Nephrocalcinosis in neonates

Authors: Jodi Smith, MD, MPH, F Bruder Stapleton, MD
Section Editors: Tej K Mattoo, MD, DCH, FRCP, Joseph A Garcia-Prats, MD
Deputy Editor: Melanie S Kim, MD

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INTRODUCTION

Nephrocalcinosis is defined as calcium salt deposition in the renal parenchyma including the tubular epithelium and interstitial renal tissue. Nephrocalcinosis occurs more frequently in neonates, especially preterm infants because of their renal tubular immaturity, and administration of medications and nutritional supplements that promote calcium salt deposition.

This topic will review the pathogenesis, etiology, risk factors, and management of neonatal nephrocalcinosis.

INCIDENCE

The reported incidence of neonatal nephrocalcinosis over the last several decades has varied from 10 to 65 percent. However, subsequent case series in preterm infants who are most susceptible to nephrocalcinosis report a lower but still significant rate of 7 to 41 percent [1-5].

PATHOGENESIS

Neonatal nephrocalcinosis is caused by calcium salt crystal formation and aggregation within the renal tubules created by an imbalance that promotes **stone producing**

factors (increased urinary excretion of calcium, oxalate, uric acid) over **stone inhibiting factors** (decreased urinary excretion of citrate and magnesium) [1,6-13]. Neonates and especially premature infants are at risk for calcium salt crystallization because of renal tubule immaturity, and increased likelihood of hypercalciuria (increased promoting factor) and hypocitraturia (loss of inhibiting factor) as discussed below.

ETIOLOGY AND RISK FACTORS

Renal tubular immaturity in preterm infants — Preterm infants are at increased risk for nephrocalcinosis due to renal tubular immaturity, which increases with decreasing birth weight [14]. Nephrogenesis is not completed until 34 to 36 weeks gestation. As a result in the developing kidney, there is continuing proliferation of renal epithelium cells within the renal tubule that are thought to be more susceptible to crystal formation and aggregation [15]. Preterm infants have a markedly low glomerular filtration rate that results in a low fluid flow rate within the tubular lumen [16,17]. This enhances crystal formation and aggregation particularly in the setting of tubular fluid supersaturation, which is promoted by hypercalciuria and hypocitraturia (commonly observed findings in preterm infants).

Very low birth weight preterm infants (birth weight <1500 g) also have decreased bicarbonate reabsorptive capacity. The increased bicarbonate excretion results in an alkaline urine pH, which directly enhances calcium phosphate precipitation [18].

Hypercalciuria — Hypercalciuria promotes crystal and stone formation and is commonly observed in preterm infants [1,4,6,7,16,19-21]. Hypercalciuria can be caused by hypercalcemia resulting in an increased filtered load of calcium to the kidney or in patients with normal calcium blood levels due to decreased calcium renal resorption.

Hypercalcemia — Neonatal nephrocalcinosis has been observed as a result of hypercalcemia and hypercalciuria in the following settings [22]:

- Subcutaneous fat necrosis – Subcutaneous fat necrosis resulting from inflammation of the subcutaneous fat is a rare complication that can occur following birth trauma, meconium aspiration or therapeutic cooling (picture 1). It is associated with severe hypercalcemia, fever and risk for nephrocalcinosis [23]. (See "Panniculitis: Recognition and diagnosis", section on 'Infants and children'.)

- Nutrition

- Calcium supplementation – Neonatal nephrocalcinosis has been associated with increased calcium and phosphate intake, especially in preterm infants receiving total parenteral nutrition [1,6,19,24].

- Vitamin D therapy – Nephrocalcinosis has been reported in infants due to excessive vitamin D supplementation resulting in hypercalcemia [17,25].

- Genetic disorders

  - Williams-Beuren syndrome – Patients with Williams-Beuren syndrome (caused by hemizygous deletion of 1.5 to 1.8 Mb on chromosome 7q11.23) often have elevated calcium levels and are at risk for developing nephrocalcinosis. Typical clinical neonatal features of this syndrome include "elfin" face, supravalvar aortic stenosis, and hypertension. (See "Williams-Beuren syndrome: Renal manifestations", section on 'Elevated calcium levels'.)

