder with a thickened trabeculated wall. In severe cases, oligohydramnios and/or pulmonary hypoplasia may result. Other obstructive urinary tract abnormalities such as ureteroceles, ureteropelvic junction obstruction, and primary obstructive megaureter, as well as cloacal anomalies, may be associated with fetal ascites, but are less common than posterior urethral valves. Adzick and colleagues reported that 12 of 44 fetuses with urinary tract obstruction had urinary extravasation that was either diffuse (urinary ascites) or localized (perirenal urinoma).

Possible mechanisms for the development of urinary ascites include transudation through the bladder wall; rupture of the fetal bladder; and in cloacal dysgenesis, urine escaping from the hydrocolpos through the fallopian tubes into the abdominal cavity. The formation of urinary ascites in utero may be beneficial because it ameliorates the degree of renal dysplasia by decompressing the high-pressure–obstructed urinary tract.

In addition to urinary tract obstructions, intrauterine infections, such as syphilis, toxoplasmosis, parvovirus, rubella, cytomegalovirus, coxsackievirus, and herpes simplex virus are common causes of isolated fetal ascites. Possible mechanisms include fetal anemia from suppression of erythrocyte production, fetal myocarditis, or fetal hepatitis. Another possible mechanism for infection-induced ascites is
from intrauterine cardiac failure because of direct viral injury to cardiomyocytes. Structural cardiac abnormalities and arrhythmias less commonly lead to isolated fetal ascites by direct cardiac tissue injury. Rather, cardiac defects more commonly lead to ascites because of increased capillary permeability and generalized fluid overload after congestive heart failure.

Laryngeal atresia is a rare congenital anomaly that may present with intrauterine ascites and voluminous lungs. Infants with laryngeal atresia probably develop ascites by obstructing venous return because of the increased intrathoracic pressure created by the overdistended lungs. Resultant esophageal pressure may decrease fetal swallowing of amniotic fluid and lead to polyhydramnios. Other causes of airway obstruction, such as congenital cystic adenomatoid malformation or bronchopulmonary sequestration, may also result in fetal ascites and/or polyhydramnios.

Meconium peritonitis occurs after a small bowel perforation complicating intestinal stenosis, intestinal atresia, or volvulus. The abdominal fluid collection from spillage of small bowel contents is sterile. In addition to the ascites found in approximately 64% of cases, fetuses with meconium peritonitis often have other ultrasonographic findings such as intra-abdominal calcifications (86%), polyhydramnios (71%), and bowel dilatation (46%). Meconium peritonitis is also found in fetuses with cystic fibrosis or a viral infection.

Some metabolic storage diseases can lead to hepatic insufficiency resulting in shifts in colloid osmotic pressure and/or portal hypertension, which, in turn, may result in fetal ascites. Fetuses with Gaucher disease, gangliosidosis, mucolipidosis, mucopolysaccharidosis, or carnitine deficiency may present with ascites.

In addition to urinary tract obstruction, cardiac failure, small bowel perforation, and hepatic insufficiency, two other mechanisms have been implicated in the intrauterine development of fetal ascites. Abnormal lymphatic drainage from a transient blockage or abnormal development of the local lymphatic system can lead to chyloperitoneum. In addition to the distortion of intrahepatic architecture and resultant portal hypertension from the extramedullary erythropoiesis observed in fetuses with anemia, decreased plasma oncotic pressure in anemic fetuses may also lead to isolated ascites. Sometimes, the cause of isolated fetal ascites is not identified and the ascites may resolve spontaneously; other cases may progress to hydrops fetalis.

References:


Morrison PJ, Macphail S, Williams, D, et al. Laryngeal atresia or stenosis presenting as second-trimester fetal ascites—diagnosis and pathology in three independent cases. Prenat Diagn.
American Board of Pediatrics Content Specification(s):

Identify the etiology and clinical manifestations of neonatal ascites

Know the differential diagnosis and the plan of management of a fetus with nonimmune hydrops
You are called to the operating room for an emergency cesarean section of a mother who just had a seizure. The obstetrician hands you a full-term hypotonic infant making only weak respiratory efforts. After an appropriate resuscitation, the infant is pink with a normal heart rate and perfusion, but still somewhat hypotonic. Over the next few hours, the weakness is accompanied by poor feeding, apnea, decreased bowel sounds, and no meconium production. Skin turgor, urine output, and serum glucose concentration are normal. Among other diagnoses, you suspect an electrolyte abnormality.

Of the following, the MOST appropriate treatment for this infant is:

1. calcium, insulin, and glucose
2. extra fluids, calcium, and loop diuretics
3. extra free water
4. normal saline, loop diuretics, hydrocortisone
5. phenylbutyrate and benzoate

You selected 3, the correct answer is 2.

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

The most likely electrolyte abnormality in this infant is hypermagnesemia. The treatment most likely to benefit a symptomatic child with hypermagnesemia includes fluids, calcium, and loop diuretics. The other treatment choices are important for cases involving hyperkalemia, hypernatremia, hypercalcemia, or hyperammonemia.

Magnesium ion passes freely across the placenta. Equilibration of maternal and fetal serum concentrations occurs with a 2-hour delay. The normal serum magnesium concentration is between 1.6 mEq/L (1.6 mmol/L) and 2.1 mEq/L (2.1 mmol/L). The most common cause of hypermagnesemia in the newborn is maternal administration of magnesium for preeclampsia, or eclampsia as in this vignette. Other causes of hypermagnesemia include renal failure, rhabdomyolysis, hypothyroidism, and excess magnesium administered by antacids, laxatives, or parenteral nutrition.

Signs and symptoms of hypermagnesemia vary by serum magnesium concentration, and neonates often are affected at lower concentrations than children or adults (Table).
Serum concentrations correlate only approximately with tissue levels and clinical signs. Signs in the neonate can last from hours to days. The elimination half-life of magnesium in premature infants with adequate urine output may be as long as 40 hours. Changes on the electrocardiogram may include sinus bradycardia; prolonged PR, QRS, and QT intervals; atrial fibrillation; heart block; and asystole. Signs and symptoms can be potentiated by the addition of weak neuromuscular blocking agents, such as gentamicin. Death has been reported in some cases, mainly from cardiac arrhythmias.

Treatment of hypermagnesemia in a neonate with good urine output requires supportive care, as well as the removal of any intravenous source of the magnesium. Severe symptomatic cases, especially those with cardiac arrhythmias, may benefit from supplemental fluid administration and loop diuretics to promote magnesium excretion. Intravenous calcium acts as a temporary magnesium antagonist and may reverse arrhythmias and electrocardiographic abnormalities. Exchange transfusion and dialysis have been used successfully in severe cases.

Calcium, insulin, and glucose are used to treat severe hyperkalemia. Bicarbonate and cation exchange resins have also been used. Weakness, ileus, and apnea, as in this vignette, are not common signs of hyperkalemia.

Extra free water in the total daily fluids, as the main treatment mode, is important in the treatment of hypernatremia. Hypernatremic neonates are often hypovolemic, and so may also require volume expanders such as normal saline. Calcium and diuretics, potentially useful for the infant in this vignette with hypermagnesemia, are not ordinarily part of the treatment of a neonate with hypernatremia. Clinical signs of hypernatremia may include irritability and hyperpnea, not present in this vignette.

Normal saline, loop diuretics, and hydrocortisone are part of the treatment of hypercalcemia. Hypercalcemia may present with poor feeding, lethargy, and constipation, as in this vignette. It is unlikely to present in the delivery room, and even less likely than hypermagnesemia, given the probable treatment of the mother with magnesium after her seizure.

Benzoate and phenylbutyrate are useful agents for the treatment of hyperammonemia. They provide alternative pathways for the excretion of waste nitrogen. Benzoate is transaminated from glycine to form hippuric acid, eliminating one nitrogen in the urine. Phenylbutyrate causes one glutamine to form phenylacetyl-glutamine, eliminating two nitrogens. Although transient hyperammonemia may manifest as hypotonia on the first day after birth, as in this vignette, it is unlikely to manifest in the delivery room.

**Table. Selected Signs and Symptoms of Hypermagnesemia**

<table>
<thead>
<tr>
<th>Serum Concentration, mEq/L</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-8</td>
<td>Sedation</td>
</tr>
<tr>
<td></td>
<td>Facial flushing</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Electrocardiographic changes</td>
</tr>
<tr>
<td>5-15</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td></td>
<td>Apnea</td>
</tr>
<tr>
<td></td>
<td>Ileus</td>
</tr>
<tr>
<td></td>
<td>Loss of deep-tendon reflexes</td>
</tr>
<tr>
<td></td>
<td>Weakness</td>
</tr>
<tr>
<td></td>
<td>Coma</td>
</tr>
<tr>
<td>20-30</td>
<td>Cardiac arrest</td>
</tr>
</tbody>
</table>

References:


Leone CR, Barbosa NO. Magnesium and perinatal asphyxia. *NeoReviews.* 2007;8:e387-e393


**American Board of Pediatrics Content Specification(s):**

Understand the etiology, clinical manifestations, and approach to therapy of hypermagnesemia

Recognize and diagnose the metabolic disorders that lead to coma

Know how to recognize inadequate or excessive water intake by analyzing water intake, urine output, weight change, and serum sodium concentration

Understand the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of the urea cycle
During rounds with the residents in the newborn nursery, you are asked to see a full-term infant born to a 25-year-old white mother. The mother's pregnancy was uncomplicated. Because of previous pregnancy losses, chorionic villus karyotype was performed and parents were told it was normal. Prenatal ultrasonography performed at 18 weeks' gestation was normal, but parents did not want to know the predicted fetal sex from either study. The infant's abnormal physical finding is seen in the Figure. The chorionic villous sampling result was 46,XY, according to the prenatal records.

Figure

Of the following, the statement that MOST accurately describes details about the evaluation and management of the infant is that:

1. circumcision is recommended in the neonatal period
2. cryptorchidism increases risk of intersexuality
3. meatal obstruction is common
4. renal ultrasound should be obtained
5. surgical repair is usually done by 2 months of age

You selected 2, the correct answer is 2.
Hypospadias, following cryptorchidism, is the second most common genital abnormality in male infants, occurring with an incidence of 0.3% to 0.8% of live births. The incidence of hypospadias has doubled since the 1960s for unknown reasons.

The anatomic location of approximately 87% of hypospadias anomalies are glandular or coronal, 10% are penile, as in the neonate in the vignette, and 3% are penoscrotal or perineal. The anatomy of a penis with hypospadias is similar to that of a normal penis except on the ventral aspect where the foreskin and urethral spongiosum are absent.

Formation of the male external genitalia is a complex process involving genetic programming, cell differentiation, hormonal signaling, enzyme activity, and tissue remodeling. Hypospadias occurs because of an arrest of urethral formation. The urethral opening can be found anywhere along the ventral midline from the perineum to the glans depending on the time during embryogenesis when fusion of the urethral folds ceases. The exact cause of hypospadias is still not known in most cases. In fewer than 5% of patients, hypospadias can be attributed to defects in androgen metabolism (5-alpha-reductase type II deficiency), androgen receptors, or known genetic factors.

Hypospadias is usually identified during the initial examination. The penile raphe is displaced from the midline and the glans tilts downward (chordee). The meatus may be the size of a pinhole but is usually not obstructed. Micturition from the ventrally placed meatus confirms the diagnosis.

Anomalies that may accompany hypospadias include meatal stenosis, hydrocele, inguinal hernia, and cryptorchidism. Evaluation of a newborn with hypospadias may include the following:

- a family history of hypospadias, endocrine, or intersex problems
- a history of possible maternal progestin or estrogen exposure
- examination to evaluate the hypospadias (urethral meatus location, chordee, scrotal folds, phallus length, presence of gonads)
- identification of other congenital abnormalities
- radiographic studies of the kidneys and pelvis if the hypospadias appears to be part of a malformation syndrome

A male infant without cryptorchidism, as in this vignette, who has an isolated urethral opening on the glans or shaft of a normal-sized phallus rarely has a dilemma of gender identity; evaluation for endocrinopathies or intersex disorders are generally not required. Cryptorchidism is defined by the failure of one or both testes to descend completely into the scrotum (at least 4 cm below the pubic crest in a term infant weighing more than 2.5 kg).

Disorders resulting in ambiguous genitalia, such as congenital adrenal hyperplasia in a virilized female, must be considered if the gonads are not palpable and especially if the defect is low on the shaft or scrotum. Congenital adrenal hyperplasia can yield marked virilization making chromosomal diagnosis essential in all cases of ambiguity with cryptorchidism. If the gonads are not palpable in a male (46,XY) neonate with hypospadias, risk of intersexuality approaches 50%. The likelihood of intersexuality is also increased among male neonates whose meatus is positioned in the scrotum or perineum.

Because cryptorchidism may result from insufficient androgen, it is not surprising that hypospadias and intersex disorders may coexist. Approximately 8% of boys with hypospadias have at least one undescended testicle with the incidence varying with the severity of hypospadias. Only 5% of genetically male neonates with distal hypospadias, as in this vignette, have cryptorchidism, compared with 32% of neonates with proximal lesions.

Hypospadias, often associated with cryptorchidism, occurs in a number of syndromes. The neonate in the vignette has mild hypospadias, defined as glandular or penile, and no other dysmorphic features. Isolated penile hypospadias without other genital abnormalities or dysmorphic features is unlikely to be associated with a chromosomal abnormality.
In the past, boys with hypospadias routinely underwent intravenous pyelography, voiding cystourethrography, and renal ultrasonography as part of their evaluation. However, even with severe hypospadias the arrest in development is after the eighth week of gestation, when the urethral bud joins the metanephros. The likelihood of detecting an upper urinary tract anomaly is low, with clinically significant abnormalities found in fewer than 5% of neonates with hypospadias. Radiographic studies may be helpful in boys who develop a urinary tract infection or those whose anomaly is part of a malformation syndrome.

The only treatment for hypospadias is surgical repair of the defect. The goal of surgical correction is to create a penis with normal function and appearance. Because the spectrum of severity is wide, ranging from glandular to perineal, and the shaft may be straight or significantly curved, it is not surprising that more than 300 operative techniques for hypospadias repair have been described. Depending on the severity of the lesion, surgical techniques can be applied sequentially or in combinations beginning at 6 months in an otherwise healthy newborn. In severe cases requiring a two-stage procedure, the second stage is performed at least 6 months after the initial repair. Neonatal circumcision is contraindicated in such cases because foreskin tissue is often used in the repair process.

References:


American Board of Pediatrics Content Specification(s):

Know how to evaluate and manage an infant with hypospadias and epispadias

Know how to evaluate and manage an infant with cryptorchidism

Know the etiology and diagnosis of an infant with ambiguous genitalia, including congenital adrenal hyperplasia
Physiologic jaundice has been defined as bilirubinemia of the newborn in which the hour-specific bilirubin concentrations do not exceed 2 standard deviations above the population mean. However, unlike serum potassium or hemoglobin concentrations, bilirubin concentrations for a defined population depend on specific genetic and environmental factors resulting in a unique physiologic jaundice curve. Population mean curves are presented below for two representative populations.

Of the following, the pair of categories BEST represented by the graph is:

<table>
<thead>
<tr>
<th>Response</th>
<th>Population A</th>
<th>Population B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asian-American</td>
<td>African-American</td>
</tr>
<tr>
<td>2</td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>3</td>
<td>Formula-fed</td>
<td>Breastfed</td>
</tr>
<tr>
<td>4</td>
<td>Term</td>
<td>Postterm</td>
</tr>
<tr>
<td>5</td>
<td>White</td>
<td>Black</td>
</tr>
</tbody>
</table>
Physiologic jaundice (nonpathologic jaundice or physiologic bilirubinemia) is the typical rise and fall in serum bilirubin concentration seen in newborn infants in the first week after birth. Before birth, the fetus produces bilirubin, detoxifies (conjugates) it, and excretes it through the biliary tree into the fetal gut. A portion of conjugated bilirubin is then hydrolyzed (deconjugated) and reabsorbed from the fetal intestines. The placenta is responsible for clearing bilirubin from the fetal circulation. Bilirubin, however, does accumulate in the meconium before birth.

Physiologic jaundice results from a temporary imbalance between bilirubin production and excretion. Production is enhanced in the newborn because the half-life of the red blood cell is shorter (~90 days) than the 120-day life span of the adult red blood cell. Bilirubin excretion depends on uptake and conjugation (detoxification) of bilirubin. Uptake of bilirubin into the hepatocyte is facilitated by a cytosolic receptor-carrier protein called ligandin, which has a higher affinity for bilirubin than serum albumin. Conjugation is effected by bilirubin-UDP-glucuronosyl transferase (UGT), an enzyme that is bound to the endoplasmic reticulum. In normal newborns excretion is somewhat hampered by (1) a likely reduction in ligandin and (2) a moderate reduction in bilirubin-UDP-glucuronosyl transferase A1A (UGT). In addition, normal infants exhibit an enterohepatic circulation of already excreted conjugated bilirubin that is deconjugated by a glucuronidase enzyme in the newborn gut and then reabsorbed.

All of the aforementioned conditions combine to raise the serum bilirubin concentration from about 2 mg/dL (34 μmol/L) at birth to about 6 mg/dL (103 μmol/L) by 2 to 4 days of age in white and African-American infants. Asian-American neonates tend to reach higher bilirubin values (up to 10-14 mg/dL [171 to 239 μmol/L]) a bit later in the first week possibly because of a higher prevalence of UGT gene promoter variations and inherited red blood cell abnormalities. The serum bilirubin concentrations of normal newborns tend to return to adult concentrations by 7 to 10 days of age as feeding increases, UGT activity and ligandin concentrations increase, and the enterohepatic recirculation of bilirubin decreases.

The physiologic jaundice curves for girls and boys are very similar, as are those for white infants compared with black infants. Postterm infants tend to have lower peak serum bilirubin concentrations, possibly because of an accelerated development of UGT activity.

The physiologic jaundice curve, however, is not the same for formula-fed infants as for breastfed infants. Breastfed infants tend to have higher peak bilirubin concentrations than formula-fed infants. This might be because of reduced feeding volumes and the presence of active β-glucuronidase (which hydrolyzes conjugated bilirubin and enhances the reabsorption of bilirubin) in human milk.

References:


**American Board of Pediatrics Content Specification(s):**

Understand the course of physiologic jaundice of the newborn infant
A female infant is born at 38 weeks' gestation via repeat cesarean section to a 34-year-old woman with two healthy children. The pregnancy was normal. Membranes ruptured at home during early labor. Birthweight is 3.8 kg, and Apgar scores are 8 and 9 at 1 and 5 minutes, respectively. Physical examination reveals persistent tachypnea and a nontender, rounded, full abdomen. There are no abdominal masses, organomegaly, or visible bowel loops. Chest radiograph is normal except for poor inflation of the lungs. Abdominal radiograph shows loops of bowel of normal size collected into the center of the abdomen on the supine view (Figure). A sample of abdominal fluid is obtained and sent to the laboratory for studies.

Of the following, the measurement MOST likely to assist in identifying the cause of this infant's condition is:

- creatinine concentration
- eosinophil count
- glucose concentration
- sodium concentration
- specific gravity

You selected 2, the correct answer is 1.
Ascites is an abnormal collection of fluid in the intraperitoneal cavity. It is an uncommon finding in newborn infants. When present, the fluid may represent a transudate or an exudate. The "common" types of isolated neonatal ascites are chylous ascites, presumably associated with congenital malformations of lymph drainage, and abdominal fluid secondary to perforation of the gastrointestinal tract, urinary tract, or biliary tract. However, sepsis, congenital infection, congenital heart disease, ovarian cyst, pancreatic cyst, or severe liver disease including storage disease can also result in ascites. Rarely, ascites has been caused by erosion of an umbilical vein catheter into the peritoneum.

Most infants with isolated ascites have abdominal distention at birth. In some cases, neonatal ascites first appears after birth. In any case, the fluid may be under enough pressure to interfere with breathing. Infants with ascites occurring as part of a more generalized fluid retention problem such as hydrops fetalis are not included in this discussion of ascites.

Ascites may be identified on fetal ultrasonography. After delivery, radiographic signs of ascites include abdominal distention often without distention of bowel loops. The abdomen appears more or less opaque, sometimes with separation of loops of bowel. Often gas-containing bowel is seen in the center of the abdomen on a supine view. The liver appears denser than the background opacity of the abdomen. Abdominal ultrasonography can also identify free fluid.

Urinary ascites is a common form of ascites and results from lower urinary tract obstruction at the lower ureter, the bladder, or the posterior urethra. Such obstruction often results in perforation of the upper urinary tract. A voiding cystourethrogram is helpful in identifying the point of obstruction. The infant in this vignette had a ureterocele obstructing the ureter and a resultant tear in the caliceal fornix. Urinary ascites is often accompanied by systemic acidosis, elevated blood urea and creatinine concentrations, electrolyte abnormalities, and possibly a history of oligohydramnios. Severe bilateral obstruction can lead to Potter syndrome. Most affected infants are male. Elevated creatinine in the ascitic fluid is diagnostic of this form. Urinary drainage and correction of the obstruction are the mainstays of management along with correction of the fluid and electrolyte imbalances. Despite the apparent success of this management, some patients may develop end-stage renal disease before adolescence.

In utero gastrointestinal tract perforation can present as neonatal ascites (also known as meconium ascites). Diagnostic clues include:

- calcifications in the abdomen
- abdominal mass or distended bowel
- history of polyhydramnios

The diagnosis is confirmed when meconium is found in the ascitic fluid. Management includes abdominal surgery to find and correct the obstruction and perforation. These infants should undergo an evaluation for cystic fibrosis because meconium peritonitis can be the first sign of cystic fibrosis.

Chylous ascites is the most common neonatal form of ascites, and it is often difficult to manage. With chylous ascites, the peritoneal fluid can be clear initially, but it becomes cloudy or milky once oral feedings are started. This fluid contains a high concentration of triglycerides especially after feeding and a high lymphocyte count (>75% of peritoneal cells). The eosinophil count is not affected. Surgical causes of chylous ascites include malrotation, volvulus, and neoplasia. Most cases, however, are thought to be associated with lymphatic malformations. Treatment consists of a diet rich in medium-chain triglycerides or intravenous alimentation allowing for bowel rest for 2 to 4 weeks. Prognosis is usually good. However, intractable cases have been treated with peritoneovenous shunts.

Biliary ascites is also a rare form of neonatal ascites. It is usually associated with mild
conjugated hyperbilirubinemia. These infants often have feeding problems in addition to their ascites. The diagnosis is confirmed if the ascitic fluid has an increased concentration of bilirubin. Nuclear medicine imaging of the biliary tree can demonstrate free radionuclide outside the biliary tree and intestines. Drainage of the biliary tree through a cholecystostomy tube is usually effective in allowing the perforation to heal.

Measuring electrolytes, specific gravity, or glucose concentration in ascitic fluid does not help to identify the underlying cause in most cases. Hyponatremia is common regardless of the cause. A high glucose concentration, along with the presence of a central venous catheter, would indicate possible migration of the catheter into the peritoneum. The infant in this vignette did not have such a catheter.

References:


American Board of Pediatrics Content Specification(s):

Identify the approaches to diagnosis and management of neonatal ascites
You are called in to evaluate a full-term newborn. The mother's pregnancy and delivery were uncomplicated. During your examination of the rectum and genitalia you note the abnormalities shown in Figure 1 (courtesy of Casey Calkins, MD, Milwaukee, Wis).

The infant's physical examination findings are normal. You observe meconium coming from the base of the scrotum (Figure 1, Arrow). A red rubber catheter placed in the rectal opening can only be advanced 0.5 cm. You discuss evaluation plans with the infant's parents and the importance of quickly determining the reason for meconium leaking from the scrotum.

Of the following, the INITIAL diagnostic study in this infant would be:

1. abdominal ultrasonography
2. contrast enema
3. spinal magnetic resonance imaging
4. upper gastrointestinal series
5. voiding cystourethrography

You selected 1, the correct answer is 1.

The neonate in the vignette has an imperforate anus, a malformation that varies widely in
appearance. Imperforate anus occurs in 1 of 4,000 to 5,000 live births and is slightly more common among male infants. Recurrence risk in families with an isolated case is approximately 1%. Imperforate anus may occur as part of a genetic syndrome or as a sporadic abnormality.

More than 80% of boys with an imperforate anus have a fistula that connects the rectum to the bladder (rectovesical), the prostatic urethra (rectoprostatic), or bulbar urethra (rectobulbar) of the urinary tract. If the fistula opens onto the skin along the midline raphe, as it did in the infant in the vignette, it is called a perineal fistula. In the infant, the lowest aspect of the rectum opens along the midline raphe (Figure 1, Arrow) anterior to the center of the external sphincter. The more proximal aspect of the rectum remains within the sphincter muscles. The perineal fistula can be located anywhere along the midline raphe. In fewer than 5% of neonates with an imperforate anus the rectum ends in a blind pouch without a fistula, and 50% of these infants have Down syndrome.

Three variants of imperforate anus are seen in females: perineal fistula, vestibular fistula, and a cloaca. The rectum opens on the skin anterior to the anal dimple in the perineal fistula variant and the posterior aspect of the introitus outside the hymen in the vestibular fistula variant. A cloaca is a congenital anomaly in which the rectum, vagina, and urethra open into a common channel of variable length.

Although certain associated defects may require urgent treatment, most cases of imperforate anus do not require immediate surgical repair. Managing life-threatening complications caused by associated anomalies and determining whether a diverting colostomy is required are two issues that need to be addressed during the initial evaluation. The initial evaluation and management of a neonate with an imperforate anus generally includes an abdominal and pelvic ultrasound, a radiograph of the spine including anteroposterior and lateral views of the sacrum, a cardiac evaluation, and insertion of a nasogastric tube (Figures 2 and 3). Subsequent evaluation and management vary based on the infant's sex.

Figure 2: Male neonate with an anorectal malformation (adapted from Principles and Practice of Pediatric Surgery [2005])
Figure 3: Female neonate with an anorectal malformation (adapted from *Principles and Practice of Pediatric Surgery* [2005])

- **Perineal inspection urinalysis**
  - Evidence of fistula (30-90%)
    - Perineal fistula
    - "Flat bottom"
  - No evidence or questionable fistula (10-20%)
    - Cross-table lateral film in prone position
      - >1 cm bowel-skin distance
      - <1 cm bowel-skin distance

- Minimally posterior sagittal anoplasty
  - Evaluate for additional abnormalities
  - Posterior sagittal anorectoplasty in 4-8 weeks
  - Minimal posterior sagittal anoplasty

- Observe 16-24 hours
  - Pelvic/abdominal ultrasound
  - Anteroposterior and lateral radiographs of spine and sacrum
  - Cardiac evaluation
  - Nasogastric tube

- Cloaca
  - Emergency Genitourinary evaluation
  - Fistula (0.5%)
    - Cross-table lateral film in prone position
      - >1 cm bowel-skin distance
      - <1 cm bowel-skin distance or questionable
      - Colostomy
  - No Fistula (5%)
    - Posterior sagittal anorectoplasty in 4-8 weeks
    - Posterior sagittal anoplasty

- Vesibular (or vaginal)
  - Cloaca, vagina, and urethra diversion if necessary
  - Colostomy

- Cutaneous
  - Evaluate for additional abnormalities
  - Posterior sagittal anorectoplasty in 4-8 weeks

- Posterior sagittal anorectoplasty in 4-8 weeks
The arrested migration of the mesoderm in the caudal eminence and abnormal resorption of the cloacal membrane are likely embryologic causes of the imperforate anus; therefore, other tissues derived from mesoderm can also be affected. The tissues derived from the paraxial and lateral mesoderm plate include the genitourinary, skeletal, muscular, and gastrointestinal system. Among neonates with imperforate anus, 22% to 72% have associated malformations, the most common of which are genitourinary malformations. Genitourinary malformations occur in 20% to 54% of cases and may include the following:

- absent, dysplastic, or horseshoe kidneys
- hydronephrosis
- hypospadias
- bifid scrotum

Fewer than 10% of neonates with perineal fistulas, as present in the infant in the vignette, have genitourinary anomalies. In contrast, 90% of infants with high fistulas (cloaca, rectobladder) have associated genitourinary anomalies compared with 30% of cases with lower fistulas (rectourethral, rectovestibular). Abdominal ultrasonography performed during the initial evaluation (Figures 2 and 3) will help identify genitourinary abnormalities, which may alter management. Voiding cystourethrography may be reserved for those infants in whom hydronephrosis is identified on ultrasonography.

Gastrointestinal malformations associated with imperforate anus may include the following:

- esophageal atresia
- duodenal atresia
- Hirschsprung disease

Gastrointestinal anomalies may occur independently or as part of the VACTERL association. If a nasogastric tube can be passed into the stomach, the common forms of esophageal atresia are absent. In the absence of bilious emesis or an abnormal abdominal radiograph, a contrast study of the upper gastrointestinal tract is not indicated during the initial evaluation (Figures 2 and 3). Although Hirschsprung disease may occur with imperforate anus, it is rare, especially among neonates with low fistulas. A biopsy can be performed at the time of definitive repair or during colostomy if Hirschsprung disease is suspected. A contrast study of the lower intestinal tract to outline the fistula is not necessary during the initial management of a male infant with imperforate anus.

Infants with imperforate anus with a high fistula have a higher risk of vertebral anomalies. Examples of the types of vertebral abnormalities that are found include the following:

- partial or complete lumbosacral agenesis
- hemivertebrae
- agenesis of thoracic vertebrae
- scoliosis
- hemisacrum or scimitar sacrum
- asymmetric sacrum
- posterior protruding sacrum
- agenesis of the coccyx

Sacral abnormalities occur in as many as 45% of neonates with imperforate anus. The severity of the sacral anomaly is correlated with the prognosis for bowel and bladder function. If two or more sacral vertebrae are missing, the prognosis is poor for normal bowel and bladder function following repair.

At least one study reported a 38% incidence of spinal cord abnormalities among infants with anal-rectal malformations. Approximately 25% of cases of imperforate anus are associated with a tethered cord. Spinal cord abnormalities associated with imperforate anus include the following:

- tethered cord
- dural sac stenosis
- narrow spinal canal
Spinal cord abnormalities are also more common among neonates with high fistulas. A lumbosacral spine evaluation with plain radiographs will help delineate skeletal abnormalities. Pelvic ultrasonography is most often performed in infants younger than 3 months of age, especially those with low fistulas, to detect abnormalities of the vertebrae, spinal cord, or canal. Spinal magnetic resonance imaging (MRI) is recommended in neonates with complex defects, myelodysplasia, cloacal extrophy, or abnormal sacral anatomy. An MRI should also be considered in an infant with a bladder fistula, a presacral mass, hemivertebrae, or a genitourinary anomaly. MRI is rarely required as part of the initial evaluation unless ultrasound or spine radiographs are abnormal.

Other rare syndromes are associated with imperforate anus. For example, cat eye syndrome, associated with trisomy or tetrasomy 22pter?q11, presents with anal atresia and ocular coloboma. Ophthalmology consultation may be warranted.

