Published in final edited form as:

Curr Opin Pediatr. 2016 April ; 28(2): 202–208. doi:10.1097/MOP.0000000000000323.

Proteinuria and Hematuria in the Neonate

Catherine Joseph¹ and Jyothsna Gattineni²

1

2

Abstract

Purpose of Review—Neonatal proteinuria and hematuria while not common can have potentially devastating consequences if left undiagnosed and untreated. It is important to distinguish between inherited and acquired causes of proteinuria to initiate appropriate and timely treatment. In regards to hematuria, it is critical to identify true hematuria from pseudo-hematuria in order to balance between thorough investigation and unnecessary laboratory work up. This review provides an overview of the common causes of hematuria and proteinuria in a neonate.

Recent Findings—Identification of genetic mutations in nephrotic syndrome has improved our understanding of the role of various proteins that play an important role in maintaining the glomerular filtration barrier. With the advancement in our ability to provide care for extreme premature neonates, the incidence of acute kidney injury has increased in these neonates along with proteinuria and hematuria.

Summary—Persistent proteinuria after neonatal acute kidney injury would be of interest in regards to the risk of developing future chronic kidney disease and hypertension.

Keywords

Congenital nephrotic syndrome; renal vein thrombosis; renal cortical necrosis

Introduction

Neonatal proteinuria and hematuria while not common can be detrimental to the health of the neonate. Although nephrogenesis is complete in humans by 36 weeks of gestation, glomerular filtration rate (GFR) is approximately 10–20 ml/min/1.73m² demonstrating the immaturity of the kidney [1]. Premature infants have an even lower GFR.

Neonatal proteinuria can be due to genetic causes, structural anomalies, infections or immune mediated. Severity of proteinuria can vary based on the etiology and will determine the clinical presentation in the neonate. Normal protein excretion in a full term neonate is 68–309 mg/m²/24hrs [2–4].

Send Reprint Requests and Correspondence to: Jyothsna Gattineni, M.D., Department of Pediatrics, U.T. Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, Texas 75390-9063, PH: (214) 648-3438, FAX: (214) 648-2034, jyothsna.gattineni@utsouthwestern.edu.

Conflicts of Interest:

The authors have no conflicts of interest.

Neonatal hematuria can be broadly classified into gross and microscopic hematuria. Microscopic hematuria is defined as >5 RBCs/HPF and is more common in premature or low birth weight infants than healthy term neonates. In the absence of any associated renal or urological anomalies, microscopic hematuria is usually transient. Gross hematuria in a neonate requires prompt evaluation and intervention based on the etiology [5]. For the purpose of this review, a neonate is defined as less than 1 month of age. In this article, we will review the common causes, clinical presentation, evaluation and management of neonatal proteinuria and hematuria.

Normal neonatal renal physiology

The neonatal kidney takes over the placental function of regulating homeostasis at the time of birth. The GFR of a term newborn baby is only 10–20 ml/min/1.73m² and it correlates closely with the gestational age [1]. By 1–2 years of age, GFR reaches adult levels [6]. Despite tubular immaturity and low GFR in the neonatal kidney, fluid and electrolyte homeostasis is maintained. The glomerular basement membrane, vascular endothelium of the capillaries and podocytes are components of the glomerular filtration barrier which prevents leakage of red blood cells (RBCs) and protein. Disruption of the glomerular filtration barrier will result in urinary losses of RBCs and protein. In a healthy neonatal kidney, the proximal tubule function is often not mature enough to prevent leak of smaller proteins and therefore it is normal to see increased urinary protein in a neonates' urine when compared to adult urine. The amount of physiologically normal protein excreted in the urine can be inversely correlated with gestational age [7].

Proteinuria

Here we will discuss the pathologic causes, evaluation and management of neonatal proteinuria. Of note, there are disease processes that have both proteinuria and hematuria and they are discussed in one of the two sections. We will describe glomerular and tubular causes of proteinuria.

Glomerular Proteinuria

Congenital Nephrotic syndrome: Nephrotic syndrome is characterized by proteinuria, hypoalbuminemia, edema and hyperlipidemia. Nephrotic syndrome presenting within 3 months of life is defined as congenital nephrotic syndrome (CNS). CNS can be broadly classified into genetic and non-genetic causes.