  - Idiopathic infantile hypercalcemia (IIH) – IIH is characterized by severe hypercalcemia with failure to thrive, vomiting, dehydration, and nephrocalcinosis. Hypercalcemia resolves during or soon after infancy. It is caused by mutations in the CYP24A1 gene that encodes the vitamin D enzyme 25-hydroxyvitamin D_3-24-hydroxylase, which leads to accumulation of the active metabolite 1,25-$(OH)_2D_3$ [26,27].

  - Congenital lactase deficiency – One small case series described nephrocalcinosis in infants with congenital lactase deficiency due to hypercalcemia and hypercalciuria [28]. (See "Etiology of hypercalcemia", section on 'Congenital lactase deficiency'.)

- Neonatal primary hyperparathyroidism – Although rare, patients with neonatal primary hyperparathyroidism have hypercalcemia (which is often severe), hypophosphatemia, a normal or increased plasma alkaline phosphatase level, and may present with respiratory distress, failure to thrive, and hypotonia [29]. Rachitic changes often occur and bone radiographs may reveal subperiosteal resorption. At least some cases of neonatal hyperparathyroidism are familial and are due to an autosomal recessive disease due to mutations of the gene that encodes the calcium-sensing protein in the parathyroid gland; heterozygotes have less severe disease and present with asymptomatic hypercalcemia and hypercalciuria. (See "Disorders of the calcium-sensing receptor: Familial hypocalciuric hypercalcemia and autosomal dominant hypocalcemia".)

Normocalcemia — The two main mechanisms that result in neonatal nephrocalcinosis associated with hypercalciuria and normal blood calcium levels are:

- Medications that alter calcium renal absorption, most commonly loop diuretics
- Genetic disorders with renal tubular dysfunction that affect calcium renal absorption

Loop diuretics — Nephrocalcinosis is a known complication of loop diuretic therapy in preterm infants due to hypercalciuria [14,19,21,30]. This effect is mediated by inhibition of sodium chloride reabsorption in the thick ascending limb and an associated decline in calcium reabsorption, as calcium transport passively follows that of sodium. Hypercalcuria may be prolonged in neonates because there is typically a slower plasma clearance of the diuretic [31,32]. (See "Diuretics and calcium balance".)

In addition, loop diuretics also may increase urinary phosphate excretion, a probable reflection of decreased proximal phosphate reabsorption induced by the mild carbonic anhydrase inhibitory activity of furosemide. Concurrent therapy with acetazolamide, which inhibits carbonic anhydrase, diminishes proximal tubular transport of calcium, phosphate, and bicarbonate. The net effect appears to be increased urinary calcium and phosphate excretion and an elevation in urine pH. In one report, for example, 7 of 11 infants treated with acetazolamide and furosemide had hypercalciuria; five of these seven infants had nephrocalcinosis [33].

Other medications — Other medications identified as risk factors for hypercalcuria and nephrocalcinosis include aminoglycosides [1,19,34] and dexamethasone [19,35].

Genetic disorders — Genetic disorders that result in renal tubular dysfunction have been associated with hypercalciuria and nephrocalcinosis and include the following:

- Bartter syndrome – Bartter syndrome is due to gene mutations of proteins that are involved in sodium chloride reabsorption in the medullary thick ascending limb of the loop of Henle. These mutations result in impaired sodium reabsorption (similar to that seen with loop diuretic therapy), which is accompanied by a decline in calcium reabsorption leading to hypercalciuria. Neonates with severe autosomal recessive disease present with polyhydramnios and prematurity. If untreated, these infants develop severe metabolic acidosis with poor growth, rickets, and nephrocalcinosis. (See "Bartter and Gitelman syndromes", section on 'Bartter syndrome'.)
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Distal (type 1) renal tubular acidosis – Genetic causes of distal renal tubular acidosis (RTA) include mutations of genes that encode the chloride-bicarbonate exchanger (AE1) or subunits of the H-ATPase pump. Infants with autosomal recessive forms of distal RTA typically have more severe diseases and if untreated develop severe metabolic acidosis, poor growth, rickets and nephrocalcinosis (table 1). (See "Etiology and clinical manifestations of renal tubular acidosis in infants and children", section on 'Distal (type 1) RTA'.)

