Renal Calcification in NICU Patients

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Author Disclosure
Dr Karlowicz has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Abstract

Sequential renal ultrasonographic studies have shown renal calcifications to be more common in neonatal intensive care unit (NICU) patients than is commonly believed, especially in extremely low-birthweight (ELBW) infants. A family history of kidney stones is an independent risk factor for renal calcifications in ELBW infants. Understanding the role of inhibitors and promoters in crystal formation helps in understanding the pathophysiology of nephrocalcinosis. Identification of the presence or absence of hypercalcemia and hypercalciuria is an effective method of directing the diagnostic evaluation of infants who have nephrocalcinosis. Fortunately, ultrasonographic renal calcifications resolve spontaneously in most NICU patients. Renal calcifications can be associated with persistent abnormalities in renal function if hypercalciuria continues, such as in the rare very low-birthweight (VLBW) infant who receives long-term furosemide therapy after hospital discharge. Only in rare cases, often inborn errors of metabolism, can renal calcifications in NICU patients progress to chronic renal injury, such as in infants who have primary hyperoxaluria that involves persistence of oxalate in the urine, a potent promoter of calcium crystal formation.

Objectives

After completing this article, readers should be able to:

1. Describe the clinical and imaging features of renal calcification in the NICU patient.
2. Review the cause of renal calcification in the NICU patient.
3. List common inhibitors and promoters of calcium crystal formation.
4. Delineate the factors that can contribute to chronic renal injury following renal calcification.

Introduction

Renal calcifications are common in VLBW infants, with estimates of at least 5,000 new cases per year in the United States. The two types of calcification associated with the urinary tract in NICU patients are urolithiasis and nephrocalcinosis. Urolithiasis, or a kidney stone, is a macroscopic calcification in the urinary collecting system. Nephrocalcinosis is a microscopic calcification in the tubules, tubular epithelium, or interstitial tissue of the kidneys. This review focuses on the causes, treatment, and outcomes of renal calcifications in NICU patients.

Clinical and Imaging Features

The clinical presentation of renal calcification in NICU patients often is asymptomatic, even with kidney stones. Renal calcification in NICU patients may be detected by renal ultrasonographic screening in high-risk infants, (1) such as those who have a history of receiving more than 20 doses of furosemide, or as part of the diagnostic evaluation of a urinary tract infection. Gross hematuria is seen occasionally with congenital urolithiasis. (2) Renal colic has been suspected in some neonates who have urolithiasis but is difficult to prove.

Renal calcifications are represented by radiopaque foci on plain radiographs or as radiolucent filling defects during voiding cystourethrography. Renal calcifications must be very large to be detected by radiography; ultrasonography is more sensitive than plain film radiography in detecting renal calcifications. The normal medullary pyramids in neonates

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are hypoechoic when compared with the renal cortex (Fig. 1). Ultrasonographic criteria for renal calculi or stones require hyperechoic foci within the renal medulla with acoustic "shadowing" (Fig. 2). Nephrocalcinosis, especially in VLBW neonates, may consist of multiple microscopic calcifications that show hyperechoic medullary foci, but unlike a solid aggregate, they may not generate an acoustic shadow. (4) Myracle and colleagues (3) recommend criteria for ultrasonographic diagnosis of nephrocalcinosis that require hyperechoic foci in the renal pyramids or calyces either producing shadowing or seeming to be at least 3 mm in diameter demonstrable in different planes. Computed tomography scan is both sensitive and specific for detection of nephrocalcinosis but lacks the portability of ultrasonography and subjects the infant to radiation exposure.

In contrast to medullary nephrocalcinosis, cortical nephrocalcinosis is rare in neonates. Detection of nephrocalcinosis by ultrasonography is hampered by the normally increased echogenicity of the renal cortex in the neonate. Cortical nephrocalcinosis develops within a few weeks of acute renal cortical necrosis and may be evident radiographically as a rim of cortical calcification. Diffuse cortical nephrocalcinosis has been reported in a 2-month-old infant who had primary hyperoxaluria. (5)