Genetic causes: Congenital nephrotic syndrome is associated with genetic mutations of proteins that are components of the glomerular filtration barrier. Nephrin and podocin are key components of the slit diaphragm that connects the foot processes of the podocytes and forms a tight barrier. Homozygous mutations in these two proteins account for the majority of the genetic causes of congenital nephrotic syndrome. Wilms tumor suppression gene (*WT1*) encodes for WT1 protein that is expressed in the podocytes, involved in kidney development, and also regulates nephrin expression. Laminin β 2 encodes for LAMB2 protein which is integral part of the glomerular basement membrane. In a European cohort, up to 85% of the children that had congenital nephrotic syndrome had mutations in podocin,

nephrin, WT1 and LAMB2 proteins [8]. With the disruption of glomerular filtration barrier, there is massive leakage of protein into the urine which results in hypoalbuminemia, and generalized edema. Renal function is normal during the first several months of life but eventually end stage renal disease ensues. Some of the described mutations are associated with non-renal malformations which may provide a clue to the specific genetic mutations. These clinical manifestations include male pseudo-hermaphroditism (WT1), microcoria (LAMB2) and microcephaly and structural brain anomalies (Mowat–Galloway) [9]. Please refer to Table 1 for commonly described genetic mutations, mutant proteins, phenotype and extra-renal manifestations.

Non genetic causes: While genetic causes of congenital nephrotic syndrome are more common in the developed world, infections can also cause nephrotic syndrome [10]. These infections include congenital syphilis, rubella, CMV, toxoplasmosis, hepatitis B and HIV [10]. Neonatal lupus has been reported in the presence and in the absence of maternal lupus [11–13]. Nephrotic syndrome has also been described in neonates due to placental transfer of Neutral-Endopeptidase (NEP) antibodies from feto-maternal alloimmunization [14,15]. NEP antibodies were identified in the maternal serum and transiently in the infant's serum. Mothers were later identified as having truncating mutations in the metalloproteinase endopeptidase (MME) gene encoding NEP protein. A prior exposure to the NEP protein from previous miscarriage or sperm triggered the production of NEP antibody. Membranous nephropathy is a common histopathological description in infants with infectious etiology and NEP antibodies.

Evaluation of infants with congenital nephrotic syndrome should include a detailed maternal history for autoimmune disease, kidney disease, medication exposure, infection screening, prenatal sonogram for amniotic fluid index, and fetal anomalies. In the genetic forms of CNS maternal serum and amniotic fluid alpha-feto-protein levels are elevated. Placental size of >25% of birth weight is seen in neonates with CNS [16]. Hypertension is noted in the presence of renal failure. Due to urinary losses of macromolecules and proteins, these babies are at increased risk of hypothyroidism, infections and thrombosis. Affected babies with neonatal lupus have elevated lupus serologies, hypocomplementemia, and can present with hematuria, hypertension, and acute kidney injury in addition to proteinuria. Babies with NEP antibodies can present with oliguria and acute kidney injury needing renal replacement therapy but in many of these patients, renal injury improves although the risk of chronic kidney disease remains [15].

Genetic tests are diagnostic and are commercially available for the common mutations. Renal biopsy is not diagnostic but may help guide genetic tests. Management options include albumin replacement with diuresis, adequate nutrition, use of medications such as indomethacin and angiotensin converting enzyme inhibitors to reduce GFR and thereby proteinuria. There is no role for immunosuppressive medications in genetic forms of nephrotic syndrome. As patients develop renal failure, nephrectomy and dialysis is performed until transplant. Renal transplantation is a definitive therapy for genetic forms of nephrotic syndrome. In the non-genetic causes, treatment of the underlying etiology will help in the resolution of nephrotic syndrome.

Acute Kidney Injury/Acute Tubular Necrosis: The incidence of acute kidney injury (AKI) in newborns is not well defined and varies from 0.4–3.5% of hospital admissions [17]. AKI occurs in the setting of perinatal asphyxia, hypoxia, hypotension, hypovolemia, sepsis, cardiac disease/surgery, and nephrotoxicity from medications [18,19]. Acute tubular necrosis (ATN) is a common cause for acute kidney injury especially in the neonatal intensive care unit and as a consequence, proteinuria can be seen in the setting of ATN.