References:


American Board of Pediatrics Content Specification(s):

Understand the embryology of rectal and anal malformations and associated anomalies

Understand the diagnosis of rectal and anal malformations and associated anomalies

Understand the management of rectal and anal malformations and associated anomalies
A 3-day-old female infant, whose birthweight was 680 g at an estimated gestational age of 24 weeks, has the following laboratory data:

<table>
<thead>
<tr>
<th>Laboratory Data</th>
<th>Patient Results (SI Values)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Arterial blood gas measurements</em></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.22</td>
</tr>
<tr>
<td>Partial pressure of oxygen, mm Hg (kPa)</td>
<td>78 (10.4)</td>
</tr>
<tr>
<td>Partial pressure of carbon dioxide, mm Hg (kPa)</td>
<td>44 (5.9)</td>
</tr>
<tr>
<td>Base deficit, mEq/L (mmol/L)</td>
<td>10 (10)</td>
</tr>
<tr>
<td><em>Serum electrolytes</em></td>
<td></td>
</tr>
<tr>
<td>Sodium, mEq/L (mmol/L)</td>
<td>135 (135)</td>
</tr>
<tr>
<td>Potassium, mEq/L (mmol/L)</td>
<td>4.9 (4.9)</td>
</tr>
<tr>
<td>Chloride, mEq/L (mmol/L)</td>
<td>111 (111)</td>
</tr>
<tr>
<td>Bicarbonate, mEq/L (mmol/L)</td>
<td>17 (17)</td>
</tr>
</tbody>
</table>

The infant is breathing spontaneously in a fraction of inspired oxygen of 0.30 and has received no methylxanthines, indomethacin, or diuretics. She is receiving trophic enteral feeds of expressed breast milk at 8 mL/kg per day and supplemental parenteral nutrition for a total fluid intake of 130 mL/kg per day. Urine measurements are: output 72 mL/kg per day, pH 7.6, and glucose ++.

Of the following, the PRINCIPAL site of developmental immaturity in the nephron in this infant is:

1. collecting duct
2. distal tubule
3. glomerulus
4. loop of Henle
5. proximal tubule

You selected 5, the correct answer is 5.

The extremely preterm infant in this vignette has evidence of metabolic acidosis. The major renal contributor to metabolic acidosis is immaturity of the proximal tubule, which results in urinary loss of bicarbonate, glucose, phosphate, and amino acids. Other contributors to metabolic acidosis include exogenous intake of acid largely from arginine and cysteine in parenteral nutrition and inadequate intake of base equivalents from enteral milk feeding. Pathologic causes of metabolic acidosis include patent ductus arteriosus, dehydration, sepsis,
hypoxemia, intraventricular hemorrhage, anemia, shock, gastrointestinal losses, and metabolic disorders such as cystinuria, tyrosinemia, galactosemia, and fructose intolerance.

The principal site of developmental immaturity in the nephron as a cause of metabolic acidosis in this infant is the proximal tubule. Cells of the proximal tubule absorb sodium via an apical membrane Na⁺/H⁺ antiporter (NHE3) (Figure 1).

![Figure 1: Proximal tubule cell: acid-base homeostasis](image)

The action of this antiporter, coupled with that of another apical membrane vacuolar H⁺ATPase, results in extrusion of H⁺ into the lumen of the proximal tubule. An apical membrane enzyme, carbonic anhydrase IV, catalyzes the conversion of extruded H⁺ and filtered HCO₃⁻ into H₂CO₃, and further into CO₂ and H₂O. The latter diffuse into the proximal tubule cell, where a cytosolic enzyme, carbonic anhydrase II, catalyzes the reconversion of CO₂ and H₂O into H₂CO₃, and further into H⁺ and HCO₃⁻. The H⁺ is extruded into the lumen as mentioned before, whereas the HCO₃⁻ is transferred across the basolateral membrane into the interstitium via a Na⁺/HCO₃⁻ cotransporter (NBC1).

Immaturity of the proximal tubule accounts for impaired excretion of H⁺ in the form of phosphate-buffered titratable acid and through generation of ammonium. This defect in urinary acidification frequently is accompanied by impaired absorption of electrolytes (sodium, potassium, chloride), minerals (calcium, phosphate), and nutrients (glucose, lactate, amino acids). The urinary acidification improves with advancing gestational and postnatal age.

The glomerular filtration rate (GFR), as measured by inulin clearance studies in the human infant, is low at birth, especially in preterm neonates. It is estimated at 13 mL/min per 1.73 m² surface area at gestational age of 28 weeks and at 20 mL/min per 1.73 m² at term. The GFR increases rapidly in the first month after birth to values estimated at 27 mL/min per 1.73 m² in the preterm neonate and at 42 mL/min per 1.73 m² in the term infant. This postnatal increase in GFR is attributed to:

- decrease in renal vascular resistance and consequent increase in renal blood flow
- increase in systemic blood pressure and consequent increase in glomerular capillary hydrostatic pressure, and
- increase in filtration coefficient associated with an increase in both glomerular basement membrane surface area and permeability

Immaturity of the glomerular function by itself is not a common cause of metabolic acidosis. However, under pathologic conditions such as hypoxemia, ischemia, hypovolemia, hypotension, ventilation abnormalities, and renal failure, the impaired glomerular function can contribute to metabolic acidosis.

Cells of the medullary thick ascending loop of Henle absorb sodium via an apical membrane Na⁺/K⁺/2Cl⁻ transporter (NKCC2) (Figure 2).

**Figure 2: Loop of Henle cell: calcium and magnesium absorption**

![Diagram of Loop of Henle cell](image)

The sodium is then transported across the basolateral membrane into the interstitium via the Na⁺/K⁺ ATPase. The chloride is transported from the cytosol into the interstitium via a basolateral Cl⁻ channel (CLC-K2). The potassium is recycled primarily into the urinary space via a lumenal K⁺ channel (ROMK). The combined activities of apical ROMK and basolateral CLC-K2 result in a lumen-positive transepithelial potential difference that drives paracellular absorption of cations, principally calcium and magnesium. Immaturity of the loop of Henle accounts for impaired absorption and consequent urinary loss of calcium and magnesium.

The distal tubule, in conjunction with the collecting duct, is important for water homeostasis. When the water intake is low and/or the water loss is excessive, the permeability of the distal tubule under the influence of arginine vasopressin from the posterior pituitary is increased, thereby promoting reabsorption of water. Conversely, when the water intake is high and/or the water loss is decreased, the distal tubule remains impermeable to water, thereby inhibiting reabsorption of water. Immaturity of the distal tubule accounts for impaired water homeostasis.

Cells of the collecting duct absorb sodium via an apical membrane Na⁺ channel (ENaC) (Figure 3).

**Figure 3: Collecting duct cell: sodium-potassium exchange**

![Diagram of Collecting duct cell](image)
The sodium is then transported across the basolateral membrane into the interstitium via the Na+/K+ ATPase. In addition, collecting duct cells express an apical membrane K+ channel that allows potassium to exit from the cells into the lumen of the nephron. Both sodium absorption and potassium excretion are closely linked and reciprocal. The ENaC expression is modulated by aldosterone, an adrenal mineralocorticosteroid hormone. The aldosterone binds to the mineralocorticoid receptor, which then increases the nuclear transcription of both ENaC and Na+/K+ ATPase. The resultant effect is increased renal absorption of sodium and renal excretion of potassium. Immaturity of the collecting duct accounts for potassium retention and resultant hyperkalemia. Nonoliguric hyperkalemia is observed in 30% to 50% of extremely preterm neonates, particularly in the first 48 to 72 hours after birth.

References:


**American Board of Pediatrics Content Specification(s):**
| Know the changes in glomerular and tubular function that occur during development, including the handling of glucose, sodium, potassium, calcium, and phosphate |
| Understand the etiology of metabolic acidosis and metabolic alkalosis in infants |
| Recognize the clinical and laboratory manifestations of metabolic acidosis and metabolic alkalosis in infants |
| Recognize the causes, diagnosis, and treatment of renal tubular acidosis in the neonate |
A 37-day-old, 1,000-g male infant is recovering from an episode of medically treated necrotizing enterocolitis. He is receiving parenteral nutrition through a central venous catheter. His nutritional intake includes:

- enteral feeds of a 20 kcal/oz formula at 15 mL/kg per day
- parenteral fluids containing 13% dextrose and 2.4% amino acids at 135 mL/kg per day
- infusion of a 20% lipid emulsion at 0.45 mL/hour

Recent laboratory data from the infant are shown. Because he has not gained weight over the past 5 days, you discuss with the residents how to increase his caloric intake to at least 110 kcal/kg per day.

Of the following, the change MOST likely to increase the daily caloric intake in this infant to at least 110 kcal/kg per day would be to increase the:

1. enteral feeds to 20 mL/kg per day
2. lipid infusion to 0.65 mL/hour
3. parenteral amino acid concentration to 3%
4. parenteral dextrose concentration to 14%
5. parenteral fluids to 140 mL/kg per day

You selected 5, the correct answer is 2.

Parenteral nutrition is often the primary source of nutritional support in critically ill neonates recovering from necrotizing enterocolitis. Although the neonate in this vignette may be receiving enough parenteral calories for a healthy low-birthweight neonate, a superimposed catabolic condition such as necrotizing enterocolitis may increase protein and nonprotein requirements and result in...
weight gain and growth that are less than those seen in utero.

Carbohydrate and fat are the primary sources of nonprotein calories in parenteral nutrition; amino acids provide protein calories. Sufficient nonprotein energy is required to maximize protein accretion and limit breakdown of endogenous protein stores for energy. Approximately 60 kcal/kg per day of nonprotein calories are required to ensure protein accretion in a stable ventilated neonate receiving 3.0 g/kg per day of amino acids. To approximate intrauterine growth and nitrogen accretion, a stable neonate will require about 90 to 100 kcal/kg per day of parenteral calories: at least 80 kcal/kg per day of nonprotein calories and 3.0 g/kg per day of amino acids. Parenteral energy requirements are less than enteral requirements because no energy is lost in the stool or during digestion. Protein and energy requirements may be higher in neonates with prior malnutrition or who have disease processes with increased nitrogen turnover.

In the absence of protein intake, glucose is more effective than fat in preventing protein breakdown. In the presence of protein, calories from both glucose and lipid are known to be protein sparing. Studies in older children have shown a positive effect of both lipid and glucose on nitrogen retention. However, the optimal carbohydrate-to-fat ratio to maximize protein accretion in ill low-birthweight neonates is not known.

Providing 40% to 65% of parenteral calories as carbohydrate and 30% to 50% as fat may help to maximize protein accretion and minimize excess energy expenditure caused by a disproportionate amount of carbohydrate calories.

Caloric content of a parenteral solution can be determined assuming:

- Dextrose = 3.4 kcal/g
- Lipids = 9.0 kcal/g
- Protein = 4.0 kcal/g

The Table summarizes calculations used to determine the infant's parenteral caloric intake.

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Nutrient Concentration, g/dL</th>
<th>Daily Volume, dL</th>
<th>Kcal/g of Nutrient</th>
<th>Total Kcal/kg/day</th>
<th>% of Total Parenteral Kcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate</td>
<td>13</td>
<td>× 1.35</td>
<td>× 3.4</td>
<td>= 60</td>
<td>65</td>
</tr>
<tr>
<td>Protein</td>
<td>2.4</td>
<td>× 1.35</td>
<td>× 4</td>
<td>= 13</td>
<td>14</td>
</tr>
<tr>
<td>Fat</td>
<td>20</td>
<td>× 0.108</td>
<td>x 9</td>
<td>= 19</td>
<td>21</td>
</tr>
</tbody>
</table>

The infant in this vignette is receiving approximately 102 kcal/kg per day (92 kcal/kg per day from parenteral fluids and 10 kcal/kg per day [0.67 kcal/mL × 15 mL/kg] from enteral feeds). Glucose at 12 mg/kg per minute provides 65% of parenteral calories; lipid at 2.2 g/kg per day of a 20% lipid emulsion provides just 21% of parenteral calories. Although the infant is receiving 80 kcal/kg per day of nonprotein calories, 3.2 g/kg per day of amino acids by parenteral route, and 10 kcal/kg per day by enteral feeds, his weight gain is likely slowed by increased metabolic needs.

Because the infant is tolerating the current lipid infusion (triglyceride concentration: 75 mg/dL [0.85 mmol/L] [Laboratory Data]), increasing the infusion would increase caloric intake. Increasing the lipid infusion by 0.2 mL/hour to 0.65 mL/hour (3.1 g/kg per day) would provide an additional 8.6 kcal/kg per day:

\[
0.20 \text{ mL/hour} \times 24 \text{ hour} \times 0.20 \text{ g/mL} \times 9 \text{ kcal/g} = 8.6 \text{ kcal/kg per day}
\]

The infant’s daily caloric intake would increase to at least 110 kcal/kg per day.

Increasing the enteral feeds by 5 mL/kg per day to 20 mL/kg per day would provide an additional 3.4 kcal/kg per day:

\[
5 \text{ mL/kg per day} \times 0.67 \text{ kcal/mL} = 3.4 \text{ kcal/kg per day}
\]

The infant’s daily caloric intake would increase to just 105 kcal/kg per day.
The infant's serum glucose and blood urea nitrogen are in the normal range (see Laboratory Data), indicating that he is tolerating the current composition of parenteral fluids. Increasing the parenteral fluids by 5 mL/kg per day to 140 mL/kg per day would provide an additional 2.7 kcal/kg per day:

Dextrose: $13 \text{ g/dL} \times 0.05 \text{ dL/day} \times 3.4 \text{ kcal/g} \times 1 \text{ kg} = 2.2 \text{ kcal/kg per day}$

Protein: $2.4 \text{ g/dL} \times 0.05 \text{ dL/day} \times 4 \text{ kcal/g} \times 1 \text{ kg} = 0.5 \text{ kcal/kg per day}$

The infant's daily caloric intake would increase to just 105 kcal/kg per day.

Increasing the parenteral amino acid concentration by 0.6% to 3% would provide an additional 3.2 kcal/kg per day:

$$0.6 \text{ g/dL} \times 1.35 \text{ dL/day} \times 4.0 \text{ kcal/g} \times 1 \text{ kg} = 3.2 \text{ kcal/kg per day}$$

The infant's daily caloric intake would be approximately 105 kcal/kg per day.

Finally, increasing the parenteral dextrose concentration by 1.0% to 14% would provide an additional 4.2 kcal/kg per day:

$$1.0 \text{ g/dL} \times 1.35 \text{ dL/day} \times 3.4 \text{ kcal/g} \times 1 \text{ kg} = 4.6 \text{ kcal/kg per day}$$

The infant's daily caloric intake would be approximately 107 kcal/kg per day.

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

References:

Adamkin DH. Nutrition management of the very low-birthweight infant. I. Total parenteral nutrition and minimal enteral nutrition. *Neoreviews*. 2006;7:e602-606

Dusick AM, Poindexter BB, Ehrenkranz RA, Lemons JA. Growth failure in the preterm infant: can we catch up? *Semin Perinatol.* 2003;27:302-310

Poindexter BB. Protein needs of the preterm infant. *Neoreviews*. 2003;4:e52-e58


American Board of Pediatrics Content Specification(s):

Understand the nutritional composition of parenteral solutions

Understand the importance of protein and nonprotein nutrients in achieving optimal utilization of energy and nitrogen

Know how to calculate the caloric content of parenteral nutrition solutions
A male infant is delivered at term gestation. Physical examination reveals the lesion shown in the Figure.

The infant spontaneously moves the lower extremities. The knee and ankle jerks are present, but the anal wink is absent. Intermittent postvoiding bladder catheterizations consistently drain 10 mL or more of urine. Mild hydrocephalus is revealed on magnetic resonance imaging of the head.

Of the following, the MOST likely long-term consequence of this infant's condition is:

1. deterioration of the urinary tract
2. mental retardation
3. moderate to severe scoliosis
4. seizures
5. wheelchair dependence

You selected 1, the correct answer is 1.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)
The infant in the vignette has a lumbosacral myelomeningocele (Figure). This primary neural tube defect results from a failure of posterior neural tube closure during the 3rd and 4th weeks of gestation. Dorsal bone and soft tissue defects permit a saccular outpouching of neural elements (neural placode), with an incomplete, although variable, dermal covering. The defect may occur at any point along the spine, however 80% of lesions involve the lumbar spinal region (thoracolumbar, lumbar, or lumbosacral). Eighty-four percent of patients with myelomeningocele develop hydrocephalus, with the incidence highest among lumbar lesions. Likewise, the Arnold-Chiari type II malformation (displacement of the medulla and crowding of the cerebellar tonsils into the foramen magnum) occurs in nearly every case of lumbar myelomeningocele, but is symptomatic in only one third of patients. Survival rates, although influenced by decisions regarding aggressiveness of early neonatal care, are approximately 90%. Mortality in the first year after birth is highest in the most severely affected patients, and is usually related to brainstem dysfunction.

The major long-term complications of myelomeningocele can be grouped into neurologic, orthopedic, and urinary tract problems. After the first year, the major cause of death and morbidity relates to urinary tract complications and renal damage. Abnormalities of bladder innervation and detrusor muscle dysfunction accompany lumbosacral lesions and lead to deterioration of the urinary tract in nearly 75% of patients. By adulthood, fewer than 40% of patients have a normal renal ultrasound and a normal serum creatinine concentration. Vescicoureteral reflux, chronic infection, and urolithiasis contribute to progressive loss of renal mass and subsequent chronic renal failure. More than 80% of young adults with myelomeningocele have social bladder incontinence. Tethering of the cord is nearly universal in older children, and likely contributes to this deterioration in urinary tract function.

About 15% to 20% of patients with myelomeningocele have mental retardation, which is usually attributable to central nervous system infection or subtle microscopic anomalies of neuronal migration and differentiation. High thoracic lesions, hydrocephalus, and ventriculoperitoneal shunts are associated with lower intellectual function. The mean intelligence quotient (IQ) for individuals with myelomeningocele and no hydrocephalus is 102. The addition of shunted hydrocephalus and infection reduces the mean IQ to 73. Up to 25% of patients develop seizures, which may contribute to impaired intellectual function.

Up to 50% of patients with myelomeningocele develop scoliosis, with the risk determined by the segmental level of the lesion. Significant scoliosis often is seen with lesions above L2, while this complication is unusual in lesions below S1.

Ambulation potential is reasonably predicted by the functional level of the lesion. Most patients with lesions below S1 ultimately walk unaided. In contrast, lesions above L2 usually result in wheelchair dependence for most activities. Intermediate lesions result in varying degrees of ambulation, with or without assistive devices, such as braces and crutches. During adolescence and young adulthood, weight gain, increased stature, and tethering of the cord lead to greater use of a wheelchair than orthotic devices.

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

References:


American Board of Pediatrics Content Specification(s):
Understand the long-term complications of myelomeningocele and encephalocele
A 72-hour-old female newborn, whose birthweight was 1,840 g at an estimated gestational age of 33 weeks, has a urine output of 0.8 mL/kg per hour. The maternal history was significant for spontaneous vaginal bleeding from acute placental abruption that led to an emergency cesarean delivery. The infant’s Apgar scores were 7 and 8 at 1 and 5 minutes after birth, respectively, and the umbilical cord blood pH was 7.28. Initial physical examination of the infant revealed pallor, poor perfusion of the skin, and low blood pressure. The infant has no apparent anomalies or dysmorphic features. She is breathing spontaneously in room air, is receiving intravenous fluids, and has received no medications other than vitamin K and topical eye prophylaxis.

Laboratory data reveal the following:

<table>
<thead>
<tr>
<th>Laboratory Studies</th>
<th>Patient Result (SI Units)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma measurements</strong></td>
<td></td>
</tr>
<tr>
<td>Urea nitrogen, mg/dL (mmol/L)</td>
<td>38 (13.6)</td>
</tr>
<tr>
<td>Creatinine, mg/dL (μmol/L)</td>
<td>1.6 (141)</td>
</tr>
<tr>
<td>Sodium, mEq/L (mmol/L)</td>
<td>138 (138)</td>
</tr>
<tr>
<td>Potassium, mEq/L (mmol/L)</td>
<td>5.6 (5.6)</td>
</tr>
<tr>
<td><strong>Urine measurements</strong></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL (mmol/L)</td>
<td>8 (0.7)</td>
</tr>
<tr>
<td>Sodium, mEq/L (mmol/L)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Osmolality, mOsm/kg (mmol/kg)</td>
<td>310 (310)</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Microscopic hematuria</td>
</tr>
<tr>
<td><strong>Renal ultrasonography</strong></td>
<td></td>
</tr>
<tr>
<td>Echogenecity</td>
<td>Increased</td>
</tr>
<tr>
<td>Corticomedullary differentiation</td>
<td>Normal</td>
</tr>
<tr>
<td>Urinary collecting system</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Of the following, the laboratory finding MOST likely to distinguish prerenal from intrinsic renal failure in this infant is:

1. fractional excretion of sodium
2. plasma urea nitrogen–creatinine ratio
3. renal ultrasonography
4. urinalysis
5. urine osmolality

You selected 2, the correct answer is 1.

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

The preterm neonate in this vignette has evidence of acute renal failure as characterized by oliguria, defined in infants as urine output less than 1.0 mL/kg per hour, and a plasma creatinine concentration...
higher than 1.5 mg/dL (133 μmol/L). The incidence of acute renal failure is estimated at 6% to 8% among neonates hospitalized for intensive care. Acute renal failure in neonates has multiple causes that can be classified broadly into three categories: prerenal, renal (intrinsic), and postrenal (obstructive) (Table). Prerenal failure is the most common type of acute renal failure in the neonate, accounting for up to 85% of the cases.

### Table. Causes of Acute Renal Failure in the Neonate

<table>
<thead>
<tr>
<th>Prerenal</th>
<th>Renal (Intrinsic)</th>
<th>Postrenal (obstructive)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypovolemic causes</strong></td>
<td>Acute tubular necrosis</td>
<td>Obstructive causes</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Hypoxia-ischemia</td>
<td>Urethral obstruction</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Drug-induced</td>
<td>Bilateral ureteral obstruction</td>
</tr>
<tr>
<td>Salt wasting</td>
<td>Toxin-mediated</td>
<td>Ureteropelvic junction obstruction</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>Malformations</td>
<td>Ureterovesical junction obstruction</td>
</tr>
<tr>
<td><strong>Cardiovascular causes</strong></td>
<td>Renal dysplasia</td>
<td>Obstructive nephrolithiasis</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Polycystic/multicystic kidney disease</td>
<td>Functional causes</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>Vascular lesions</td>
<td>Neurogenic bladder</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>Renal artery thrombosis</td>
<td></td>
</tr>
<tr>
<td><strong>Distributive causes</strong></td>
<td>Renal vein thrombosis</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>Cortical necrosis</td>
<td></td>
</tr>
<tr>
<td>Hypoproteinemia</td>
<td>Infective causes</td>
<td></td>
</tr>
<tr>
<td>Tissue trauma</td>
<td>Sepsis</td>
<td></td>
</tr>
<tr>
<td>Capillary leakage</td>
<td>Pyelonephritis</td>
<td></td>
</tr>
<tr>
<td><strong>Drug-induced causes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostaglandin synthetase inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasodilators</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The history and clinical course in the infant in this vignette are suggestive of prerenal failure resulting from hypovolemia secondary to perinatal blood loss. In prerenal failure, the renal function is decreased from impaired renal perfusion, but the kidney is intrinsically normal. When renal perfusion is decreased, at least two compensatory mechanisms are set in motion. First, the glomerular afferent arteriole relaxes to decrease renal vascular resistance and to maintain glomerular blood flow. This effect is mediated largely by vasodilatory prostaglandins, including prostacyclin. Second, the glomerular efferent arteriole constricts to increase the hydrostatic pressure in glomerular capillaries and to maintain glomerular filtration. This effect is mediated largely by vasoconstrictive angiotensin II. Prerenal failure occurs when these compensatory mechanisms fail to maintain perfusion of the renal microvasculature.

Prerenal failure results from either true blood volume contraction or decreased effective blood volume. The true blood volume contraction results from causes that include hemorrhage, dehydration from gastrointestinal loss, salt-wasting renal or adrenal disease, central or nephrogenic diabetes insipidus, increased transdermal fluid loss, and disease states associated with extravascular fluid loss such as sepsis, hypoproteinemia, tissue trauma, and capillary leakage. Prerenal failure may also occur in the face of normal or increased blood volume when renal perfusion is impaired from diseases such as congestive heart failure, cardiac tamponade, and hepatorenal syndrome. Postnatal administration of medications such as prostaglandin synthetase inhibitors and angiotensin-converting enzyme inhibitors can cause prerenal failure by impairing renal perfusion in the presence of normal blood volume. Whether prerenal failure is caused by true blood volume contraction or decreased effective blood volume, correction of the underlying disturbance and restoration of renal perfusion results in a prompt return of renal function to normal.

Several laboratory tests have been proposed to differentiate between prerenal failure and intrinsic renal failure. This differentiation is based on the concept that in prerenal failure, the renal tubules function normally and therefore are able to reabsorb salt and water appropriately, whereas in intrinsic
renal failure the renal tubules are injured and therefore are unable to conserve salt and water.

Among the laboratory tests in this vignette, the fractional excretion of sodium (FE\(_{Na}\)) is the test most likely to distinguish prerenal failure from intrinsic renal failure. The FE\(_{Na}\) is calculated by using the following equation:

\[
FE_{Na} (\%) = \frac{UNa \times PCr}{PNa \times UCr} \times 100
\]

where UNa is urine sodium (mEq/L), PCr is plasma creatinine (mg/dL), PNa is plasma sodium (mEq/L), and UCr is urine creatinine (mg/dL).

In prerenal failure, the FE\(_{Na}\) in neonates is often 2.5% or lower, indicative of renal tubular conservation of sodium, whereas in intrinsic renal failure, the FE\(_{Na}\) is often greater than or equal to 3.0%, indicative of failed renal tubular reabsorption of sodium. The FE\(_{Na}\) in the infant in this vignette is calculated at approximately 1.4%. This value is consistent with the diagnosis of prerenal failure.

The plasma urea nitrogen–creatinine ratio (mg/mg) has been proposed as a measure to distinguish prerenal failure from intrinsic renal failure. In prerenal failure, the renal tubules retain the capacity to reabsorb sodium and water, which promotes passive reabsorption of urea. The net effect is an increased plasma urea nitrogen–creatinine ratio (>30). Conversely, in intrinsic renal failure, the renal reabsorption of urea is decreased from impaired tubular reabsorption of sodium and water. Moreover, the plasma concentration of creatinine often is higher than in prerenal failure. The net effect is a decreased plasma urea nitrogen–creatinine ratio (<20). The plasma urea nitrogen–creatinine ratio in the infant in this vignette is calculated at approximately 24. This value is not helpful in discriminating between prerenal and intrinsic renal failure.

In prerenal failure, the renal tubules retain the capacity to reabsorb water, and therefore the urine osmolality tends to be high (>350 mOsm/kg [350 mmol/kg]). Conversely, in intrinsic renal failure, the renal osmolality is relatively low (<300 mOsm/kg [300 mmol/kg]). The urine osmolality in the infant in this vignette is 310 mOsm/kg (310 mmol/kg). This value is not helpful in discriminating between prerenal and intrinsic renal failure.

In prerenal failure, the urinalysis is usually normal or may show minor changes such as microscopic hematuria. In intrinsic renal failure, impaired sodium reabsorption by injured tubular epithelial cells increases sodium concentration in the tubular lumen. The increased intratubular sodium polymerizes Tamm-Horsfall protein, a protein normally secreted by the loop of Henle, which contributes to the formation of casts. Presence of such casts, in addition to sloughed epithelial cells and red blood cells, often suggests intrinsic renal failure. The finding of microscopic hematuria on urinalysis in the infant in this vignette is not helpful in differentiating prerenal from intrinsic renal failure.

Renal ultrasonography findings are usually normal in prerenal failure, and, may be normal or reveal increased echogenicity with loss of corticomedullary differentiation in intrinsic renal failure. The finding of increased echogenicity on renal ultrasonography in the infant in this vignette is subjective and not sensitive or specific for discriminating between prerenal and intrinsic renal failure.

References:


Andreoli SP. Acute renal failure in the newborn. Sem Perinatol. 2004;28:112-113


American Board of Pediatrics Content Specification(s):

Know the common causes of acute renal failure in the neonate

Know the clinical manifestations and laboratory features of acute renal failure in the neonate
A 6-week-old infant has an average daily weight gain of 30 g. Following his birth at full term and with a birthweight of 3 kg, he has been healthy and breastfeeding exclusively.

Of the following, the energy cost of growth, as a percentage of total energy requirement, for this infant is CLOSEST to:

- 10%
- 25%
- 35%
- 50%
- 65%

You selected 2, the correct answer is 3.

Energy requirement for an individual may be defined as the level of dietary energy intake that will balance energy expenditure. In addition, for infants, derivation of energy need requires an estimate of the energy needed for growth. This relationship can be represented by the following equation:

\[
\text{Energy Requirement} = \text{Total Energy Expenditure} + \text{Energy Cost of Growth}
\]

Total energy expenditure (TEE) is the sum of the energy needed for basal metabolic functions, the thermic effect of feeding, physical activity, and thermoregulation. The basal metabolic rate (BMR) refers to energy expenditure for vital processes during physical, emotional, and digestive rest. In the infant, BMR represents approximately 45% of TEE, but is affected by changes in body size and composition, as well as the presence of disease. The thermic effect of feeding refers to the energy needed for food ingestion and nutrient digestion, absorption, transport, and deposition. This metabolic response to food increases the TEE by approximately 10% of the BMR. The contribution of physical activity is variable, comprising approximately 10% of TEE in the neonate, and peaking at 6 months of age to as much as 40% of TEE. Subsequent voluntary muscular control becomes increasingly coordinated, resulting in more efficient energy expenditure. Typically, the contribution of thermoregulation on TEE is minimal; however, outside the thermoneutral temperature range, an additional 10% of TEE may be required to maintain body temperature.

The energy cost of growth (ECG) may be subdivided into the energy needed for synthesis of new tissue and the energy stored in new tissue. Therefore, the ECG may be computed from the separate costs of protein and fat deposition (carbohydrate content is insignificant), and ranges from 4 to 6 kcal/g (16.7-25.1 kJ/g) of tissue gained. Because the composition of tissue synthesized changes with development, the ECG varies with age. During the first year, the percentage of fat mass peaks at 3 months followed by a gradual decrease, while the percentage of protein mass decreases in the first 6 months and increases thereafter. Protein
synthesis is a high-energy-requiring process with an energetic efficiency of 42% (1 kcal [4.2 kJ] deposited per 2.38 kcal [11.7 kJ] used). On the other hand, fat deposition has an energetic efficiency of 85% (1 kcal [4.2 kJ] deposited per 1.17 kcal [4.9kJ] used).

Relative to maintenance energy requirements, the ECG is small, except during the first month of age, and decreases markedly during the first year. Between birth and 2 months, ECG is approximately 35% of the total energy requirement, and decreases to approximately 12% at 6 months. By 18 to 24 months of age, the ECG only represents approximately 2.5% of the child’s total energy requirement. In terms of energy cost per gram of tissue gained, at 1 to 2 months, the ECG is 5.9 kcal/g (25 kJ/g), decreasing to 3.4 kcal/g (14 kJ/g) at 9 to 12 months.

Satisfactory growth is a sensitive indicator of energy balance. The precise caloric requirements for growth are unknown, and vary by age and body composition. Net energy intake must exceed TEE for growth to be possible. Gross energy intake exceeds that of dietary energy available, because most foods are not completely absorbed, and protein is incompletely oxidized. Metabolizable energy is between 88% and 92% of dietary intake. During the first 4 months, the healthy breastfed infant adequately grows on 85 to 100 kcal/kg per day (356-418 kJ/kg per day). The formula-fed infant has a higher energy requirement, 100 to 110 kcal/kg per day (418-460 kJ/kg per day), because of less efficient digestion and absorption of fat. At 12 months of age, energy requirements are closer to 80 kcal/kg per day (335 kJ/kg per day).