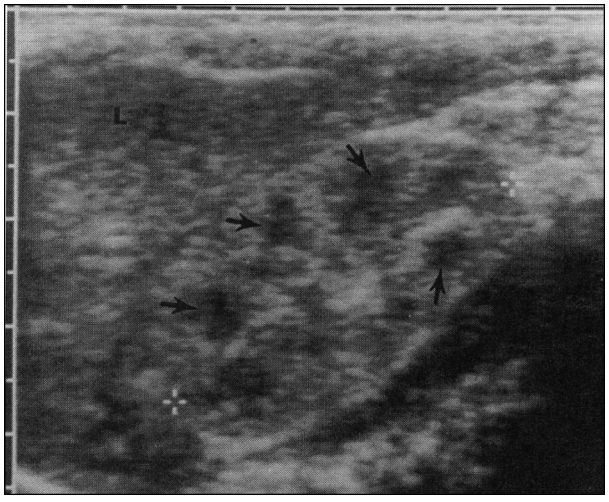

Figure 1. Ultrasonography showing that normal medullary pyramids in neonates are hypoechoic (arrows) when compared with the renal cortex. From Shackelford GD, Kees-folts D, Cole BR. Imaging the urinary tract. *Clin Perinatol.* 1992;19: 85–119. Reprinted with permission from Saunders, Inc.

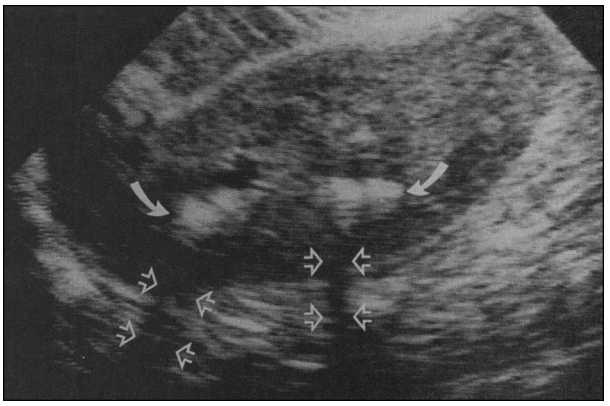

Figure 2. Ultrasonography demonstrating the features required to diagnose renal calculi or stones: hyperechoic foci (long curved white arrows) with acoustic "shadowing" (short white hollow arrows) in the renal medulla. From Myracle MR, et al. *J Clin Ultrasound.* 1986;14:285. (3) Reprinted with permission from John Wiley & Sons, Inc.

Causes

Not all cases of medullary hyperechoic foci in NICU patients represent renal calcification. The differential diagnosis includes transient acute renal injury, pyelonephritis, granuloma, fibrosis, and urate deposits.

The most striking examples of medullary echogenic foci in NICU patients *not* caused by renal calcification involve neonates who have acute renal injury. Several investigators have reported nonasphyxiated neonates who had transient anuric/oliguric acute renal injury with hyperechoic renal medullary pyramids that returned to normal hypoechoic appearance within 4 to 6 days as well as full clinical recovery and normalization of all laboratory test results. (6) The acute renal injury and hyperechoic renal pyramids are believed to be caused by excess production of Tamm-Horsfall proteins, causing transient renal tubular obstruction.

Pyelonephritis may cause medullary hyperechogenicity, but it tends to be more diffuse than focal. *Candida* or cytomegalovirus infections may cause granulomas or chronic inflammation that appears as medullary hyperechoic foci. (7) Renal medullary fibrosis has been reported as focal areas of medullary hyperechogenicity in a 30-week preterm infant who died at 10 weeks of age from gram-negative sepsis. (8) Histology of the renal pyramids showed fibrosis and amorphous tubular casts without calcification. Urate deposits in the renal pyramids have been reported as medullary hyperechoic foci in an infant who had hypoxanthine guanine phosphoribosyl transferase deficiency (Lesch-Nyhan syndrome) and presented with gout and renal failure at 1 month of age. (9)

It is helpful to separate the causes of renal calcification in NICU patients (Table) into three groups: 1) normocalcemic hypercalciuric, 2) hypercalcemic hypercalciuric, and 3) normocalcemic normocalciuric. VLBW infants often have multifactorial causes (eg, acute renal injury, chronic furosemide, corticosteroids) for nephrocalcinosis.