The premature infant in whom nephronogenesis is incomplete at the time of birth is particularly at risk for low nephron number, glomerular hyperfiltration and proteinuria in childhood which in turn can lead to CKD [20]. If there is nephron loss due to AKI, the premature infant is at an even higher risk for CKD. In these infants, persistent proteinuria can be an early marker for the development of chronic kidney disease.

Tubular proteinuria—The majority of protein that is filtered by the glomerulus is reabsorbed by the proximal tubule. The protein that is not reabsorbed is excreted in urine and identified as low molecular weight protein [21]. Owing to tubular immaturity, neonates tend to have generalized aminoaciduria that is compounded in the face of prematurity [22,23].

Hereditary conditions associated with tubular low molecular weight proteinuria include hereditary forms of Fanconi syndrome including cystinosis, Dent's disease, Lowes Syndrome and mitochondriopathies. Since there is generalized proximal tubular dysfunction, the proteinuria in these conditions is accompanied by glucosuria, phosphaturia, hypercalciuria and metabolic acidosis. Neonatal presentation of these above condition however is uncommon.

Hematuria

In this section we will review the common causes, evaluation and management of neonatal hematuria. Gross hematuria in a newborn in general requires immediate evaluation but it is important to determine that it is actually hematuria. For instance, urate crystals in the diaper present as a reddish-brown or pink discoloration and is more commonly seen in states of volume depletion especially in breast fed neonates [24]. These urate crystals are benign and improve with increased fluid intake. Vaginal discharge due to maternal hormonal withdrawal can be mistaken for gross hematuria. Diaper rash causing skin break down or rectal bleeding can also present as blood in the diaper and misdiagnosed as gross hematuria. In rare instances porphyria can present with pink discoloration of the diaper. In all these conditions discussed above, urine analysis will be negative for blood. Myoglobinuria is rarely seen in neonates but has been reported in a patient with severe perinatal asphyxia [25]. Hemoglobinuria although rare in neonates can be seen with ABO blood group incompatibility from intravascular hemolysis [26]. In myoglobinuria and hemoglobinuria, urinalysis will be positive for blood but urine microscopy will be negative for red blood cells. Common causes of neonatal hematuria are described below.

Trauma—Gross hematuria can be seen after instrumentation from urethral catheterization, suprapubic tap or cystoscopy [27]. Hematuria is usually self-limited and intervention is

seldom required. It is important to ensure that there is no obstruction to the urinary flow due to blood clots. Neonates with traumatic birth can also present with gross hematuria [28].

Hematological Disorders and Vascular Thrombosis—Neonates are at increased risk of thrombosis and hemorrhage due to the imbalance between anticoagulant and pro-coagulant factors. In addition, neonates have poor flow states with small caliber vasculature predisposing to thrombosis. Additional neonatal risk factors include sepsis, polycythemia, umbilical catheterization, hypoxia, hypotension, and dehydration. Maternal risk factors include diabetes, anti-phospholipid syndrome, thrombotic states and chorioamnionitis. A German study concluded that neonates with renal vein thrombosis had increased incidence of pro-thrombotic risk factors including factor V mutation and elevated Lipoprotein a [29]. Renal vascular thrombosis although not common can have detrimental consequences including hypertension, renal atrophy and chronic kidney disease. Renal vein thrombosis is more common than renal artery thrombosis. It is more common in males and usually occurs on the left side [30]. The classic presentation of renal vein thrombosis includes, gross hematuria, abdominal mass, and thrombocytopenia although this triad is not present in all of the patients [31]. Renal artery thrombosis is often associated with umbilical artery catheterization and is also associated with an aortic thrombus. Patients with renal artery thrombosis present with gross hematuria, thrombocytopenia, and in addition have hypertension.

Ultrasound with Doppler, a commonly used imaging modality has its own limitations as the clot is often not visible and there are non-specific findings like poor cortico-medullary differentiation and renal enlargement. Doppler study might demonstrate reversal of diastolic flow. CT angiogram is gold standard but it has inherent risks of contrast nephropathy in the neonate. DMSA scan can be used to diagnose renal atrophy with differential renal function. As umbilical catheterization is a major risk factor associated with renal vascular thrombosis, correct placement of catheter tip and the use of heparin infusion through the umbilical artery can decrease the incidence of thrombosis. Treatment options include supportive therapy, removal of inciting causes and anticoagulation [30].