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

References:


American Board of Pediatrics Content Specification(s):

Understand how body composition changes during the growth and development of full-term infants

Understand how to ascertain and calculate the caloric requirements to ensure optimal growth of full-term infants
A full-term male infant weighing 3.4 kg was born via repeat cesarean delivery after spontaneous rupture of membranes. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Physical examination was normal 3 hours after birth. Feedings were started with standard infant formula. On day 3, the infant became pale and lethargic. His heart rate increased to 196 beats per minute and respiratory rate was 72 breaths per minute. His skin temperature was 35°C; systolic blood pressure was 35 mm Hg and diastolic, 12 mm Hg. Heart sounds were normal. A chest radiograph was obtained (Figure).

The rest of the physical examination findings were normal. Laboratory findings showed his white blood cell count was $3 \times 10^3/\mu L$ ($3 \times 10^9/L$) and C-reactive protein was abnormally high. Cerebrospinal fluid findings were normal. Findings on blood gases and electrolytes were as follows.

<table>
<thead>
<tr>
<th>Laboratory Findings</th>
<th>Patient Results (SI Values)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood gases</strong></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>6.9</td>
</tr>
<tr>
<td>Bicarbonate, mmol/L</td>
<td>7</td>
</tr>
<tr>
<td>Partial pressure of arterial carbon dioxide, mm Hg (kPa)</td>
<td>37 (4.9)</td>
</tr>
<tr>
<td>Partial pressure of arterial oxygen, mm Hg (kPa)</td>
<td>82 (10.9)</td>
</tr>
<tr>
<td><strong>Electrolytes</strong></td>
<td></td>
</tr>
<tr>
<td>Sodium, mEq/L (mmol/L)</td>
<td>140</td>
</tr>
<tr>
<td>Potassium, mEq/L (mmol/L)</td>
<td>5</td>
</tr>
<tr>
<td>Chloride, mEq/L (mmol/L)</td>
<td>110</td>
</tr>
</tbody>
</table>

Of the following, the MOST likely underlying mechanism for the acidemia is:
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>excess exogenous acid load</td>
</tr>
<tr>
<td>2</td>
<td>increased endogenous inorganic acid(s)</td>
</tr>
<tr>
<td>3</td>
<td>increased endogenous organic acid(s)</td>
</tr>
<tr>
<td>4</td>
<td>loss of bicarbonate through the kidneys</td>
</tr>
<tr>
<td>5</td>
<td>respiratory insufficiency</td>
</tr>
</tbody>
</table>

You selected 2, the correct answer is 3.

**Do you want to add anything to your Learning Plan?**

(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

The infant in the vignette has early-onset sepsis and pneumonia, as manifested by pallor and lethargy, temperature instability, tachypnea and tachycardia, systemic hypotension, mild hypoxemia, and metabolic acidosis with only partial respiratory compensation. The chest radiograph is consistent with pneumonia (Figure).

The acidosis is primarily metabolic and is only partially compensated. The anion gap defined as $[\text{Na}] - ([\text{Cl}] + [\text{HCO}_3^-])$ is large at 23 mmol/L (normal = 6-15 mmol/L). An increased anion gap indicates the presence of an anion (ie, acid) that is not yet measured. The metabolic acidosis of sepsis is primarily because of the accumulation of lactic acid. Lactic acidosis occurs when the mitochondria cannot complete the oxidation of carbohydrates to carbon dioxide and water via the tricarboxylic acid cycle (also known as the citric acid cycle or the Krebs cycle). This cycle uses pyruvate, the end-product of glycolysis, and oxygen in a series of steps that yield carbon dioxide, water, and adenosine triphosphate. The tricarboxylic acid cycle produces over 90% of the adenosine triphosphate energy derived from carbohydrate oxidation. If the mitochondria are deprived of oxygen because of poor perfusion or hypoxemia or if they are unable to use oxygen because of a genetic error or toxin, pyruvic acid accumulates and is preferentially converted to lactic acid.

The underlying mechanism(s) for the lactic acidosis seen in sepsis have been proposed to be:

- Increased lactate production
- Decreased lactate clearance
- Inhibition of pyruvate dehydrogenase

The first two mechanisms can be explained in part by tissue hypoperfusion.

The infant in the vignette was being fed a standard infant formula that does not provide a large acid load. Small premature infants nourished via parenteral nutrition may receive an acid load in excess of the clearance capabilities of their immature kidneys which can cause a metabolic acidosis. In this latter case, the addition of acetate to the intravenous alimentation might prevent metabolic acidosis.

Metabolic acidosis can be caused by an increased release of inorganic acids (nitrogen, sulfate, or phosphorous-based acids) into the circulation because of cellular necrosis. In an infant who is moribund from sepsis, this mechanism can contribute to metabolic acidosis. The infant in the vignette is very sick, but no signs of massive tissue necrosis are described.

Newborn infants, especially very prematurely born infants, have a tendency to lose more bicarbonate in their urine than older individuals. This bicarbonate loss partially explains the slightly lower concentrations of bicarbonate in the blood of normal newborn infants. However, severe acidosis results from the loss of bicarbonate only in cases with an inborn error (renal tubular acidosis) or chronic diarrhea. No evidence of either condition was presented in the infant in the vignette.
The infant in the vignette does have some measure of respiratory insufficiency but it is not the primary cause of his acidosis. The partial pressure of arterial carbon dioxide (PaCO₂) is 37 mm Hg when the value should have been between 16.5 and 20.5 mm Hg if the infant were fully able to compensate for his metabolic acidosis with increased breathing. The formula for this value is:

\[
\text{PaCO}_2(\text{expected}) = (1.5 \times [\text{HCO}_3^-]) + 8 \pm 2
\]

If the infant were able to effect respiratory compensation to that degree, he would have corrected the pH to around 7.2. However, the combination of pneumonia and sepsis impaired his ability to compensate effectively.

What should be done in addition to the prompt administration of intravenous antibiotics? The low extracellular pH primarily results from poor perfusion and the accumulation of lactic acid. To achieve better tissue perfusion, fluid boluses of isotonic saline could be used. If these boluses are ineffective, cardiac function should be assessed and measures taken to improve cardiac output.

Administration of sodium bicarbonate might be considered, but there is no evidence that treatment of metabolic acidosis with this drug has improved the short-term or long-term outcomes of newborn infants. Sodium bicarbonate also can act as an extracellular volume expander, but it is not superior to isotonic saline. Repeated administration is associated with a risk of hypernatremia. In addition, the administration of sodium bicarbonate in the situation described in the vignette will raise the PaCO₂ and reduce the pH of the extracellular and intracellular fluid. Carbon dioxide diffuses freely to all the fluid spaces of the body. Initiating ventilatory assistance to reduce the PaCO₂ moderately will improve pH in all compartments while the infection is being addressed.

References:


American Board of Pediatrics Content Specification(s):

Know how to manage metabolic acidosis and metabolic alkalosis in the neonate
Fat is the most abundant source of energy in the diet of premature infants. Premature infants fed their mother’s milk, absorb a higher proportion of the fat in their diet than those fed cow milk–based premature infant formula. Consequently, the stools of premature infants fed mother’s milk contain smaller quantities of lipids than of those fed formula.

Of the following, the difference in fat absorption between human milk and infant formula can be BEST attributed to:

- 1. bile salt–stimulated lipase
- 2. fatty acid composition
- 3. gastric emptying time
- 4. size of fat globules
- 5. white blood cells

You selected 2, the correct answer is 1.

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

The primary sources of energy in human milk or premature infant formula are fat, carbohydrate, and protein. About 45% of the fuel energy in mature human milk and most premature infant formulas is derived from fat. Most of the fat energy is in the form of triglycerides. Triglycerides are constructed with a three-carbon glycerol backbone (Figure).
The three hydroxyl radicals of glycerol are esterified with fatty acids of various lengths and degrees of unsaturation (based on number of double bonds between carbon atoms).

Absorption of energy-rich fatty acids and glycerol requires prior hydrolysis (digestion) of the ester bonds connecting the fatty acids with the glycerol backbone. In older children and adults, digestion occurs primarily in the upper small intestine and is facilitated by the emulsification of fats by bile salts and the hydrolytic action of pancreatic lipase. Newborn term and preterm infants are relatively deficient in both bile salts and pancreatic lipase.

In the newborn, lipolysis starts in the stomach with lingual lipase made by serous glands at the base of the tongue and gastric lipase secreted by gastric glands. These two lipases are present by 25 weeks' gestation, and they are resistant to acid denaturation and are active in the pH range found in the infant stomach after a feeding. They tend to release one fatty acid (from one end of the glycerol backbone), leaving a diglyceride and a fatty acid. The fatty acids initially released act as substitute emulsifiers for the rest of the dietary fat.

Breast milk contains lipases that are not present in bovine milk or in infant formula. As a consequence, fat is absorbed more efficiently from breast milk than from bovine milk or infant formula. Whether breast milk is fresh or heat-treated affects fat absorption. Fat absorption amounts to approximately 75% with fresh breast milk in contrast to 50% with heat-treated breast milk. The relative deficiency of fat absorption with heat-treated breast milk is attributed to loss of enzyme activity associated with heat treatment.

Most of the lipolytic activity in breast milk comes from bile-salt–stimulated lipase (BSSL). This enzyme is resistant to acid denaturation and is inactive in the absence of its cofactor, bile salt. The low concentrations of bile salt found in premature and term infants are enough to activate BSSL in the upper small bowel. BSSL is able to hydrolyze the fatty acid moiety at the end and middle positions of the triglyceride backbone, complementing the actions of lingual lipase, gastric lipase, and pancreatic lipase.

Other lipases in human milk include lipoprotein lipase which is probably leaked into the milk from the mother's circulation. This lipase is serum-activated and probably not important to the digestion process of infants. Other minor lipases/esterases have also been described in human milk.
The composition of fatty acids in human milk depends somewhat on the mother’s diet. Fatty acid absorption tends to increase as chain length decreases and as the degree of unsaturation (number of double bonds) increases. Therefore, medium chain triglycerides (MCTs) are digested more readily than long chain triglycerides (LCTs). Human milk contains about 10% MCTs and modern premature infant formulas contain added MCTs, leading to minimal difference from human milk.

Premature infants fed breast milk have a shorter gastric emptying time (by half) than those fed infant formula or breast milk fortified with a premature infant fortifier. Shorter emptying time may decrease the gastric phase of lipid digestion and cannot account for the improved absorption from unheated breast milk.

The size of fat globules in a milk feeding can influence the efficiency of lipolysis, because small globules present more surface area for digestion per gram of fat thus improving efficiency. Colostrum fat globules at less than 12 hours postpartum have a diameter of about 9 μm. The milk fat globule diameter decreases over time such that mature human milk contains fat globules measuring about 3 to 4 μm in diameter. The fat droplets in infant formula are much smaller, measuring 0.4 μm in diameter and, therefore have the most surface area per gram of fat. This increase in available surface area does have an effect on the efficiency of fat digestion; however, the percentage of fat absorbed from formula is still lower than from fresh human milk (although higher than from heated human milk).

Human milk, unlike formula, contains live white blood cells that have been implicated in promoting resistance to infection. Although these leukocytes produce esterase, such esterases are not designed for triglyceride hydrolysis and are produced in very small amounts. They are not responsible for the improved fat absorption from fresh breast milk compared with infant formula.

References:


Ewer AK, Durbin GM, Morgan MEI, Booth IW. Gastric emptying in preterm infants. *Arch Dis Childhood.* 1994;71:F24-F27


**American Board of Pediatrics Content Specification(s):**

Understand the physiology of fat digestion, absorption, and metabolism in newborn infants
At 1 month of age, a full-term infant is healthy and demonstrates adequate weight gain. His enteral intake provides approximately 100 kcal/kg per day (418 kJ/kg per day).

Of the following, the upper limit of carbohydrate requirement for this infant, assuming minimal intake of other macronutrients, is CLOSEST to:

1. 50 kcal/kg per day (167 kJ/kg per day)
2. 65 kcal/kg per day (209 kJ/kg per day)
3. 80 kcal/kg per day (293 kJ/kg per day)
4. 100 kcal/kg per day (418 kJ/kg per day)
5. 120 kcal/kg per day (502 kJ/kg per day)

You selected 4, the correct answer is 2.

In the human body, glucose is the primary circulating carbohydrate and a preferred metabolic fuel. Specifically, glucose serves as the main source of energy for the brain, renal medulla, and erythrocyte. In addition, glucose provides an important carbon source for de novo synthesis of fatty acids and nonessential amino acids. In the liver, dietary carbohydrates are converted to glucose. Amino acids and glycerol also can be converted to glucose, but this process is not metabolically efficient. Glucose not immediately oxidized can be polymerized and stored in the liver and skeletal muscle as glycogen. The term newborn has glycogen stores sufficient to meet energy needs during the first few days after birth. In contrast, the preterm infant’s reserves are limited and will be rapidly depleted during periods of fasting. Other forms of carbohydrate in the body include mucopolysaccharides; glycoproteins; glycolipids; and components of nucleic acids, various hormones, and enzymes.

Although an infant’s metabolic energy requirement can be met by carbohydrates, protein and fat are obligatory requirements for growth and essential nutrients. The total energy requirement is the sum of the total energy expenditure and the energy cost of growth. The total energy expenditure represents the energy needed for basal metabolic functions, the thermic effect of feeding, and physical activity. Between birth and 2 months of age, the energy cost of growth is approximately 35% of the total energy requirement. Therefore, the upper limit of carbohydrate requirement, assuming a minimal intake of protein and fat, approximates 65% of the total energy requirement. For the infant in this vignette, with an intake of 100 kcal/kg per day (418 kJ/kg per day), the upper limit of carbohydrate needed would be approximately 65 kcal/kg per day (272 kJ/kg per day). Excess glucose is metabolized and stored mainly as fat, and a high carbohydrate intake may predispose to obesity and insulin resistance.

At a minimum, carbohydrate intake must meet the energy needs of the brain and other glucose-dependent organs, minimize loss of protein and nitrogen, minimize gluconeogenesis, and prevent ketosis. Based on endogenous rates of glucose production, and cerebral glucose utilization rates, the minimal glucose requirement for newborn infants is estimated at 4 to 6
mg/kg per minute. Because of an increased brain-to-body weight ratio, decreased fat stores, and increased total energy requirement, the preterm infant’s minimal glucose need is estimated to be higher, 5 to 8 mg/kg per minute.

References:


American Board of Pediatrics Content Specification(s):

Understand the carbohydrate requirements of preterm and full-term infants

Understand the physiology of carbohydrate metabolism in newborn infants
A 32-week-gestation infant with bowel obstruction is transferred to your hospital 7 days after birth. She is fed nothing by mouth, with surgery planned for the next morning. Intravenous administration of dextrose 10% was started at the referring hospital. After you order new intravenous fluids for her, you discuss with the residents the relationship between a child's energy needs and nitrogen balance. You point out the nutritional priorities for maintaining body nitrogen on one hand, and achieving an intrauterine growth rate on the other.

Of the following, the parenteral fluid order that comes CLOSEST to providing sufficient energy and nitrogen to maintain body nitrogen stores for this infant is:

<table>
<thead>
<tr>
<th>Fluid Rate (mL/kg/d)</th>
<th>Dextrose (%)</th>
<th>Amino Acids (%)</th>
<th>Lipids (g/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>160</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>120</td>
<td>12.5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>110</td>
<td>10</td>
<td>2.5</td>
<td>2</td>
</tr>
<tr>
<td>100</td>
<td>10</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>120</td>
<td>10</td>
<td>1.5</td>
<td>1</td>
</tr>
</tbody>
</table>

You selected 1, the correct answer is 5.
For most premature infants, the absence of nitrogen intake results in a loss of 1 to 1.2 g/kg per day of endogenous body protein, estimated as 1% of total body protein. To forestall this loss, an amino acid intake of at least 1.5 g/kg per day is needed, as well as a nonprotein energy intake of at least 50 kcal/kg per day. Of the fluid orders given, the one that comes closest to these needs of the infant in the vignette is dextrose 10% and amino acids 1.5% at 120 mL/kg, and lipids at 1 g/kg, per day. This dosage of parenteral fluid will deliver 1.8 g/kg of amino acids per day and 50 kcal/kg of nonprotein energy per day. The Table shows the energy and the protein provided by the solutions listed in the vignette.

### Table: Energy and Protein Calculations

<table>
<thead>
<tr>
<th>Response</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid rate, mL/kg/d</td>
<td>160</td>
<td>120</td>
<td>110</td>
<td>100</td>
<td>120</td>
</tr>
<tr>
<td>Dextrose, %</td>
<td>15</td>
<td>12.5</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Dextrose, g/kg/d</td>
<td>24</td>
<td>15</td>
<td>11</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Dextrose energy, kcal/kg/d</td>
<td>82</td>
<td>51</td>
<td>37</td>
<td>34</td>
<td>41</td>
</tr>
<tr>
<td>Lipids, g/kg/d</td>
<td>0</td>
<td>3.0</td>
<td>2.0</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Lipid energy, kcal/kg/d</td>
<td>0</td>
<td>27</td>
<td>18</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Total nonprotein energy, kcal/kg/d</td>
<td>82</td>
<td>78</td>
<td>55</td>
<td>34</td>
<td>50</td>
</tr>
<tr>
<td>Amino acids, %</td>
<td>0</td>
<td>3.0</td>
<td>2.5</td>
<td>1.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Amino acids, g/kg/d</td>
<td>0</td>
<td>3.6</td>
<td>2.8</td>
<td>1.8</td>
<td>1.8</td>
</tr>
</tbody>
</table>

*Glucose = 3.4 kcal/g and lipids = 9 kcal/g*

The nutritional energy of a parenteral solution can be computed using conversion factors for the main constituents. Carbohydrates provide 4 kcal/g, unless glucose is used. Glucose crystals provide only 3.4 kcal/g because they are weighed in the hydrated state. Lipids provide 8 to 10 kcal/g. Protein, when catabolized for energy, provides 4 kcal/g. Because of the complexity of protein metabolism in the growing premature infant and the many variables that determine how much delivered protein is turned over, accreted, or excreted, discussion of amino acids often is excluded when calculating parenteral energy delivery. Enteral feeding calculations, however, usually include the protein energy content.

The resting metabolic rate of the third-trimester fetus is estimated at 50 to 60 kcal/kg per day. Meeting this need in a premature infant, and replacing the 1% daily loss of nitrogen seen when no amino acids are given, is likely to prevent loss of endogenous body protein. The metabolic linkage between energy and amino acids requires that both be provided. However, this level of nutritional support does not result in substantial growth.

Parenteral nutrition that does not provide the minimum rate of nonprotein energy (response 4) or amino acids (response 1) results in a negative nitrogen balance and loss of endogenous body protein.

Providing additional amino acids when nonprotein energy is near the minimum level of 50 kcal/kg per day (response3) will give some growth, but only at a fraction of the fetal growth rate.
More energy is needed to process the additional amino acids and achieve the fetal and early neonatal accretion rate for nitrogen, estimated as 2 to 3 g/kg per day. A growth rate paralleling the intrauterine growth rate in a clinically stable infant can be achieved with a parenteral nonprotein energy intake of about 80 kcal/kg per day and a protein intake of 2.5 to 3.5 g/kg per day (response 2).

Many variables are involved in predicting the nitrogen accretion and growth rate of an individual child. Nutritional needs increase during stresses, such as hypothermia, sepsis, or surgery. Administered glucocorticoids or catecholamines can disrupt normal metabolism. Expressed mother’s milk may vary widely in its fat and energy content. The studies used to estimate the nutritional needs of the premature infant represent group averages only, but they do allow a starting point to begin parenteral and enteral feedings.

References:


American Board of Pediatrics Content Specification(s):

Understand the importance of protein and nonprotein nutrients in achieving optimal utilization of energy and nitrogen

Understand the consequences of feeding low-birthweight infants too little or too much protein

Know how to calculate the caloric content of parenteral nutrition solutions
A full-term newborn is admitted for evaluation of ambiguous genitalia (Figure 1). You are discussing with medical students the stages of normal fetal sex differentiation and the hormones involved in the process.

**Figure 1: Ambiguous genitalia**

Of the following, the hormone CRITICAL for the differentiation of the external genitalia in a male fetus is:

1. antimüllerian hormone
2. dihydrotestosterone
3. insulinlike hormone
4. luteinizing hormone
5. testosterone

You selected 4, the correct answer is 2.

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

Fetal sex differentiation is defined as the acquisition of male or female characteristics in anlage that are initially similar regardless of the genetic sex. Normally, genetic sex, gonadal sex, and somatic sex are concordant with one another and with the sex that is assigned to the neonate based on external genital appearance. If this concordance is lost, ambiguity of sex is the result, as in the infant in this vignette.

Normal fetal sex differentiation occurs in four successive, overlapping stages of sex development.

1. Genetic sex determination: The genetic (chromosomal) sex is established at the time of gamete fertilization. A fetus with a 46,XY karyotype is destined to follow the male pathway of
sex differentiation characterized by the development of testes and other features of masculinization. A fetus with a 46,XX karyotype is destined to follow the female pathway of sex differentiation characterized by the development of ovaries and other features of feminization.

2. Gonadal sex differentiation: The stage of gonadal sex differentiation begins in the first few weeks of gestation with the development of a primordial, bipotential gonad. This gonad develops from condensation of a ridge of mesenchymal tissue located near the mesonephros accompanied by penetration of the mesenchyme by proliferating coelomic epithelium. The coelomic epithelium constitutes the outer cortex and the mesenchyme constitutes the inner medulla in this primitive gonad. Under the influence of complex interacting genes, some established and others putative, the medulla develops and the cortex regresses in the 46,XY fetus, resulting in the formation of a testis, whereas the cortex develops and the medulla regresses in the 46,XX fetus, resulting in the formation of an ovary (Figure 2).

![Figure 2: Gonad formation](http://emb.aap.org/courseprodv2/Index.asp)

The key genes involved in the formation of the testis from the primordial gonad are sex-determining region of the Y (SRY) gene and SRY homeoboxlike (SOX9) gene. The SRY gene is a 3.8-kb single-exon gene located on chromosome Y (Yp11.3). The SOX9 gene is a 3.9-kb single-exon gene located on chromosome 17 (17q24.25). The formation of the testis from the primordial gonad requires an active SRY gene and an active SOX9 gene.

The key gene involved in the formation of the ovary from the primordial gonad is wingless type MMTV integration (WNT4) gene. The WNT4 gene is a 25-kb five-exon gene located on chromosome 1 (1p35). The formation of the ovary from the primordial gonad requires an active WNT4 gene and a suppressed SOX9 gene.

The timetable for the gonadal sex differentiation during gestation is different between the male and female fetuses. The differentiation of the primordial gonad into testis occurs around 6 weeks of gestation, whereas the differentiation of the primordial gonad into ovary occurs around 10 weeks of gestation.

3. Gonaductal (internal somatic) sex differentiation: The stage of gonaductal (internal somatic) sex differentiation begins in the first few weeks of gestation with the development of two sets of embryonic internal genital tracts—wolffian and müllerian ducts (Figure 3).

![Figure 3: Gonaduct formation](http://emb.aap.org/courseprodv2/Index.asp)
Masculinization of the internal genital tract involves stabilization of the wolffian duct and resorption of the müllerian duct. Wolffian duct stabilization requires exposure to testosterone secreted by Leydig cells of the fetal testis. Müllerian duct reabsorption requires exposure to antimüllerian hormone (AMH) secreted by Sertoli cells of the fetal testis. The wolffian duct differentiates into epididymides, vasa deferentia, and seminal vesicles.

Feminization of the internal genital tracts involves stabilization of the müllerian duct and resorption of the wolffian duct. Both müllerian duct stabilization and wolffian duct resorption occur in the absence of testosterone and AMH. The müllerian duct differentiates into fallopian tubes, uterus, and upper vagina.

The timetable for the gonaductal (internal somatic) sex differentiation during gestation is different between the male and female fetuses. In the male fetus, the wolffian duct differentiates between 9 and 12 weeks of gestation, whereas in the female fetus, the müllerian duct differentiates between 10 and 13 weeks of gestation.

4. Genital (external somatic) sex differentiation: The stage of genital (external somatic) sex differentiation begins in the first few weeks of gestation with the development of an undifferentiated, ambisexual external genital (Figure 4).

Figure 4: Formation of external genitalia
This structure includes a urogenital sinus surrounded by urethral folds and labioscrotal folds on the two sides and a genital tubercle at its ventral end. Under the influence of an androgen (primarily dihydrotestosterone [DHT]) in the male fetus, the genital tubercle elongates to form the body of the penis, the urethral folds fuse from behind forward to form the penile urethra, and the labioscrotal folds fuse in the midline to form the scrotum. DHT also induces the urogenital sinus to differentiate as the prostate.

In the absence of the androgen (primarily DHT) in the female fetus, the genital tubercle elongates only slightly to form the clitoris, the urethral folds do not fuse but develop into labia minora, and the labioscrotal folds enlarge but remain unfused to form the labia majora.

The timetable for the genital (external somatic) sex differentiation during gestation is different between the male and female fetuses. The differentiation of the external genitalia in the male fetus occurs between 8 and 13 weeks of gestation, whereas in the female fetus it occurs between 10 and 14 weeks of gestation.

Among the hormones listed, the androgen DHT is critical for the differentiation of the external genitalia in the male fetus. DHT is derived from testosterone by a reaction catalyzed by the microsomal enzyme 5α-reductase. There are two isoenzymes of 5α-reductase encoded by separate genes: 5α-reductase1 by SRD5A1 gene located on chromosome 5(5p15) and 5α-reductase2 by SRD5A2 gene located on chromosome 2 (2p23). In the context of fetal sex differentiation, the more important of these two enzymes is 5α-reductase2, which mediates the conversion of testosterone to DHT in androgenic target tissue.

Testosterone is produced from cholesterol by Leydig cells in the fetal testicular interstitium. In the context of fetal sex differentiation, testosterone is critical for stabilization of the wolffian duct and the resultant formation of male gonaductal structures.

Antimüllerian hormone is a member of the transforming growth factor b family. AMH is a glycoprotein dimer linked by disulfide bonds and encoded by a 2.8-kb gene located on chromosome 19. AMH is produced by Sertoli cells in the fetal testis and is critical for resorption of the müllerian duct. A combination of testosterone and AMH stabilizes the wolffian duct and the resultant formation of male gonaductal structures.

Luteinizing hormone does not play a major role in fetal sex differentiation. It plays a role in conjunction with testosterone in promoting normal penile growth in the third trimester of gestation.

Insulinlike hormone, a member of the insulin/relaxin hormone family, secreted by Leydig cells in the fetal testis, does not play a major role in fetal sex differentiation. It may play a role in the control of testicular descent as suggested by the occurrence of cryptorchidism in patients with mutations of this hormone.
Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:


American Board of Pediatrics Content Specification(s):

Understand normal fetal sexual differentiation

Differentiate among disorders of testicular hormone synthesis or action

Understand the etiology of abnormal sexual differentiation
May: Question 6

A 750-g infant is born at 26 weeks’ gestation. The infant receives surfactant in the delivery room and begins receiving nasal continuous positive airway pressure. The infant’s care is provided in an incubator setting, with a humidity hood over the infant. He is given parenteral fluids at 2.5 mL/hour using a 10% dextrose solution containing 4 g of amino acids per 100 mL.

Of the following, the MOST likely effect of this fluid solution on the infant is:

1. continued in utero rate of weight gain from birth
2. hyperaminoacidemia
3. hyperkalemia
4. improved glucose tolerance
5. metabolic acidosis

You selected 4, the correct answer is 4.

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

Very-low-birthweight infants who receive only glucose-containing fluids after birth may rapidly develop adverse nutritional consequences (“metabolic shock”) from the decline in concentrations of key amino acids, especially arginine and leucine. Early administration of amino acid–containing fluids results in improved endogenous insulin secretion and improved glucose tolerance because insulin secretion depends on the concentrations of glucose, arginine, and lysine. Lack of amino acids leads to hyperglycemia, because secretion of insulin and insulinlike growth factors decreases and endogenous glucose production increases. Infants lose weight after birth for two predominant reasons. Clearance of excess extracellular fluid accounts for about 50% of weight loss; this loss is part of the adaptation to extrauterine life and is of no consequence nutritionally. In preterm and other sick infants, catabolism of endogenous protein and fat stores results in lost tissue mass and intracellular fluid, and weight decreases. The goal of early amino acid administration is to avert these losses and shorten the time to the return to birthweight. Very-low-birthweight infants who receive 3 g/kg per day of parenteral amino acids do not face the complication of hyperaminoacidemia; threonine and lysine concentrations actually remain low.

Fetal energy at 26 weeks’ gestation is derived mostly from glucose and amino acids transported to the fetus by the placenta. Up to 50% of amino acids taken up by the fetus are oxidized to provide energy. Lipids provide little nutritional benefit for the fetus early in gestation. During the third trimester, however, lipids assume a more important nutritional role.

Insulin and insulinlike growth factors regulate glucose and amino acid uptake at the cell membrane. Na+, K+ ATPase activity requires adequate glucose and amino acid uptake at the cell membrane. If glucose and amino acid uptake are inadequate, Na+, K+ ATPase activity is impaired and contributes to intracellular energy failure. Leakage of intracellular potassium leads to nonoliguric hyperkalemia, which can be prevented by early amino acid administration.

In studies of early parenteral amino acid administration, no recognizable metabolic complications such as metabolic acidosis, hyperammonemia, or abnormal serum amino acid concentrations have been reported.
profiles (aminogram) were found. Because amino acids provide a significant fraction of total energy for the midtrimester fetus, urea production exceeds that of the term infant and adult. Serum urea nitrogen concentrations show no reliable correlation with protein intake. Infants having serum urea nitrogen concentrations exceeding 40 mg/dL have significantly lower birthweights and higher incidences of hypotension, clinically significant patent ductus arteriosus, and higher Score for Neonatal Acute Physiology Perinatal Extension (SNAPPE), suggesting that serum urea nitrogen may correlate with the severity of illness rather than function as a marker of excess protein administration.

(Content revised August 31, 2009)

References:

Adamkin DH. Nutrition management of the very low-birthweight infant: I, total parenteral nutrition and minimal enteral nutrition. NeoReviews. 2006;7:e602-e607


American Board of Pediatrics Content Specification(s):

Understand the protein requirements of preterm and full-term infants

Understand the consequences of feeding low-birthweight infants too little or too much protein

Determine the nutrients and the relative amounts required for normal fetal growth
In 1889, William Perry Northrup, MD, of New York City described a series of 114 infants between the ages of 7 and 14 months, mostly from affluent families, who presented with weakness, irritability, tachypnea, failure to thrive, and diarrhea. More specifically, they had symmetrical swelling of their extremities and marked tenderness over long bones. Typically they were found to be lying in bed quietly in the frog-leg position and fearful of the approaching doctor. Petechial hemorrhages in skin and mucous membranes were also common findings. Some cases were fatal. Northrup eventually identified the cause of this disease through postmortem examination.

Of the following, the MOST likely diagnosis for the infants reported by Northrup was:

1. battered child syndrome
2. hemorrhagic disease
3. rickets
4. scurvy
5. tuberculosis

You selected 2, the correct answer is 4.

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

The infants described in the vignette have scurvy, which is caused by a nutritional deficiency of vitamin C (ascorbic acid). Although not mentioned specifically, several would have had swollen, bleeding gums. The typical posture they exhibited is known as pseudoparalysis which is caused by the extreme pain associated with movement. Anemia would have been common because of blood loss and the role of ascorbic acid in hemoglobin synthesis. Most of the typical symptoms of scurvy are the result of defects in collagen synthesis.