Normocalcemic Hypercalciuric Nephrocalcinosis

Distal renal tubular acidosis is characterized by the inability of the distal nephron to acidify urine below pH 5.5 and the presence of hypercalciuria. Urine citrate concentrations are often low or undetectable, so affected patients lack an important inhibitor of renal calcification. Alkaline pH favors calcium-phosphate crystallization. The combination of high urine pH, hypercalciuria, and low urine citrate makes nephrocalcinosis a common finding in distal renal tubular acidosis. (10) A variant of renal tubular acidosis with nephrocalcinosis characterized by extensive glomerular immaturity and nephrogenic diabetes insipidus has been reported in three infants. (11)

Bartter syndrome is a renal tubular disorder characterized by hypokalemic metabolic alkalosis, hyperreninemia, hyperaldosteronism, normal blood pressure, and hypertrophy of the juxtaglomerular apparatus. A prostaglandin-independent defect in chloride reabsorption in the loop of Henle is the most likely cause of the abnormalities. (12) Hypercalciuria and nephrocalcinosis are present in more than 50% of cases. An autosomal recessive, early-onset form of Bartter syndrome occurs in preterm infants and is associated with polyhydramnios due to fetal polyuria. (13) Failure to thrive is common, and nephrocalcinosis may occur in early infancy. Neonatal Bartter syndrome may be caused by a mutation in the gene encoding the Na-K-2CL cotransporter (*NKCC2*) or the outwardly rectifying potassium channel (*ROMK*), a regulator of NKCC2. (14)

Acquired Bartter-like syndrome has been associated with gentamicin therapy in a case series of four adult women ages 35 to 82 years. (15) Symptoms included marked paresthesia, muscle weakness, and tetany that persisted for 2 to 6 weeks after receiving a total gentamicin dose ranging from 1.2 to 2.6 g. Serum immunereactive parathyroid hormone concentrations were low despite hypocalcemia. Biochemical abnormalities included hypercalciuria, hypocalcemia, hypermagnesuria, hypomagnesemia, metabolic alkalosis, and hypokalemia. The polyvalent cationic gentamicin molecule is believed to induce the action of the calcium-sensing receptor in the thick ascending loop of Henle and distal convoluted tubule. (15) The net result is renal wasting of Ca^{2+}, Mg^{2+}, Na^{+}, K^{+}, and Cl^{-}. Two 4-month-old infants have been reported with acquired Bartter-like syndrome associated with gentamicin therapy, but neither infant had renal calcifications, probably due to the transient nature of the hypercalciuria, which lasted only a few weeks. (16)(17)

In Cushing syndrome, normocalcemic hypercalciuria develops because cortisol increases urinary calcium excretion. Nephrocalcinosis and osteoporosis occur in association with Cushing syndrome when adrenal tumors become symptomatic in the first 6 months after birth. (18) In addition, adrenocorticotropic hormone therapy for infantile spasms frequently is complicated by osteoporosis and nephrocalcinosis. (19)

Long-term furosemide therapy for chronic lung disease in preterm infants is the most common recognized cause of hypercalciuria and nephrocalcinosis in NICU patients and was reported initially by Hufnagle and colleagues. (20) Calcifications range in size from microscopic renal calcifications to staghorn calculi in the renal pelvis. Several investigators have reported that nephro-

Table. Causes of Renal Calcifications in NICU Patients

Normocalcemic Hypercalciuric
• Distal renal tubular acidosis
• Bartter syndrome
• Hyperprostaglandin E syndrome
• Cushing syndrome
• Adrenocorticotropic hormone therapy for infantile spasms
• Long-term furosemide therapy
• Idiopathic hypercalciuria
• Familial hypomagnesemia
Hypercalcemic Hypercalciuric
• Hyperparathyroidism
• Subcutaneous fat necrosis
• Hypophosphatasia
• Williams syndrome
• Paraneoplastic phenomenon
• Idiopathic infantile hypercalcemia
• Vitamin D intoxication
Normocalcemic Normocalciuric
• Primary hyperoxaluria
• Short bowel-associated hyperoxaluria
• Renal candidiasis
• Rhabdoid tumors of the kidney
• Dystrophic calcification
• Long-term acetazolamide therapy
• Melamine-contaminated formula

calcinosis occurs in more than 50% of VLBW infants receiving chronic furosemide therapy. The association of renal calcification with furosemide was considered to occur only in preterm infants until Alon and coworkers (21) reported nephrocalcinosis and nephrolithiasis in other NICU patients treated with chronic furosemide for congestive heart failure.