Hemorrhagic disease of the newborn although rare in the developed world can be seen in newborns that did not receive Vitamin K prophylaxis and/or in babies who are exclusively breast fed. Babies of mothers on anticonvulsants or warfarin are also at increased risk. Gross or microscopic hematuria although not a common site of bleeding can be seen in newborns with hemorrhagic disease of the newborn. Vitamin K administration is the primary mode of therapy along with supportive therapy with blood transfusions and fresh frozen plasma [32,33].

Infections—Urinary tract infections (UTI) can present as hematuria in a neonate although hematuria is not a common presenting symptom. Presenting complaints include decreased feeding, vomiting, lethargy, irritability, fever and prolonged jaundice. UTI prevalence can be as high as 20% in hospitalized premature neonates and these neonates with UTI are at risk of bacteremia and sepsis [34]. Neonates with urosepsis with organisms other than E.Coli are at increased risk of having a structural abnormalities including vesicoureteric reflux [34,35]. Hematuria with adenovirus and BK virus has been reported in immunocompetent

children and should be considered in a neonate even though there are no published reports [36,37].

Glomerulonephritis—Neonatal glomerulonephritis although rare has been reported. Neonatal lupus commonly presents as congenital heart block or dermatopathy. In the vast majority of the patients, the mother has lupus although neonates have been reported to present with lupus in the absence of maternal lupus. Presenting features include gross hematuria, nephrotic range proteinuria, edema, and hypertension. Laboratory work up will reveal hypocomplementemia, positive antinuclear antibody and anti-double stranded DNA antibody. Renal biopsy findings can be variable and can demonstrate changes consistent with membranous nephropathy, membrano-proliferative glomerulonephritis or “full house glomerulonephritis” with glomerular immunoglobulin (IgM, IgG, IgA) and complement deposition (C1q). Treatment includes immunosuppressive therapy in consultation with the rheumatologist [38,39].

Neonatal hemolytic uremic syndrome (HUS) is characterized by a triad of hemolytic anemia, thrombocytopenia and impairment of renal function. While shiga toxin induced HUS is the common cause of HUS in older children, it is rare in neonates with one case report of maternal transfer of E.coli 0157 [40]. The differential diagnosis for neonatal HUS would include HUS due to mutations in the alternate complement pathway, congenital thrombotic thrombocytopenic purpura due to mutation in the ADAMTS 13 gene (Upshaw Shulman syndrome), inborn errors of cobalamin metabolism, methylmalonic aciduria associated HUS, or drugs [41,42]. Treatment options include plasma infusion/plasma exchange and supportive therapy with blood transfusions and renal replacement therapy. Recently eculizumab, a monoclonal antibody to C5 that prevents the generation of C5b and the membrane attack complex has been used in neonatal atypical HUS with success. [41]

Nephrocalcinosis/Nephrolithiasis—Nephrocalcinosis refers to deposition of calcium phosphate or calcium oxalate crystals within the interstitium of the kidney and has been reported to occur in 7–40% of preterm infants [43]. Nephrocalcinosis can be associated with hematuria. Risk factors for nephrocalcinosis in premature infants include use of loop diuretics, low birth weight, relative hypercalcemia, hypocitraturia, parenteral nutrition and metabolic acidosis [43]. Nephrocalcinosis of prematurity typically resolves with cessation of inciting factors although it can take up to 7–8 years for complete resolution to occur. Nephrocalcinosis can also be seen in term neonates who have distal renal tubular acidosis, primary hyperparathyroidism or Dents disease and they are associated with hypercalciuria. Conditions of hypercalciuria can be treated with a thiazide diuretic. While citrate therapy in older children and adults has been shown to decrease the incidence of renal stones, the use of citrate did not decrease the incidence of nephrocalcinosis in preterm neonates [44]. It is unclear if nephrocalcinosis in neonates leads to an increased risk of hypertension and chronic kidney disease and therefore long term follow up is warranted [45–47].