- Other genetic diseases associated with hypercalcemia and subsequent later development of nephrocalcinosis beyond the neonatal period include Dent disease and Lowe oculocerebrorenal syndrome. (See "Nephrocalcinosis", section on 'Inherited tubulopathies' and "Dent disease (X-linked recessive nephrolithiasis)" and "Dent disease (X-linked recessive nephrolithiasis)", section on 'Lowe syndrome' and "Disorders of the calcium-sensing receptor: Familial hypocalciuric hypercalcemia and autosomal dominant hypocalcemia".)

- Hypophosphatasia is an autosomal recessive condition, which occurs due to mutations in gene encoding the *ALPL* gene. Affected neonates present with defective bone mineralization leading to rickets, osteomalacia, fractures, and severe periodontal disease, as well as hypercalcemia, hypercalciuria, and nephrocalcinosis [36] (See "Epidemiology and etiology of osteomalacia", section on 'Hypophosphatasia'.)

Hypocitraturia — Citrate is a potent inhibitor of calcium stone formation, primarily by combining with calcium to form a nondissociable but highly soluble complex (see "Risk factors for calcium stones in adults"). In very low birth weight infants (birth weight <1500 g), low urinary citrate excretion is a common finding in patients with nephrocalcinosis [8]. Urinary citrate excretion decreases in patients with persistent metabolic acidosis, which often occurs in ill preterm infants.

Increased urine oxalate excretion — Primary hyperoxaluria type 1 is a rare autosomal recessive inborn error of glyoxylate metabolism, caused by a deficiency of the liver-specific enzyme alanine glyoxylate aminotransferase. The disorder results in overproduction and excessive urinary excretion of oxalate, which may cause nephrocalcinosis in neonatal period [37]. (See "Primary hyperoxaluria", section on 'Primary hyperoxaluria type 1'.)

CLINICAL PRESENTATION

Nephrocalcinosis is an asymptomatic condition. It is discovered as an incidental finding when abdominal or chest imaging is performed for another reason or when renal ultrasound screening is performed for at-risk infants. This includes the following clinical settings:

- Chronic loop diuretic therapy, which is typically reserved for ventilator-dependent infants with severe bronchopulmonary dysplasia who are not responsive to modest fluid restriction and/or thiazide therapy. (See "Bronchopulmonary dysplasia: Management", section on 'Diuretics'.)
- Persistent hypercalcemia resulting in hypercalcuria such as in patients with hypervitaminosis D. (See 'Hypercalcemia' above.)
- Patients with hypercalcuria due to genetic diseases that result in hypercalcemia (eg, Williams-Beuren syndrome) or renal tubular dysfunction (eg, Bartter syndrome). (See 'Genetic disorders' above.)

Laboratory studies — Urinalysis for patients with neonatal nephrocalcinosis is not useful, as the findings are usually benign. On occasion, urinalysis may reveal nonspecific findings of hematuria or sterile pyuria.

DIAGNOSIS

The diagnosis of nephrocalcinosis is made by imaging. In the neonate, renal ultrasound is the modality that is usually used to make the diagnosis of nephrocalcinosis (image 1), although nephrocalcinosis can also be detected by abdominal or whole body radiography or computed tomography [38,39].

DIAGNOSTIC EVALUATION

A diagnostic evaluation is initiated to determine the underlying cause and includes the following:

- Medical history
  - History of consanguinity or positive family history for renal tubular dysfunction or stone disease may be indicative of an underlying genetic disorder
  -

Review of medications or nutritional intake that increase urinary calcium excretion (eg, loop diuretics, dexamethasone, and supplemental calcium and vitamin D)

- Medical conditions associated with nephrocalcinosis (eg, prematurity, subcutaneous fat necrosis, or history of polyhydramnios [Bartter syndrome])

- Physical examination for features suggestive of an underlying genetic disorder such as Williams-Beuren syndrome (elfin facies, supravalvular aortic stenosis, hypertension) (see "Williams-Beuren syndrome: Renal manifestations")

- Laboratory evaluation

  - Serum electrolytes – Hypokalemia and metabolic acidosis are features observed with distal renal tubular acidosis (RTA); hypokalemia and metabolic alkalosis are features of Bartter syndrome.

  - Calcium – Hypercalcemia leads to hypercalciuria. (See 'Hypercalcemia' above.)