Idiopathic hypercalciuria is a cause of urolithiasis in children. Most studies of calcium excretion in VLBW neonates who had nephrocalcinosis have been confounded by long-term furosemide therapy. However, Karlowicz and colleagues (22) reported significantly increased calcium excretion in VLBW infants who had nephrocalcinosis and did not receive long-term furosemide therapy.

Hypercalcemic Hypercalciuric Nephrocalcinosis

Nephrocalcinosis is common in NICU patients who have severe primary hyperparathyroidism, which is characterized by elevated serum parathyroid hormone concentrations and striking hypercalcemia, with serum calcium values often more than 17 mg/dL (4.25 mmol/L). This condition is frequently life-threatening, with vomiting and seizures, and often requires parathyroidectomy. (23) A milder form of neonatal familial hyperparathyroidism is associated with distal renal tubular acidosis, hypercalciuria, and nephrocalcinosis. (24) Hypercalcemia resolves by 2 years of age in affected infants without the need for parathyroidectomy, but the nephrocalcinosis and renal tubular acidosis persist. Secondary hyperparathyroidism also has been reported in VLBW infants receiving long-term furosemide therapy. (25)

A potentially fatal form of hypercalcemia in NICU patients is subcutaneous fat necrosis. In this condition, firm subcutaneous nodules and plaques form on the back, buttocks, cheeks, chin, arms, and thighs within a few weeks of birth. A history of perinatal distress and hypoperfusion is common. The lesions range in size from a few millimeters to several centimeters. A few weeks after the appearance of the subcutaneous nodules, some infants develop symptomatic severe hypercalcemia with vomiting, irritability, failure to thrive, and seizures. (26) Some NICU patients who have subcutaneous fat necrosis die from it or develop persistent seizures and blindness.

The nephrocalcinosis in NICU patients who have subcutaneous fat necrosis is associated with severe hypercalcemia and hypercalciuria. (27) Corticosteroid therapy leads to resolution of the hypercalcemia, nephrocalcinosis, and sclerotic bone lesions. 1, 25-dihydroxyvitamin D concentrations have been reported as elevated in an infant who had subcutaneous fat necrosis and hypercalcemia. (28) The response of hypercalcemia to corticosteroid therapy, leading to resolution of the fat necrosis and normalization of 1, 25-dihydroxyvitamin D, supports the hypothesis that granulomatous inflammation of the fat necrosis is the source of elevated 1, 25-dihydroxyvitamin D concentrations. The hypercalcemia may be caused by unregulated extrarenal 1, 25-dihydroxyvitamin D production by macrophages in the zones of subcutaneous fat necrosis. (29)

Hypophosphatasia is another cause of hypercalcemia, hypercalciuria, and nephrocalcinosis. It is a group of autosomal recessive disorders characterized by defective skeletal mineralization due to deficiency of tissue-nonspecific alkaline phosphatase. The neonatal form of hypophosphatasia is the most severe, with almost complete lack of bone mineralization that results in either stillbirth or early death due to respiratory failure. The infantile form of hypophosphatasia is also severe; often fatal; and characterized by failure to thrive, fractures, short stature, premature craniosynostosis, and respiratory infections. Defective mineralization results in reduced calcium uptake by bone, leading to hypercalcemia, suppression of parathyroid hormone production, hypercalciuria, and nephrocalcinosis. (30)

Hypercalcemic paraneoplastic phenomena are rare in childhood. Nevertheless, a 2-month-old infant has been reported who had mesoblastic nephroma, severe hypercalcemia (20 mg/dL [5 mmol/L]), and bilateral medullary nephrocalcinosis. (31) A humoral factor secreted by the tumor may have been responsible for the hypercalcemia because serum calcium concentrations normalized soon after removal of the mesoblastic nephroma.