Structural Malformations—Posterior urethral valves are usually diagnosed prenatally with bilateral hydronephrosis, however some patients present later in life with a poor urinary stream, urinary tract infections or chronic kidney disease. Gross hematuria has been noted in

a small percentage of neonates within the first month of life with posterior urethral valves [31,48]. The precise mechanism of hematuria is unclear.

Congenital ureteroplevic junction obstruction causes hydronephrosis and can present with neonatal gross hematuria. Many theories have been proposed as to the etiology of hematuria including birth trauma, relatively large size kidneys in the neonate, poorly developed Gerota's fascia and perinephric fat [48]. However, the incidence reported is 4 per 100,000 admissions indicating that neonatal gross hematuria due to a hydronephrotic kidney is quite rare [31].

Inherited forms of cystic kidney disease including autosomal recessive polycystic kidney disease (ARPKD) and autosomal dominant polycystic kidney disease (ADPKD) can present in a neonate with microscopic/gross hematuria and or proteinuria. The dominant form of PKD is due to mutations in PKD1 and PKD2 genes. While ADPKD typically presents in adulthood, it can also present in the neonatal period with enlarged hyperechoic kidneys with macrocysts [49,50]. Having a family member with early onset ADPKD increases the risk of early presentation of the disease in the child [49]. Patients with ARPKD have enlarged and diffusely echogenic kidneys on ultrasound, decreased amniotic fluid and respiratory compromise due to pulmonary hypoplasia. Macrocysts are typically absent in the neonatal period in ARPKD [51]. Patients with ARPKD will require renal replacement therapy or transplantation when they develop end stage renal disease [51].

Tumors—Neonatal renal tumors are rare and they constitute <10% of the neonatal tumors [52]. Despite advances in fetal sonography, neonatal renal tumors are commonly diagnosed during routine neonatal examinations or in the presence of other congenital anomalies. Renal tumors are also associated with syndromes like Beckwith-Weidemann syndrome, WAGR (Wilm's tumor, aniridia, genital anomalies, mental retardation), and Denys-Drash (nephropathy, gonadal dysgenesis, intersex and Wilm's tumor). It is critical to perform serial sonogram in these syndromic conditions to monitor for the development of renal tumors. While a palpable abdominal mass is a common presenting symptom, neonates can present with hematuria. Other signs and laboratory findings include polyhydramnios, hypertension, hypercalcemia, anemia and elevated renin levels [52,53]. Congenital mesoblastic nephroma is the most common neonatal renal tumor and the survival rate is very good. Wilms tumor is the second most common neonatal renal tumor and most of them are low grade. For both tumors, nephro-ureterectomy is the primary treatment of choice [52]. Although bladder hemangioma is rare, it should be considered in the differential of neonatal gross hematuria [54].

Renal cortical necrosis—Renal cortical necrosis is seen in neonates with severe hypoxic/ischemic injury leading to microvascular injury and the initiation of the coagulation cascade. Presenting signs include gross or microscopic hematuria, elevated creatinine, abnormal electrolytes, oliguria/anuria and hypertension. Renal sonogram at the time of injury will likely be normal but follow up sonogram will show atrophy of the kidney. The diagnostic test is radionucleotide scan which will show absence of perfusion of the affected kidney. There is no recovery of renal function after renal cortical necrosis [19].

Conclusion

A thorough prenatal and postnatal history along with physical examination will guide the clinician towards a focused work up of neonatal proteinuria and hematuria. Urinalysis with microscopy is an essential first step of the laboratory work up. Complete blood count will be useful to diagnose infections, bleeding disorders and thrombocytopenia. Electrolytes, serum albumin and renal function and urine culture should also be performed. Initial imaging study should include a renal sonogram with doppler study to evaluate renal flow and structural anomalies of the kidneys. Further work up can include coagulation studies, urine albumin/creatinine ratio, urinary calcium/creatinine ratio, CT scan, voiding cystourethrogram and urological procedures like cystoscopy. A timely evaluation and diagnosis can prevent long term complications.

Acknowledgments

None

Financial Support:

This work was supported by NIH grants K08DK089295 (J.G) and R03DK105298 (J.G).