  - Urine calcium-to-creatinine ratio – Infants have a higher urinary calcium excretion rate and urine calcium/creatinine ratio. Hypercalciuria for infants less than six months of age is defined as a ratio >0.8 mg/mg (2.25 mmol/mmol) [40]. (See 'Hypercalciuria' above.)

  - Urinalysis – Urine pH >5.3 with a low serum bicarbonate are features of distal RTA. A low specific gravity may be indicated of impaired ability for urinary concentration, which is a feature in Bartter syndrome.

If a diagnosis is still not established after this initial evaluation, further laboratory testing may be performed and include:

- Urine anion gap – A positive urine anion gap in presence of normal anion gap metabolic acidosis is suggestive of distal RTA. (See "Approach to the child with metabolic acidosis", section on 'Urine electrolytes and anion gap'.)

- Urinary oxalate level – Elevated urinary oxalate is suggestive of primary hyperoxaluria type 1. (See "Primary hyperoxaluria", section on 'Primary hyperoxaluria type 1'.)

- Serum alkaline phosphatase level – Patients with hypophosphatasia have low alkaline phosphatase levels. (See "Epidemiology and etiology of osteomalacia", section on 'Hypophosphatasia'.)

- Genetic testing if there is a strong suspicion for an underlying genetic disorder such as distal RTA, Bartter syndrome, or Williams-Beuren syndrome. (See "Etiology and clinical manifestations of renal tubular acidosis in infants and children", section on 'Distal (type 1) RTA' and "Bartter and Gitelman syndromes", section on 'Bartter syndrome' and "Williams-Beuren syndrome: Renal manifestations".)

- In patients with hypercalcemia, serum vitamin D or parathyroid hormone levels may be helpful to diagnosis hypervitaminosis D or hyperparathyroidism.

MANAGEMENT

The initial management of neonatal nephrocalcinosis is directed to treating the underlying cause, if possible:

- For patients with nephrocalcinosis secondary to loop diuretic therapy (eg, furosemide), hypercalciuria is eliminated by stopping loop diuretic therapy. Administration of a thiazide diuretic can used as an alternative if diuretic therapy is still needed [38,41]. This change may not be tolerated in ventilator-dependent infants with severe bronchopulmonary dysplasia. In these patients, a short course of furosemide may be used in combination with chronic thiazide diuretic therapy. (See "Bronchopulmonary dysplasia: Management", section on 'Diuretics'.)

  Discontinuation of loop diuretic therapy typically results in resolution of nephrocalcinosis over time [2,7,38,42-45]. (See 'Outcome' below.)

- For patients with high calcium and phosphorus dietary intake, modification of dietary intake (especially total parenteral nutrition) by lowering calcium and phosphorus intake should be undertaken if possible.

- Therapy for the following genetic disorders is directed towards addressing metabolic abnormalities that contribute to renal tubular calcium salt deposition.

  - Distal renal tubular acidosis (RTA) – Correction of metabolic acidosis with alkali therapy (eg, sodium bicarbonate or sodium citrate) minimizes calcium deposition. (See "Treatment of distal (type 1) and proximal (type 2) renal tubular acidosis", section on 'Distal (type 1) renal tubular acidosis'.)

  - Bartter syndrome – Treatment is supportive and is focused on minimizing metabolic abnormalities caused by the underlying genetic defect. Primary initial intervention consists of administration of nonsteroidal anti-inflammatory drugs

and the addition of agents that block distal tubule sodium-potassium exchange (eg, spironolactone or amiloride). (See "Bartter and Gitelman syndromes", section on 'Primary therapeutic approaches'.)

- Williams-Beuren syndrome – Therapy is directed towards correcting hypercalcemia. Supportive measures include fluid administration, furosemide treatment, and calcium restriction. Case reports have shown bisphosphonates may be helpful in severe cases, however, it remains unclear whether these agents are both efficacious and safe. (See "Williams-Beuren syndrome: Renal manifestations", section on 'Elevated calcium levels'.)

- Idiopathic infantile hypercalcemia – Therapy includes phosphate supplementation, and restriction of calcium and vitamin D supplementation [26,27].

- Additional supportive measures to reduce urinary calcium concentration in patients with hypercalciuria may be needed and include increasing fluid intake and administration of thiazide diuretics.

