Neonatal Hypocalcemia: Common, Uncommon, and Rare Etiologies

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EDUCATION GAPS

- Hypocalcemia is among the most common metabolic conditions in NICU patients.
- Appropriate surveillance, prevention, and treatment strategies for NICU patients with hypocalcemia require understanding of the underlying physiology.
- Late-onset neonatal hypocalcemia is often symptomatic and often caused by conditions that are less commonly encountered in practice.

OBJECTIVES *After completing this article, readers should be able to:*

1. Explain key features of fetal regulation of calcium metabolism.
2. Describe the features of normal and abnormal calcium homeostasis of the neonate.
3. Explain the etiologies and treatment strategies of early- and late-onset neonatal hypocalcemia.

ABSTRACT

Calcium homeostasis in the neonatal period is a reflection of the transition from placental regulation to hormonal maturation in the newborn. Hypocalcemia occurring within the first 72 hours after birth, termed *early-onset hypocalcemia* (EOH), is more common and often asymptomatic. Hypocalcemia occurring beyond 72 hours of age is termed *late-onset hypocalcemia* (LOH). LOH is less common than EOH, and affected patients are more likely to be symptomatic. To prevent and treat hypocalcemia in the newborn, neonatal clinicians should be familiar with the common, uncommon, and rare etiologies of EOH and LOH, as summarized in this review.

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ABBREVIATIONS

EOH	early-onset hypocalcemia
iCal	ionized calcium
IDM	infant of diabetic mother
LOH	late-onset hypocalcemia
PTH	parathyroid hormone
PTHrP	parathyroid hormone–related protein
tCal	total calcium

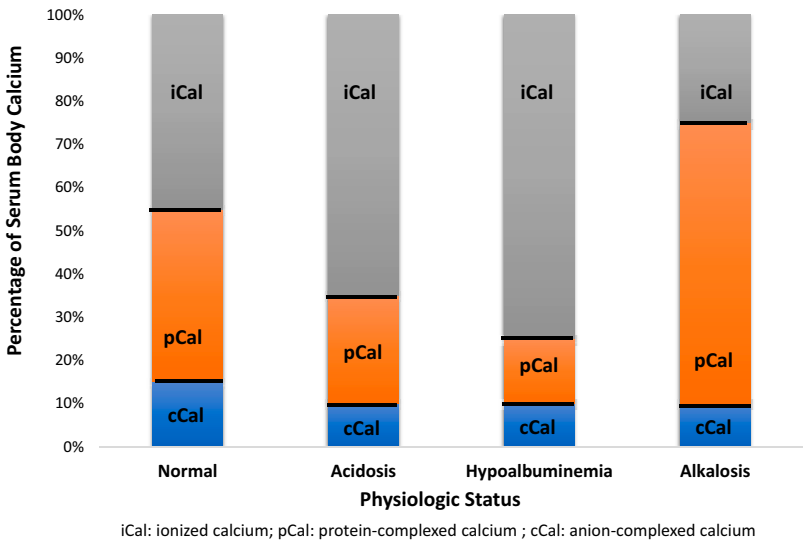

Figure. Relative shifts in total body calcium concentrations depending on overall physiologic status. iCal=ionized calcium, pCal=protein-complexed calcium, cCal=anion-complexed calcium.

INTRODUCTION

Hypocalcemia is a common metabolic condition seen among neonates. As calcium plays a vital role in multiple biochemical processes, severely low calcium levels can lead to life-threatening situations. Hypocalcemia is defined based on low levels of total serum calcium or of its ionized fraction. Serum calcium represents a small proportion of the total body calcium as most of the total body calcium remains sequestered in the developing bones. (1) Ionized calcium (iCal) is the physiologically active component of total calcium (tCal) and is responsible for hypocalcemic symptoms. (2) In a physiologic steady state, iCal is typically the largest fraction of tCal. The remaining serum calcium is biologically inert and includes the protein-bound and anion-complexed fractions. (2)(3) Total serum calcium does not always correlate well with iCal as the tCal can be affected by various factors such as acid-base status and plasma albumin concentration. (4) These relationships are summarized in the Figure. The iCal is the preferred measurement; however, if it is unavailable, tCal can be corrected to assess if the low tCal is the result of a low albumin state. A commonly used correction formula is:

Corrected Total Calcium (in milligrams per deciliter) = Measured Total Calcium (in milligrams per milliliter) + (0.8 × [4.0 – measured serum albumin, grams per deciliter]) in which albumin is assumed to be a normal value of 4.0 g/dL (40 g/L). (5)

The threshold for defining hypocalcemia is determined by birthweight and gestational age (Table 1). In term infants and preterm infants with birthweights greater than 1,500 g, hypocalcemia is defined as tCal less than 8 mg/dL (2 mmol/L) or iCal less than 4.4 mg/dL (1.1 mmol/L). (6) In preterm infants with birthweights less than 1,500 g, hypocalcemia is defined as tCal less than 7 mg/dL (1.75 mmol/L) or iCal less than 4 mg/dL (1 mmol/L). (6) Each cutoff reflects values 2 standard deviations below the mean nadir in each group adjusted for age. (2)(3) A notable limitation is that values at or near these thresholds do not generally correlate with the onset of symptoms. Observational studies have noted that very low-birthweight infants are often asymptomatic until the iCal values drop below 3.2 mg/dL (0.8 mmol/L) or lower. (3)(7)

Determining the etiology of hypocalcemia requires an understanding of the uniqueness of calcium metabolism among neonates. Calcium homeostasis involves a delicate balance among the parathyroid gland, bones, and kidneys. The mature parathyroid gland is the chief modulator of calcium homeostasis. Parathyroid hormone (PTH) is released when calcium levels fall below a threshold recognized by calcium-sensing receptors in parathyroid tissue. PTH communicates with the bones to liberate calcium and phosphorus from the matrix into the serum. It acts

Table 1. Hypocalcemia Thresholds (6)

Gestational Age and Birthweight	Calcium Levels
Term or preterm with birthweight >1,500 g	tCal <8 mg/dL (2 mmol/L)
	iCal <4.4 mg/dL (1.1 mmol/L)
Preterm with birthweight ≤1,500 g	tCal <7 mg/dL (1.75 mmol/L)
	iCal <4 mg/dL (1 mmol/L)

on the kidneys to increase calcium retention at the expense of phosphorus lost in the urine. PTH also increases the 1α-hydroxylation of calcidiol (25-hydroxyvitamin D) in the kidneys to synthesize calcitriol. Calcitriol (1,25-dihydroxyvitamin D) is the biologically active vitamin D metabolite that increases intestinal calcium absorption by increasing the presence of calcium transport proteins along the small intestinal lumen. Absorption across these calcium channels is the only mechanism to increase total body calcium stores, making the intestines the most important site of calcium acquisition. Before the intestines become the chief organ of calcium absorption, the placenta serves as the critical regulator of mineral homeostasis in fetal life. (8)(9) This transition from maternal-fetal to postnatal mineral regulation matures in the neonatal period and allows for unique causes of hypocalcemia when disrupted.

PERINATAL CALCIUM METABOLISM

Fetal calcium metabolism is marked by dependence on the active transport of calcium across the placenta. The kidneys and intestines are not important fetal mineral sources, though the ingestion-absorption-excretion cycling of calcium through a renal-amniotic-intestinal loop may contribute to maintaining a positive calcium balance. (10)(11) The 2 primary goals of fetal calcium homeostasis are successful mineralization of the developing skeleton and accretion of calcium against the electrochemical gradient to maintain a relatively high serum calcium level. (12) During the third trimester, approximately 150 mg/kg of calcium is actively transported daily across the placenta to the fetus. (9) Fetal serum calcium levels are maintained approximately 1.2 to 2 mg/dL (0.3–0.5 mmol/L) higher than that of the pregnant person in the latter half of pregnancy. (10)(12) This state of relative hypercalcemia in fetal life also appears to be protective against a precipitous drop in calcium levels after birth due to separation from the constant maternal supply. (13)