There are two forms of idiopathic hypercalcemia in NICU patients. Williams syndrome is the more severe and is characterized by "elfin" facies, short stature, cardiac defects (especially supravalvar aortic stenosis), and intellectual disability. Nephrocalcinosis can appear as early as 2 months of age when hypercalcemia is present. (32) The hypercalcemia often resolves before 2 years of age, and the cause of the hypercalcemia has not been determined. Possible causes include deficient inactivation of vitamin D (33) or impaired secretion of calcitonin. (34) Idiopathic infantile hypercalcemia is the milder form of idiopathic hypercalcemia and is manifested by hypercalcemia, hypercalciuria, and nephrocalcinosis without dysmorphic facies or heart defects. (35) Hypercalcemia develops because of generalized maturational delay of calcium homeostasis, deficient suppression of parathyroid hormone and 1, 25-dihydroxyvitamin D secretion, and deficient stimulation of calcitonin and 24, 25-dihydroxyvitamin D secretion. Calcitonin corrects

hypercalcemia within hours, but a high-phosphate diet and thiazides may be needed to stop hypercalciuria.

Vitamin D intoxication is another cause of hypercalcemia, hypercalciuria, and nephrocalcinosis. Symptomatic hypercalcemia due to excess vitamin D was common before the understanding that a dose of 400 IU is sufficient to prevent vitamin D-deficient rickets. Unfortunately, renal calcification caused by vitamin D intoxication continues to occur, especially in developing countries. (36)

Normocalcemic Normocalciuric Nephrocalcinosis

Nephrocalcinosis may occur in the absence of hypercalciuria or hypercalcemia, especially when there are excess promoters or deficient inhibitors of renal calcification. For example, primary hyperoxaluria is an autosomal recessive disorder of organic acid metabolism associated with increased synthesis and excretion of oxalate, a well-known kidney stone promoter. Before the advent of dialysis and renal transplantation, most patients who had hyperoxaluria died from chronic progressive renal injury in their 20s and 30s due to the cumulative effects of calcium-oxalate deposition. A more severe form of primary hyperoxaluria occurs in 3- to 4-month-old infants and manifests as poor appetite, failure to thrive, seizures, nephrocalcinosis, and end-stage renal failure. (37) Nephrocalcinosis in Shwachman syndrome may be due to increased urinary oxalate excretion. (38)

Hyperoxaluria also can result from malabsorption in association with short bowel syndrome. Malabsorption of fatty acids leads to saponification of enteral calcium, thereby blocking binding to oxalate and resulting in large amounts of unbound oxalate entering the colon. Bile acid malabsorption increases colonic permeability to oxalate. Increased oxalate absorption results in hyperoxaluria. Urolithiasis with gross hematuria has been reported in a 6-month-old infant who had short bowel syndrome that was treated with oral cholestyramine and chlorothiazide. (39)

One example of decreased inhibitor production is found with acetazolamide therapy, which reduces citrate excretion. Nephrocalcinosis in VLBW infants has been associated with acetazolamide and furosemide therapy when the combination was used in an attempt to reduce cerebrospinal fluid production in the treatment of posthemorrhagic hydrocephalus, (40) a drug combination that has been shown to be both ineffective and unsafe.

In a small case series of infants younger than 6 months of age who had rhabdoid tumors of the kidneys, computed tomography scans demonstrated calcifications outlining the tumor lobules in the kidneys. (41)

Recently, exposure to melamine-contaminated formula in China was reported to be associated with urinary stones in infants, who lacked typical signs and symptoms of urolithiasis. (42)

Nephrocalcinosis in VLBW Infants

Long-term furosemide (>20 mg/kg cumulative dose) therapy has been associated with renal calcification in VLBW infants, (20) but nephrocalcinosis also can occur in VLBW infants without long-term furosemide therapy. The highest prevalence (41%) of renal calcification in VLBW infants was reported by Jacinto and colleagues (43) but probably was caused by very high parenteral doses of calcium. Short and Cooke (44) reported no difference in the mean total dose of furosemide given to infants who did or did not have nephrocalcinosis when nephrocalcinosis was detected. It was suggested that long-term furosemide therapy frequently is prescribed for NICU patients who are already at risk for renal calcification. In support of this suggestion, Karlowicz and colleagues (22) found a 28% prevalence of renal calcification (both nephrocalcinosis and urolithiasis) in a prospective study of 50 consecutive VLBW infants who underwent serial renal ultrasonography every 3 weeks until 9 weeks of age and in whom the median cumulative dose of furosemide was only 1 mg/kg during the 9 weeks in the NICU. Furthermore, they reported the renal calcification in their population of VLBW infants to be significantly and independently associated with white ethnicity (67% versus 16%) and a family history of kidney stones (78% versus 17%). (22) Calcium excretion in infants who had renal calcification was significantly increased, but no other promoters or inhibitors of renal calcification were measured. Calciuria occurs in parenterally fed VLBW infants if phosphorus intake is low, resulting in hypophosphatemia. Increasing phosphorus intake lowers calcium excretion.