- Other possible modalities, which have not been well evaluated, include the administration of sodium citrate, potassium citrate-citric acid, or oral phosphate. The use of citrate therapy has been proposed as a means of preventing nephrocalcinosis. However, in a randomized controlled trial of 74 preterm infants with a gestational age less than 32 weeks, there was no difference in the incidence of nephrocalcinosis between infants who received sodium citrate and control infants (34 versus 44 percent) [12]. (See "Diuretics and calcium balance" and "Prevention of recurrent calcium stones in adults".)

Follow-up after NICU discharge — Follow-up after neonatal intensive care unit (NICU) discharge involves ongoing and comprehensive re-assessment of the patient's renal status. Timing of follow-up is based on the severity of the nephrocalcinosis, renal function, and therapy. Any neonate who is receiving medical management should be seen within a month of discharge. Subsequent visits are scheduled based on individual clinical factors. Follow-up includes:

- Serial renal ultrasonography with annual imaging for the first few years. Subsequent evaluations are based on the progress or resolution of nephrocalcinosis.

- Measurement of renal function (serum creatinine) and urine calcium-to-creatinine ratio (detect and monitor hypercalcuria) at each outpatient visit.

OUTCOME

The outcome of neonatal nephrocalcinosis is determined by the underlying cause. In most cases of nephrocalcinosis that occur in preterm infants without an underlying genetic defect, there is spontaneous resolution in the first several years of life [2,7,44]. In particular, nephrocalcinosis induced by loop diuretics resolves over time in the majority of infants after cessation of the diuretic [2,7,38,42-45].

It remains uncertain whether nephrocalcinosis affects renal function and growth as data are limited and results are conflicting.

- Several studies have shown no evidence of renal impairment associated with nephrocalcinosis [7,9,45]:
  - In one case series, 14 children who were preterm infants with nephrocalcinosis had similar renal function as normal matched controls (sex, gestational age, and birth weight) at five to seven years of age [7]. Of note, three patients had evidence of persistent nephrocalcinosis.
  - In a second case series, there was no difference in renal size urinary calcium excretion or renal concentration ability between preterm survivors with neonatal nephrocalcinosis compared with matched controls at four to five years of age [45].
- In contrast, other studies have reported an association between neonatal nephrocalcinosis and long-term renal dysfunction:
  - In one study, creatinine clearance at one to two years of age was lower in 10 preterm survivors with renal calcifications associated with furosemide therapy compared with two control groups: group 1 with no furosemide therapy or renal calcification and group 2 who were treated with furosemide but had no renal calcifications [43].
  - In a relatively large case series, 6 of 40 preterm survivors with neonatal nephrocalcinosis had a glomerular filtration rate (GFR) below 85 mL/min per 1.73 m^2 compared with 2 of 32 controls without nephrocalcinosis at a mean age of 7.5 years [44]. Children with neonatal nephrocalcinosis compared with controls also had lower tubular phosphate reabsorption and plasma bicarbonate levels.

- Mixed results were reported in a large case series of 63 children with neonatal nephrocalcinosis and matched controls at two years of life [46]. In this cohort, there was no difference between the two groups regarding serum creatinine levels and estimated GFR, however children with neonatal nephrocalcinosis had shorter kidney length (detected by renal ultrasound) for both kidneys at one year of age and only for the right kidney at two years of age.

As a result, we continue to recommend long-term follow-up to monitor both kidney growth and function until more definitive outcome data are available. (See 'Follow-up after NICU discharge' above.)

SUMMARY AND RECOMMENDATIONS

Nephrocalcinosis is defined as deposits of calcium salts in the renal parenchyma. Nephrocalcinosis occurs more frequently in neonates, especially preterm infants because of their renal tubular immaturity and administration of medications and nutritional supplements that promote calcium salt deposition.