Increased maternal intestinal absorption and fetal bone resorption of calcium help facilitate the fetal supply while maintaining adequate maternal levels throughout pregnancy. Maternal PTH levels start low but rise throughout pregnancy into the third trimester, augmented by maternal vitamin D and calcium intake. (14) Maternal PTH does not cross the placenta but does affect calcium supply to the fetus through maintenance of maternal serum calcium levels. (10) Calcium transport across the placenta increases exponentially during the third trimester. Approximately 80% of calcium transport occurs after the 24th week of pregnancy as fetal accretion increases 6-fold. (15)(16) Studies have shown that total body calcium accretion is exponentially related to gestational age and linearly related to weight in appropriate-for–gestational age preterm and term infants. (17)(18)(19) At term gestation, the fetus should have accrued approximately 30 g of calcium or about 1% of its bodyweight. (13)(15)

The developing calcium-PTH-vitamin D axis appears to play a burgeoning role in regulating fetal serum calcium levels. Fetal parathyroid glands are functionally active as early as 12 weeks of gestation and respond to the state of fetal hypercalcemia by suppressing PTH production. (10)(12)(16) Low PTH suppresses fetal renal 1α-hydroxylase activity, effectively diminishing production of fetal calcitriol despite the passive transport of maternally derived calcidiol across the placenta. Fetal levels of the PTH antagonist calcitonin are also upregulated, complementing a hormonal environment appropriate for bone mineral deposition over resorption. (20) Bioassays on human cord blood show that despite low concentrations of intact PTH, high PTH-like activity is present in fetal life. (21) PTH-related protein (PTHrP), which is synthesized by maternal and fetal tissues including the fetal parathyroid gland and placenta, plays a role similar to PTH in the regulation of fetal iCal. (10)(22) Upregulation of fetal PTHrp in the absence of a hypocalcemic stimulus suggests that unlike PTH, PTHrp is secreted autonomously. (22) The 2 hormones likely work together with a net effect of facilitating placental mineral transfer, bone differentiation and mineralization, and maintenance of high fetal serum mineral levels. (10)(12)(22)

EARLY-ONSET HYPOCALCEMIA

Neonatal hypocalcemia is defined as early onset if it occurs before 72 hours of age. Early-onset hypocalcemia (EOH) can be generalized as an inappropriate physiologic response to the calcium nadir. This impaired response may be due to suboptimal fetal calcium accretion and calcium reserve, an impaired ability to increase calcium absorption in response to the physiologic nadir, or an insufficient supply of exogenous calcium. Table 2 summarizes etiologies of EOH.

Common Causes of EOH

Preterm infants are at higher risk for EOH as they have lower calcium accretion levels compared with their term counterparts. In addition, they experience a more rapid and significant postnatal calcium drop as the magnitude of the nadir is inversely related to gestational age. (13)

Table 2. Common, Uncommon, and Rare Causes of Neonatal Hypocalcemia

	Early-Onset Hypocalcemia	Late-Onset Hypocalcemia
Common	Prematurity/small for gestational age	Nutrition: hyperphosphatemia (cow's milk formula), low calcium intake
	Intrauterine growth restriction, very low birthweight	Neonatal vitamin D deficiency (low vitamin D stores)
		Neonatal hypomagnesemia (transient vs primary/permanent)
	Neonatal hypomagnesemia	
	Maternal diabetes mellitus	
Uncommon	Perinatal asphyxia (tissue injury), sepsis	Renal insufficiency (renal hypoplasia or obstructive nephropathies)
	Maternal medications: anticonvulsants, alkali, magnesium, antacids	Gastrointestinal malabsorption
	Maternal vitamin D or calcium deficiency	Hepatobiliary disease (hyperbilirubinemia/phototherapy and exchange transfusion)
	Medications: diuretics, citrated blood products, aminoglycosides	
	Hyperventilation (respiratory alkalosis)	
Rare	Hypoparathyroidism (transient, DiGeorge/CATCH-22 syndromes)	Primary hypoparathyroidism (transient, DiGeorge/CATCH 22 syndromes)
	Osteopetrosis type 2	Secondary hypoparathyroidism (from maternal hyperparathyroidism)
	Maternal hyperparathyroidism/hypercalcemia	Pseudohypoparathyroidism (parathyroid hormone insensitivity)
		Hypercalciuric hypocalcemia (calcium sensor receptor mutations)
		Autoimmune polyglandular syndrome type I (autoimmune polyglandular syndrome)
		Syndromes: Kenny-Caffey (sensorineural deafness, renal dysplasia), Kearns-Sayre, Sanjad-Sakati, Barakat, Blomstrand (osteochondrodysplasia)
		Mitochondrial (long chain fatty acid) disorders