Ascorbic acid, a water-soluble vitamin (Figure), acts as a cofactor in several hydroxylation and amidation reactions by providing reducing equivalents (transferring electrons to enzymes) for oxidation-reduction reactions. Ascorbic acid is essential for the conversion of proline and lysine residues in procollagen to hydroxyproline and hydroxylysine. It also promotes the absorption of iron from the stomach. Defective collagen synthesis leads to excessive capillary fragility and rupture of capillaries in mucous membranes and in the periodontal and periosteal membranes.

Figure
W. P. Northrup was a contemporary of William Osler and Thomas Morgan Rotch. Dr Rotch was famous for many advances in the care of infants and children including his infant formulas. He recommended using his unique and popular “percentage method” for home-made recipes. His “scientific” formulas were composed of cow’s milk, water, cream, and carbohydrate (sugar or honey) in precise ratios. Some of the well-to-do of New York adopted these modern views for “dry nursing,” while poor people continued to breastfeed or use wet nurses.

The minimum daily requirement of vitamin C for infants is 40 mg. Human milk contains 40 to 60 mg/L of ascorbic acid and even more with high maternal intakes. Cow’s milk, on the other hand, contains only 20 to 25 mg/L of ascorbic acid, a borderline concentration to start with. In addition, infantile bacterial diarrhea was common, and pasteurization was already popular by the 1880s. Parents themselves were likely to heat batches of formula and then store them in ice boxes. Although commercial pasteurization itself (30 minutes’ exposure to 145°F or 63°C followed by rapid cooling) does not destroy significant amounts of ascorbic acid, higher temperatures and exposure for longer periods degrade an increasing percentage of the vitamin. Furthermore, ascorbic acid concentrations in milk exposed to air have been shown to fall dramatically after being stored in the refrigerator even for a day or in a freezer for a week.

Battered child syndrome (BCS) was first described in the 20th century, but many such children were mistakenly diagnosed as having other diseases before the features of BCS became well known. The syndrome is not exclusive to any particular economic class. The injuries in BCS are usually not symmetrical and pseudoparalysis is not a feature. Petechial hemorrhages in skin can be consistent with BCS but not in mucous membranes.

Hemorrhagic disease of the newborn is usually seen in the first week after delivery in infants who have not had prophylactic vitamin K at birth. Typical cases are breastfed. Bleeding usually starts at the umbilicus, or from mucous membranes, gastrointestinal tract, or wounds such as circumcision. Subperiosteal bleeding is not described.

Rickets in infancy is usually the result of dietary vitamin D deficiency. It presents as bony deformities, including nodular enlargements along the costochondral junctions of the ribs (rachitic rosary), enlargement of wrists and ankles, and bowing of weight-bearing long bones. Bleeding and pain are not features.

Tuberculosis (often miliary in infancy) can mimic many conditions. Failure to thrive is common, as are weakness, irritability, fatigue, and generalized lymphadenopathy. Signs of meningitis are common, but bleeding and swollen limbs are not.

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

References:


Holmes AD, Lindquist HG, Jones CP, Wertz AW. Effect of high-temperature-short-time


**American Board of Pediatrics Content Specification(s):**

Understand the clinical and laboratory manifestations of deficiencies of water-soluble vitamins
July: Question 4

A male infant born at 30 weeks’ gestation is 12 days old. He is receiving full volume enteral feedings with preterm infant formula.

Of the following, the MOST important mechanism of fat digestion and absorption in this infant is:

1. bile acid emulsification
2. carnitine production
3. chylomicron hydrolysis
4. intragastric lipolysis
5. micelle formation

You selected 4, the correct answer is 4.

Effective digestion and absorption of dietary fats is important for energy production, growth, and development. Because dietary fats are insoluble in the aqueous intestinal environment, they first need to be solubilized (or emulsified). Bile salts synthesized in the liver and secreted from the gallbladder emulsify ingested fats. These emulsified fats are then degraded by pancreatic lipases, generating monoglycerides, fatty acids, phospholipids, and cholesterol. In the presence of bile acids, these products of fat digestion form aggregates, known as micelles.

The micelles permit transport of these compounds from the intestinal lumen into mucosal cells. Within the intestinal cells, triglycerides are resynthesized from monoglycerides and fatty acids. The triglycerides are then solubilized by the formation of lipoprotein complexes, or chylomicrons, composed of lipid droplets surrounded by polar lipids and an outer layer of proteins. Chylomicrons from the intestine are then released into the lymphatic system, and fat by-products can be delivered to tissues. Carnitine plays an important role in the β-oxidation of long-chain fatty acids in intracellular compartments.

Adequate fat digestion is critical for the growth of preterm infants because fat comprises 40% to 50% of the available calories in formula and is the major energy source for the growing infant. While adults absorb more than 95% of dietary fat, preterm infants absorb between 65% and 80% of ingested fat. This decreased fat absorption in preterm infants is attributed to low pancreatic lipase activity and impaired solubilization of lipids as a result of low bile salt concentrations.

To compensate for these insufficiencies, the preterm infant relies on lingual and gastric lipase secretion for fat digestion. While absorption of long chain triglycerides (LCTs) mostly requires adult mechanisms of fat breakdown, including pancreatic lipase activity, micelle and chylomicron formation, and carnitine availability, breakdown of medium chain triglycerides (MCTs) relies on intragastric lipolysis. Because lingual and gastric lipases prefer acidic environments and do not require fat emulsification by bile salts, hydrolysis of MCTs in the preterm infant is initiated in the stomach. Delayed gastric emptying time in preterm newborns allows for even longer periods of intragastric MCT digestion. Indeed, preterm infants fed by nasojejunal route have lower fat absorption compared with infants fed...
directly into the stomach. After intragastric lipolysis, most of the MCT by-products can then be absorbed directly into the serum without the assistance of micelles. Thereafter, medium chain fatty acids bind to albumin and are then transported directly to the liver. Independent of carnitine, these products can then enter cellular mitochondria for \( \beta \)-oxidation. Thus, intragastric lipolysis is the most important mechanism of fat digestion and absorption for the infant in this vignette.

Because preterm infants can digest and absorb MCTs both faster and more easily than LCTs, preterm formulas are now composed of higher amounts of MCTs. One disadvantage of this change in formula composition is a lowered amount of ingested long-chain polyunsaturated fatty acids, which are thought to be important for retinal development and visual acuity. However, these fatty acids make up only a small proportion of the total LCTs in preterm formulas. Data derived from eight randomized controlled trials suggest that there is no difference in short-term growth of preterm infants fed high versus low MCT formula. Further data are needed to determine differences in long-term growth and neurodevelopmental outcomes.

Bile acid emulsification is limited in the preterm infant because of decreased bile salt concentrations. Preterm infants compensate for impaired lipid solubilization by using lingual and gastric lipases.

Carnitine is synthesized from lysine and is important in the transfer of fatty acids across the inner mitochondrial membrane for \( \beta \)-oxidation of long-chain fatty acids and the production of adenosine triphosphate. Preterm infants are prone to carnitine deficiency because most of carnitine is acquired transplacentally during the third trimester. Thus, preterm infants rely on exogenous carnitine intake rather than carnitine production.

Intravascular chylomicron hydrolysis requires an adequate lipoprotein lipase concentration. Although this enzyme is slightly decreased in preterm infants, it does not appear to affect chylomicron hydrolysis in these infants. It is unknown whether the assembly and/or secretion of chylomicrons are rate-limiting in fat absorption in the preterm infant.

Micelle formation is impaired in the preterm infant because of decreased bile salt concentrations. While micelles are still required for digestion and absorption of all ingested LCTs, most of the ingested MCTs can be absorbed directly after intragastric lipolysis, without the need for micelle formation.
Understand the role of medium-chain triglycerides in neonatal nutrition
August: Question 4

A 700-g infant regained her birthweight 14 days after birth. She is receiving 120 kcal/kg per day (503 kJ/kg/day) of fortified infant formula. Three weeks later, she is noted to be growing at 10 g/kg per day, and her head circumference has increased 1 cm during the past 2 weeks. She requires 24% supplemental oxygen, has normal radiographic findings, and generally appears healthy. Blood cell count, electrolytes, and blood gases are normal.

Of the following, the BEST nutritional strategy for this infant would be to add:

1. carbohydrate
2. lipid
3. nothing
4. protein
5. volume

You selected 4, the correct answer is 4.

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

Although appearing well, this infant is growing suboptimally. Once having regained their birthweights, very-low-birthweight infants should demonstrate a weight gain of more than 18 g/kg per day, and their head growth should exceed 0.9 cm per week. As weight gain increases from 12 g/kg per day to 21 g/kg per day, the incidences of cerebral palsy, Bayley II Mental Developmental Index and Psychomotor Developmental Index scores less than 70, abnormal neurologic findings, neurodevelopmental impairment, and need for rehospitalization decrease. Gain in head circumference shows similar correlations, suggesting best outcomes with increases of more than 0.9 cm per week. When lower-than-desirable growth velocity is observed and not accounted for by comorbidities, nutritional adjustment by increasing the protein-energy ratio may be the best strategy.

Shortly after birth, preterm infants uniformly show weight loss. Part of this weight loss, approximately 50%, is the desirable loss of extracellular fluid required for extrauterine adaptation. The remainder reflects loss of lean body mass and intracellular fluid associated with inadequate nutrition. Early use of parenteral amino acid/glucose solutions and early enteral feeding may minimize this loss. The times for the infant to reach nadir weight and then to regain birthweight are inversely proportional to this loss of body mass and are directly proportional to the child's energy and protein deficits.

Had this infant remained in utero, she would have gained more than 15 g/kg of weight per day and accumulated approximately 3 g/kg of protein per day. Preterm infant formula or fortified breast milk provided at 120 kcal/kg per day (503 kJ/kg/day) can reasonably be predicted to meet her energy needs and to compensate for her energy deficit. Currently, energy intakes in excess of 120 kcal/kg per day are not considered desirable so as to avoid excess fat accretion. On the other hand, current feedings may not provide sufficient protein for adequate growth, especially when a significant protein deficit must be overcome, as in the infant in this vignette. Protein intakes up to 3.6 g/100 kcal per day (4.3 g/kg/day if fed 120 kcal/kg/day) result in an increase in the protein-energy ratio.
Supplementing her feedings with calories in the form of carbohydrate or lipid would decrease the protein-energy ratio and not facilitate better rates of restoring lean body mass. Increasing volume would increase both caloric intake and protein, but leave the nutritional composition unchanged. In the face of a low growth velocity, making no change in the nutritional strategy would not be the wisest approach.

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

References:


American Board of Pediatrics Content Specification(s):

Understand how to ascertain and calculate the caloric requirements to ensure optimal growth of preterm infants

Understand the protein requirements of preterm and full-term infants

Understand the consequences of feeding low-birthweight infants too little or too much protein

Know the interventions used to prevent mental retardation and their effects on cognitive outcome
A 5-hour-old newborn, who weighs 1,250 g at an estimated gestational age of 27 weeks, has respiratory distress. Maternal history was significant for spontaneous rupture of membranes about 3 days before delivery and subsequent onset of preterm labor. The mother is a carrier of group B *Streptococcus* and has had a history of *Chlamydia* infection. Administration of corticosteroids and antibiotics was completed before delivery. Apgar scores were 3 and 7 at 1 and 5 minutes after birth, respectively. The resuscitation included endotracheal intubation, positive pressure ventilation, and administration of surfactant. The infant is supported with a mechanical ventilator and has umbilical arterial and venous access. Narcotic analgesia is used for these procedures, but the infant remains irritable and has frequent oxygen desaturations when manipulated. You are considering adding midazolam for further sedation.

Of the following, the most likely EXPECTATION if midazolam is given to this infant is that it will:

1. be safe without serious side effects
2. block g-aminobutyric acid binding in the brain
3. have a half-life of less than 4 hours
4. have less bioavailability than in the adult if given orally
5. provide effective sedation

You selected 1, the correct answer is 5.

Midazolam is a short-acting benzodiazepine that provides sedation and muscle relaxation in adults and children. The structure of midazolam is shown in the Figure.
This drug can be administered intravenously, orally, sublingually, or nasally. Midazolam has come into wide use as a sedative for neonatal intensive care patients in recent years. Randomized controlled trials, using behavioral and physiologic outcome measures in premature infants of varying gestational ages and weights, have shown midazolam to be more effective than placebo. However, these trials were relatively small and did not specifically investigate whether the most immature infants responded as well as more mature infants.

Moreover, the safety of midazolam in premature infants has come under question, because adverse events including death, possible seizures, severe intracranial hemorrhage, and periventricular leukomalacia have occurred more frequently with midazolam use than with placebo. Such adverse outcomes, however, have not been consistently found. Further controlled trials are needed, especially in small and sick premature infants.

The mode of action of midazolam is to promote the binding of g-aminobutyric acid (GABA) to the GABA_A receptor by attaching itself to the benzodiazepine-binding site of that receptor. GABA acts as a central nervous system inhibitor (sedative) and the GABA_A receptor functions as a ligand-gated transmembrane chloride channel.

The observed increases in adverse neurologic outcomes of premature infants treated with midazolam as compared with placebo are understandable when considering data from controlled studies of immature animals. These studies show that the effect of midazolam and its side effects are highly dependent on the maturity of the animal brain so exposed. Three-day-old rat pups (with brain development roughly comparable with that of premature infants of 24-28 weeks’ gestation) receive no sedative effect from midazolam. Midazolam produces heightened sensitization to noxious stimuli in these immature animals. On the other hand, 10-day-old rats (comparable with term newborn infants) are sedated by midazolam. The introduction of midazolam to the early developing mammalian brain (before maturation of GABA_A receptors) results in stimulation of neural activity (not inhibition) and an excess of neuronal apoptosis, similar to the effects of ethanol on the developing brain.

The half-life of midazolam in adults is 1.9 to 3.2 hours, justifying its reputation as a “short-acting” sedative. Metabolism and elimination kinetics depend on the following steps: demethylation and hydroxylation at the 1-position of midazolam; catalyzed by the mixed function oxidase, cytochrome P450 3A4 (CYP3A4); and subsequent glucuronidation of the same hydroxyl radical. CYP3A4 is found in adult liver and intestines but is absent from either tissue in the fetus. After parturition, CYP3A4 activity remains far below adult levels in premature and newborn infants. Consequently the half-life of midazolam in premature infants is considerably longer, with mean estimates of 6.3 hours (intravenous) to 7.6 hours (oral). Of interest, because of the similar developmental course of intestinal CYP3A4, almost half of a dose of midazolam administered orally to a premature infant is absorbed intact, while only one fourth survives to absorption in adults.

Midazolam clearance can be altered by interactions with other drugs. Reduced clearance of midazolam has been reported in the presence of CYP3A4 inhibitors such as cimetidine, fluconazole, and erythromycin. Infants treated with indomethacin, on the other hand, have been reported to clear midazolam more efficiently because of either the drug interaction or the patent ductus arteriosus itself.

References:


de Wildt SN, Kearns GL, Hop WC, Murry DJ, Abdel-Rahman SM, van den Anker JN.


American Board of Pediatrics Content Specification(s):

Understand the mechanisms by which various drugs are metabolized

Identify the factors involved in the disposition of a drug and understand the differences between drug distribution in infants and adults
A growth-restricted female infant born at term gestation is being discharged from the newborn nursery 6 days after birth. Newborn screening shows that she has a high risk for cystic fibrosis and is scheduled to have a buccal smear. The infant’s mother expresses her desire to have her infant drink a soy protein–based formula. She explains that the infant’s sibling, a male born at term gestation, had severe colic and after several months of trying different formulas and potential remedies, a change to soy formula led to resolution of his colic. This child now has severe eczema and allergies to several foods. In addition to preventing colic and allergies, the mother would like to transition to soy formula because she has recently become a vegetarian and wishes that her children abide by this diet.

Of the following, the MOST appropriate indication for initiating soy protein–based formula in this infant is to:

1. maintain a vegetarian diet
2. minimize malabsorption
3. maximize fat intake
4. obviate allergies
5. prevent colic

You selected 5, the correct answer is 1.

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

Formulas with soy protein were developed to assist infants who were unable to tolerate milk protein. The popularity of soy protein–based infant formula doubled during the late 1980s to early 1990s. By the late 1990s, sales of soy formulas accounted for approximately 20% of the formula market in the United States. To clarify the indications for these formulas, the American Academy of Pediatrics (AAP) established specific recommendations in 1998, which were revised in 2008, for the use of soy formulas. The AAP recommends the use of soy formulas instead of cow milk–based formulas for the following infants:

- Term infants with galactosemia
- Term infants with hereditary lactase deficiency
- Term infants with a secondary lactose intolerance
- Term infants whose care providers are instituting a vegetarian diet

In this vignette, the mother’s interest in maintaining a vegetarian diet for her infant is an indication for the use of a soy protein–based formula.

Protein hydrolysate formulas, rather than soy formulas, are the preferred diet for infants with significant malabsorption from gastrointestinal or hepatobiliary diseases such as cystic fibrosis, short gut syndrome, biliary atresia, or protracted diarrhea. Because the milk protein
(either casein or whey) is heat-treated and enzymatically hydrolyzed, hydrolysate formulas contain free amino acids and peptides that are easily absorbed. In addition, these formulas contain medium-chain triglycerides to facilitate fat absorption. Polysaturated vegetable oil is added to supply essential fatty acids. Most of the protein hydrolysate formulas are lactose-free and the carbohydrate component contains various amounts of sucrose, tapioca starch, corn syrup solids, and/or cornstarch.

Because soy formulas contain the same amount and type of fats as found in cow milk–based formulas, soy formulas will not improve the growth of the growth-restricted term infant in this vignette. However, these two formulas have certain distinctive nutritional components. As expected, the source of protein in soy formulas is soy instead of cow milk protein. Methionine, taurine, and carnitine are added to soy formulas to compensate for the low concentration of these amino acids in soy protein. To avoid possible contamination with milk proteins, lactose is not used in soy formulas. Instead, the carbohydrate component of soy formulas consists of sucrose, cornstarch hydrolysates, or a mixture of these two. Similar to cow milk formulas, soy protein–based formulas meet the iron, vitamin, mineral, and electrolyte content specifications for feeding term infants that has been established by the US Food and Drug Administration. However, unlike cow milk–based formulas, soy formulas contain soy phytoestrogens; at present, there is no conclusive evidence that these compounds affect human development, reproduction, or endocrine function.

Some studies suggest that soy protein–based formulas can have a calming benefit for infants with colic but controlled trials of cow milk and soy formulas have not shown a significant benefit with soy exposure. Soy formulas have not been shown to prevent colic.

While studies have suggested that soy protein–based formulas can be useful to treat infants with a documented cow milk protein allergy, approximately 10% to 14% of these allergic infants will also have a soy protein allergy. Thus, the AAP recommends that clinicians should consider recommending hydrolyzed protein formulas instead of soy formulas to these infants. There is no evidence that a soy formula diet can obviate allergies.

The AAP guidelines also emphasize that soy protein–based formulas are not indicated for preterm infants. Studies have shown that preterm infants receiving a soy formula diet have lower serum phosphorus concentrations, higher alkaline phosphatase concentrations, and a greater degree of osteopenia than preterm infants receiving a cow milk protein–based formula.

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

References:


Berseth CL, Johnston WH, Stolz SI, Harris CL, Mitmesser SH. Clinical response to 2 commonly used formulas occurs within 1 day [published online ahead of print October 2, 2008]. Clin Pediatr [Phila].


American Board of Pediatrics Content Specification(s):

Understand the benefits and risks of formulae that contain soy proteins
Understand the benefits and risks of formulae that contain hydrolyzed proteins
Human milk is uniquely suited to meet the needs of the newborn infant, providing bioavailable nutrients, as well as bioactive and immunoprotective factors. Although the protein content of human milk is only approximately 25% that of cow milk, the qualitative differences in protein composition make human milk superior for the neonate.

Of the following, the PREDOMINANT human whey protein is:

1. α-lactalbumin
2. β-lactoglobulin
3. immunoglobulin A
4. lactoferrin
5. lysozyme

You selected 5, the correct answer is 1.

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

Human milk supplies the newborn with bioavailable nutrients as well as bioactive and immunoprotective factors. Adapting to the needs of the newborn, human milk provides digestive enzymes, immunoglobulin A (IgA), taurine, nucleotides, and long-chain polyunsaturated fatty acids. Postcolostrum or mature milk is mostly composed of water (88%), followed by carbohydrates (5.6%-6.9%), lipids (3.4%-4.4%), and proteins (1.7%-2.2%).

The protein content of mature human milk is approximately 0.9 g/dL, with the constituents being a mixture of mucins as well as whey and casein proteins. Also known as milk fat globule membrane proteins, mucins contribute to the membranes that surround milk fat globules. The proportion of protein in human milk attributed to mucin is very small. Caseins are proteins with low solubility in acid media. Whey proteins promote more rapid gastric emptying, and remain in solution after acid precipitation, facilitating their digestion. Mature human milk is whey predominant, but the proportion of whey and casein components varies throughout lactation. Early in lactation, the whey-to-casein ratio may be 80:20, and as casein production increases later in lactation, the ratio approaches 50:50. On average, human milk is considered to have a whey-to-casein ratio of 60:40.

The major proteins in human milk are listed in the Table. The mammary gland synthesizes most proteins, but serum albumin comes from the maternal circulation.

Table: Major Proteins in Human Milk
The chief fraction of whey protein in human milk is made up of α-lactalbumin, amounting to 41% of the whey protein and 28% of the total protein. α-Lactalbumin has both biochemical and nutritional roles for the mother-infant dyad. Two proteins produced by the mammary gland, α-lactalbumin and galactosyltransferase, form the enzyme complex lactose synthase, which catalyzes the synthesis of lactose from glucose and galactose. Subsequently, α-lactalbumin dissociates from the enzyme complex to become an integral part of the protein content of human milk. The nutritional value of α-lactalbumin relates to its high proportion of essential amino acids, particularly tryptophan, cysteine, and lysine. In addition, α-lactalbumin binds minerals such as calcium and zinc, facilitating their absorption from the gut.

Additional whey proteins found in high quantities in human milk, and involved in host defense, include secretory immunoglobulin A (IgA), lactoferrin, and lysozyme. β-Lactoglobulin is the major whey protein in casein-predominant cow milk (whey-to-casein ratio of 18:82), and is not measurable in human milk. Fourfold higher in colostrum than mature milk, IgA is the main immunoglobulin component of human milk, and is resistant to proteolysis. Additional functional advantages of IgA include four to eight antigen-binding sites, carbohydrate moiety-mediated antiadherence proteins, and inhibition of complement activation. The immunoprotective effect of IgA is mainly at the mucosal surface, where it plays an important role in first-line epithelial defense.

Nonimmune innate protection is provided by many milk proteins. Lactoferrin is bactericidal, antiviral, and anti-inflammatory, and it modulates cytokine function. In addition, lactoferrin reduces intestinal infections and the development of protein allergy via the mediation of mechanisms involved in neonatal intestinal growth, hepatic protein synthesis, intestinal recovery from injury, and stimulation of growth of probiotic intestinal bacteria. Lysozyme, the only protective protein that increases in concentration throughout lactation, cleaves bacterial walls and lyases gram-positive and some gram-negative bacteria.

The milk protein composition from a mother of a preterm infant (preterm milk) differs from that of a mother of a full-term infant, particularly during the first 2 weeks of lactation. The protein content of preterm milk is twice that of term milk, containing 2.0 g/100 mL at 1 week. Preterm milk has been shown to contain twice as much IgA, but also increased concentrations of lactoferrin and lysozyme compared with term milk, adapting to the increased immunologic needs of the preterm infant. The absolute concentration of the nutritional proteins beta-casein and lactalbumin is initially lower in preterm than term milk. After a few weeks, the nutritional proteins increase and immunologic constituents decrease to concentrations of term milk.

### References:


American Board of Pediatrics Content Specification(s):

Know the difference between the composition of the breast milk of the mother of a preterm infant and that of a full-term infant

Understand the differences in the nutritional composition of human milk and cow milk
A 1-week-old male infant who was delivered at 24 weeks' gestational age is in the neonatal intensive care unit (NICU). The infant is receiving continuous positive pressure ventilation, parenteral nutrition, minimal enteral feeds, and vitamin A. He is not receiving any other medications. He is voiding normally and has normal renal function. The first-year pediatric resident expresses his concern that the serum potassium concentrations as reported by the laboratory have been high for the last several days even in blood specimens that showed no hemolysis. You review with the resident the normal ranges for potassium concentrations in preterm and term infants and adults and the reference values used by the laboratory to designate abnormal results (Table 1).

### Table 1

<table>
<thead>
<tr>
<th>Potassium, mEq/L (mmol/L)</th>
<th>Range</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm infants, 1 week chronologic age</td>
<td>4.6-6.7 (4.6-6.7)</td>
<td>5.6 (5.6)</td>
<td>0.5</td>
</tr>
<tr>
<td>Laboratory reference value</td>
<td>3.4-5.0 (3.4-5.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For most infants in the NICU, blood chemistries are tested serially.

Of the following, the MOST likely percentage of serum potassium findings for preterm infants this age that would be reported as abnormally high by the laboratory is:

- 10
- 30
- 50
- 70
- 90

You selected 4, the correct answer is 5.

The serum potassium concentrations in the preterm infant in this vignette are likely to be designated as abnormally high in approximately 90% of the test results based on the laboratory reference ranges.

Serum potassium concentrations are an example of normally distributed data (Figure 1).
A normal distribution is a very important statistical pattern found in many natural phenomena, such as height, blood pressure, body temperature, shoe sizes, lengths of objects produced by machines, and tree diameters. Mathematicians de Moivre and Laplace used this distribution in the 1700s. In the early 1800s, German mathematician and physicist Karl Gauss used it to analyze astronomical data, and it consequently became known as the Gaussian distribution among the scientific community. The shape of the normal distribution resembles that of a bell, so it sometimes is referred to as the “bell curve.”

Normally distributed data exhibit predictable traits and probabilities. These include the following characteristics (Figure 1):

- Symmetry
- Unimodality
  - Extension to +/- infinity
  - Area under the curve = 1 (100% of the population)

The normal distribution can be completely specified by two parameters:

- Mean (μ)
- Standard deviation (σ)

The mean is located at the center of the symmetric curve and is the same as the median. Fifty percent of the distribution lies to the left of the mean and 50% lies to the right. The standard deviation controls the spread of a normal curve. Figure 2 shows two normal curves with different values of σ. The curve with the larger σ is more spread out. The height of the curve represents the probability of the measurement at that given distance away from the mean.

Figure 2: Two normal curves, showing the mean (μ) and standard deviation (σ)
In general, the normal distribution curve is described by the following probability density function:

$$f(x) = \frac{1}{\sqrt{2\pi}\sigma} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$

Of note, the equation of the curve is completely determined by the mean and standard deviation.

Given the mean and standard deviation of a data set that follows the normal distribution, the spread of the data can be quickly estimated using the empirical rule (Figure 3).

**Figure 3: The Empirical Rule: The 68-95-99.7 rule for normal distributions**

The empirical rule states that for a normal distribution:
68% of the distribution lies within 1 standard deviation of the mean.

- 95% of the distribution lies within 2 standard deviations of the mean.
- 99.7% of the distribution lies within 3 standard deviations of the mean.

An empiric estimate for the percentage of potassium concentration alerts can be determined by understanding the empiric rule and plotting the upper end of the potassium concentration reporting range on a normal curve with mean 5.6 mEq/L and standard deviation of 0.5 (Figure 4):

- Potassium distribution above the mean = 50%
- 5.0 mEq/L is near 1 standard deviation from the mean (5.6–0.5 mEq/L)
- Distribution between the mean and 1 standard deviation of the mean = 0.5×68% = 34%
- 50% + 34% = 84%, closest to the 90% listed among the answer choices

Figure 4: The Empirical Rule: The 68-95-99.7 rule for normal distributions

A more precise determination of the percentage of potassium values that are reported can be made using the z score and the Standard Normal Table. All normal distributions are the same if measured in units of size σ about the mean μ as center. Changing to these units is called standardizing. The standard normal distribution has μ = 0 and σ = 1 (Figure 5).

Figure 5
If $x$ is an observation from a distribution with a mean ($\mu$) and standard deviation ($\sigma$), the standardized value of $x$, also known as the $z$ score is:

$$z = \frac{x - \mu}{\sigma}$$

Standardizing is a linear transformation that transforms the data into the standard scale of $z$ scores. This allows comparison of observations belonging to different normal distributions, such as potassium concentrations at different ages.

The Standard Normal Table is a table of areas under the standard normal curve and is found in statistical texts and software. The table entry for each value of $z$ is the area under the curve to the left of $z$ (Figure 4).

The mean potassium concentrations for infants such as the infant in the vignette is 5.6 with $\sigma$ of 0.5 and range of 4.6 to 6.7 mEq/L. The laboratory uses an upper limit cutoff of 5.0 mEq/L to designate abnormal concentrations. Assuming that serum potassium concentrations are normally distributed, a serum potassium concentration of 5.0 corresponds to a $z$ score of $-1.2$:

$$z = \frac{5.0 - 5.6}{0.5} = -1.2$$

Based on the Standard Normal Table (Table 2), we can determine that 11.51% of the observations in this distribution will lie below a $z$ score of $-1.2$; therefore $(100 - 11.51) = 88.49\%$ of the observations will lie above (Figure 6).

Table 2: Standard Normal Table
Thus, using the laboratory reference standards, approximately 90% of the serial serum potassium concentrations in preterm infants at this age will be designated as abnormally high by the laboratory.

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

References:


http://www.math.unb.ca/~knight/utility/NormTble.htm


American Board of Pediatrics Content Specification(s):

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

You are called to the emergency department to evaluate a 3,500-g, 4-day-old female infant who has distressed breathing, dusky, and poor perfusion. She was discharged from the hospital 45 hours after delivery following an uncomplicated pregnancy. At home she had been eating poorly, sleeping longer, and acting listless. In addition to breathing support begun on arrival at the hospital, she was given 70 mL of normal saline and antibiotics. Laboratory serum studies reveal a sodium concentration of 142 mEq/L (142 mmol/L), bicarbonate concentration of 8 mEq/L (8 mmol/L), and an anion gap of 21 mEq/dL (21 mmol/L). Blood gas values reveal a pH of 7.01; partial pressure of carbon dioxide of 30 mm Hg (4.0 kPa), and partial pressure of oxygen of 110 mm Hg (14.7 kPa). As you consider further management, you are asked if you would like to give intravenous sodium bicarbonate, to which you answer “no.”

Of the following, the MOST significant physiologic concern regarding the use of sodium bicarbonate for metabolic acidosis is the associated:

- A. diffusion of bicarbonate into cells
- B. intracellular hypocarbia
- C. intracellular hypo-osmolality
- D. upward shift of the apparent pKa
- E. weak buffer capacity

Incorrect:  
Correct Answer: E

Although sodium bicarbonate has been widely used and often has been recommended for the treatment of metabolic acidosis, studies of its effectiveness and safety have not demonstrated better outcomes, either in the situation of cardiopulmonary resuscitation or in the treatment of metabolic acidosis. A review of the bicarbonate/carbonic acid buffer system is helpful in understanding both the limited ability of sodium bicarbonate to ameliorate metabolic acidosis in the physiologic setting and the potential negative consequences associated with its use.