References

* of special interest

** of outstanding interest

1. Guignard JP, John EG. Renal function in the tiny, premature infant. *Clin Perinatol.* 1986; 13:377–401. [PubMed: 3720168]
2. Galaske RG. Renal functional maturation: renal handling of proteins by mature and immature newborns. *Eur J Pediatr.* 1986; 145:368–371. [PubMed: 3792381]
3. Cooper, S. The Harriet Lane Handbook. Nineteenth. Tschudy MMA, KM., editor. Elsevier; 2012.
4. Cruz C, Spitzer A. When you find protein or blood in urine. *Contemp Pediatr.* 1988; 15:89.
5. Jernigan SM. Hematuria in the newborn. *Clin Perinatol.* 2014; 41:591–603. [PubMed: 25155729] **
This author discusses the different etiologies, pathophysiology and therapeutic options for neonatal hematuria.
6. Arant BS Jr. Postnatal development of renal function during the first year of life. *Pediatr Nephrol.* 1987; 1:308–313. [PubMed: 3153294]
7. Ojala R, Ala-Houhala M, Harmoinen AP, Luukkaala T, Uotila J, Tammela O. Tubular proteinuria in pre-term and full-term infants. *Pediatr Nephrol.* 2006; 21:68–73. [PubMed: 16550364]
8. Hinkes BG, Mucha B, Vlangos CN, Gbadegesin R, Liu J, Hasselbacher K, Hangan D, Ozaltin F, Zenker M, Hildebrandt F, et al. Nephrotic syndrome in the first year of life: two thirds of cases are caused by mutations in 4 genes (NPHS1, NPHS2, WT1, and LAMB2). *Pediatrics.* 2007; 119:e907–e919. [PubMed: 17371932]
9. Rheault MN. Nephrotic and nephritic syndrome in the newborn. *Clin Perinatol.* 2014; 41:605–618. [PubMed: 25155730] ** This review article provides the reader with a detailed outline of the common causes of nephrotic and nephritic syndrome in the neonate. Evaluation and therapeutic options are well discussed.