- The reported incidence of nephrocalcinosis in preterm infants ranges from 7 to 41 percent. (See 'Incidence' above.)
- Risk factors for neonatal nephrocalcinosis include prematurity, administration of loop diuretics, increased dietary calcium, and vitamin D supplementation. Genetic disorders associated with neonatal nephrocalcinosis include those with hypercalcemia (Williams-Beuren syndrome and idiopathic infantile hypercalcemia) and those with hypercalcuria in the setting of normal blood levels of calcium (distal renal tubular acidosis [RTA] and Bartter syndrome).
- Neonates with nephrocalcinosis are asymptomatic. Nephrocalcinosis presents as either an incidental finding when renal imaging is performed for another reason or when renal ultrasound screening is performed for at-risk infants. (See 'Clinical presentation' above.)
- The diagnosis is typically made by renal ultrasound (image 1), although nephrocalcinosis can be detected by whole body or abdominal radiography or computed tomography. (See 'Diagnosis' above.)
- An initial diagnostic evaluation is performed for all neonates with nephrocalcinosis to determine the underlying cause (if possible). It includes a focused medical history,

and laboratory evaluation that includes urine and blood tests to detect hypercalcemia, hypercalciuria, impaired urinary concentrating ability or distal renal acidification, and alterations in acid/base status (eg, metabolic acidosis and alkalosis). (See 'Diagnostic evaluation' above.)

- The initial management of neonatal nephrocalcinosis is directed towards treating the underlying cause. (See 'Management' above.)
  - For infants with nephrocalcinosis due to medications (eg, loop diuretics) or nutritional supplementation (eg, calcium or vitamin D), elimination of the causative agent is usually sufficient to stop further progression of calcium salt deposition and begin nephrocalcinosis resolution. For furosemide-associated nephrocalcinosis in preterm infants, we recommend that furosemide be discontinued and replaced by a thiazide diuretic (**Grade 1C**).
  - For infants with genetic disorders, therapy is directed towards addressing the metabolic abnormalities that contribute to the development of nephrocalcinosis.
- Although nephrocalcinosis resolves in the majority of cases, it remains unclear whether nephrocalcinosis results in significant chronic kidney injury. As a result, continued follow-up of affected patients is required to ascertain the long-term renal effect of neonatal nephrocalcinosis. (See 'Outcome' above and 'Follow-up after NICU discharge' above.)

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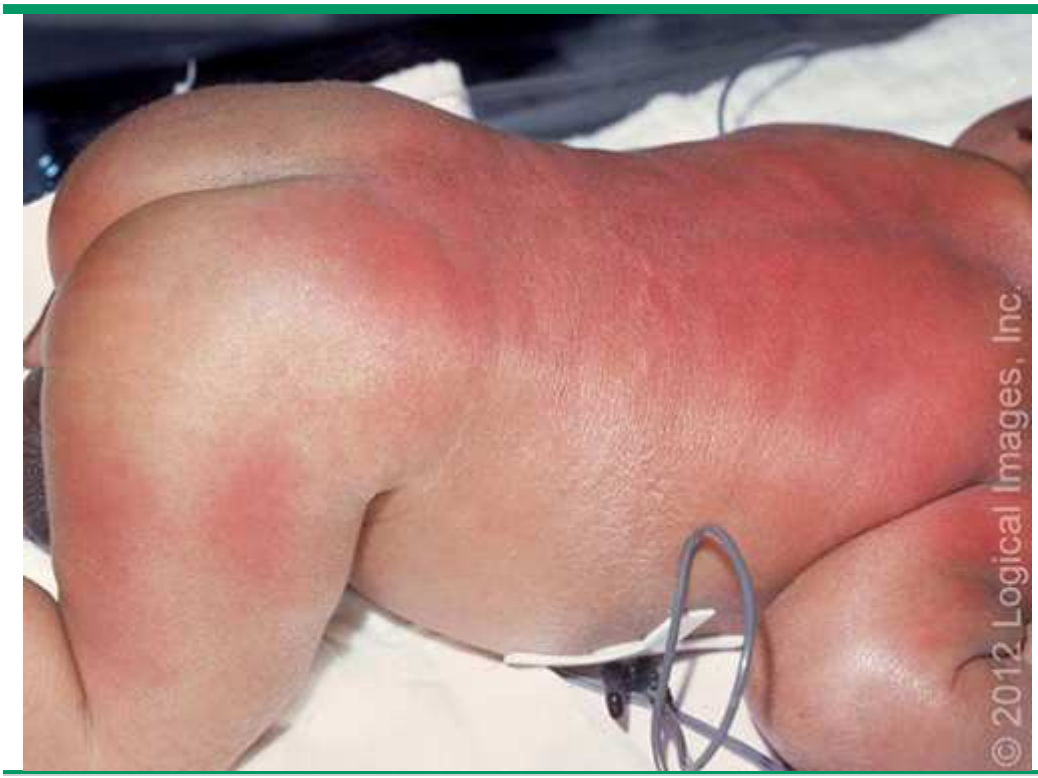
GRAPHICS

Subcutaneous fat necrosis of the newborn



Erythematous nodules and plaques in subcutaneous fat necrosis of the newborn.