In considering the benefit-risk balance, the potential for a treatment to be effective is measured against its potential side effects. What is our understanding of sodium bicarbonate as a treatment for metabolic acidosis in newborn infants? Sodium bicarbonate is not a base, that is, it does not contribute a
hydroxyl group (OH\(^{-}\)) when in solution. Sodium bicarbonate is the salt of a weak acid, and its impact depends on its ability to form a buffer (resist pH change when titrated). According to the Henderson-Hasselbach equation, when the concentrations of salt and acid are equal, a solution of a weak acid will be, by definition, at its pKa.

\[ \text{pH} = \text{pKa} + \log \left( \frac{[\text{salt}]}{[\text{acid}]} \right) \]

Buffering capacity is best within 1 pH unit of the pKa, which for the bicarbonate/carbonic acid system is 6.1. When pH is higher than 7.0, buffering capacity is nearly exhausted, as the ratio of salt to acid is near 10:1. Hence, weak buffering capacity is a major concern regarding lack of efficacy of sodium bicarbonate in the setting presented in this vignette.

What are the potential risks associated with sodium bicarbonate? Concerns involve the rate of clearance of carbon dioxide; adverse effect of increases in carbon dioxide, especially at the intracellular level; changes in osmolality; and potential distraction from diagnosis of underlying causes of acidosis.

An important feature of the bicarbonate/carbonic acid system involves the role of carbon dioxide. Many years ago, in vitro demonstrations showed that the following equation can be effectively blocked if the resultant gas, CO\(_2\), is not able to escape the system:

\[
\text{(H}^+\text{)} + (\text{NaHCO}_3) \leftrightarrow (\text{Na}^+) + (\text{H}_2\text{CO}_3) \leftrightarrow (\text{Na}^+) + (\text{H}_2\text{O}) + (\text{CO}_2 \text{ gas})
\]

Accumulation of carbon dioxide has important secondary effects that affect the clinical setting.

- The pKa, to remain at 6.1, requires immediate elimination of carbon dioxide. Because carbonic acid is not stable, it spontaneously dissociates into carbon dioxide and water. As carbon dioxide accumulates, the apparent pKa (now called pKa prime, indicated as pKa') declines, bringing the apparent pKa further away from the physiologic setting and further impairing the buffering effect.
- Carbon dioxide diffuses rapidly into the intracellular fluid space, resulting in a decrease in intracellular pH. Sodium bicarbonate has been shown to distribute in the extracellular fluid, hence the intracellular movement of carbon dioxide is not balanced and the aforementioned reaction is driven to the left in the intracellular fluid.

Use of hypertonic sodium bicarbonate solutions increases serum osmolality, which independently lowers the pKa values of physiologic buffer systems. Fever has a similar effect.

Metabolic acidosis has many causes. Clinically effective treatment follows ascertainment of the underlying cause. An ineffective treatment has the potential to shift the focus away from the diagnostic challenges associated with metabolic acidosis. Notably, acidosis following hypoxia and/or ischemia responds well to support of perfusion, such as normal saline administration and restoration of oxygenation. With gradually improving acid-base status, continued attention to specific measures addressing the underlying condition is much preferred. Of the other causes of acute metabolic acidosis, such as sepsis likely in the infant in this vignette, each has its own unique management challenges.

**References:**


Related readings from Neoreviews.org

Dagli AI, Zori RT, Heese BA. Testing strategy for inborn errors of metabolism in the neonate.
**American Board of Pediatrics Content Specification(s):**

07_Water_Salt_Renal: Know how to manage metabolic acidosis and metabolic alkalosis in infants

18_Pharmacology: Know the general mechanisms by which various drugs are metabolized and the clinical implications of how this changes in the newborn period
Question 9

A 15-day-old female infant, who weighed 990 g at birth at an estimated gestational age of 29 weeks, is receiving full gavage feeds of fortified expressed breast milk. She is breathing spontaneously in room air without distress. Her physical examination findings, including cardiovascular status, are normal. Head ultrasonography shows no intraventricular hemorrhage. Her hematocrit is 39%, and the reticulocyte count is 4%. You discuss with the house staff the need for supplemental iron in preterm infants.

Of the following, the RECOMMENDED age at which iron supplements should be initiated in preterm infants is:

- A. 2 weeks
- B. 1 month
- C. 4 months
- D. 6 months
- E. 12 months

Incorrect:

Correct Answer: B

Iron deficiency, the most common nutritional deficiency, has negative effects on children’s motor and mental development that may not be reversible with iron treatment. Iron deficiency can also increase lead absorption, an additional cause of neurologic and developmental deficits. The total body iron content of a newborn infant at term gestation is approximately 75 mg/kg; approximately 60% of iron is accreted during the third trimester of gestation. The distribution of iron in the body is as follows: 75% to 80% in red blood cells (RBC) as hemoglobin, approximately 10% in tissues as iron-containing proteins (myoglobin and cytochromes), and the remaining 10% to 15% as storage iron (ferritin and hemosiderin). The storage iron content increases progressively and is reflected by an umbilical cord serum ferritin concentration higher than 60 μg/L at term gestation.

The period soon after birth is characterized by a 30% to 50% decrease in hemoglobin concentration secondary to cessation of erythropoiesis, lysis of senescent fetal RBCs, and expansion of the vascular volume. During this physiologic anemia, the hemoglobin concentration can reach a nadir of 100 to 110 g/L between 6 and 8 weeks of age. In preterm infants, the hemoglobin...
concentration nadir can be as low as 60 to 80 g/L, occur 1 to 4 weeks earlier than in full-term infants, and is called anemia of prematurity. The iron released during lysis of senescent RBCs (3.47 mg/g of hemoglobin) is stored for future use. In full-term infants, this stored iron supports the iron needs of the ensuing erythropoiesis and growth until 4 to 6 months of age.

Preterm birth deprives the fetus of the significant iron accretion that occurs after 32 weeks of gestation. The total body and tissue iron contents and hemoglobin and serum ferritin concentrations are lower in the preterm infant. Early onset of postnatal erythropoiesis, greater postnatal growth velocity, uncompensated phlebotomy losses, exclusive use of breast milk, and delayed or inadequate iron supplementation predispose the preterm infant to iron deficiency. Extremely low birthweight (<1,000 g), intrauterine growth restriction, and use of recombinant human erythropoietin without adequate iron supplementation are additional risk factors. Without an external source of iron, iron stores in preterm infants who do not receive blood transfusions will sustain effective erythropoiesis only until they have doubled their birthweight, that is, until approximately 2 months of age. Without iron supplementation, extremely low-birthweight infants may experience negative iron balance during the first month.

Primary prevention of iron deficiency among infants means ensuring that they have an adequate intake of iron. Iron fortification of infant formula reduces the risk for iron deficiency among formula-fed infants; however, the American Academy of Pediatrics (AAP) and others recommend that infants be fed breast milk exclusively during these early months, in part because breast milk provides infants with essential immunologic factors in addition to nutrients. Although iron is absorbed efficiently from breast milk, the iron concentration of breast milk is inadequate to meet the increased iron requirement of infants aged 6 months or more. Therefore, the AAP recommends that full-term breastfed infants receive 1 mg/kg per day of supplemental iron, preferably from food, beginning at approximately 4 to 6 months of age. Good dietary sources of iron include iron-fortified infant cereal and meat. The AAP recommends an average of two servings per day from these sources. If full-term breastfed infants are unable to consume sufficient iron from their diet after 6 months of age, they should be given a daily oral supplement of elemental iron of 1 mg/kg per day. Regardless of dietary iron intake, the AAP recommends that preterm breastfed infants be given an oral iron supplement of 2 mg/kg per day starting at 1 month of age, with supplementation continuing through 12 months of age. Because preterm discharge formulas provide approximately 1.8 to 2.2 mg/kg of iron per day, assuming a typical consumption of 150 to 160 mL per kg per day, the AAP Committee on Nutrition recommends that formula-fed preterm infants receive 1 mg/kg per day of supplemental iron from 1 to 12 months of age. Iron supplements may not be necessary in preterm infants who have received multiple transfusions with packed RBCs.

In an analysis of the data from the 2005-2007 Infant Feeding Practices Study II, a longitudinal study of mothers and infants followed from late pregnancy through the first year of their infant’s life, Dee and associates found that a substantial percentage of mothers of breastfed infants do not follow AAP recommendations regarding the introduction of infant cereal or meat or the use of iron supplements. Among full-term infants who were exclusively breastfed, 23% had no supplemental iron source at 6 months, and 70% received infant cereal, meat, or iron supplements less frequently than recommended. Only 6.5% of the mothers of late preterm, exclusively breastfed infants followed recommendations for oral iron supplementation at 6 months; none did so during their first 2 months and 13% or fewer did so at any period from 7.5 to 10.5 months.

Therefore, it is important for pediatricians to advise parents to:

- give oral iron supplements to:
  - breastfed full-term infants aged 6 months or more who are not consuming at least two daily servings of iron-rich food
  - all preterm infants between the ages of 1 and 12 months
- give only iron-fortified formula to infants receiving formula

References:


Related readings from Neoreviews.org


**American Board of Pediatrics Content Specification(s):**

14_Hematology_Oncology: Understand the mechanism and gestational timing of placental transfer of iron to the fetus and its effect on iron stores in newborn infants

14_Hematology_Oncology: Recognize the causes of iron deficiency anemia and various prevention measures

14_Hematology_Oncology: Recognize the clinical and diagnostic features, laboratory findings, management, and long-term consequences of iron deficiency anemia
August

ASSESSMENT PROGRESS: Total Questions: 10 Questions Answered: 4 Correct Answers: 2

Question 4

During rounds with your team in the neonatal intensive care unit you see a 14-day-old infant born at 28 weeks' gestation. The infant weighs 900 g and is receiving her mother's milk mixed with a powdered fortifier. The nutritionist on your team suggests adding a protein supplement. You explain the variability of the protein content of human milk. You then ask the team how best to monitor the delivery of enough protein to this child.

Of the following, the value MOST useful to know in the daily adjustment of protein delivery to a preterm infant is the child's:

- A. blood urea nitrogen
- B. linear growth
- C. serum albumin
- D. serum prealbumin
- E. serum transferrin

Preterm infants require parenteral protein delivery of 3 to 3.5 g/kg per day for adequate growth. Enteral requirements, 3.5 to 4 g/kg per day, are higher because of losses in digestion and absorption. A lower protein intake results in poor growth and development. Intake of more than 5 g/kg per day may be associated with acidosis, aminoacidemia, and cylindruria.

Human milk is the food of choice for preterm children. Fortification is needed because of the greater demands of the preterm infant for protein, minerals, and vitamins. These demands are not met by human milk alone until the child is closer to term or beyond. In general, low protein intake is thought to be the limiting factor in the growth of premature infants.

The protein content of human milk can vary dramatically. The protein content in milk from mothers of term newborns is often in the range of 15 to 20 g/L. Protein in mothers' milk of preterm newborns initially can be 20 to 30 g/L. Protein in mature milk (i.e., after the first 2 weeks) ranges between 8 and 14 g/L. Concentrations in this range are found in most samples of donor milk.

Of the choices in the vignette, the blood urea nitrogen (BUN) has been used most...
successfully in adjusting the daily amount of protein delivered to the preterm infant.

Blood urea nitrogen is the concentration of nitrogen in the blood that specifically comes from urea, a product of nitrogen metabolism (Figure).

Figure: Urea molecule

During the first few days after birth and at other times of stress, BUN is most affected by renal or fluid derangements. In contrast, when examined in a stable growing premature infant, BUN signals the adequacy of delivered dietary protein. A change in dietary protein is reflected in a few hours by a similar change in BUN.

Several studies have taken advantage of this linkage to develop regimens of breast milk fortification based on BUN. The most quoted regimen used twice-weekly BUN measurements to adjust protein fortification, using a target concentration range of 9 to 14 mg/dL (3.2 -5 mmol/L). A BUN below the target range prompted an increase in protein supplementation. In other regimens, a lower limit of 6 mg/dL (2.1 mmol/L) was used.

Randomized trials have found that these adjustable fortification regimens resulted in greater gains in weight and head circumference than in controls.

One retrospective study found an association between BUN and later development. In a large group of infants born before 28 weeks’ gestation and fed mainly fortified human milk, the likelihood of a good developmental quotient at 36 months was positively correlated with a BUN-based “area under the curve.”

The other measures listed as response choices are used as valid tools to assess nutritional status. These measures suffer, however, from time lag problems. After a change is made in the dietary protein delivered, changes in these measures may take weeks to be reliably seen. A change in the linear growth rate of a child’s length, for instance, takes 3 to 4 weeks to detect.

Albumin has a half-life of 2 to 3 weeks, so the serum albumin concentration varies very slowly after a change in delivered dietary protein. Similarly, prealbumin (also called transthyretin) and transferrin have half-lives of 2 and 8 days, respectively, and are slower than BUN in changing their serum concentrations after a change in dietary protein.

The serum concentration of retinol-binding protein, with a half-life of 12 hours, may prove to be clinically useful as a guide to protein delivery, but is not now easily available.

All of these nutritional indicator proteins have the handicap of being negative acute phase reactants. During periods of inflammation in the body, these proteins will decrease in concentration without regard to the availability of dietary protein or the child’s nutritional status.
The ideal value to know, when matching the supplied milk to the child’s protein needs, is the protein content of the mother’s milk. This determination can be done on a research basis, but is not generally available clinically.

References:


Ziegler EE. Protein requirements of very low birth weight infants. J Pediatr Gastroenterol Nutr. 2007;45:S170-S174

Related readings from Neoreviews.org


American Board of Pediatrics Content Specification(s):

06_Nutrition: Know the protein requirements of preterm and full-term infants

06_Nutrition: Know the consequences of feeding preterm infants too little or too much protein

06_Nutrition: Know the physiology of protein/amino acid digestion (absorption and metabolism) in newborn infants

06_Nutrition: Know that human milk needs to be fortified in order to meet the nutritional needs of preterm infants
August

ASSESSMENT PROGRESS: Total Questions: 10 Questions Answered: 5 Correct Answers: 2

Question 5

A 10-week-old white male infant, whose birthweight was 690 g and estimated gestational age at birth 24 weeks, is receiving daily furosemide treatment for chronic lung disease. Prior clinical course is characterized by episodes of feeding intolerance requiring sustenance with parenteral nutrition, episodes of sepsis requiring antimicrobial treatment including aminoglycosides, and a course of dexamethasone treatment for weaning ventilator support and high fraction of inspired oxygen. As a part of surveillance, a renal ultrasonograph is obtained (Figure), which shows bright echogenic foci in the renal parenchyma.

Figure: Renal ultrasonogram (arrow indicates bright echogenic foci)

Of the following, the factor MOST likely to contribute to the renal ultrasonographic findings in this infant is the increased urinary excretion of:

A. calcium oxalate
The renal ultrasonographic findings in the infant in this vignette are consistent with the diagnosis of nephrocalcinosis. Since the first description of nephrocalcinosis in 1982 by Hufnagel and associates, the incidence of the disease among very-low-birthweight (birthweight <1,500 g), preterm (gestational age <32 weeks) infants is reported to be between 17% and 64% in North American studies and between 16% and 41% in European studies. The infant in this vignette has many of the predisposing risk factors for the development of nephrocalcinosis. These risk factors include:

- low birthweight
- low gestational age
- bronchopulmonary dysplasia
- long-term furosemide treatment
- postnatal glucocorticosteroid treatment
- aminoglycoside treatment
- male sex
- white race
- family history of urolithiasis

In common with urolithiasis from different causes in children, nephrocalcinosis represents a deposition of particulate material of mineral origin within the renal parenchyma. The deposit consists largely of calcium oxalate crystals and is located predominantly in the tubules and the interstitium of the renal medulla.

The process of nephrocalcinosis begins with precipitation of mineral solutes in the urine in the form of crystals, followed by growth, aggregation, and adherence of the crystals to the renal tubular epithelium. Although the concentration of the mineral solutes in the urine is the principal determinant, other factors, such as ionic strength, urinary acidity/alkalinity, urine flow velocity, and renal tubular epithelial integrity, also influence the development of nephrocalcinosis. In addition, several factors have been recognized as either promoters or inhibitors of nephrocalcinosis (Table).

<table>
<thead>
<tr>
<th>Factors Promoting Nephrocalcinosis</th>
<th>Factors Inhibiting Nephrocalcinosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalciuria</td>
<td>Urinary inhibitors</td>
</tr>
<tr>
<td>High calcium intake</td>
<td>Citrate</td>
</tr>
<tr>
<td>Low phosphorus intake</td>
<td>Pyrophosphate</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Magnesium</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td></td>
</tr>
<tr>
<td>Methylxanthine</td>
<td></td>
</tr>
</tbody>
</table>
Vitamin D
Glucocorticosteroid

Hyperoxaluria
High precursor intake
Ascorbic acid
Glycine
Secondary hyperoxaluria
Fat malabsorption

Urinary macromolecules
Osteopontin
Nephrocalcin
Glycosaminoglycan
Tamm-Horsfall protein
Medications
Thiazide

Major factors in the development of nephrocalcinosis in preterm infants are hypercalciuria, especially related to the use of furosemide for chronic lung disease, and hyperoxaluria related to prolonged parenteral nutrition. Hypercalciuria can be diagnosed by means of calcium and creatinine measurements in random urine samples. The typical urine calcium concentration is less than 0.8 mg/mg of creatinine (2.3 mmol/mmol) in infants younger than 6 months of age. However, the urine calcium concentration often exceeds this limit in preterm infants, especially those with high dietary calcium intake, low dietary phosphorus intake, vitamin D excess, metabolic acidosis, and exposure to medications including furosemide.

Hyperoxaluria can occur in preterm infants receiving parenteral nutrition that contains ascorbic acid and glycine—precursors of oxalate—in high concentrations. Hyperoxaluria also can occur from fat malabsorption in preterm infants receiving enteral nutrition. Unabsorbed fat in the lumen of the gut binds to calcium, makes less calcium available for binding to oxalate, and promotes the binding of oxalate to sodium in lieu of calcium. The sodium-oxalate complex is more readily absorbed in the gut than calcium-oxalate complex, which increases the circulating load of oxalate and its renal excretion. Hyperoxaluria can be diagnosed by means of oxalate and creatinine measurements in random urine samples. Although the typical urine oxalate concentration ranges between 0.12 and 0.21 mg/mg of creatinine (0.15-0.26 mmol/mmol) in infants younger than 1 year of age, it often exceeds these limits in preterm infants, especially those receiving prolonged parenteral nutrition.

Magnesium is a low-molecular-weight chelator, which in the urine forms complexes with oxalate that are more soluble than calcium oxalate. Likewise, pyrophosphate in the urine inhibits calcium oxalate crystallization. Thus, both magnesium and pyrophosphate may have therapeutic potential in the prevention and treatment of nephrocalcinosis.

Osteopontin is a glycoprotein macromolecule, which in the renal tubules binds to crystals of calcium oxalate and inhibits its accumulation. Urinary osteopontin concentration is significantly lower in preterm infants than in adults, which may explain in part the predisposition of preterm infants to nephrocalcinosis.

Citrate is a naturally occurring inhibitor of calcium oxalate crystallization. Deficiency of urinary citrate often accompanies hypokalemia and metabolic acidosis, and may lead to a predisposition to urolithiasis in adults. Hypocitraturia may be a risk factor for nephrocalcinosis in preterm infants, but this observation remains unconfirmed. A small randomized clinical trial of sodium citrate supplementation in preterm infants has shown that such treatment is safe and promotes a favorable urinary mineral profile. However, this treatment has had no beneficial effect on the development of nephrocalcinosis.

Tamm-Horsfall protein is a glycoprotein macromolecule actively secreted by the tubular cells in the ascending thick limb of the loop of Henle. It is an inhibitor of calcium oxalate crystallization. Its role in the development of nephrocalcinosis in preterm infants has not been studied.

References:


Sikora P, Roth B, Kirbs A, Michalk DV, Hesse A, Hoppe B. Hypocitraturia is one of the major risk factors for nephrocalcinosis in very low birth weight (VLBW) infants. Kidney Int. 2003;63:2194-2199


Related readings from Neoreviews.org


American Board of Pediatrics Content Specification(s):

03_Cardiovascular: Know the therapeutic indications for, and toxicity of, commonly used diuretic drugs in preterm and term infants with cardiovascular disease

04_Respiratory: Know the management of bronchopulmonary dysplasia/chronic lung disease

06_Nutrition: Know the physiology of fat digestion (and) absorption (and metabolism) in newborn infants

06_Nutrition: Know the potential adverse effects of pharmacologic use of fat soluble vitamins

07_Water_Salt_Renal: Know the effects of various illnesses on renal function

18_Pharmacology: For therapeutic drugs commonly used in the neonate (eg, opiates, methylxanthines, barbiturates, etc), know indications for their use, clinical effects, pharmacokinetics, side effects, and toxicity
Question 8

A 760-g infant born at 26 weeks’ gestation is now 3 days of age. Vigorous from birth, his condition is stable with the administration of nasal continuous positive airway pressure at 26% oxygen in an incubator. He weighed 720 g yesterday, and is 700 g today. He is receiving total parenteral nutrition. Urine specimen is negative for glucose and protein. He is receiving nothing by mouth pending evaluation for patent ductus arteriosus.

Selected clinical and laboratory data are summarized in Table 1.

<table>
<thead>
<tr>
<th>Component</th>
<th>Yesterday</th>
<th>Today</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>720</td>
<td>700</td>
</tr>
<tr>
<td>Glucose, mg/dL (mmol/L)</td>
<td>80 (4.44)</td>
<td>120 (6.66)</td>
</tr>
<tr>
<td>Sodium, mg/dL (mmol/L)</td>
<td>134 (134)</td>
<td>139 (139)</td>
</tr>
<tr>
<td>Serum urea nitrogen, mg/dL (mmol/L)</td>
<td>20 (7.14)</td>
<td>25 (8.93)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL (mmol/L)</td>
<td>80 (0.90)</td>
<td>88 [0.99]</td>
</tr>
<tr>
<td>Urine specific gravity</td>
<td>1.007</td>
<td>1.013</td>
</tr>
<tr>
<td>Urine output, mL/kg per hour</td>
<td>4.0</td>
<td>2.5</td>
</tr>
</tbody>
</table>

The infant’s proposed parenteral nutrition orders are presented for your review. A number of modifications have been suggested for your approval or adjustment (Table 2).

<table>
<thead>
<tr>
<th>Component</th>
<th>Current</th>
<th>Proposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid rate, mL/h</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Dextrose, %</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Protein, g/dL</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>20% lipids, mL/h</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Sodium, mEq/L (mmol/L)</td>
<td>0.3</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Of the following, the BEST approach to the proposed new parenteral fluid order would be to
change:

- A. base solution to dextrose 10% in 0.2 N sodium chloride
- B. dextrose concentration to 8%
- C. fluid rate to 4.5 mL/h
- D. nothing; accept as written
- E. protein concentration to 3.5 g/dL (35 g/L)

**Incorrect:**

Correct Answer: B

---

Prompt response to nutritional needs of the very-low-birthweight infant is needed to avoid postnatal stresses associated with suboptimal intake leading to postnatal growth restriction. As parenteral nutrition is presented and advanced, careful attention to the infant’s response is essential. Current recommendations for very-low-birthweight infant nutrition suggest beginning glucose and amino acid–containing parenteral fluids as soon as practicable to avoid energy starvation and negative nitrogen balance; starting intravenous lipids promptly to avert essential fatty acid deficiency; and advancing intakes in a balanced manner toward full nutrient and energy sufficiency to avert postnatal growth retardation. Nutrition is most commonly begun parenterally; enteral intake using minimal enteral feedings can begin early as well, but enteral feeding often is influenced by other factors, such as concern regarding the ductus arteriosus and its treatment, as presented in this vignette.

The major components of parenteral nutritional fluids begun in the first week after birth are summarized in **Table 3**.

### Table 3: Components of Early-Onset Parenteral Fluids for Very-Low Birthweight Infants Not Receiving Enteral Nutrition*

<table>
<thead>
<tr>
<th>Component</th>
<th>Initiation and Advancement</th>
<th>Goal Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid rate, mL/hour</td>
<td>• 60-80 mL/kg/d (1st d), increase by 10-20 mL/kg/d max ~ 140 mL/kg/d</td>
<td>• 140-150 mL/kg/d (Variable depending on total fluid needs, etc)</td>
</tr>
<tr>
<td>Dextrose, %</td>
<td>• 6 – 8 mg/kg/min: Up to 10 mg/kg/min @ day 10 (blood glucose 45 - 120 mg/dL)</td>
<td>• D10 @ 140 mL/kg/day = 14.4 g or 49 cal per day</td>
</tr>
<tr>
<td>Protein, g/dL</td>
<td>• 3 g/kg/d ASAP; May increase up to 4 g/kg/d, in 0.5 to 1.0 g/kg steps</td>
<td>• Up to 4 g/d=16 cal/day</td>
</tr>
<tr>
<td>Sodium, mEq/dL</td>
<td>• Added when &lt;130 mEq/dL</td>
<td>• 3 mEq/kg/d – adjusted prn. For [Na+] 130-145</td>
</tr>
<tr>
<td>20% Lipids, mL/h</td>
<td>• 0.5-1 g/kg/d (@ no &gt;0.125 g/kg/h);</td>
<td>• 3.0 g/d= 15 mL/d=30 cal/d</td>
</tr>
</tbody>
</table>
Increase to 3 g/kg/d by 0.5-1 g/kg/d steps

Caloric deliveries: 3.4 cal/g dextrose; 4 cal/g protein; 2 cal/mL 20% lipid emulsion.

*Adapted from Adamkin (2009).

The appropriate fluid composition and delivery rate are determined based on an analysis of the patient’s clinical and laboratory studies, combined with review of current and proposed intakes. To do so, the current and proposed parenteral fluid composition and rates of administration are analyzed and compared, the infant’s responses reviewed, and projected patient needs considered. Because of the confounding influence of early neonatal weight loss, fluid and nutrient intakes are calculated using the birthweight until the infant regains birthweight. Current weight is used thereafter. Table 4 lists the current and proposed total parenteral nutrition (TPN) solutions.

**Table 4: Component Delivery of Total Parenteral Nutrition (TPN) Solutions: Current and Proposed**

<table>
<thead>
<tr>
<th>Component</th>
<th>Solution</th>
<th>Component Delivery*</th>
<th>Solution</th>
<th>Component Delivery*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPN fluid rate</td>
<td>3 mL/h</td>
<td>95 mL/kg/d</td>
<td>4 mL/h</td>
<td>126 mL/kg/d</td>
</tr>
<tr>
<td>Dextrose</td>
<td>10%</td>
<td>6.6 mg/kg/min</td>
<td>10%</td>
<td>8.8 mg/kg/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(32 cal/kg/d)</td>
<td></td>
<td>(43 cal/kg/d)</td>
</tr>
<tr>
<td>Protein</td>
<td>2.5 g/dL</td>
<td>2.4 g/kg/d</td>
<td>2.5 g/dL</td>
<td>3.2 g/kg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(9.6 cal/kg/d)</td>
<td></td>
<td>(12.6 cal/kg/d)</td>
</tr>
<tr>
<td>Sodium</td>
<td>0 mEq/dL</td>
<td>0 mEq/kg/d</td>
<td>0 mEq/kg/d</td>
<td>0 mEq/kg/d</td>
</tr>
<tr>
<td>Caloric density</td>
<td>44 cal/dL</td>
<td>42 cal/kg/d</td>
<td>44 cal/dL</td>
<td>59 cal/kg/d</td>
</tr>
<tr>
<td>20% Lipids, cc/hour</td>
<td>0.3 mL/h</td>
<td>1.95 g/kg/d</td>
<td>0.4 mL/h</td>
<td>2.53 g/kg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(19 cal/kg/d)</td>
<td></td>
<td>(25 cal/kg/d)</td>
</tr>
<tr>
<td>Caloric delivery</td>
<td>61 cal/kg/d</td>
<td>81 cal/kg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water from lipid</td>
<td>7.2 mL/d</td>
<td>9.5 mL/kg/d</td>
<td>9.6 mL/d</td>
<td>12.6 mL/kg/d</td>
</tr>
<tr>
<td>lipid solution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total water</td>
<td>79 mL/d</td>
<td>104 mL/kg/d</td>
<td>105.6 mL/d</td>
<td>139 mL/kg/d</td>
</tr>
</tbody>
</table>

* Component delivery based on a birthweight of 760 g.

Decision making can be broken down by focusing on each of the components of the TPN order:

- **Fluid administration.** Water balance can be tricky in the early days after birth. Basal needs are determined by neonatal size, gestational age, postnatal age, concurrent treatments, and environment. Initial and subsequent fluid administration rates are influenced by hydration, as assessed physically through changes in body weight, skin turgor, mucous membrane wetness, or fontanelle fullness; clinically by urine volume and/or composition; or biochemically through concentrations of electrolytes, blood urea nitrogen (BUN), or creatinine. For the infant in the vignette, weight loss pattern shows a further 20-g drop from yesterday’s weight. In addition, urine output is down and urine specific gravity is higher, just above the upper limit for normal hydration (1.012). Serum sodium concentration, although in normal limits, is rising in spite of having none in parenteral fluids. These data suggest an increase in the total daily fluid administration rate by more than the usual 20 mL/kg per day. The proposed solution suggests an increase in total fluid intake to 105.6 mL/d (139 mL/kg per day): 126
mL/kg from TPN and 12.6 mL/kg from lipid solution). This 32% increase is reasonable for this situation. A greater increase to more than 50% above the current volume, as would result from a TPN rate of 4.5 mL/hour with lipids at 0.4 mL/hour, is likely not needed and could become problematic if a patent ductus is confirmed.

- **Glucose.** At the current delivery of 6.6 mg/kg per minute, central in the recommended 6 to 8 mg/kg per minute range, the infant’s blood glucose concentration remains within acceptable limits (45-120 mg/dL as recommended by Adamkin [2009]). Nevertheless, the blood glucose concentration has risen at this infusion rate. The proposed orders would maintain the base solution at 10% dextrose and, with the new infusion rate, raise glucose delivery to 8.8 mg/kg per minute. With the increase in blood glucose concentrations over the past day from 80 mg/dL to 120 mg/dL, maintaining glucose administration near its current, tolerated level is suggested. This can be accomplished by reducing the glucose concentration of the proposed solution to 8% with resultant glucose infusion rate at 7 mg/kg per minute. Caloric content from glucose concentration thereafter is calculated as:

  - (Glucose, g/dL) × 3.4 calories/g = (8 × 3.4) cal/dL = 27.4 cal/dL
  - Caloric delivery = 27.4 cal/100 mL × 126 mL/kg per day = 34.5 cal/kg per day

- **Protein (amino acids).** Very-low-birthweight infants require protein intakes of 0.5 to 1.0 g/kg per day to avoid negative nitrogen balance and the related catabolic state. In utero, about one half of amino acids transferred into the fetus are used for energy rather than for growth. Recent studies demonstrate greater tolerance to parenteral amino acids, with restoration of positive nitrogen balance similar to that seen in utero at a protein intake of 3 to 4 g/kg per day. BUN is a poor measure of protein tolerance, especially in the first week after birth. The small increase in BUN noted in the vignette is consistent with normal metabolism. The proposed new fluid order would increase protein intake from 2.4 g/kg per day to 3.2 g/kg per day, reaching intakes suggested in recent reports. In an example using 2.5 g amino acid per 100 mL solution, the caloric content from protein for the proposed solution is calculated as:

  - (Protein g/dL) × 4 calories/g = (2.5 × 4) cal/dL = 10 cal/dL
  - Caloric delivery = 10 cal/100 mL × 126 mL/kg/d = 12.6 cal/kg/d

Increasing protein administration further by increasing the fluid concentration to 3.5 g/dL, in addition to the volume increase, would yield a total protein intake of 4.4 g/kg per day, in excess of current recommendations.