Renal stone formation has been reported to follow renal candidiasis in VLBW infants in the absence of furosemide therapy. In some cases, renal calcifications were misinterpreted to be persistence of renal fungal balls, resulting in inappropriately prolonged systemic antifungal therapy. (7)

Increased concentrations of promoters and decreased concentrations of inhibitors of renal calcification in NICU patients may be factors contributing to the increased prevalence of nephrocalcinosis in VLBW infants. Parenteral nutrition in VLBW infants may cause elevated urinary oxalate concentrations via metabolism

of ascorbate and glycine, and such hyperoxaluria may contribute to renal calcification. (45) Some formula-fed VLBW infants have higher ascorbate intake than human milk-fed infants. (46) Ascorbate is an oxalate precursor and can contribute to higher urinary oxalate excretion, which can predispose infants to nephrocalcinosis. Chronic lung disease in VLBW infants is associated with decreased urinary citrate, which can increase the risk of renal calcification. (47) In summary, there is a vulnerable period for many VLBW infants during which the transient aggregation of several risk factors can cause renal calcification. (48)

Outcome of Renal Calcification

The only long-term outcome data available for renal calcifications in NICU patients are limited to small case series associated with long-term furosemide therapy. Ezzedeen and colleagues (48) reported persistent renal calcifications in five of nine infants receiving long-term furosemide followed for 4 years. Serum creatinine concentrations and calculated glomerular filtration rates were abnormal in four of the infants. Continuing furosemide treatment in VLBW infants after discharge from the NICU is associated with some morbidity in the first year after discharge, including persistent renal calcification, urinary obstruction from urolithiasis requiring nephrolithotomy, and recurrent urinary tract infections. (49) However, longer-term follow-up at 4 to 5 years of 11 preterm infants who developed renal calcifications in the NICU, when compared with matched preterm controls who did not have renal calcifications in the NICU, showed that the renal calcifications, independent of other complications of NICU hospitalization, did not result in long-term renal injury. (50)

Differential Diagnosis

History, physical examination, and laboratory tests help identify the cause of renal calcifications in NICU patients. Simultaneous serum and urine calcium and creatinine values are extremely helpful in directing further testing. Hypercalcemia is defined as total serum calcium concentrations of more than 10.5 mg/dL (2.6 mmol/L), although the values frequently are much higher. Serum total and ionized calcium should be measured on more than one occasion because of daily variation in calcium concentrations in some NICU patients who have renal calcification.

The definition of hypercalciuria in NICU patients has been controversial. Random urine samples typically are used to determine calcium-creatinine ratios because collecting complete 24-hour urine samples from young, and especially VLBW infants, is very difficult in most NICUs. This is a valid approach because random urine calcium-creatinine ratios have been shown to correlate closely with 24-hour calcium excretion in healthy children and children who have urolithiasis. (51)

Hypercalciuria in children has been traditionally defined (>95th percentile) as a urine calcium-creatinine ratio of more than 0.18 mg/mg, but the study population included very few infants and no females younger than 2 years of age. (52) Definitions of hypercalciuria in older children may not apply to young infants. When Sargent and colleagues (53) determined normal random urine calcium-creatinine ratios in 143 healthy term infants, they defined hypercalciuria (>95th percentile) as a urine calcium-creatinine ratio of more than 0.86 mg/mg in the first 6 postnatal months.