Elevated fetal levels of calcitonin facilitate in utero bone mineralization and are typically more than double that in a term newborn. This elevation can persist after delivery, contributing to EOH. (13)(20) In addition, the immature parathyroid glands in premature neonates are unable to release sufficient PTH, whereas the immature renal tubules do not respond adequately to PTH. (12) When present, concomitant hypomagnesemia further diminishes the hypocalcemic response. The combination of these factors is often referred to as *early hypocalcemia of prematurity*. Despite having a low tCal, preterm infants are frequently asymptomatic because of the preservation of their iCal levels. Although the exact mechanism of preserving iCal levels is unknown, the relative acidosis and hypoproteinemia associated with prematurity are likely contributory. (3)

Similarly, growth-restricted infants are at higher risk of developing EOH. Decreased transfer of calcium and other minerals in utero can be a consequence of placental pathology, particularly when associated with ischemia. (23) Chronic fetal hypoxia and prolonged suboptimal nutritional supply lead to ineffective metabolic adaptations that impair appropriate intestinal absorption and bone resorption, leading to hypocalcemia. (20)(23) Severity of growth restriction directly correlates with the severity of hypocalcemia. (2)(24)

In infants of diabetic mothers (IDM), EOH may occur as frequently as in 50% of births. (25) These infants experience an exaggerated postnatal calcium nadir that correlates with the severity of poor maternal glycemic control. (3) Glycosuria in diabetic mothers is associated with increased urinary magnesium loss, leading to maternal and fetal hypomagnesemia. Magnesium is essential for the synthesis and appropriate release of PTH. (10) Functional hypoparathyroidism secondary to hypomagnesemia is the suspected mechanism of hypocalcemia in IDM. (2) Concomitant hyperphosphatemia may be present and aligns with features of hypoparathyroidism. The underlying mechanism is likely multifactorial as magnesium supplementation has not demonstrated a decreased incidence of hypocalcemia among these neonates. (26) Increased risk for perinatal asphyxia, prematurity, and increased calcium demand in macrosomic infants have been suggested as factors contributing to EOH among IDM. (25)

Uncommon Causes of EOH

Severe cardiorespiratory depression at birth can be associated with severe EOH. The hypocalcemia in this scenario

is multifactorial. Slow and impaired PTH secretion and increased phosphate load secondary to decreased glomerular filtration rate are suggested factors. (2)(3) Perinatal asphyxia is also associated with increased calcitonin levels, blunting the response to the calcium nadir. (3) It appears unclear if the severity of EOH correlates with the severity of hypoxic-ischemic encephalopathy. Decreased calcium intake with delayed initiation of enteral feeds is also contributory. With correction of metabolic acidosis, the iCal level will drop as more calcium binds to serum albumin.

Chronic maternal serum calcium derangement may increase an infant's risk of developing EOH. Although the fetal-placental unit can adapt to brief fluctuations in maternal calcium levels, prolonged exposure to maternal hypercalcemia or hypocalcemia can result in neonatal hypocalcemia. Two uncommon causes of maternal hypercalcemia leading to EOH are untreated maternal hyperparathyroidism and excessive maternal calcium consumption. Maternal hyperparathyroidism with hypercalcemia can significantly affect the neonate and cause symptoms in roughly 50% of such infants. (10)(27) Although maternal PTH cannot cross the placenta, maternal calcium does flow across to the fetus. Prolonged exposure to maternal hypercalcemia suppresses the fetal parathyroid glands. This suppression persists postnatally and can present as either EOH or LOH. (10) Severe neonatal hypocalcemia may be the presenting feature of an undiagnosed maternal parathyroid disease.

Maternal hypercalcemia due to excess nutritional calcium intake has been reported as contributory to EOH. Excessive ingestion of calcium carbonate–containing antacids can cause fetal hypoparathyroidism due to maternal hypercalcemia. (28)(29)(30) Maternal medications implicated in EOH and their suspected pathophysiology are summarized in Table 3.