10. Jalanko H. Congenital nephrotic syndrome. *Pediatr Nephrol.* 2009; 24:2121–2128. [PubMed: 17968594]
11. Massengill SF, Richard GA, Donnelly WH. Infantile systemic lupus erythematosus with onset simulating congenital nephrotic syndrome. *J Pediatr.* 1994; 124:27–31. [PubMed: 8283373]
12. Buyon JP, Clancy RM. Neonatal lupus: review of proposed pathogenesis and clinical data from the US-based Research Registry for Neonatal Lupus. *Autoimmunity.* 2003; 36:41–50. [PubMed: 12765470]
13. Dudley J, Fenton T, Unsworth J, Chambers T, MacIver A, Tizard J. Systemic lupus erythematosus presenting as congenital nephrotic syndrome. *Pediatr Nephrol.* 1996; 10:752–755. [PubMed: 8971898]
14. Debiec H, Nauta J, Coulet F, van der Burg M, Guignon V, Schurmans T, de Heer E, Soubrier F, Janssen F, Ronco P. Role of truncating mutations in MME gene in fetomaternal alloimmunisation and antenatal glomerulopathies. *Lancet.* 2004; 364:1252–1259. [PubMed: 15464186]
15. Debiec H, Guignon V, Mougnot B, Decobert F, Haymann JP, Bensman A, Deschenes G, Ronco PM. Antenatal membranous glomerulonephritis due to anti-neutral endopeptidase antibodies. *N Engl J Med.* 2002; 346:2053–2060. [PubMed: 12087141]
16. Patrakka J, Kestila M, Wartiovaara J, Ruotsalainen V, Tissari P, Lenkkeri U, Mannikko M, Visapaa I, Holmberg C, Rapola J, et al. Congenital nephrotic syndrome (NPHS1): features resulting from different mutations in Finnish patients. *Kidney Int.* 2000; 58:972–980. [PubMed: 10972661]
17. Walker MW, Clark RH, Spitzer AR. Elevation in plasma creatinine and renal failure in premature neonates without major anomalies: terminology, occurrence and factors associated with increased risk. *J Perinatol.* 2011; 31:199–205. [PubMed: 20651693]
18. Selewski DT, Charlton JR, Jetton JG, Guillet R, Mhanna MJ, Askenazi DJ, Kent AL. Neonatal Acute Kidney Injury. *Pediatrics.* 2015; 136:e463–e473. [PubMed: 26169430]
19. Andreoli SP. Acute renal failure in the newborn. *Semin Perinatol.* 2004; 28:112–123. [PubMed: 15200250]
20. Askenazi DJ, Ambalavanan N, Goldstein SL. Acute kidney injury in critically ill newborns: what do we know? What do we need to learn? *Pediatr Nephrol.* 2009; 24:265–274. [PubMed: 19082634]
21. Gattineni J. Highlights for the management of a child with proteinuria and hematuria. *Int J Pediatr.* 2012; 2012:768142. [PubMed: 22844302]
22. Dustin JP, Moore S, Bigwood EJ. Chromatographic studies on the excretion of amino acids in early infancy. *Metabolism.* 1955; 4:75–79. [PubMed: 13235324]
23. Brodehl J, Gellissen K. Endogenous renal transport of free amino acids in infancy and childhood. *Pediatrics.* 1968; 42:395–404. [PubMed: 5677481]
24. Kupeli S, Yurdakok M, Kilinc G, Bilgetekin E. Urinary uric acid levels and discoloration of diapers in healthy neonates. *Pediatr Nephrol.* 2005; 20:1361–1362. [PubMed: 15942785]
25. Sirota L, Levi J, Landman J, Dulizky F. Myoglobinuric renal failure in a newborn after traumatic delivery. *Isr J Med Sci.* 1988; 24:317–318. [PubMed: 3403227]
26. Waldron P, de Alarcon P. ABO hemolytic disease of the newborn: a unique constellation of findings in siblings and review of protective mechanisms in the fetal-maternal system. *Am J Perinatol.* 1999; 16:391–398. [PubMed: 10772197]
27. Akierman AR. Suprapubic bladder aspiration in neonates. *Can Fam Physician.* 1987; 33:2099–2100. [PubMed: 21263980]
28. Newman B, Smith S. Unusual renal mass in a newborn infant. *Radiology.* 1987; 163:193–194. [PubMed: 3547494]
29. Kosch A, Kuwertz-Broking E, Heller C, Kurnik K, Schobess R, Nowak-Gottl U. Renal venous thrombosis in neonates: prothrombotic risk factors and long-term follow-up. *Blood.* 2004; 104:1356–1360. [PubMed: 15150075]
30. Resontoc LP, Yap HK. Renal vascular thrombosis in the newborn. *Pediatr Nephrol.* 2015 *The diagnosis and treatment options of renal vascular thrombosis is well described in this article.