- **Sodium.** Because of the excess sodium-containing extracellular fluid in the newborn infant, sodium is retained as the excess extracellular water is excreted in a relatively dilute state, giving infants sufficient sodium in the early days after birth. As seen in this vignette, serum sodium concentrations often rise without supplementation. After serum concentrations fall below 130 mEq/dL, inclusion in the TPN formulation is recommended. Thus, for this infant, switching to a base solution of 10% dextrose in 0.2 normal saline is not needed at this time.

- **Lipids.** As noted earlier, essential fatty acid deficiency occurs rapidly unless supplementation with linoleic acid is begun. Thus, current guidelines allow intravenous lipids to be begun early, and gradual advancement to 3 g/kg per day is suggested. The increase of lipids suggested in the proposed order would bring the intake to 2.5 g/kg per day. At intakes up to 3 g/kg per day, no adverse effects on bilirubin binding or on pulmonary function have been confirmed. There would be no need to change this portion of the proposed orders, but the increase in fluid volume administered must be factored into total water intake calculations. Caloric delivery from 20% lipid emulsion (0.2 g/mL) yields 1.8 cal/mL from fat and 0.2 cal/mL from glycerol. Thus, lipid emulsion provides 2 cal/mL, and for practical purposes all such calories are generally counted as fat. Total caloric delivery is calculated from lipid emulsion in the proposed order as follows:

  - (rate, mL/h) × 2 cal/mL × 24 h/d = (0.4 × 2 × 24) cal/d = 19.2 cal/d
  - Divide this value by the weight in kilograms to get calories (from lipid emulsion) per kilogram per day = 19.2/0.76 = 25.3 cal/kg per day

For the infant in the vignette, a change in the base solution for the new TPN formulation to 8% dextrose can bring fluid and component administration within expected limits and will likely be tolerated by the infant. The calculations for the components of the revised solution are presented in Table 5.
Table 5: Component Delivery of Revised Nutrient Orders

<table>
<thead>
<tr>
<th>Component</th>
<th>Revised Order</th>
<th>Solution</th>
<th>Component Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total parenteral nutrition fluid rate, mL/h</td>
<td>4 mL/h</td>
<td>126 mL/kg/d</td>
<td></td>
</tr>
<tr>
<td>Dextrose, %</td>
<td>8%</td>
<td>7 mg/kg/min</td>
<td>(34.5 cal/kg/d)</td>
</tr>
<tr>
<td>Protein, g/dL</td>
<td>2.5 g/dL</td>
<td>3.15 g/kg/d</td>
<td>(12.6 cal/kg/d)</td>
</tr>
<tr>
<td>Caloric density</td>
<td>37 cal/dL</td>
<td>47.1 cal/kg/d</td>
<td></td>
</tr>
<tr>
<td>Sodium, mEq/dL</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>20% Lipids, mL/h</td>
<td>0.4 mL/h</td>
<td>2.5 g/kg/d</td>
<td>(25.3 cal/kg/d)</td>
</tr>
<tr>
<td>Fluid delivery-lipid solution</td>
<td>9.6 mL/d</td>
<td>12.6 mL/kg/d</td>
<td></td>
</tr>
<tr>
<td>Total calories</td>
<td></td>
<td>72.4 cal/kg/d</td>
<td></td>
</tr>
<tr>
<td>Total fluids</td>
<td>105.6 mL/d</td>
<td>139 mL/kg/d</td>
<td></td>
</tr>
</tbody>
</table>

For short-term support with parenteral nutrition, supplementation with vitamins or trace elements, with the possible exception of zinc, is not essential. Addition of electrolytes is determined based on periodic biochemical monitoring. Enteral feedings are recommended as soon as clinically feasible, and after a period of trophic feedings, gradually advanced as parenteral calories are decreased. Using balanced and complementary enteral and parenteral feeding, some of the adverse nutritional consequences of very-low-birthweight may be averted.

References:

Adamkin DH. Nutrition management of the very low-birthweight infant: I, total parenteral nutrition and minimal enteral nutrition. *NeoReviews*. 2006;7:e602-e607


American Board of Pediatrics Content Specification(s):

06_Nutrition: Know the nutritional composition of parenteral solutions

06_Nutrition: Know the importance of protein and non-protein nutrients in achieving optimal utilization of energy and nitrogen

06_Nutrition: Know how to calculate the caloric content of parenteral nutrition solutions
November

Overview
Editorial Board
My Learning Plan
January
February
March
April
May
June
July
August
September
October
November
December

Overview
Editorial Board
My Learning Plan
January
February
March
April
May
June
July
August
September
October
November
December

November

Overview
Editorial Board
My Learning Plan
January
February
March
April
May
June
July
August
September
October
November
December

November

Overview
Editorial Board
My Learning Plan
January
February
March
April
May
June
July
August
September
October
November
December

Question 2

A 14-day-old infant, who weighed 1,250 g at birth at an estimated gestational age of 30 weeks, is receiving full enteral feeds of human milk. The infant is breathing spontaneously in room air, being housed in a thermoneutral range inside an incubator, and receiving no medications other than supplemental vitamins. The recent weight gain has been only 8.0 g/kg per day, which prompts you to enrich the milk with nutrient fortifiers, including supplemental protein. The laboratory data reveal a serum total protein concentration of 4.0 g/dL (40 g/L) and serum albumin concentration of 2.2 g/dL (22 g/L). You review the capacity of the newborn to digest the protein as compared with that of an adult in considering the choice of nutrients for fortification of the milk.

Of the following, the digestive function MOST similar between the newborn and the adult is:

- A. cholecystokinin-stimulated trypsinogen secretion
- B. chymotrypsin activity in the small intestine
- C. enterocyte absorption of amino acids
- D. gastric acid secretion
- E. pepsin activity in the stomach

The processing of proteins is slower and less complete in the newborn than in the adult; it even allows a few large peptides to reach the small intestine undigested. Once a protein is digested to tripeptides, dipeptides, and amino acids, absorption by the enterocytes is as quick and efficient in the newborn as in the adult.

Protein digestion begins with the denaturation of proteins by gastric acid. This unfolding opens proteins to attack by endopeptidases and exposes more amino or carboxy ends to attack by exopeptidases. Cooking of food often includes heat denaturation, and begins the process of unfolding before ingestion. Newborn gastric acid secretion is lower than in adults, and is even lower in preterm newborns. Acid secretion increases in the first few hours to days, and reaches adult levels during the first few months.

Pepsin is a protease secreted in the form of pepsinogen by the chief cells of the stomach. Pepsin is cleaved from pepsinogen in an acid environment. It hydrolyzes large proteins to smaller peptides and a small proportion of amino acids. Because of low rates of acid and pepsinogen secretion in the newborn, there is no significant digestion of protein in the
stomach during the first week after birth.

Trypsin is a serine protease secreted as trypsinogen by the pancreas in response to cholecystokinin. Trypsin is cleaved from trypsinogen in the duodenum by the action of enteropeptidase (formerly enterokinase), an action that is facilitated by bile acids. Trypsin then activates the other pancreatic zymogens, including chymotrypsinogen, proelastase, and procarboxypeptidase.

Compared with adults, newborns have a blunted response to cholecystokinin and a lower pancreatic secretion rate of proteases. In addition, breast milk contains substantial amounts of protease inhibitors. This results in lower chymotrypsin activity in the small intestine of newborns.

The newborn deficiency in protein digestion relative to the adult allows a few intact proteins to enter the small intestine undigested. This permits absorption by pinocytosis of biologically important molecules such as lactoferrin and immunoglobulin. Unfortunately, it can also result in absorption of proteins associated with food allergies, such as beta-lactoglobulin from cow milk.

Absorption of amino acids by newborn enterocytes is efficient. The products of protein digestion are mainly absorbed into the enterocytes as dipeptides and tripeptides, with only about one third absorbed directly as amino acids. These dipeptides and tripeptides are then hydrolysed inside the enterocytes, so that it is mainly amino acids that are transported into the splanchnic circulation. Transport of amino acids and oligopeptides is energy dependent, relying on proton or sodium ion gradients driven ultimately by a sodium-potassium-adenosine triphosphatase in the basolateral membrane of the enterocytes.

References:


Related readings from Neoreviews.org


American Board of Pediatrics Content Specification(s):

06. Nutrition: Know the physiology of protein/amino acid digestion (absorption and metabolism) in newborn infants
11_Gastroenterology: Know the changes that occur in gastric acidity in term and preterm infants during the immediate neonatal period

11_Gastroenterology: Know the factors involved in protein digestion and absorption
Question: 8

An 800-g male infant was born at 26 weeks’ gestation via cesarean delivery because of maternal abruptio placentae. He had signs of respiratory distress immediately and was treated with endotracheal surfactant and assisted with positive pressure ventilation. He was fed initially with parenteral nutrition via a central venous catheter plus small feedings of expressed breast milk. Parenteral nutrition was weaned gradually as enteric intake was increased. Early on the seventh day, he began to have increasing gastric residuals. He later developed abdominal distention. An abdominal radiograph revealed a small area of pneumatosis intestinalis and no free air. Perfusion was good; blood pH and bicarbonate were normal. Enteric feedings were stopped, antibiotics initiated, and intravenous feedings ordered with the intention to provide adequate calories for maintenance and growth. He received a solution containing 3.5 g/100 mL of amino acids, 15% glucose, and appropriate electrolytes, minerals, and multivitamins infused at a rate of 3.7 mL/hour. In addition, he received a 20% lipid solution infused at a rate of 0.3 mL/hour.

Of the following, the CLOSEST estimate of the number of kilocalories (kilojoules) being delivered per kilogram of body weight per day is:

- A. 120 (28.7)
- B. 110 (26.3)
- C. 100 (23.9)
- D. 90 (21.5)
- E. 80 (19.1)

The infant in the vignette was stressed around the time of birth and developed necrotizing enterocolitis on the seventh day. Because his condition is being treated with bowel rest, he needs to receive his total nutrient supply via a central venous catheter. The goal is to provide enough water, electrolytes, vitamins, minerals, and fuel. Fuel, expressed in energy units such as kilocalories (kcal) or kilojoules (kJ), is needed for metabolic maintenance, growth, and protein-sparing. In addition, enough protein is needed to produce a positive nitrogen balance (about 3 g/kg per day for full-term infants and 3.5 g/kg per day for premature infants). One kilocalorie is equal to 4.1868 kJ.

Water requirement is roughly calculated from measurable losses (stool, urine) and estimations of insensible loss (evaporation through the skin and respiratory tract). Urine output is often estimated at 50 to 80 mL/kg per day (2 to 3.3 mL/kg per hour). Stool losses average 5 to 10 mL/kg per day. An expected daily weight gain of 1% to 2% of current weight would require 7 to 14 mL/kg of additional water because about 70% of new weight is water.

The quantity of insensible water loss is highly variable, being maximal just after birth and decreasing as the
Infant’s skin matures. It was recently estimated to be 55 to 65 mL/kg per day at 7 days in infants weighing less than 1 kg at birth (extremely low-birthweight [ELBW]). Using the aforementioned estimates, the water requirements for a 7-day-old ELBW infant would range from 117 to 172 mL/kg per day. These estimates are not very useful for an individual infant who requires periodic clinical evaluation, including monitoring of body weight and measurements of output and serum sodium concentration.

To calculate the energy content of parenteral nutrition, one needs to add the energy provided by each potential fuel: carbohydrate, amino acids, and lipids. The glucose concentration in the vignette was 15% (ie, each 100 mL of solution contains 15 g of “glucose”). A gram of pure or anhydrous glucose (C6H12O6, molecular weight 180.1) would yield 3.75 kcal (15.7 kJ) when metabolized. However, the solution provided is actually 15% hydrated glucose (dextrose monohydrate), with a molecular weight of 198.2, yielding 3.4 kcal/g (14.2 kJ/g). Therefore, each milliliter of 15% glucose yields 0.51 kcal (2.14 kJ) which is calculated from the following equation:

\[
\frac{15 \text{g}}{100 \text{ml}} \times \frac{3.4 \text{kcal}}{\text{g}} = \frac{51 \text{kcal}}{100 \text{ml}} = 0.51 \text{kcal/ml}
\]

A gram of amino acids yields 4 kcal (16.7 kJ). Therefore, each milliliter of 3.5% amino acids provides 0.14 kcal (0.59 kJ) calculated as follows:

\[
\frac{3.5 \text{g}}{100 \text{ml}} \times \frac{4 \text{kcal}}{\text{g}} = \frac{14 \text{kcal}}{100 \text{ml}} = 0.14 \text{kcal/ml}
\]

The glucose/amino acid combination (0.51 kcal/mL + 0.14 kcal/mL) provides 0.65 kcal/mL (2.7 kcal/mg). The infant in the vignette is scheduled to receive 3.7 mL/hour or 88.8 mL/day. The caloric content is 57.7 kcal/day (241.7 kJ/day). Dividing by the body weight of 0.8 kg, the infant will receive 111 mL/kg per day and 72 kcal/kg (302 kJ/kg) per day from the nonlipid part of the intravenous infusion.

The energy content of the intravenous lipid provided in the vignette is 10 kcal/g (41.87 kJ/g) or 2 kcal/mL (8.4 kcal/mL) for a 20% solution. This is derived from the following equation:

\[
\frac{20 \text{g}}{100 \text{ml}} \times \frac{10 \text{kcal}}{\text{g}} = \frac{200 \text{kcal}}{100 \text{ml}} = 2 \text{kcal/ml}
\]

The infant in the vignette is to receive 0.3 mL/hour of the lipid solution or 7.2 mL/day containing 14.4 kcal/day (60.3 kJ/day). Correcting for body weight, the infant will receive 18 kcal/kg (75.4 kJ/kg) per day from the lipid infusion. Total calories for the infant in the vignette would be the sum of all sources: 90 kcal/kg (376.8 kJ/kg) per day.

The energy provided with the current infusions may not be enough to support growth and maintenance nutrition requirements. At 7 days of age, the requirement for water is anticipated to be closer to 130 to 150 mL/kg per day or more depending on clinical and environmental conditions. The daily requirement for calories is anticipated to be closer to 125 kcal/kg (523 kJ/kg). The glucose infusion rate ordered is more than 11 mg/kg per minute, within maximal guidelines of up to 12 to 15 mg/kg per minute. However, starting at this rate might lead to hyperglycemia. As ordered, the amino acids delivered would be about 3.9 g/kg per day, which is within the range generally recommended for premature infants (3.5 to 4.0 g/kg per day). The lipid infusion rate is 1.8 g/kg per day, which is enough to prevent essential fatty acid deficiency (0.25 to 0.5 g/kg per day) but could be advanced to provide more calories. Finally, sick newborn infants often need more water and calories than those who are well.

The Table provides shortcuts for energy contents in kilocalories or kilojoules per milliliter of various glucose and amino acid combinations as well as a listing for the usual 20% lipid solution. Once one calculates the volume per kilogram of each solution, multiplying by energy per milliliter simplifies the process of calculating total caloric intake.

<table>
<thead>
<tr>
<th>Table: Parenteral Infusion Mixtures and Their Energy Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, %</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>12.5</td>
</tr>
<tr>
<td>12.5</td>
</tr>
<tr>
<td>15</td>
</tr>
<tr>
<td>15</td>
</tr>
<tr>
<td>Lipid, %</td>
</tr>
<tr>
<td>20</td>
</tr>
</tbody>
</table>

Notes:

1. The term “calorie” is often used in discussions of nutrition to be synonymous with kilocalorie (the heat energy needed to raise the temperature of a kilogram of water by 1°C). For example, 20-calorie infant formula actually provides 20 kcal/oz.
2. Traditionally, the caloric contents of carbohydrate, protein, and lipid are taught to be 4, 4, and 9.
kcal/g, respectively. These figures are estimates based on a mixed diet. The figures for caloric contents presented in the critique are specific to the formulations available for intravenous alimentation.

**References**


**American Board of Pediatrics Content Specification(s)**

Nutrition: Know how to calculate the caloric content of parenteral nutrition solutions

Nutrition: Know the indications and advantages of total parenteral nutrition (TPN) solutions and combined enteral and parenteral nutrition

Nutrition: Know the nutritional composition of parental solutions

Nutrition: Know the importance of protein and non-protein nutrients in achieving optimal utilization of energy and nitrogen
A 30-week-gestation female infant is now 28 days old and has been growing poorly over the last 2 weeks. Her birthweight was 1,300 g and she now weighs 1,600 g. She was given intravenous nutrition from the first day and has made a transition to fortified mother’s milk at 0.8 kcal/mL, taking about 150 mL/kg per day. A week ago another supplement was added to the milk to increase the protein concentration to 3.5 g/kg per day. She has no history of vomiting, diarrhea, or abnormal urine output. She did have constipation relieved by glycerin suppositories on occasion. Physical examination findings were normal except for mild tachypnea and poor growth. Laboratory findings on the 28th day are as follows:

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Patient Result (SI Units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium, mEq/L (mmol/L)</td>
<td>137 (137)</td>
</tr>
<tr>
<td>Potassium, mEq/L (mmol/L)</td>
<td>4.8 (4.8)</td>
</tr>
<tr>
<td>Chloride, mEq/L (mmol/L)</td>
<td>113 (113)</td>
</tr>
<tr>
<td>Blood pH</td>
<td>7.26</td>
</tr>
<tr>
<td>Pco2, mm Hg</td>
<td>32</td>
</tr>
<tr>
<td>Bicarbonate, mEq/L (mmol/L)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Serum urea nitrogen, mg/dL (mmol/L)</td>
<td>5 (1.8)</td>
</tr>
<tr>
<td>Creatinine, mg/dL (μmol/L)</td>
<td>3.2 (17.7)</td>
</tr>
<tr>
<td>Urine pH</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Of the following, the MOST likely basis for this infant’s growth failure is:

- A. aldosterone deficiency or resistance
- B. excessive acid load
- C. faulty tubular reabsorption of bicarbonate
- D. insufficient renal hydrogen ion secretion
- E. thyroxine deficiency

The infant in the vignette was born at an appropriate weight for gestation and gained an average of 7 g/kg per day over the next month, assuming that she regained birthweight by about 10 days after birth. An appropriately growing premature infant of that gestation would gain weight at twice that rate. She failed to gain adequate weight even though enough calories and protein were provided. Because she has had no vomiting, diarrhea, or polyuria, abnormal nutrient losses do not explain her failure to thrive.

The laboratory tests are important clues to the underlying problem. Metabolic acidosis, if persistent, is a
known cause of failure to thrive. Determining the cause of the metabolic acidosis is the next step. Calculating the anion gap ([Na\(^+\)] – [Cl\(^-\)] – [HCO\(_3\)] \(\text{mol/L}\)) can narrow the list of possibilities. The anion gap for this infant is 10 mEq/L (normal is ≤15 mEq/L). A normal anion gap eliminates several underlying causes, including lactic acidosis, methylmalonic acidemia, aldosterone deficiency or resistance, and late metabolic acidosis of prematurity.

Infants with failure to thrive and persistent metabolic acidosis with a normal anion gap are likely to have one of the following conditions:

- Distal renal tubular acidosis
- Congenital hypothyroidism
- Obstructive uropathy
- Early uremic acidosis
- Bicarbonate loss
  - Proximal renal tubular acidosis
  - Diarrhea
  - Intestinal fistula
  - Ureterosigmoidostomy
- Drug toxicity: cholestyramine, magnesium sulfate, calcium chloride
- Acid loading
  - Ammonium chloride
  - Arginine hydrochloride

The infant in the vignette has a urine pH greater than 5.5 in the face of metabolic acidosis. This is consistent with distal renal tubular acidosis (type I RTA), which is characterized by a failure to excrete hydrogen ion (H\(^+\)) into the distal renal tubule in exchange for bicarbonate. Infants with this condition cannot acidify their urine as a compensation for systemic acidosis. Distal RTA produces potassium wasting, which can lead to constipation, lethargy, and eventually vomiting, but the serum potassium concentration can be normal. Distal RTA is also associated with calcium wasting and low urinary citrate concentrations with a high probability of nephrocalcinosis and nephrolithiasis.

Distal RTA can occur sporadically. It can also be inherited as an autosomal recessive disorder associated with deafness because of a defect in H\(^+\)-adenosine triphosphatase, or as an autosomal dominant disorder involving a defect in the chloride-bicarbonate exchanger. Distal RTA can also occur as a sequel of obstructive nephropathy or as a toxic side effect of a drug, such as amphotericin.

Type II or proximal RTA is caused by an abnormally low threshold for bicarbonate reabsorption in the proximal renal tubule. The normal threshold is 26 mEq/L so that 85% of bicarbonate in the glomerular filtrate is reabsorbed from the proximal tubule. The remaining 15% is retrieved by the distal tubule in exchange for hydrogen ion. In type II RTA, the threshold is reduced to approximately 15 mEq/L, leading to significant loss of bicarbonate. Because the distal tubular hydrogen secretion function is intact, the urine is still acidified when the serum bicarbonate concentration is less than 15 mEq/L and becomes alkaline when exogenous citrate or bicarbonate is administered.

Newborn infants tend to have slightly higher serum potassium concentrations and lower sodium concentrations than do adults. This has been explained as a physiologic partial aldosterone resistance at birth associated with a developmentally low concentration of mineralocorticoid receptors in the normal newborn kidney. However, aldosterone deficiency as seen in cases of congenital adrenal hyperplasia or severe aldosterone resistance (pseudohypoaldosteronism) leads to massive sodium wasting and severe hyperkalemia as well as hypovolemia (leading to shock) and lactic acidosis with a high anion gap.

Thyroxine deficiency might be suspected in an infant with failure to thrive and constipation, but acidosis is not a feature of hypothyroidism.

Late metabolic acidosis of prematurity describes otherwise healthy premature infants between 1 and 3 weeks of age with impaired growth and mild to moderate metabolic acidosis. The original series consisted of infants fed cow milk providing a protein mixture that was primarily casein. The acidosis has been attributed to a net acid load (products of protein catabolism) that exceeds renal clearance capacity. These infants typically excreted acidic urine (pH <5.5). Late metabolic acidosis of prematurity is less commonly seen today because the dietary proteins currently in use have a more physiologic amino acid composition than does cow milk and are processed more efficiently.

References

<table>
<thead>
<tr>
<th>American Board of Pediatrics Content Specification(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water Salt Renal: Recognize the causes, diagnosis, and treatment of renal tubular acidosis in the neonate</td>
</tr>
<tr>
<td>Water Salt Renal: Be able to differentiate between proximal, distal, and transient renal tubular acidosis</td>
</tr>
<tr>
<td>Water Salt Renal: Know the changes in glomerular and tubular function that occur during development, including the handling of glucose, sodium, potassium, calcium, and phosphate</td>
</tr>
<tr>
<td>Water Salt Renal: Recognize the clinical and laboratory manifestations of metabolic acidosis and metabolic alkalosis in infants</td>
</tr>
<tr>
<td>Water Salt Renal: Know the causes and differential diagnosis of metabolic acidosis and metabolic alkalosis in infants</td>
</tr>
</tbody>
</table>


Question: 10

You are asked to see a woman whose fetus has a left cystic kidney identified on routine fetal ultrasonography at 16 weeks' gestation (Figure). Further imaging reveals a normal right kidney, abnormal left renal parenchyma, and no cysts in the liver or pancreas. You are asked to discuss possible diagnoses and neonatal outcomes for this fetus.

Figure: Sagittal view, Left kidney

Of the following, the MOST likely diagnosis in this fetus is:

- A. autosomal dominant polycystic kidney disease
- B. autosomal recessive polycystic kidney disease
- C. medullary cystic kidney disease
- D. multicystic dysplastic kidney disease
- E. nephronophthisis

Renal cystic disorders may result from a congenital abnormality or they can be acquired later in life (Table 1).

Table 1: Developmental Timing of Selected Renal Cystic Disorders

<table>
<thead>
<tr>
<th>Developmental Period</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before nephrogenesis</td>
<td>Multicystic dysplastic kidney</td>
</tr>
<tr>
<td>During nephrogenesis</td>
<td>Dysplastic kidney with cysts</td>
</tr>
<tr>
<td></td>
<td>• isolated</td>
</tr>
</tbody>
</table>
Cysts are defined as spherical, thin-walled, fluid-filled structures that can be single or multiple. Cysts develop from segments of renal tubules that grow and then detach from the parent tubule. The development and growth of cysts is attributed to increased proliferation of tubular epithelium, tubular cilia abnormalities, and/or excessive fluid secretion. Cysts may be restricted to the kidney or may involve other organs, particularly the liver. Renal cystic disorders may be associated with a primary renal parenchymal abnormality while other renal cystic diseases lead to destruction of the renal parenchyma as the cysts enlarge.

Ultrasoundography is the ideal diagnostic tool to identify and classify renal cysts but other imaging modalities may be useful:
- magnetic resonance imaging to provide additional information, such as extrarenal involvement
- voiding cystourethrography to assess for vesicoureteral reflux
- scintigraphy to measure renal function of each kidney

The fetus in this vignette most likely has multicystic renal dysplasia or multicystic dysplastic kidney (MCDK) disease because of early intrauterine detection of cysts, isolated unilateral renal cyst involvement, and abnormal renal parenchyma (Table 2).

Table 2: Comparison of Renal Cystic Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Incidence</th>
<th>Genetics</th>
<th>Characteristics of Cysts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal recessive polycystic kidney disease</td>
<td>1 in 20,000 to 40,000 live births</td>
<td>Autosomal recessive</td>
<td>Bilateral microcysts, typically after 20 weeks' gestation, associated with large kidneys, often with hepatic fibrosis</td>
</tr>
<tr>
<td>Autosomal dominant polycystic kidney disease</td>
<td>1 in 800-1,000 live births</td>
<td>Autosomal dominant</td>
<td>Bilateral macrocysts, rarely noted prenatally or in neonatal period, associated with large kidneys, additional cysts in liver, pancreas, spleen</td>
</tr>
<tr>
<td>Medullary cystic kidney disease</td>
<td>Extremely rare</td>
<td>Autosomal dominant</td>
<td>Cystic dilation of medullary part of renal collecting ducts</td>
</tr>
<tr>
<td>Multicystic dysplastic kidney</td>
<td>Unilateral: 1 in 1,000 live births, Bilateral: 1 in 5,000 live births</td>
<td>Sporadic</td>
<td>Usually large cysts, unilateral more common than bilateral, associated with abnormal renal parenchyma, abnormal renal shape, absent or atretic ureter, observed prenatally, typically by 20 weeks' gestation</td>
</tr>
<tr>
<td>Nephronophthisis</td>
<td>1 in 100,000</td>
<td>Autosomal recessive</td>
<td>Cysts detected at later stage of renal disease</td>
</tr>
</tbody>
</table>

MCDK disease is the most common renal cystic disease among infants. This disease usually affects only one kidney, with an incidence of 1 in 1,000 live births, but can affect both kidneys with an incidence of 1 in 5,000 live births. In contrast to polycystic kidney disease, MCDK disease is usually an incidental finding without significant familial occurrence. The causes of MCDK disease can be explained by two possible theories. The first theory suggests that abnormal differentiation of the metanephros leads to dysplastic renal parenchyma with resultant nonuniform cysts that increase in size and compress adjacent renal tissue. A second theory proposes that MCDK disease results after intrauterine ureteral obstruction leading to renal cyst formation. In support of both possibilities, MCDK has been linked to mutations in genes involved in ureteric bud development.

In 71% of cases, affected individuals with MCDK disease present with abnormal prenatal ultrasound findings. The cysts in MCDK disease are usually large and radiographically visible by 20 weeks' gestation and...
observed as early as 16 weeks’ gestation (Figure). Because of additional abnormalities in branching and differentiation of the uterine bud, affected individuals also exhibit a dysplastic collecting system and abnormal renal parenchyma. While bilateral MCDK disease is usually fatal in the newborn period because of the associated pulmonary hypoplasia, infants with unilateral MCDK disease have good outcomes with involution of the involved kidney occurring over months to years. Nephrectomy is considered in infants with hypertension, malignant transformation of the kidney, or an unusually large involved kidney. The function and radiographic image of the contralateral kidney should be monitored closely because this kidney is at increased risk (20%-40%) for minor malformations, such as vesicoureteral reflux.

Autosomal dominant polycystic kidney disease (ADPKD) is the most common renal cystic disease occurring in 1 in 800 to 1 in 1,000 live births. This autosomal dominant disorder is attributable to mutations in polycystin, with alterations of the PKD1 or PKD2 gene leading to ciliary abnormalities of the renal tubular epithelium. Prenatal ultrasonography may show nonspecific bilateral abnormalities, such as increased echogenicity of the renal cortex and increased corticomedullary differentiation. Because cysts are rarely seen prenatally, the diagnosis of ADPKD is unlikely in the fetus in the vignette.

Bilateral cysts usually become apparent during the second decade of life in patients with ADPKD and increase in number and size with advancing age, leading to hypertension and/or renal failure. A small subgroup of patients with ADPKD may develop cysts with symptoms earlier in life, and are often misdiagnosed with autosomal recessive polycystic kidney disease (ARPKD). This is a rare, neonatal presentation that is usually fatal. The diagnosis of ADPKD can be confirmed by finding an autosomal dominant inheritance pattern of cystic renal disease. Adults with ADPKD usually have extrarenal manifestations, such as mitral valve ballooning, cerebral or aortic aneurysm, hepatic fibrosis, and/or cyst formations in the liver, spleen, or pancreas. Patients with ADPKD display a large clinical variability, thought to be attributable to genetic, environmental, and hormonal modifiers.

Autosomal recessive polycystic kidney disease is a rare cystic disorder occurring in 1 in 20,000 to 40,000 live births. This autosomal recessive disorder is caused by mutations in the PKHD1 gene, leading to abnormalities in fibrocystin, which is involved in tubular cilia formation in the renal collecting tubules and biliary tree. After 20 weeks’ gestation, prenatal ultrasonography reveals multiple small cysts in both kidneys that are usually confined to the collecting ducts, enlarged kidneys with increased echogenicity, and decreased corticomedullary differentiation. Because affected individuals with ARPKD have bilateral renal involvement and cysts are not usually observed before 20 weeks’ gestation, the fetus in the vignette is unlikely to have ARPKD.

If ARPKD is not diagnosed prenatally, affected individuals usually present within the first year after birth with an enlarging abdominal mass, respiratory difficulties as a result of limited diaphragmatic mobility, failure to thrive in the setting of renal failure, hypertension, and/or urinary tract infections. ARPKD has a wide clinical outcome including intrauterine fetal demise, Potter syndrome, or early renal failure with hypertension. If affected individuals survive the neonatal period, more than half require renal transplantation before age 20 years. Less commonly, affected individuals may have normal renal function into adulthood or enlarging cysts during adulthood with progressive hepatic fibrosis and portal hypertension. This clinical variability is not completely understood but thought partly attributable to the distinct mutations in the fibrocystin gene.

Nephronophthisis is a rare autosomal recessive cystic renal disease with an incidence of 1 in 100,000 live births. Patients with nephronophthisis have mutated NPHP genes that encode proteins critical for primary cilia function. Affected individuals may have clinical symptoms during infancy, childhood, or adolescence. Initially the kidneys are normally shaped but have decreased corticomedullary differentiation. The associated chronic renal insufficiency leads to the presentation of polyuria, polydipsia, anemia, and failure to thrive. Cysts are seldom evident during the initial stage of the disease, and usually appear when end-stage renal failure is diagnosed.

Medullary cystic kidney disease has an autosomal dominant inheritance pattern that presents clinically during adulthood. Mutations in the MCKD1 and MCKD2 genes induce cystic dilation of the medullary portion of the collection ducts. Fetal diagnosis is not possible; rather, individuals with medullary cystic kidney disease present with gout, hyperuricemia, and renal failure during adulthood.