On the opposite end of the spectrum, maternal hypocalcemia may also lead to EOH. Long-term exposure to decreased maternal calcium levels can increase fetal PTH levels, leading to greater bone resorption resulting in EOH.

Rare Causes of EOH

Osteopetrosis is a rare congenital disorder that can often be fatal without hematopoietic stem cell transplantation. Dysregulated osteoclast activity results in abnormal bone remodeling, which is prone to fracturing and can narrow

Table 3. Effect of Maternal and Neonatal Medications on Neonatal Calcium Levels

Maternal Medications	Proposed Mechanism
Anticonvulsants	
Phenytoin Phenobarbital	Enzyme induction leading to increased catabolism of vitamin D in both pregnant person and fetus causes decreased bone mineralization and insufficient stores to maintain calcium homeostasis in the newborn (48)(49)
Topiramate	Interference with calcium-sensing receptors on parathyroid gland leads to depletion of parathyroid hormone levels and deficient bone deposition, hence a lack of calcium stores to preserve calcium stability after birth (50)(51)
Calcium-based antacids	
Calcium carbonate	Excessive calcium ingestion results in maternal hypercalcemia and triggers fetal and neonatal hypoparathyroidism (28)(29)(30)(52)
Neonatal Medications	**Proposed Mechanism**
Aminoglycosides	Sensitization of parathyroid cell calcium-sensing receptors results in decreased parathyroid hormone secretion in addition to direct inhibition of calcium transport in the proximal tubules, both of which increase renal excretion of calcium (33)(34)
Anticonvulsants	
Phenytoin Phenobarbital	Enhanced metabolism of vitamin D produces lower vitamin D levels and consequently decreases calcium absorption (53)(54)(55)
Bicarbonate	Increased blood pH results in amplified calcium-albumin binding and reduction in ionized calcium (2)(56)
Glucocorticoids	Reduced intestinal calcium absorption and enhanced renal elimination; more common in patients with hypoparathyroidism (57)(58)(59)
Loop diuretics	Enhanced urinary excretion of calcium (60)
Lipids	Elevated free fatty acids accentuate calcium-albumin binding causing a reduction in ionized calcium levels (61)(62)
Phosphate load	
Phosphate enema	Excessive phosphate decreases vitamin D absorption and precipitates with circulating calcium thereby lowering serum calcium levels (63)

the cranial nerve foramen, causing nerve compression. The typical presentation of osteopetrosis is fractures, visual impairment from optic nerve compression, and bone marrow failure. (3) The dysregulated osteoclasts are unable to mobilize calcium from trabecular bone, resulting in hypocalcemia with elevated PTH levels. (31)

Acute respiratory alkalosis is associated with a 0.16 mg/dL (0.04 mmol/L) decline in iCal with each 0.1 increase in pH. (2) Alkalosis correction may also cause rapid decline in iCal levels by increasing the protein-bound fraction. Neonates with severe hyperbilirubinemia have been noted to have lower iCal levels. (32) Infusion of citrated blood products used in exchange transfusion treatments lowers iCal levels by increasing the anion-complexed fraction of calcium despite the calcium present in transfused blood. (32)

Medications such as aminoglycosides have been noted to cause hypocalcemia through increased renal calcium excretion. (33) Although it is unlikely that renal tubular injury from aminoglycoside exposure leads to hypocalcemia, it is unclear if this mechanism of action is due to hyperphosphatemia or phosphate accumulation secondary to renal injury. (34) Additional medications and interventions implicated in hypocalcemia are summarized in Table 3.

LATE-ONSET HYPOCALCEMIA

Late-onset hypocalcemia (LOH) is defined as low calcium levels that occur after 72 hours of age. Most cases of LOH present before the end of the first postnatal week. Compared with EOH, LOH has a higher association with severe iCal derangements, with patients more likely to be symptomatic. Fortunately, LOH is less prevalent than EOH, with many causes rarely encountered in clinical practice. Causes of LOH are summarized in Table 2.

Common Causes of LOH

One of the most common causes of LOH is hyperphosphatemia due to a diet consisting of cow milk formula. It is suggested that the increased serum phosphorus results in poorly soluble calcium salts, which limits its intestinal absorption. (8)(35) A higher phosphate load also leads to increased calcium bone deposition, resulting in hypocalcemia.