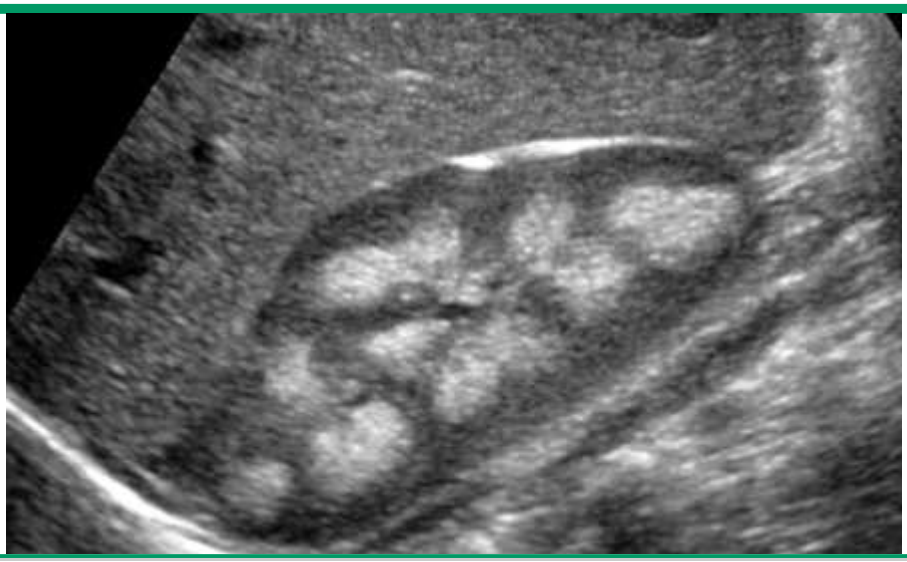
Graphic 83790 Version 5.0

Inherited primary causes of renal tubular acidosis (RTA)

	Gene	Gene location	Protein	Features
Type 1 (distal) RTA				
Autosomal recessive with deafness	*ATP6V1B1*	2p13	B1 subunit of H-ATPase	Presents in infancy with severe metabolic acidosis, poor growth, rickets, and nephrocalcinosis
Autosomal recessive without deafness	*ATP6V0A4*	7q33-q34	a4 subunit of H-ATPase	Presents in infancy with severe metabolic acidosis, poor growth, rickets, and nephrocalcinosis
Autosomal dominant	*SLC4A1*	17q21-q22	Chloride-bicarbonate exchanger	Presents later in life (eg, adolescence and adulthood) with mild/moderate metabolic acidosis, hypercalciuria, nephrolithiasis or nephrocalcinosis, osteomalacia, and erythrocytosis; may be associated with hereditary spherocytosis and ovalocytosis
Type 2 (proximal) RTA				
Autosomal recessive	*SLC4A4*	4q21	Sodium bicarbonate cotransporter	Severe hypokalemic, hyperchloremic, metabolic acidosis, growth retardation, and ocular abnormalities (glaucoma, cataracts, and band keratopathy)
Autosomal dominant	Unknown	Unknown	Unknown	Short stature and metabolic acidosis
Type 3 (mixed) RTA				
Autosomal recessive	Carbonic anhydrase II	8q22	Carbonic anhydrase II	Mixed RTA, osteopetrosis, cerebral calcification, and mental retardation

Graphic 59008 Version 4.0

Ultrasound demonstrating nephrocalcinosis in a neonate



Courtesy of Patrick Niaudet, MD.

Graphic 106015 Version 1.0

Contributor Disclosures

Jodi Smith, MD, MPH Nothing to disclose **F Bruder Stapleton, MD** Nothing to disclose **Tej K Mattoo, MD, DCH, FRCP** Consultant/Advisory Boards: Kite Medical Limited [Vesicoureteral reflux (Bioimpedance)]. **Joseph A Garcia-Prats, MD** Nothing to disclose **Melanie S Kim, MD** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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