References


**American Board of Pediatrics Content Specification(s)**

- Water Salt Renal: Recognize the clinical manifestations of anatomic abnormalities of the kidneys and urinary tract in infants
- Water Salt Renal: Know how to diagnose specific anatomic abnormalities of the kidneys and urinary tract in infants
- Water Salt Renal: Know how prenatal diagnosis of renal abnormalities effects postnatal management

Complete Assessment
A male infant born at 24 weeks' gestation is now 4 months old with a postmenstrual age of 40 weeks. His hospital course was complicated by surfactant deficiency; patent ductus arteriosus that closed with indomethacin treatment; chronic lung disease that was treated with prolonged ventilator support, glucocorticoid and diuretic administration; apnea of prematurity treated with caffeine; and feeding immaturity that required prolonged gavage feedings. Renal ultrasonography showed bilateral nephrocalcinosis.

Of the following, the factor MOST likely to exacerbate nephrocalcinosis is:

A. elevated serum osteopontin
B. elevated urinary citrate
C. magnesium supplementation
D. metabolic acidosis
E. thiazide administration

Nephrocalcinosis occurs in 7% to 41% of preterm neonates born before 32 weeks of gestation. This wide prevalence is attributable to differences in study populations, ultrasound and technician detection rate, and criteria for diagnosis. Typically, nephrocalcinosis in premature infants is localized to the medulla and consists of calcium oxalate crystals. Renal stone formation in the preterm population has various causes. Because premature infants have well-developed deep nephrons with a long loop of Henle and low urine velocity, crystals can form easily and then stick to the surface, grow, and aggregate. Subsequently, an imbalance of factors—an increase in stone-promoting factors and lowering of stone-inhibiting factors—triggers renal stone formation (~Table~).

<table>
<thead>
<tr>
<th>Promoting Factors</th>
<th>Inhibiting Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalciuria</td>
<td>Medications (eg, thiazides)</td>
</tr>
<tr>
<td>Acidosis</td>
<td>Citrate</td>
</tr>
<tr>
<td>High calcium intake</td>
<td>Other possibilities (not proven)</td>
</tr>
<tr>
<td>Low phosphorous intake</td>
<td>Magnesium</td>
</tr>
<tr>
<td>Total parenteral nutrition</td>
<td>Tamm-Horsfall protein</td>
</tr>
<tr>
<td>Medications (eg, loop diuretics, methyloxanthines, glucocorticoids)</td>
<td>Nephrocalcin</td>
</tr>
<tr>
<td></td>
<td>Osteopontin</td>
</tr>
<tr>
<td>Hyperoxaluria</td>
<td></td>
</tr>
</tbody>
</table>
Episodic periods of respiratory and metabolic acidosis have been shown to increase the risk of renal stone formation in adults. Similarly, recent studies have shown that preterm infants with more extensive nephrocalcinosis have experienced longer periods of acidosis. This association can be explained by multiple mechanisms. Evidence suggests that preterm infants exhibit an increase in urinary calcium excretion during acidosis. This occurs partly because acidosis induces calcium release from bone in an attempt to buffer the acidic environment, which results in inhibition of osteoblastic activity and stimulation of osteoclastic activity. In addition to higher serum calcium delivery to the kidneys, acidosis also directly increases urinary excretion of calcium and phosphorous, with both mechanisms increasing the risk of stone formation in the preterm infant. Serum acidosis has also been shown to increase reabsorption of urinary citrate in the proximal tubules, decreasing urinary citrate and limiting the protective effect of urinary citrate. In the infant in this vignette, a metabolic acidosis potentially could incite further formation of renal stones.

Urine contains macromolecules, including osteopontin, nephrocalcin, and Tamm-Horsfall protein (uromodulin). Osteopontin, originally identified in bone, is a glycoprotein involved in mineralization, signaling, and cell adhesion. By binding and coating calcium oxalate crystals in renal tubules, it has been suggested that osteopontin may prevent renal calcium oxalate accumulation. However, recent data showed that osteopontin was localized to the luminal surface of distal tubular cells in preterm neonates before crystal retention, which is the first step to nephrocalcinosis. Thus, further data are needed to support the inhibitory role of osteopontin. The role of other macromolecules in preterm neonates and renal stone formation has not been investigated.

Citrate plays an important role in preventing calcium stone formation by forming complexes with calcium that are more soluble than calcium oxalate and calcium phosphate compounds. Indeed, some studies have found that preterm infants with nephrocalcinosis have a lower urine citrate-calcium ratio compared with infants without renal stones. Because renal citrate excretion has been shown to inhibit renal calcification in the preterm infant and children with hyperoxaluria have been treated successfully with citrate, one study investigated the impact of citrate supplementation on preventing stone formation in preterm infants. In this randomized controlled trial, preterm neonates received oral citrate from 7 days after birth until term gestational age. In the treated group of infants, the urinary citrate-calcium ratio was observed to increase, but the prevalence of nephrocalcinosis did not decrease significantly. Although citrate administration may not prevent further nephrocalcinosis in the infant in this vignette, it is unlikely to cause additional stone formation.

Magnesium is a low-molecular-weight chelator that, similar to citrate, forms complexes with oxalate, increasing formation of soluble magnesium oxalate instead of the less-soluble calcium oxalate. The role of urinary magnesium excretion in the development of nephrocalcinosis in the preterm infant has not been studied.

Thiazides are diuretics that block the thiazide-sensitive sodium chloride cotransporter and inhibit sodium absorption in the distal tubules. These medications also decrease urinary secretion of calcium by increasing proximal calcium and sodium reabsorption in response to the distal natriuretic effect. Thiazides also lead to direct calcium reabsorption. Although thiazides are generally known to inhibit nephrocalcinosis, preterm neonates treated with thiazides can still develop nephrocalcinosis. In contrast to thiazide, furosemide administration is thought to be an important cause of nephrocalcinosis in preterm infants. By inhibiting the Na⁺K⁺Cl⁻ carrier in the apical membrane, furosemide induces a corresponding reduction in calcium reabsorption, thereby leading to hypercalciuria. This may be prolonged in preterm infants because of the slower plasma clearance found in this population.

In addition to treatment with furosemide, preterm infants exposed to glucocorticoids postnatally are also at increased risk of developing nephrocalcinosis secondary to hypercalciuria. Similarly, methylxanthines induce a hypercalciuric effect, possibly by increasing diuresis and natriuresis, increasing prostaglandin synthesis, and altering renal blood flow. The preterm infant diet, composed of high calcium, ascorbic acid, and glycine, also contributes to the development of nephrocalcinosis.

References


**American Board of Pediatrics Content Specification(s)**

Water Salt Renal: Know the recommended supportive and corrective treatment of anatomic abnormalities of the kidneys and urinary tract in infants
A male infant is born to a mother with limited prenatal care at 33 weeks' gestation with very little amniotic fluid at the time of delivery. The infant requires endotracheal intubation and breathing support for persistent grunting, flaring, retractions, and cyanosis. Physical examination reveals a firm distended abdomen, flat face, flat nose, low-set flattened ears, and positional deformities of his feet. After umbilical catheters are placed you obtain a radiograph of his chest and abdomen (Figure 1).

His first arterial blood gas while he is receiving oscillator support reveals a pH of 7.19, Paco2 of 81 mm Hg (10.7 kPa), and a Pao2 of 30 mm Hg (4 kPa). His serum creatinine and sodium concentrations are 3.5 mg/dL (309 μmol/L) and 138 mg/dL (138 mmol/L), respectively. Forty milliliters of clear yellow fluid are obtained via a paracentesis and the specimen is sent for analysis. The infant’s abdominal ultrasound obtained after the paracentesis is shown in Figures 2 through 4.
Of the following, the paracentesis fluid obtained from this infant is MOST likely to contain:

- A. 55 mEq/L (55 mmol/L) of sodium
- B. 4.1 mg/dL (362.4 μmol/L) of creatinine
- C. 1,600 mg/dL (18.1 mmol/L) of triglycerides
- D. 90% lymphocytes
- E. 3.7 g/dL (37.0 g/L) of protein

Incorrect
Correct Answer: B

The infant in the vignette has ascites, an accumulation of an abnormal amount of intraperitoneal fluid. In most cases ascites is caused by an imbalance between capillary and interstitial hydrostatic and oncotic pressures or an obstruction of the lymphatic or urine flow. Abnormalities of the urinary tract, biliary tract, or lymphatic system are the most common causes of ascites in neonates. Neonatal ascites also may occur after a gastric or intestinal perforation. Rare causes of ascites include cardiac anomalies (arrhythmias, right-sided obstructive lesions) and pancreatic injury from infections or trauma. Disorders of the urinary tract, as found in the infant in the vignette, are responsible for at least 40% of all cases of neonatal ascites. The creatinine concentration of ascites fluid is most likely to be similar to that of serum.

Posterior urethral valves, similar to those present in the neonate in the vignette, occur in 1 of 5,000 to 8,000 live male neonates. The obstruction at the urethra results in obstruction to fetal urine flow and oligohydramnios. Pulmonary hypoplasia, as was present in the neonate, is a direct result of oligohydramnios. Oligohydramnios is responsible for the facial features and limb abnormalities (Potter syndrome) noted in the infant. Additional clinical findings of obstructed valves noted in the neonate include a distended trabeculated bladder with thick walls (Figure 5), severe hydroureteronephrosis (Figures 6 and 7), and urinary ascites.

Figure 5: Ultrasonogram of bladder and left ureter. Two arrows point to thickened trabeculated bladder walls. The single arrow points to the dilated left ureter.
Figure 6: Ultrasonogram of left kidney. Transverse view of the kidney shows severe hydronephrosis. The calyces (two arrows) and renal pelvis are dilated.

Figure 7: Ultrasonogram of right kidney. Transverse view of the kidney shows severe hydronephrosis (two arrows), parenchymal thinning, and increased echogenicity of the parenchyma (single arrow).
Urinary ascites occurs in neonates with posterior urethral valves because the elevated intraluminal pressure from the obstruction causes a perforation of the bladder or kidney or extravasation of urine across the renal fornix. Urine that extravasates across the fornix first enters the retroperitoneum and then travels across the peritoneum into the abdominal cavity as a transudate. Although the urinary concentrations of sodium and creatinine are dissimilar from serum concentrations, the electrolyte and creatinine concentrations of urinary ascites are more similar to serum concentrations because the large absorptive mesothelial surface serves to quickly equilibrate these values with those of serum, masking the true origin of the ascitic fluid.

In most instances transudates such as urinary ascites are the result of mechanical forces of hydrostatic or oncotic pressure that favor fluid filtration in excess of absorption. They usually do not directly involve the pleural or mesentery surfaces. Transudates are usually clear or pale yellow, as opposed to exudates which may be cloudy from an abundance of neutrophils or have a milky white opalescent color because of the presence of chyle. Transudative fluids in the pleural space or peritoneum, including urinary ascites, will have a protein concentration that is less than 3 g/dL (16.95 mmol/L). Transudates contain primarily lymphocytes, neutrophils, and monocytes whereas exudates tend to have higher cell counts with a preponderance of polymorphonuclear neutrophils.

Chyle is a rare cause of ascites in neonates and is not likely to present in association with urinary obstruction. Most cases of chylous ascites are idiopathic, but a congenital lymphatic abnormality is thought to be the usual underlying cause. Chylous ascites fluid would be expected to have an elevated triglyceride content in excess of 1,500 mg/dL (16.95 mmol/L) and a predominance of lymphocytes (>75%). Note that among neonates who have never been fed enterally, the peritoneal fluid triglyceride concentrations may be low but the lymphocyte predominance will remain.

References
<table>
<thead>
<tr>
<th>Water/Salt/Renal: Know the causes of renal failure in the neonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water/Salt/Renal: Know the clinical manifestations, imaging, and laboratory features of renal failure in the neonate</td>
</tr>
<tr>
<td>Water/Salt/Renal: Recognize the clinical manifestations of anatomic abnormalities of the kidneys and urinary tract in infants</td>
</tr>
<tr>
<td>Water/Salt/Renal: Know how to diagnose specific anatomic abnormalities of the kidneys and urinary tract in infants</td>
</tr>
</tbody>
</table>
A family practitioner calls you about a 6-day-old infant she is seeing in her office. The infant was born at home to a young primigravida living with her husband in a remote homestead. Breastfeeding was attempted, but was not very successful. The child is 10% to 15% below the estimated birthweight. The serum glucose concentration is 30 mg/dL (1.67 mmol/L), yet the infant is active, alert, and smiling. The family practitioner asks you, "How can this be?"

Of the following, the metabolic response to starvation that is MORE important in the neonate than in the adult is:

- A. ammonia production
- B. autophagy
- C. gluconeogenesis
- D. glycogenolysis
- E. ketogenesis

Correct

The newborn human at term is born prematurely compared with other mammals as a consequence of the metabolic demands of her large brain. Until regular breastfeeding is established, the neonate undergoes the most severe period of starvation she is likely to encounter throughout life.

Several mechanisms have evolved to help the human newborn to adapt to the demands of this period of starvation, including autophagy, ketogenesis, gluconeogenesis, and ammonia production. Of these, ketogenesis is the process that is more important in the newborn than in the adult.
Ketogenesis is the production of ketone bodies, such as β-hydroxybutyrate and acetoacetic acid, from triglycerides (Figure 1). The process takes place in the liver. The human brain can metabolize ketone bodies as well as glucose for energy; other organs are dependent on glucose.

Ketogenesis is important for the newborn because of the large metabolic demands of the brain, which account for 60% to 70% of the total metabolism at birth. Newborns can produce ketone bodies faster than humans at any other age (Figure 2). The ketone bodies provide more than half the metabolic demands of the newborn brain, and continue to do so during starvation. As in the vignette, the serum glucose level may be low without the brain necessarily being deprived, if sufficient ketone bodies are available.

Maternal colostrum is well suited to supply the metabolic demands of the newborn brain, with abundant triglyceride and little lactose. Infants of diabetic mothers, however, are at a disadvantage, because their high insulin levels after birth inhibit the production of ketone bodies.

Other species, and humans at other ages, need less than 5% of their metabolism to operate their brains. During starvation in these species, lipolysis provides enough glycerol for gluconeogenesis, and some ketone bodies. Thus, the hibernating bear does not need to become ketogenic to sustain its brain.

Gluconeogenesis is the production of glucose from other molecules (Figure 3). Sources in starvation include glycerol from lipolysis and alanine from protein breakdown. Lactate and pyruvate, from red cells and the renal medulla, can be turned into glucose via the Cori cycle. These processes take place in the liver. During starvation, the kidneys also can make glucose from glutamine.

Autophagy is the cellular process of self-digestion of proteins. A portion of each cell's cytoplasm is sequestered in an autophagosome and fused with a lysosome. The resulting amino acids are then fed into the gluconeogenesis pathway. Autophagy has recently been described in mice as an immediate source of amino acids for gluconeogenesis immediately after birth or sudden starvation. The process is not known to be different from the adult process in scope or quality.

Ammonia production by the kidneys is a by-product of gluconeogenesis from glutamine (Figure 4). Although ammonia production is more energy efficient than urea production as a means of eliminating waste nitrogen, the accumulating ammonium ion is toxic to cells. Because of this toxicity, this process becomes primary only with the dire needs of starvation. It is seen in newborns and adults after several days of starvation.

Glycogenolysis (Figure 5) as a source of glucose is important in the first day of adult starvation. Low glycogen stores render glycogenolysis less important in the newborn human.

Suggested Readings


**American Board of Pediatrics Content Specification(s)**

Endocrine/Metabolic/Thermal: Know the metabolic consequences of starvation in the neonatal period

Copyright © 2013 American Academy of Pediatrics. All rights reserved.
Figure 1: Ketogenesis. β-hydroxy-butyrate and acetoacetic acid are made from triglyceride breakdown.

Triglyceride

β-Hydroxybutyrate

Acetoacetate
Figure 2: β-hydroxy-butyrate is produced during starvation more quickly in the newborn than at other ages. (Adapted from Cahill [2006].)

β-Hydroxybutyrate in Starving Subjects

- Newborn
- Infant
- Child
- Adult

β-Hydroxybutyrate, mM

Hours
Figure 3: Gluconeogenesis. Glucose is made from triglyceride and protein breakdown.
Figure 4: During starvation, gluconeogenesis from protein breakdown produces ammonium in the kidneys as well as urea in the liver.
Figure 5: Glycogen breakdown produces glucose.
A pediatric colleague consults you about a 2-day-old child with clonic seizures. She has no details of the case beyond low serum calcium and magnesium concentrations: 5.5 mg/dL (1.4 mmol/L) and 0.7 mg/dL (0.3 mmol/L), respectively.

Of the following, the cause of early hypocalcemia that is MOST likely to involve hypomagnesemia is:

- A. intrauterine growth restriction
- B. maternal diabetes
- C. maternal phenytoin use
- D. perinatal asphyxia
- E. prematurity

Of the following, the cause of early hypocalcemia that is MOST likely to involve hypomagnesemia is:

Early neonatal hypocalcemia is most often caused by intrauterine growth restriction, maternal diabetes, maternal phenytoin use, perinatal stress or asphyxia, or prematurity. The mechanisms by which these conditions cause hypocalcemia are diverse. The condition most likely to involve hypomagnesemia as part of the mechanism causing hypocalcemia is maternal diabetes.

Neonatal hypocalcemia is considered significant when the serum ionized calcium is less than
4 mg/dL (1.0 mmol/L), when total serum calcium is less than 6.5 mg/dL (1.6 mmol/L), or when symptoms occur. Possible symptoms are listed in the Table. Early neonatal hypocalcemia is defined as hypocalcemia in the first 3 or 4 days after birth.

Maternal diabetes causes magnesium losses in the maternal urine. Transplacental transfer of magnesium is by active transport against a concentration gradient, but is markedly reduced in maternal diabetes. Mild maternal hypomagnesemia is magnified in the fetus. Magnesium deficiency in the fetus and newborn reduces the secretion of parathyroid hormone (PTH) and induces resistance to PTH in the end organs. The hypoparathyroidism causes hypocalcemia that is unresponsive to calcium administration, until the hypomagnesemia is corrected.

Prematurity is associated with immature parathyroid glands that release inadequate amounts of PTH in response to the abrupt drop in umbilical calcium influx at birth. The immature renal tubular cells do not react appropriately to what little PTH is secreted, resulting in hypercalciuria and hypocalcemia. End-organ resistance to calcitriol may also play a role. The premature infant, relative to the term infant, is protected from the effects of low total serum calcium concentrations. A greater proportion of the total calcium in the premature infant is in the form of free biologically active ionized calcium, because of a lower serum protein concentration and a lower pH.

Perinatal stress or asphyxia lowers serum calcium concentration via a low glomerular filtration rate. The lower renal clearance of phosphate causes hyperphosphatemia. The higher phosphate concentration precipitates calcium, interferes with bone resorption and calcium release, and inhibits the production of calcitriol, resulting in hypocalcemia.

Intrauterine growth restriction does not by itself cause hypocalcemia. It is, however, closely associated with prematurity, stress, and asphyxia, each of which is a cause of hypocalcemia.

Maternal use of phenytoin or phenobarbital induces production in the liver of microsomal enzymes of the cytochrome P450 and mixed-function oxidase systems. These enzymes increase the hepatic elimination of calcitriol and its precursor, 25-hydroxyvitamin D₃ (calcidiol), causing low maternal serum concentrations. Calcitriol does not seem to cross the placenta, but calcidiol does cross, by diffusion down a concentration gradient. Chronic maternal calcidiol deficiency results in fetal calcidiol and calcitriol deficiencies, similar to postnatal rickets, leading to hypocalcemia in the newborn. Vitamin D supplements are recommended for mothers taking phenytoin or phenobarbital during pregnancy.

**Suggested Readings**


Maternal-Fetal Medicine: Know the effects on the fetus and/or newborn infant of maternal diabetes mellitus (including gestational diabetes) and their management.
Print

Table: Symptoms of Early Neonatal Hypocalcemia

- Jitteriness
- Hyperactivity
- Hyperacusis
- Tetany
- Seizures
- Apnea
- Laryngospasm
- Wheezing (bronchospasm)
- Vomiting (pylorospasm)
- Tachycardia
Question 5

A 33-week-gestation male infant with a distended abdomen and Potter features requires high-frequency ventilation and nitric oxide to maintain adequate oxygenation and ventilation. At delivery, the abdomen was firm and markedly distended. A paracentesis was performed to remove 45 mL of fluid from the abdomen. The creatinine concentration of the fluid was 4.1 mg/dL (362.4 μmol/L). The infant’s serum creatinine concentration was 3.5 mg/dL (309 μmol/L). A radiograph of his chest and abdomen is shown (Figure 1). The infant’s abdominal ultrasound is shown in Figures 2 through 4. After reviewing the ultrasonography findings with the resident team you discuss the most appropriate immediate management of the infant’s condition.

Figure 1
Of the following, the MOST appropriate next step in the treatment of this infant is:

- **A.** creation of a vesicostomy
- **B.** insertion of bladder catheter
- **C.** placement of a peritoneal drain
- **D.** urinary diversion with a pyelostomy
- **E.** valve ablation

**Correct**

The neonate in the vignette has posterior urethral valves, one of the most devastating anomalies of the urinary tract. Posterior urethral valves occur in 1 of 5,000 to 8,000 live male neonates and make up a majority of congenital urethral obstructions and 10% of urinary obstructions diagnosed in utero. Posterior urethral valves are among the few urinary obstructions that can be life-threatening in the neonatal period. Initial management requires immediate drainage of the bladder with a 3.5 or 5 French catheter.

The term *valve*, which seems to imply function, is a misnomer. The one-way obstructive membrane creates a passive barrier to urine flow, has no active function, and is not a developmental stage in the embryology of the urethra. The term was coined in 1919 by Hugh Hampton Young after he noted that a urethral sound could pass easily from the urethral meatus into the bladder in a retrograde fashion but would not pass in an antegrade manner out of the bladder and down the urethra.
The embryology of posterior urethral valves is not well established, but may be related to an abnormal insertion of the mesonephric ducts into the fetal cloaca. Timing of valve development is also speculative, but it appears that they become obstructive during or after the eighth week of gestation.

Obstruction of the urethra will result in damage to the entire urinary tract proximal to the level of the obstruction. Injury to the lower tract appears to be caused by high-pressure urine storage. The urethral wall is thickened and the lumen is dilated. The bladder shows hypertrophy (Figure 3) and hyperplasia of the detrusor muscle. Treatment will reduce wall thickness and bladder compliance, but seldom do valve bladders ever achieve normal function. Ureter damage is usually severe. Virtually all patients with posterior urethral valves have hydrourerteronephrosis.

Renal damage in boys with posterior urethral valves appears to have two components. Obstructive uropathy associated with persistently high pressure can be ongoing and progressive, but can be reversed when the obstruction is relieved. Because recovery is thought to be time sensitive, early relief of the obstruction is imperative. Renal dysplasia, a type of damage that is not reversible, may be the result of elevated pressure during kidney development or abnormal embryologic development. Because dysplasia is not reversible, the amount of dysplasia at diagnosis is a major determinant of eventual renal function.

Most patients with posterior urethral valves are diagnosed with prenatal ultrasonography. If they are not diagnosed in utero, the most severely affected patients will present signs in the newborn period. The most significant and immediate clinical problem neonates face is pulmonary hypoplasia, the result of oligohydramnios. Infants with pulmonary hypoplasia, such as the neonate in the vignette, often require aggressive respiratory support after birth. Pulmonary hypoplasia is responsible for most mortality during the neonatal period in infants with posterior urethral valves. Mortality in neonates with posterior urethral valves has decreased during the past two decades with improvements in management of pulmonary hypoplasia. Neonates with obstructive posterior urethral valves often have intrauterine growth restriction and may have classic signs of oligohydramnios such as Potter facies and positional deformities of the limbs with pressure dimples over the knees and elbows.

Bladder catheterization helps to establish immediate drainage of the high pressure system. The bladder can become so irritable when a catheter is placed that wall spasms obstruct urine flow into the bladder. Effective drainage of the bladder with the catheter must be established and documented with irrigation of the catheter or by imaging of the bladder. A one-shot cystogram is often necessary to aid and document placement of the catheter.

After successful initial bladder drainage and stabilization of the neonate’s medical conditions, the next step in treatment is to permanently destroy the valves. This may occur several weeks after birth, especially in preterm infants whose urethral meatus may be too small to accommodate the smallest of cystoscopes. Such neonates may require gradual urethral dilation while their medical condition improves so that a cystoscope can be passed to destroy the valves.

Infants who are too small for safe instrumentation for a valve ablation may require placement of a cutaneous vesicostomy. Vesicostomies provide adequate drainage of the upper urinary tract in more than 90% of cases. They are not without complications. Noe and colleagues reported an 8.6% reoperation rate of vesicostomies. In general, primary ablation is the preferred surgical procedure to treat posterior urethral valves; vesicostomies are reserved for very small ill infants. Either procedure is done after the bladder has been catheterized and adequate drainage has been established.

Upper tract diversion with an ureterostomy or pyelostomy was used in the past as initial management of posterior urethral valves. Although upper diversion effectively decompressed the upper tracts and controlled infections, future urinary tract reconstructive procedures were more difficult. Current consensus is that an upper tract diversion and
primary valve ablation yield similar long-term results, but that infants with upper diversions need more surgical procedures. Upper tract diversion is usually limited to neonates who fail to respond to bladder drainage. If the creatinine concentration remains above 2.0 mg/dL (177 μmol/L) after 10 to 14 days of adequate bladder decompression, and hydronephrosis has not improved, upper tract diversion is often considered.

The infant in the vignette has urinary ascites, which at times may be difficult to diagnose. Urinary ascites occurs in neonates with posterior urethral valves because the elevated intraluminal pressure from the obstruction causes a perforation of the bladder or kidney, or extravasation of urine across the renal fornix. Electrolyte and creatinine concentrations of urinary ascites are often similar to serum concentrations as the large absorptive surface of the mesothelium serves to normalize these values, masking the origin of the ascitic fluid. Upper tract diversion with nephrostomies may be required to establish and treat the cause of ascites. Peritoneal drains are not used to treat urinary ascites.

**Suggested Readings**


**American Board of Pediatrics Content Specification(s)**

Water/Salt/Renal: Know the causes of renal failure in the neonate

Water/Salt/Renal: Know the clinical manifestations, imaging, and laboratory features of renal failure in the neonate

Water/Salt/Renal: Recognize the clinical manifestations of anatomic abnormalities of the kidneys and urinary tract in infants

Water/Salt/Renal: Know how to diagnose specific anatomic abnormalities of the kidneys and urinary tract in infants

Water/Salt/Renal: Know the recommended supportive and corrective treatment of anatomic abnormalities of the kidneys and urinary tract in infants

Water/Salt/Renal: Know the clinical manifestations, imaging, and laboratory features of renal failure in the neonate
An infant is born at 29 weeks’ gestation following labor induced because of severe maternal preeclampsia. You wish to initiate enteral feedings, but his mother’s milk supply is limited. As an alternative, you discuss use of donor human milk and explain to the parents that the processes involved in donor milk banking, including freezing and pasteurization, make this a safe alternative, while preserving nutritional and immunologic benefits unique to human milk.

Of the following, the component of human milk MOST preserved during the process of Holder pasteurization is/are:

- A. immunoglobulin M
- B. lactoferrin
- C. lipases
- D. lysozyme
- E. oligosaccharides

Incorrect
Correct Answer: E

Human milk is recognized as uniquely superior for infant feeding, providing nutritional and immunologic benefits important for normal growth, development, and general good health. Bioactive factors in human milk provide host defense against infections, actively modulate immune responses, and modify intestinal bacterial colonization.

When a mother is unable to pump milk, or her supply of milk is insufficient, donor human milk is an alternative to formulas. Evidence shows that the clinical
benefits of donor human milk may be comparable to an infant’s own mother’s milk, particularly related to feeding intolerance and necrotizing enterocolitis (NEC). A 2007 Cochrane Review found that feeding with formula compared with donor breast milk resulted in a higher incidence of NEC in the formula-fed group (relative risk 2.5; 95% confidence interval 1.2-5.1). A recent randomized controlled trial demonstrated a 50% reduction in the incidence of NEC among preterm infants fed an exclusive human milk diet compared with infants fed diets containing bovine milk–based products, including nutrient fortification. Furthermore, the number needed to treat with an exclusively human milk–based diet to prevent one case of NEC was estimated at 10.

Donor human milk banking involves the collection, screening, and pasteurization of expressed milk from lactating women. In the United States, donor milk banks follow guidelines set forth by the Human Milk Banking Association of North America. Potential milk donors are screened for human immunodeficiency virus, human T-cell lymphoma virus, hepatitis B and C, and syphilis. Donated milk is kept frozen until processed by the milk bank. Processing involves performing cultures for bacterial contamination, and subsequently discarding unacceptable milk. Donor milk is then pasteurized at 62.5°C for 30 minutes using the Holder method, a reliable method for eliminating bacteria and viruses, including cytomegalovirus.

However, Holder pasteurization affects immunologic properties of human milk. Lymphocytes, alkaline phosphatase, cytokines, some growth factors, and lipoprotein and bile salt–actived lipases are destroyed. Lactoferrin concentration is reduced by at least 50% and lysozyme by 25%. Immunoglobulins are variably affected, with 67% to 100% of immunoglobulin A preserved, up to 70% of immunoglobulin G preserved, but all immunoglobulin M destroyed.

Several important components of human milk are preserved through pasteurization, and may contribute to the protective health benefits common to donor and mother’s own milk. Preserved components include oligosaccharides; vitamins A, D, and E; lactose; long-chain polyunsaturated fatty acids; and epidermal growth factor. Human milk oligosaccharides are the third largest solid component in human milk and modulate immunity in several ways. These oligosaccharides exert a prebiotic function, as they resist digestion and serve as substrate for colonic flora. Also, human milk oligosaccharides act as analogs to epithelial receptors for specific microbes, exert a trophic effect on intestinal mucosa through their fermentation products, and interact directly with cells of the immune system. Long-chain polyunsaturated fatty acid metabolites induce eicosanoid production and alter gene expression and T-cell signaling, thereby influencing cytokine profiles.

**Suggested Readings**


**American Board of Pediatrics Content Specification(s)**

- Nutrition: Know the immunologic constituents in human milk and their physiologic effects
- Nutrition: Recognize the effects of different methods of processing of human milk, such as freezing, pasteurization, sterilization
- Nutrition: Realize the common problems associated with breast milk production in the NICU, and their management
Fetal ultrasonography performed at 33 weeks’ gestation detects a pelvic mass. Fetal magnetic resonance imaging shows that the mass is most consistent with hydrometrocolpos. A neonatologist meets with the family to discuss the cause, potential complications, and management of this mass.

Of the following, the MOST likely complication that can occur in this infant is:

- A. ascites
- B. congestive heart failure
- C. decreased lower limb movement
- D. urinary tract obstruction
- E. vaginal bleeding

Hydrometrocolpos is the collection of fluid (hydro) in the uterus (metro) and vagina (colpos). This condition occurs when a vaginal blockage coexists with an excess of vaginal fluid production. The incidence is between 1 in 16,000 and 1 in 30,000 live births.

During embryologic development, the cephalic ends of the müllerian ducts remain separate and with modifications, develop into the fallopian tubes. In contrast, the caudal ends of the müllerian ducts fuse in the midline, and the resulting solid cord of epithelial cells needs to degenerate to form the uterus and vagina, usually during the fifth or sixth gestational month. Failure of degeneration of the distal epithelial plate results in an imperforate hymen, while persistence of the solid rod of cells above this level results in vaginal atresia. Incomplete degeneration of these cells leads to formation of a vaginal septum. An imperforate hymen, high vaginal septum, vaginal atresia, or urogenital sinus causes a vaginal blockage, placing the fetus or neonate at risk for a
hydrometrocolpos.