Neonatal vitamin D deficiency can present as LOH, hypophosphatemia, elevated alkaline phosphatase, and secondary hyperparathyroidism. This deficiency can result from low maternal vitamin D levels or from poor neonatal absorption. If maternal vitamin D stores are low, the neonate is at a greater risk of also being vitamin D deficient. Several reports have noted a high incidence of vitamin D–deficient mothers among infants presenting with hypocalcemic tetany. (36)(37)(38) Malabsorption, hepatobiliary disease, and renal failure are common causes of neonatal vitamin D deficiency. (2) Vitamin D absorption is chylomicron dependent. Any fat malabsorptive condition will increase the neonate's risk of developing vitamin D deficiency. (39)

Transient neonatal hypomagnesemia can often present with hypocalcemia. Magnesium deficiency inhibits PTH secretion as well as reduces its responsiveness. Transient hypomagnesemia may also occur secondary to renal magnesium wasting due to urinary tract obstruction, acute renal failure, and certain medications such as aminoglycosides and loop diuretics. (3) Primary hypomagnesemia is a rare autosomal recessive disorder resulting in intestinal magnesium transport defects. In affected infants, hypocalcemia will be refractory to treatment until the magnesium concentration is corrected.

Uncommon Causes of LOH

Parathyroid dysfunction causing LOH in neonates is classified into 3 categories: primary hypoparathyroidism, secondary hypoparathyroidism, and pseudohypoparathyroidism. Primary hypoparathyroidism is a rare cause of LOH and will be discussed in the next section.

Secondary hypoparathyroidism may result from untreated maternal hyperparathyroidism, intrauterine growth restriction, maternal magnesium deficiency, neonatal intestinal transport disorders, and neonatal renal excretion disorders of magnesium.

Rare Causes of LOH

Primary hypoparathyroidism generally is rare in the neonatal population. Microdeletion of chromosome 22q11 noted in the spectrum of DiGeorge syndrome is an important cause of hypoplasia or aplasia of the parathyroid glands. Microdeletion 22q11 occurs in about 1 in 4,000 live births. Hypocalcemia has been reported in as many as 70% of infants with DiGeorge phenotype. (40) Clinical features of this syndrome include abnormal facies, cleft palate, thymic aplasia, and congenital heart disease with conotruncal defects. Other causes of congenital hypoparathyroidism are exceedingly rare. Few cases of isolated or idiopathic primary hypoparathyroidism have been reported. (23) Autosomal dominant inheritance of activating mutations of the calcium-sensing

receptor can cause hypocalcemia with inappropriate calciuria, nephrocalcinosis, and LOH. (41) Kenny-Caffey syndrome is a rare disorder characterized by skeletal, optic, otic, and renal abnormalities with both autosomal recessive and dominant forms presenting with impaired PTH production. (42) Infants are typically small for gestational age and may experience recurrent episodes of hypocalcemia with onset late in the neonatal period. (2)

Pseudohypoparathyroidism is an uncommon, heterogeneous group of disorders characterized by hypocalcemia and hyperphosphatemia despite elevated PTH levels. This pattern reflects end-organ resistance to PTH. In neonates, this etiology is suspected when these aberrations remain despite adequate calcium and vitamin D supplementation. Reported neonatal cases are transient, and immaturity of PTH1R signaling has been postulated to be causative. (43)

CLINICAL PRESENTATION OF NEONATAL HYPOCALCEMIA

Hypocalcemia can be potentially life-threatening. Although EOH is typically clinically silent, LOH tends to be symptomatic. Neonates can present acutely with neuromuscular irritability. Premature neonates may present with subtle manifestations such as jitteriness, exaggerated startle reflex, myoclonic jerks, or generalized/focal seizures. (32)(44) Electroencephalographic findings associated with hypocalcemia include presence of fast rhythms and generalized spike-and-wave discharge. (45) Electrocardiography can show prolonged QTc due to lengthening of the ST interval. While the cardiac changes correlate with the degree of hypocalcemia, other nonspecific symptoms such as apnea, tachypnea, cyanosis, and laryngospasm are unrelated to the severity of hypocalcemia. (46)