Fewer data are available on normal calcium excretion in VLBW infants. Karlowicz and colleagues (22) reported significantly increased random urine calcium-creatinine ratios in VLBW infants who had nephrocalcinosis as 0.49 mg/mg compared with 0.11 mg/mg in the control group of VLBW infants. The normal range of random urine calcium-creatinine ratios reported by these investigators (22) was similar to values reported in older children, which were in contrast to reports by Sargent and colleagues. (53) Additional studies are needed of healthy preterm and term infants who have documented normal serum calcium and phosphorus values and normal bone mineralization to define clearly the normal random calcium-creatinine ratios.

For NICU patients who have hypercalcemia and renal calcification, clinicians should look for subcutaneous fat necrosis or clinical features of Williams syndrome. If skeletal survey shows hypomineralization, serum phosphate and serum alkaline phosphatase should be measured. If vitamin D intoxication is suspected, vitamin D values should be obtained.

NICU patients who have renal calcification, normocalcemia, and hypercalciuria should undergo a different battery of testing. Urine and serum pH and urine citrate are obtained to look for evidence of distal renal tubular acidosis. Cushing syndrome is identified by a history of adrenocorticotropic hormone therapy or elevated serum cortisol values, which now can be measured with point-of-service testing. The history of long-term (cumulative dose >20 mg/kg) furosemide use is a common cause of renal calcification in NICU patients. Bartter syndrome requires the presence of hypokalemic metabolic alkalosis, hyperreninemia, and hyperaldosteronism. Idiopathic hypercalciuria occurs in some NICU patients who have renal calcification, no history of chronic furosemide use,

and normal urine pH and normal serum chemistries, but who often have a family history of kidney stones. (22)

NICU patients who have renal calcification without either hypercalcemia or hypercalciuria should be evaluated for hyperoxaluria, especially if there is progressive renal injury. Those who have short bowel syndrome and nephrocalcinosis should have their urine oxalate determined. Urine citrate should be measured in patients who have a history of chronic acetazolamide therapy. Urolithiasis can follow renal candidiasis. Finally, dystrophic renal calcification can be a consequence of nephrotoxins or acute renal injury.

Summary

Renal ultrasonography has shown that renal calcification is more common in NICU patients than was previously believed. Understanding the role of inhibitors and promoters of calcium crystal formation helps elucidate the pathophysiology of nephrocalcinosis and urolithiasis. Early identification of hypercalcemia and hypercalciuria effectively directs the diagnostic evaluation and therapy of NICU patients who have renal calcification.

Fortunately, renal calcifications resolve in 85% of NICU patients in the first postnatal year. (54) If hypercalciuria persists, such as in VLBW infants discharged with long-term furosemide therapy, persistent progressive renal injury can develop. Renal calcification can contribute to chronic renal injury in some NICU patients, especially in those who have primary hyperoxaluria, because persistently elevated concentrations of oxalate in the urine is a potent promoter of calcium crystal formation in neonates' kidneys.

American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications

- Know the effects of various illnesses on renal function.
- Know the etiology and clinical manifestations of neonatal hypercalcemia.

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NeoReviews Quiz

7. Renal calcification in neonates can be classified into three categories: normocalcemic hypercalciuric, hypercalcemic hypercalciuric, and normocalcemic normocalciuric. Of the following, the *most* common cause of normocalcemic hypercalciuric nephrocalcinosis in preterm infants is:

   A. Bartter syndrome.
   B. Distal renal tubular acidosis.
   C. Familial hypomagnesemia.
   D. Hyperprostaglandin E syndrome.
   E. Long-term furosemide treatment.

8. Hypercalcemic hypercalciuric nephrocalcinosis in neonates hospitalized in intensive care units has several causes and can vary in severity from benign to fatal disease. Of the following, the *most* severe and often fatal cause of hypercalcemic hypercalciuric nephrocalcinosis in neonates is:

   A. Idiopathic infantile hypercalcemia.
   B. Infantile hypophosphatasia.
   C. Paraneoplastic phenomenon.
   D. Subcutaneous fat necrosis.
   E. Vitamin D intoxication.

9. Nephrocalcinosis may occur in the absence of hypercalcemia or hypercalciuria, especially in the presence of excess promoters or deficient inhibitors of renal calcification. Of the following, nephrocalcinosis in infants who have short bowel syndrome is *most* likely caused by increased urinary excretion of:

   A. Citrate.
   B. Oxalate.
   C. Phosphate.
   D. Tamm-Horsfall protein.
   E. Urate.

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