A hydrometrocolpos can form in a female fetus or neonate with a vaginal obstruction if the fetal reproductive tract is sufficiently stimulated by maternal estrogens, causing an excess of vaginal fluid. The retained fluid arises from stimulated cervical mucous glands of the vagina and uterus and is typically serous or mucoid and rarely contains blood. If vaginal secretions are not excessive, the vaginal obstruction will remain undiagnosed until puberty. At that time, the patient’s own hormones will induce secretion of fluid from the cervical and uterine glands, leading to a hydrometrocolpos. This fluid collection increases even further at the time of menarche with a hematocolpos being superimposed on the hydrometrocolpos.

The clinical signs and symptoms seen in an infant with hydrometrocolpos depend on the cause of the obstruction and the degree of uterovaginal distention. In some cases, a pelvic mass is palpable. A translucent bulge from an imperforate hymen may be evident on physical examination, being more prominent when the infant cries or when pressure is exerted on the abdominal mass. If an infant has vaginal atresia, the enlarging proximal vagina may retract the atretic portion of the vagina into the pelvis and the external genitalia may appear normal. Patients with vaginal atresia have a high incidence of associated abnormalities, such as urinary tract or skeletal anomalies. Additional associated anomalies include congenital heart disease and postaxial polydactyly, found in patients with McKusick-Kaufman syndrome. Bardet-Biedl syndrome is associated with similar clinical features but also with retinitis pigmentosa, obesity, and learning disabilities later in childhood.

If the amount of fluid in the hydrometrocolpos is large, the mass can obstruct nearby structures. Obstruction of the adjacent urinary tract system is the most common secondary finding in an infant with hydrometrocolpos, and thus the most likely complication in the infant in the vignette. If the urinary tract obstruction is severe, the infant may develop acute renal failure and less commonly, urinary ascites. Infants with a large hydrometrocolpos may also have adjacent venous and/or intestinal obstruction. A secondary infection in the vagina or uterus, known as pyometrocolpos, can occur and may lead to signs and symptoms of sepsis. In rare cases, the mass can be so large that it compresses the diaphragm with associated respiratory distress.

Unless the infant also has congenital heart disease, congestive heart failure is not associated with hydrometrocolpos. Although the adjacent intestinal and urinary systems can be altered by mass effect, the spine is not typically affected and leg mobility is usually normal. Interestingly, lower limb edema as a result of mass-induced pressure on the inferior vena cava has been reported. External vaginal bleeding is not apparent because the vaginal tract is obstructed.

The diagnosis of hydrometrocolpos can sometimes be established prenatally with fetal ultrasonography, which shows a pelvic mass. Fetal magnetic resonance imaging may help to distinguish a hydrometrocolpos from an intestinal duplication cyst, ovarian cyst, sacrococcygeal teratoma, dermoid cyst, or anterior sacral meningocele. The Figure reveals a pelvic mass that is most likely a hydrometrocolpos (dashed line). The diagnosis can be confirmed with pelvic ultrasonography after birth. Ultrasonography is also helpful to evaluate for possible hydronephrosis and/or hydroureter. A voiding cystourethrogram may be needed to assess for an urethrovaginal fistula. In rare cases, hysterovaginography may be needed if the diagnosis is uncertain.

Management is aimed at vaginal drainage and excision of the vaginal obstruction. In cases of imperforate hymen, bedside incision and drainage by hymenectomy will remove the hydrometrocolpos. Laparotomy is indicated for vaginal atresia or if there are other abdominal anomalies or complications.

**Suggested Readings**


**American Board of Pediatrics Content Specification(s)**

Gastroenterology: Know the etiology, clinical and laboratory features, and management of abdominal masses in the neonate

---

Copyright © 2013 American Academy of Pediatrics. All rights reserved.
Figure: This T2-weighted axial magnetic resonance imaging scan shows a pelvic mass highlighted by the dashed line. Anteriorly, the bladder is full and slightly displaced (solid line). The mass is not connected with the bladder, spine, or rectum and has a different consistency than urine. This mass is most consistent with a hydrometrocolpos.
### Table: Composition of Maternal Human Milk and Renal Infant Formula*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Human Milk (Preterm)</th>
<th>Human Milk (Mature)</th>
<th>Renal Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume, kcal/mL (kcal/oz)</td>
<td>0.67 (20)</td>
<td>0.69 (20)</td>
<td>0.67 (20)</td>
</tr>
<tr>
<td>Protein, g/L</td>
<td>14</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Carbohydrate, g/L</td>
<td>66</td>
<td>72</td>
<td>69</td>
</tr>
<tr>
<td>Fat, g/L</td>
<td>39</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td>Sodium, mEq/L (mmol/L)</td>
<td>11 (11)</td>
<td>7 (7)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Potassium, mEq/L (mmol/L)</td>
<td>15 (15)</td>
<td>13 (13)</td>
<td>15 (15)</td>
</tr>
<tr>
<td>Calcium, mg/L (mmol/L)</td>
<td>248 (62)</td>
<td>280 (70)</td>
<td>378 (95)</td>
</tr>
<tr>
<td>Phosphorus, mg/L (mmol/L)</td>
<td>128 (41)</td>
<td>147 (47)</td>
<td>189 (61)</td>
</tr>
</tbody>
</table>

*Adapted from Chua and Sarwal (2005).

---

**ASSESSMENT PROGRESS:**  
Total Questions: **10**  
Questions Answered: **10**  
Correct Answers: **8**

**Question: 7**

A 3-week-old male infant born at 33 weeks’ gestation with posterior urethral valves and pulmonary hypoplasia has been weaned from nitric oxide and high-frequency ventilation to continuous positive airway pressure (6 cm). A 6-French catheter is in place to drain his bladder and he is scheduled for valve ablation. Over the last several days the infant's urine...
output has been 5.5 mL/kg per hour. His systolic and diastolic blood pressures have been consistently above 105 and 85 mm Hg, respectively. Twenty-four hours after birth his serum creatinine concentration was 3.5 mg/dL (309 μmol/L). Current laboratory values obtained from a radial artery are as follows.

<table>
<thead>
<tr>
<th>Laboratory Findings</th>
<th>Patient Results (SI Values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine, mg/dL (μmol/L)</td>
<td>1.9 (168)</td>
</tr>
<tr>
<td>Ionized calcium, mg/dL (mmol/L)</td>
<td>1.3 (0.33)</td>
</tr>
<tr>
<td>Phosphorous, mg/dL (mmol/L)</td>
<td>7.1 (2.3)</td>
</tr>
<tr>
<td>Sodium, mEq/L (mmol/L)</td>
<td>134 (134)</td>
</tr>
<tr>
<td>Potassium mEq/L (mmol/L)</td>
<td>6.7 (6.7)</td>
</tr>
<tr>
<td>pH</td>
<td>7.18</td>
</tr>
<tr>
<td>Paco₂, mm Hg (kPa)</td>
<td>35 (4.6)</td>
</tr>
<tr>
<td>Bicarbonate, mEq/L (mmol/L)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Random urine sodium, mEq/L (mmol/L)</td>
<td>70 (70)</td>
</tr>
</tbody>
</table>

Abdominal ultrasonography reveals significant dysplasia and bilateral hydronephrosis (Figures 1 and 2), which has improved over the past 3 weeks. He is currently receiving 140 mL/kg per day of expressed breast milk. You discuss the immediate management of the infant’s condition with the resident team.

**Figure 1:** Ultrasonogram of left kidney. Transverse view of the kidney shows severe hydronephrosis. The calyces (two arrows) and renal pelvis are dilated.
Figure 2: Ultrasonogram of right kidney. Transverse view of the kidney shows severe hydronephrosis, parenchymal thinning, and increased echogenicity of the parenchyma (arrow).

Of the following, you would MOST likely recommend:

- A. angiotensin-converting enzyme inhibitor
- B. fluid restriction
- C. low-phosphorus infant formula
- D. peritoneal dialysis
The neonate in the vignette has posterior urethral valves with renal dysplasia, hydrenephrosis, and renal failure. Congenital renal dysplasia or hypoplasia with or without urinary tract obstruction is the most common cause of end-stage renal disease in infancy and childhood. Shortly after birth the infant's serum creatinine concentration is normally equal to that of the mother and usually less than 1 mg/dL (88 mmol/L). The concentration subsequently declines during the first week after birth. Most investigators define neonatal renal failure as a serum creatinine concentration of 1.5 mg/dL (132.6 µmol/L) or greater. Renal insufficiency should be suspected in any newborn when the plasma creatinine concentration increases or fails to decrease during the week after birth. Renal failure is most commonly oliguric (urine output less than 1 mL/kg per hour) but can be nonoliguric, such as in the neonate in the vignette, depending on the reduction in glomerular filtration rate and the degree of tubular reabsorption. Thirty percent to 50% of neonates with acute renal failure are nonoliguric.

Acute and chronic renal insufficiency is often associated with a number of laboratory and clinical abnormalities that may include hyponatremia, hyperkalemia, hyperphosphatemia, hypocalcemia, acidosis, and hypertension. Because the kidney serves to excrete acids generated by metabolism and diet, metabolic acidosis is common in both acute and chronic renal failure. Metabolic acidosis normally occurs when the glomerular filtration rate is less than 50% of normal. The degree of acidosis at varying filtration rates is influenced by nutritional intake, catabolism, and alterations in electrolyte balance. Chronic metabolic acidosis interferes with calcium deposition in the bone and absorption from the intestine. In experimental animal models, uremia with metabolic acidosis creates a state of growth hormone insensitivity, which can contribute to impaired longitudinal growth. Renal failure with metabolic acidosis acts to alter growth by:

- increasing glucocorticoid production
- increasing protein breakdown
- downregulating secretion of pituitary growth hormone
- lowering growth hormone concentrations
- decreasing insulin-like growth factor concentrations

Severe metabolic acidosis is defined by a plasma bicarbonate concentration of 12 mEq/L (12 mmol/L) or less or a plasma pH less than 7.2. Sodium bicarbonate replacement in neonates with renal failure and severe metabolic acidosis promotes calcium deposition to bone and absorption from the intestine. The acidosis of renal failure can be treated by adding sodium bicarbonate to maintenance intravenous fluids, supplementing with oral bicarbonate, or maximizing sodium acetate in parenteral nutrition.

Metabolic bone disease is common among children with renal failure because the kidney plays an important role in the balance of calcium, phosphorus, and magnesium. The kidney is also responsible for the final step in synthesis of calcitriol (1,25 hydroxyvitamin D, the active form of vitamin D) and the degradation of parathyroid hormone. Hypocalcemia and hyperphosphatemia because of calcitriol insufficiency begin to occur...
when about 50% of kidney function is lost. Although the serum phosphorus and calcium concentrations in the infant in the vignette are in the normal range, a low-phosphorous diet and vitamin D supplementation are important to prevent hyperphosphatemia and hypocalcemia. Because human milk is low in phosphorous and has a low renal solute load (Table), it is suitable for the neonate in the vignette; there is no need to change to a low phosphorus infant formula.

Approximately 10% to 20% of neonates with renal failure will develop hypertension, most commonly from fluid overload. Neonates with obstructive uropathy, such as the neonate in the vignette, can also develop hypertension. Angiotensin-converting enzyme (ACE) catalyzes the conversion of angiotensin I to angiotensin II and the degradation of the peptide bradykinin. ACE inhibitors reversibly inhibit ACE, and by doing so, cause vasodilation and decreased sympathetic nervous system activity. ACE inhibitors are considered the drug of choice for most infants with mild to moderate renal failure and are generally well tolerated in neonates at low doses. Monitoring is required to avoid potential severe side effects, which may include hypotension, worsening renal failure, oliguria/anuria, and hyperkalemia. Because the infant in the vignette has hyperkalemia, a known side effect of ACE inhibitors, it would be prudent to use a different antihypertensive drug to treat the infant’s hypertension until the hyperkalemia is treated.

Hyponatremia is often the result of excessive fluid that cannot be excreted by neonates with intrinsic renal failure. Treatment consists of restricting free water intake, which will usually lead to a gradual return of the serum sodium to a normal concentration. Accurate measurement of urine and extrarenal fluid losses is imperative for optimal management of acute renal failure among neonates with oligoanuric renal failure. Depending on the situation, replacement of all or a part of the infant’s ongoing losses along with insensible losses may be necessary to attain negative fluid balance.

The neonate in the vignette has nonoliguric renal failure. Renal tubular damage from the pressure created by the obstructed valves reduces the ability of the kidney to concentrate and acidify the urine. Fifty-nine percent of patients with posterior valves will fail to concentrate and acidify their urine. Concentrating defects can result in the excessive urinary output and sodium losses noted in the neonate in the vignette, irrespective of the state of hydration. Infants with a salt-losing nephropathy will typically have high obligatory fluid output and require high fluid intakes to prevent dehydration. Restricting fluid intake would not be indicated.

Indications for renal replacement treatment (peritoneal dialysis or hemodialysis) for renal failure in newborns and octogenarians are similar, as is the need to assess the ethics of escalating treatment of renal failure. One of the most difficult questions faced by pediatric nephrologists is whether renal replacement treatment should be offered to all infants. Although the progression of renal failure varies, neonates with renal dysplasia or hypoplasia usually show a decline in renal function with time. The decision to begin or continue dialysis for a neonate who will develop chronic renal failure, such as the neonate in the vignette, is more difficult to make than the decision to initiate such treatment for a neonate whose renal failure is more self-limited. Chronic dialysis in such cases can be used as a “bridge” to renal transplantation. Indications for renal replacement treatment include biochemical abnormalities that cannot be controlled by medications, fluid management, and diet. Indications for peritoneal dialysis may include:

- worsening uremia
- refractory hyperkalemia or persistent acid base abnormalities
- refractory calcium and/or phosphate disturbances
- fluid overload that leads to clinical compromise
- increased fluid requirements to achieve adequate nutrition in oliguric patients
Although the infant in the vignette is hyperkalemic and acidemic, peritoneal dialysis would not be indicated at this point without a trial of conservative management.

**Suggested Readings**


**American Board of Pediatrics Content Specification(s)**

- Water/Salt/Renal: Recognize the clinical manifestations of anatomic abnormalities of the kidneys and urinary tract in infants
- Water/Salt/Renal: Know the recommended supportive and corrective treatment of anatomic abnormalities of the kidneys and urinary tract in infants
- Water/Salt/Renal: Know the clinical manifestations, imaging, and laboratory features of renal failure in the neonate
- Water/Salt/Renal: Know the management of renal failure in the neonate, including the use of hemofiltration, peritoneal dialysis, and hemodialysis
November

Question View:  

ASSESSMENT PROGRESS:  
Total Questions: 10  
Questions Answered: 10  
correct Answers: 9

Question: 8

A 4-hour-old full-term female infant inadvertently underwent a plasma glucose concentration measurement (sent to the laboratory on ice and within 10 minutes of sampling). The glucose concentration is 28 mg/dL (1.6 mmol/L). The infant is asymptomatic; she breastfed briefly at 45 minutes of age and for a total of 10 minutes at 3 hours of age. The infant’s mother is fit and trim and glucose screening results during pregnancy were normal. Her two siblings were also breastfed, both through the first year after birth. The infant’s parents ask what the glucose concentration means. You discuss fetal and neonatal glucose metabolism and measurement in detail.

Of the following, the factor that MOST likely is associated with the infant’s glucose concentration is:

- [ ] A. breast milk feeding
- [ ] B. glucose production rate
- [ ] C. ketone body formation
- [ ] D. red blood cell glycolysis
- [ ] E. fetal gluconeogenesis

Correct

Understanding fetal and neonatal glucose homeostasis is complicated because there is no lower threshold value that defines hypoglycemia and predicts central nervous system energy deficiency, central nervous system damage, and long-term disability. Thus, there is no threshold concentration of glucose or duration of low glucose concentration on which to intervene to prevent brain damage, the primary concern.
associated with low blood glucose concentrations. For pragmatic reasons, operational threshold values for blood glucose measurements have been arbitrarily defined. The understanding of fetal and neonatal glucose homeostasis is also complicated by measurement technique complexities and inability to measure blood glucose longitudinally; blood glucose measurements over time have been derived from cross-sectional data.

Plasma glucose concentrations randomly obtained during the first week after birth in healthy full-term infants with birthweights of 2.5 to 4.0 kg range from 40 to 100 mg/dL (2.2–5.6 mmol/L) with an average of 80 mg/dL (4.4 mmol/L) (Figure). The plasma glucose concentration decreases by about 50% to a nadir at 30 to 90 minutes after birth.

In healthy full-term infants who have fasted for up to 9 hours, the plasma glucose concentration ranges from 40 to 80 mg/dL. Plasma glucose concentrations in breastfed, small-for-gestational age, and preterm infants are somewhat lower than in healthy full-term infants. Breastfed infants, such as that in the vignette, have plasma glucose concentrations that average 37 mg/dL (2.1 mmol/L) with a range of 21 to 61 mg/dL (1.2-3.4 mmol/L) during the first 24 hours after birth. During this time frame, about half of all breastfed infants have plasma glucose concentrations that are below 36 mg/dL (2 mmol/L).

In response to the decrease in plasma glucose concentrations immediately after birth, counter-regulatory hormone activity is induced (elevations in concentrations of epinephrine, norepinephrine, glucagon, and growth hormone; decline in insulin concentration) and glucose production increases from endogenous stores, amino acids (such as alanine), fat, and lactate; glucose concentrations subsequently rise and stabilize. Glucose production rates in full-term and preterm infants range from 4 to 6 mg/kg per minute, significantly higher than that of adults. The relatively high glucose production compensates for the loss of maternal glucose supply and lowered glucose concentration after birth in the newborn infant, and is necessary to provide the brain, the major glucose-using organ, with adequate substrate for energy production.

Ketone bodies such as beta-hydroxybuterate and acetoacetate can be used to supply the brain with energy during periods of fasting when glucose supply is low. In animal models of hypoglycemia-induced neuronal injury, ketone bodies have been found to be neuroprotective. Breastfed infants have higher concentrations of ketone bodies than formula-fed infants. Hypothetically, such ketone bodies are acting to provide an alternative energy source for the brain during the initial hours to days after birth when plasma glucose concentrations are relatively low compared with subsequent days after birth.

Measurement of blood glucose concentrations is fraught with potential error. Whole blood glucose concentrations are 10% to 14% lower than that found in plasma because of red blood cell mass; thus it is important to know whether whole blood or plasma/serum glucose is being measured. Many point-of-care measurements are often made on whole blood samples. Furthermore, point-of-care devices are less reliable and less accurate at lower glucose concentrations. Although automatic analysis techniques for measurement of plasma or serum glucose are very accurate, the measurement within a sample may be hampered by the action of red blood cell glycolytic enzymes that are found to be in higher concentrations in neonates than adults. Collection of blood samples in tubes that contain a proteolytic agent (e.g., zinc hydroxide) or enzyme inhibitor (e.g., fluoride) and placement of the collection tube on ice for transport can reduce the action of red blood cell glycolysis on glucose measurements. Continuous glucose monitoring through subcutaneously placed microdialysis sensors are being evaluated and may be useful in neonatal glucose monitoring.

In an uncomplicated normal pregnancy the fetus receives glucose nearly exclusively from
the mother. No fetal gluconeogenesis occurs. Gluconeogenic capacity in fetuses is present, but the concentrations of key enzymes are generally lower than in adults. In animal models of acute hypoglycemia during pregnancy which causes fetal hypoglycemia, the sheep fetus can produce glucose from alternative fuels. Whether glucose production in human fetuses is induced during maternal hypoglycemia is yet to be established.

**Suggested Readings**


**American Board of Pediatrics Content Specification(s)**

Endocrine/Metabolic/Thermal: Recognize the clinical and laboratory features of neonatal hypoglycemia

Endocrine/Metabolic/Thermal: Know the fuels used for brain metabolism

Endocrine/Metabolic/Thermal: Recognize the clinical and laboratory features of neonatal hypoglycemia

Endocrine/Metabolic/Thermal: Recognize the approach to therapy and prevention of neonatal hypoglycemia

Endocrine/Metabolic/Thermal: Know the normal range of endogenous glucose production in term and preterm infants

Endocrine/Metabolic/Thermal: Know the causes (including hyperinsulinemic hypoglycemia) of neonatal hypoglycemia syndromes

---

Copyright © 2013 American Academy of Pediatrics. All rights reserved.
Question: 8

A 4-hour-old full-term female infant inadvertently underwent a plasma glucose concentration measurement (sent to the laboratory on ice and within 10 minutes of sampling). The glucose concentration is 28 mg/dL (1.6 mmol/L). The infant is asymptomatic; she breastfed briefly at 45 minutes of age and for a total of 10 minutes at 3 hours of age. The infant’s mother is fit and trim and glucose screening results during pregnancy were normal. Her two siblings were also breastfed, both through the first year after birth. The infant’s parents ask what the glucose concentration means. You discuss fetal and neonatal glucose metabolism and
Of the following, the factor that MOST likely is associated with the infant’s glucose concentration is:

- [x] A. breast milk feeding
- B. glucose production rate
- C. ketone body formation
- D. red blood cell glycolysis
- E. fetal gluconeogenesis

Understanding fetal and neonatal glucose homeostasis is complicated because there is no lower threshold value that defines hypoglycemia and predicts central nervous system energy deficiency, central nervous system damage, and long-term disability. Thus, there is no threshold concentration of glucose or duration of low glucose concentration on which to intervene to prevent brain damage, the primary concern associated with low blood glucose concentrations. For pragmatic reasons, operational threshold values for blood glucose measurements have been arbitrarily defined. The understanding of fetal and neonatal glucose homeostasis is also complicated by measurement technique complexities and inability to measure blood glucose longitudinally; blood glucose measurements over time have been derived from cross-sectional data.

Plasma glucose concentrations randomly obtained during the first week after birth in healthy full-term infants with birthweights of 2.5 to 4.0 kg range from 40 to 100 mg/dL (2.2-5.6 mmol/L) with an average of 80 mg/dL (4.4 mmol/L) (Figure). The plasma glucose concentration decreases by about 50% to a nadir at 30 to 90 minutes after birth.

In healthy full-term infants who have fasted for up to 9 hours, the plasma glucose concentration ranges from 40 to 80 mg/dL. Plasma glucose concentrations in breastfed, small-for-gestational age, and preterm infants are somewhat lower than in healthy full-term infants. Breastfed infants, such as that in the vignette, have plasma glucose concentrations that average 37 mg/dL (2.1 mmol/L) with a range of 21 to 61 mg/dL (1.2-3.4 mmol/L) during the first 24 hours after birth. During this time frame, about half of all breastfed infants have plasma glucose concentrations that are below 36 mg/dL (2 mmol/L).

In response to the decrease in plasma glucose concentrations immediately after birth, counter-regulatory hormone activity is induced (elevations in concentrations of epinephrine, norepinephrine, glucagon, and growth hormone; decline in insulin concentration) and glucose production increases from endogenous stores, amino acids (such as alanine), fat, and lactate; glucose concentrations subsequently rise and stabilize. Glucose production rates in full-term and preterm infants range from 4 to 6 mg/kg per minute, significantly higher than that of adults. The relatively high glucose production compensates for the loss of maternal glucose supply and lowered glucose
concentration after birth in the newborn infant, and is necessary to provide the brain, the major glucose-using organ, with adequate substrate for energy production.

Ketone bodies such as beta-hydroxybuterate and acetoacetate can be used to supply the brain with energy during periods of fasting when glucose supply is low. In animal models of hypoglycemia-induced neuronal injury, ketone bodies have been found to be neuroprotective. Breastfed infants have higher concentrations of ketone bodies than formula-fed infants. Hypothetically, such ketone bodies are acting to provide an alternative energy source for the brain during the initial hours to days after birth when plasma glucose concentrations are relatively low compared with subsequent days after birth.

Measurement of blood glucose concentrations is fraught with potential error. Whole blood glucose concentrations are 10% to 14% lower than that found in plasma because of red blood cell mass; thus it is important to know whether whole blood or plasma/serum glucose is being measured. Many point-of-care measurements are often made on whole blood samples. Furthermore, point-of-care devices are less reliable and less accurate at lower glucose concentrations. Although automatic analysis techniques for measurement of plasma or serum glucose are very accurate, the measurement within a sample may be hampered by the action of red blood cell glycolytic enzymes that are found to be in higher concentrations in neonates than adults. Collection of blood samples in tubes that contain a proteolytic agent (eg, zinc hydroxide) or enzyme inhibitor (eg, fluoride) and placement of the collection tube on ice for transport can reduce the action of red blood cell glycolysis on glucose measurements. Continuous glucose monitoring through subcutaneously placed microdialysis sensors are being evaluated and may be useful in neonatal glucose monitoring.

In an uncomplicated normal pregnancy the fetus receives glucose nearly exclusively from the mother. No fetal gluconeogenesis occurs. Gluconeogenic capacity in fetuses is present, but the concentrations of key enzymes are generally lower than in adults. In animal models of acute hypoglycemia during pregnancy which causes fetal hypoglycemia, the sheep fetus can produce glucose from alternative fuels. Whether glucose production in human fetuses is induced during maternal hypoglycemia is yet to be established.

Suggested Readings


American Board of Pediatrics Content Specification(s)

Endocrine/Metabolic/Thermal: Recognize the clinical and laboratory features of neonatal hypoglycemia

Endocrine/Metabolic/Thermal: Know the fuels used for brain metabolism

Endocrine/Metabolic/Thermal: Recognize the clinical and laboratory features of neonatal hypoglycemia

Endocrine/Metabolic/Thermal: Recognize the approach to therapy and prevention of neonatal hypoglycemia

Endocrine/Metabolic/Thermal: Know the normal range of endogenous glucose production in term and preterm infants

Endocrine/Metabolic/Thermal: Know the causes (including hyperinsulinemic hypoglycemia) of neonatal hypoglycemia syndromes

Complete Assessment

Copyright © 2013 American Academy of Pediatrics. All rights reserved.
Question: 2

A full-term male infant is found at 2 hours of age to have jitteriness, mild hypotonia, and poor responsiveness. His birthweight was 1,560 g. Most of his laboratory findings are normal, except for serial plasma glucose concentrations that range from 12 to 36 mg/dL (0.7-2.0 mmol/L) during the subsequent 18 hours despite treatment. By 24 hours of age, treatment with intravenous glucose at 12 mg/kg per minute raises the plasma glucose concentration to 54 mg/dL (3.0 mmol/L).

Of the following, the MOST likely cause for the dissociation between abnormal neurologic findings and brain energy metabolism during hypoglycemia is:

- [ ] A. elevated acetylcholine
- [x] B. hyperammonemia
- [ ] C. hypercalcemia
- [ ] D. increased ketone bodies
- [ ] E. increased lactate

Correct

Hypoglycemia and subsequent brain injury in neonates are unusual today because of close monitoring and intervention in high risk and symptomatic infants. However, if hypoglycemia is present, the severity of neuronal injury is proportional to degree and duration of hypoglycemia. Clinical symptoms such as stupor, jitteriness, seizures, apnea, irritability, and hypotonia are the most common neurologic findings. Seizures particularly portend a poor prognosis. Electroencephalographic features may progress from diffuse slowing to a burst-
suppression pattern and seizures. Major neuroradiographic findings of severe hypoglycemia and its sequelae frequently, though not exclusively, involve the parietal-occipital cortex and central white matter. Microcephaly, widened sulci, atrophic gyri, poorly myelinated white matter, and dilated ventricles are seen. With severe hypoglycemia, multicystic encephalomalacia also has been reported. Disabilities associated with these radiographic findings include cognitive delay, seizures, attention deficit disorder, and visual impairment. The clinical and radiographic associations with milder degrees of hypoglycemia are not well described; however, in one report 42% of preterm infants with prolonged (more than 3 days) moderate hypoglycemia (~~47 mg/dL [2.6 mmol/L]) had neurodevelopmental impairment and microcephaly compared with infants with lesser duration of moderate hypoglycemia.

The mechanisms of brain injury caused by severe hypoglycemia have been extrapolated from animal models and supported by clinical studies such as that described herein. Biochemical, clinical, and electroencephalographic changes in the first hours after onset of severe hypoglycemia in neonates often reflect dissociation between brain dysfunction and brain energy (e.g., adenosine triphosphate [ATP]) concentrations in whole brain, cerebral cortex, and other brain regions. A similar acute phenomenon occurs after a hypoxic-ischemic insult. Both such dissociative events may represent adaptive responses to low brain glucose or brain oxygen concentrations, respectively, as brain activity decreases to conserve energy supplies.

The proposed mechanisms for the dissociation between brain function and brain ATP concentrations involve development of hyperammonemia and impairment of acetylcholine synthesis. Concentrations of amino acids in the brain are consumed to produce ATP after the acute onset of hypoglycemia; ammonia then accumulates to concentrations known to produce stupor. In addition, acetylcholine synthesis is acutely impaired, even after the onset of moderate hypoglycemia with resultant lowering, not elevated, concentrations of acetylcholine in the cortex and striatum. Brain acetylcholine, an important neurotransmitter, is acutely reduced before ATP concentrations fall substantially.

Severe and prolonged hypoglycemia uncompensated by increased cerebral blood flow, glycogen metabolism within astrocytes, and/or glucose supply leads to neuronal death from necrosis and apoptosis. Increased intracellular calcium and extracellular potassium concentrations are present with loss of electrical activity of the brain and onset of coma. These ionic changes occur as the energy-dependent sodium/potassium pump fails. Intracellular sodium rises and potassium falls. The sodium/calcium exchange system is then activated and results in extrusion of sodium from and influx of calcium into the cytosol.

Calcium influx into the cytosol is largely mediated by glutamate receptors N-methyl-5-methyl-aspartate and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, voltage-dependent calcium channels, and glutamate stimulation of the metabotropic G-protein receptor. Glutamate receptor activation by aspartate (hypoglycemia) and glutamate (hypoxia-ischemia) increases intracellular sodium, chloride, and water content. Cell swelling and lysis may follow. Calcium release from the endoplasmic reticulum into the cytosol is stimulated by inositol triphosphate liberated by glutamate action on the metabotropic receptor. Calcium reuptake into the endoplasmic reticulum is inhibited by ATP depletion and reduced action of the energy-dependent uniport system. Calcium is also released into the cytosol from mitochondria by way of a sodium/hydrogen-dependent antiport system.

Increased cytosolic calcium acts to cause cell disintegration through several pathways. Free radicals are generated by stimulation of xanthine oxidase and nitric oxide synthetase. Membrane injury results from free radical action. Lipases are also activated by cytosolic calcium and contribute to membrane injury. The cytoskeleton is disrupted by cytosolic calcium-induction of proteases and microtubule disassembly. Nucleases are
also activated and are directly cytotoxic. Of interest, the mechanism of hypoxia-ischemia-induced neuronal injury follows a similar final common pathway.

Ketone bodies and lactate accumulate rapidly after the onset of hypoglycemia. Both of these fuels are important during the initial acute phase of hypoglycemia for preserving oxidative metabolism and brain energy content. Neither ketone bodies nor lactate in the brain have been proposed to be important mediators for the dissociation between brain activity and energy content.

**Suggested Readings**


**American Board of Pediatrics Content Specification(s)**

Endocrine/Metabolic/Thermal: Recognize the clinical and laboratory features of neonatal hypoglycemia

Endocrine/Metabolic/Thermal: Know the fuels used for brain metabolism

Copyright © 2013 American Academy of Pediatrics. All rights reserved.