Table 4. Management of Neonatal Hypocalcemia

Drug	Dose[a]	Monitoring
Symptomatic Hypocalcemia		
Calcium gluconate (IV)	100–200 mg/kg/dose over 10–20 min[b] (3)(5)(32)(39)	Obtain iCal level every 4–6 hours until stable
Calcium chloride (IV)	10–20 mg/kg/dose[c] (3)(5)	
Maintenance Therapy		
Calcium gluconate (IV) 1,000 mg salt = 93 mg elemental Ca	50–75 mg/kg per day elemental calcium (2.5–3.75 mEq/kg per day) in IV maintenance fluid (3)(64)(65)(66)	Assess iCal level frequently until serum calcium normalized, every 1–2 days with dose de-escalation (if applicable), then 1–2 days after discontinuation (3)(39)
Calcium carbonate (oral) 1,000 mg salt = 400 mg elemental Ca	30–80 mg/kg per day elemental calcium divided every 4–6 hours (3)(5)(32)(39)	
Calcium glubionate (oral)[d] 1,000 mg salt = 63.8 mg elemental Ca		
Calcium gluconate 10% (oral use of IV formulation) 1,000 mg salt = 93 mg elemental Ca		
Hypomagnesemia		
Magnesium sulfate (IV)	25–50 mg/kg per dose (0.2–0.4 mEq/kg per dose) IV over 2 hours every 8–12 hours[e] (3)(5)(37)	Obtain magnesium level every 8–12 hours until resolution (Mg > 1.5 mg/dL [0.62 mmol/L]) (3)
Vitamin D Deficiency		
Cholecalciferol (vitamin D3) (oral)	25–50 μg (1,000–2,000 units) once daily × 6 weeks (3)(5)(39)(66)	Recheck vitamin D [25-OH] in 6 weeks; once vitamin D [25-OH] exceeds 20 ng/mL (49.9 nmol/L), start maintenance of 10–25 μg (400–1,000 units) once daily (5)(66)
Ergocalciferol (vitamin D2) (oral)	25–50 μg (1,000–2,000 units) once daily × 6 weeks (5)(39)(66)(67)	
Calcitriol[f] [1, 25-$(OH)_2$] (oral)	0.25–1 μg QD (5)(37) Or 0.08–0.1 μg/kg QD (39)(67)	

iCal=ionized calcium, IV=intravenous, QD=every day.
[a]Dosages are the same regardless of gestational age.
[b]Dose expressed in milligrams of calcium gluconate.
[c]Dose expressed in milligrams of calcium chloride.
[d]High osmolality can cause diarrhea.
[e]Dosage expressed in milligrams of magnesium sulfate.
[f]Recommended in cases of hypoparathyroidism.

Patients with LOH may present with seizures. Unlike seizures in older children, neonates tend to present with multifocal seizures because their neurological system is less able to sustain any organized, generalized epileptiform activity. (28)

MANAGEMENT OF NEONATAL HYPOCALCEMIA

Before initiating treatment of neonatal hypocalcemia, appropriate laboratory investigations should be performed. The recommended studies should include blood samples for iCal, phosphate, magnesium, alkaline phosphatase, albumin, intact PTH, creatinine, and 25-hydroxyvitamin D, and urine for calcium-creatinine ratio. (31) Pseudohypocalcemia may present in a state with low albumin and low total calcium, which supports the use of iCal over tCal levels.

There is debate as to whether asymptomatic hypocalcemia should be treated. For asymptomatic patients, starting oral supplementation is an option. A common practice for patients who are not taking full enteral nutrition is to increase the amount of calcium given through their intravenous fluids. If treating asymptomatic hypocalcemia with an intermittent dose of intravenous calcium gluconate, it should be infused slowly over an hour.

In considering correction for symptomatic patients, treatment will depend on its severity as well as the underlying cause. Acute symptomatic treatment can be administered more quickly over 10 to 20 minutes with a second dose considered if there is no clinical response within 10 to 20 minutes. For continuous infusions and maintenance therapy, it is important to calculate the dose based on the elemental calcium content rather than the calcium salt content. (31) Table 4 outlines symptomatic hypocalcemia management.

Calcium gluconate should be preferably administered via a central line. If given peripherally, calcium gluconate extravasation may cause subcutaneous necrosis. Therefore, frequent skin checks around the peripheral intravenous site are recommended. (47) When beginning the infusion, close cardiovascular monitoring is necessary as arrhythmias may occur with rapid calcium infusions. (32) Serum calcium levels should be assessed regularly as additional doses may be necessary.

Once an appropriate calcium level has been achieved, daily supplementation may be required to maintain this range. The maintenance therapy may be gradually weaned provided the neonate's serum calcium level remains normalized.

CONCLUSION

Hypocalcemia is a relatively common condition seen in the neonatal period. It is essential to understand the calcium homeostasis in terms of both maternal and neonatal hormonal, renal, and intestinal regulation of the calcium-PTH-vitamin D axis. While this review presents common, uncommon, and rare causes of EOH and LOH, there is a certain degree of overlap among these categories. Understanding the mechanisms of EOH and LOH is important for the management of neonatal hypocalcemia.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the etiology and clinical manifestations of early and late neonatal hypocalcemia.
- Know the laboratory features and approach to therapy of early and late neonatal hypocalcemia.
- Know normal calcium, phosphorous, and magnesium metabolism during the prenatal and postnatal periods, including fetal accretion rates.
- Know the interrelated effects of various hormones, including parathyroid hormone, calcitonin, and vitamin D on calcium, phosphorus, and magnesium metabolism in the fetus and neonate.

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NEO QUIZ

1. Hypocalcemia, particularly early-onset hypocalcemia, is common in neonates. Ionized calcium (iCal) represents the physiologically active component of total calcium (tCal) and is responsible for the clinical symptoms associated with hypocalcemia. Total serum calcium levels do not correlate well with iCal because of lower plasma albumin concentration and/or altered acid-base status in neonates. Which of the following definitions of neonatal hypocalcemia is correct?

   A. A tCal less than 8.5 mg/dL (2.12 mmol/L) in a term or preterm infant with birthweight greater than 1,500 g.
   B. A tCal less than 8 mg/dL (2 mmol/L) in a preterm infant with birthweight less than or equal to 1,500 g.
   C. An iCal less than 3.5 mg/dL (0.87 mmol/L) in a term or preterm infant with birthweight greater than 1,500 g.
   D. An iCal less than 4.4 mg/dL (1.1 mmol/L) in a preterm infant with birthweight less than or equal to 1,500 g.
   E. An iCal less than 4 mg/dL (1 mmol/L) in a preterm infant with birthweight less than or equal to 1,500 g.

2. Fetal calcium metabolism is characterized by active transport of calcium across the placenta with 80% of calcium transport occurring after 24 weeks' gestation. What is the approximate calcium accretion in a term newborn?

   A. 15 g of calcium.
   B. 20 g of calcium.
   C. 30 g of calcium.
   D. 35 g of calcium.
   E. 40 g of calcium.

3. Early-onset hypocalcemia is defined as hypocalcemia occurring in the first 72 hours after birth. Infants of diabetic mothers are at increased risk of developing early-onset hypocalcemia. What is the postulated mechanism of early-onset hypocalcemia in infants of diabetic mothers?

   A. Functional hypoparathyroidism secondary to hypomagnesemia.
   B. Decreased transplacental transfer of calcium.
   C. Increased phosphate load secondary to decreased glomerular filtration rate.
   D. Increased fetal parathyroid hormone levels.
   E. Vitamin D deficiency.

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4. Medication exposures, both pre- and postnatal, can alter neonatal calcium levels. Which of the following medications can lead to hypocalcemia by enhancing vitamin D metabolism?

    A. Bicarbonate.
    B. Phenobarbital.
    C. Aminoglycosides.
    D. Furosemide.
    E. Dexamethasone.

5. A term infant is transferred to your NICU for further evaluation of tetralogy of Fallot. Your physical examination reveals a cleft palate, narrow palpebral fissures, prominent nose, and mild micrognathia. The infant is also noted to be jittery and laboratory evaluations reveal an iCal level of 3.5 mg/dL (0.87 mmol/L). Which of the following is the most likely diagnosis?

    A. Kenny-Caffey syndrome.
    B. Albright hereditary osteodystrophy.
    C. Infantile osteopetrosis.
    D. DiGeorge syndrome.
    E. CHARGE syndrome.