31. Emanuel B, Aronson N. Neonatal hematuria. *Am J Dis Child*. 1974; 128:204–206. [PubMed: 4368951]
32. Shearer MJ. Vitamin K deficiency bleeding (VKDB) in early infancy. *Blood Rev*. 2009; 23:49–59. [PubMed: 18804903]
33. Rana MT, Noureen N, Iqbal I. Risk factors, presentations and outcome of the haemorrhagic disease of newborn. *J Coll Physicians Surg Pak*. 2009; 19:371–374. [PubMed: 19486577]
34. Baracco R, Mattoo TK. Diagnosis and management of urinary tract infection and vesicoureteral reflux in the neonate. *Clin Perinatol*. 2014; 41:633–642. [PubMed: 25155732] *The current guidelines for evaluation and treatment of neonatal UTIs are discussed in detail.
35. Beetz R. Evaluation and management of urinary tract infections in the neonate. *Curr Opin Pediatr*. 2012; 24:205–211. [PubMed: 22227782]
36. Allen CW, Alexander SI. Adenovirus associated haematuria. *Arch Dis Child*. 2005; 90:305–306. [PubMed: 15723924]
37. Feder HM Jr, Solomon B, Gavin LD. Polyoma virus hemorrhagic cystitis in an otherwise normal child. *Pediatr Infect Dis J*. 2008; 27:948–949. [PubMed: 18776826]
38. Kreindler J, Ellis D, Vats A, Kurland G, Ranganathan S, Moritz ML. Infantile systemic lupus erythematosus presenting with pulmonary hemorrhage. *Pediatr Nephrol*. 2005; 20:522–525. [PubMed: 15717168]
39. Lam C, Imundo L, Hirsch D, Yu Z, D'Agati V. Glomerulonephritis in a neonate with atypical congenital lupus and toxoplasmosis. *Pediatr Nephrol*. 1999; 13:850–853. [PubMed: 10603135]
40. Ulinski T, Lervat C, Ranchin B, Gillet Y, Floret D, Cochat P. Neonatal hemolytic uremic syndrome after mother-to-child transmission of *Escherichia coli* O157. *Pediatr Nephrol*. 2005; 20:1334–1335. [PubMed: 16010598]
41. Besbas N, Gulhan B, Karpman D, Topaloglu R, Duzova A, Korkmaz E, Ozaltin F. Neonatal onset atypical hemolytic uremic syndrome successfully treated with eculizumab. *Pediatr Nephrol*. 2013; 28:155–158. [PubMed: 22956028]
42. Joseph C, Gattineni J. Complement disorders and hemolytic uremic syndrome. *Curr Opin Pediatr*. 2013; 25:209–215. [PubMed: 23399570]
43. Schell-Feith EA, Kist-van Holthe JE, van der Heijden AJ. Nephrocalcinosis in preterm neonates. *Pediatr Nephrol*. 2010; 25:221–230. [PubMed: 18797936]
44. Schell-Feith EA, Moerdijk A, van Zwieten PH, Zonderland HM, Holscher HC, Kist-van Holthe J, van der Heijden BJ. Does citrate prevent nephrocalcinosis in preterm neonates? *Pediatr Nephrol*. 2006; 21:1830–1836. [PubMed: 17039333]
45. Kist-van Holthe JE, van Zwieten PH, Schell-Feith EA, Zonderland HM, Holscher HC, Wolterbeek R, Veen S, Frolich M, van der Heijden BJ. Is nephrocalcinosis in preterm neonates harmful for long-term blood pressure and renal function? *Pediatrics*. 2007; 119:468–475. [PubMed: 17332199]
46. Porter E, McKie A, Beattie TJ, McColl JH, Aladangady N, Watt A, White MP. Neonatal nephrocalcinosis: long term follow up. *Arch Dis Child Fetal Neonatal Ed*. 2006; 91:F333–F336. [PubMed: 16705005]
47. Schell-Feith EA, Kist-van Holthe JE, van Zwieten PH, Zonderland HM, Holscher HC, Swinkels DW, Brand R, Berger HM, van der Heijden BJ. Preterm neonates with nephrocalcinosis: natural course and renal function. *Pediatr Nephrol*. 2003; 18:1102–1108. [PubMed: 14523633]
48. Diamond DA, Ford C. Neonatal gross hematuria as a presenting sign of posterior urethral valves. *Urology*. 1992; 40:267–269. [PubMed: 1523754]
49. Boyer O, Gagnadoux MF, Guest G, Biebuyck N, Charbit M, Salomon R, Niaudet P. Prognosis of autosomal dominant polycystic kidney disease diagnosed in utero or at birth. *Pediatr Nephrol*. 2007; 22:380–388. [PubMed: 17124604]
50. Shamshirsaz AA, Reza Bekheirnia M, Kamgar M, Johnson AM, McFann K, Cadnapaphornchai M, Nobakhtaghghi N, Schrier RW. Autosomal-dominant polycystic kidney disease in infancy and childhood: progression and outcome. *Kidney Int*. 2005; 68:2218–2224. [PubMed: 16221221]
51. Katherine MacRae Dell, WES.; Avner, Ellis D. *Polycystic Kidney Disease*. Avner WEH, Ellis D., editor. Patrick Niaudet: Norishige Yoshikawa: Springer; 2009.

52. Powis M. Neonatal renal tumours. *Early Hum Dev.* 2010; 86:607–612. [PubMed: 20888153]
53. Glick RD, Hicks MJ, Nuchtern JG, Wesson DE, Olutoye OO, Cass DL. Renal tumors in infants less than 6 months of age. *J Pediatr Surg.* 2004; 39:522–525. [PubMed: 15065020]
54. Fernandes ET, Manivel JC, Reinberg Y. Hematuria in a newborn infant caused by bladder hemangioma. *Urology.* 1996; 47:412–415. [PubMed: 8633412]
55. Vodopiutz J, Seidl R, Prayer D, Khan MI, Mayr JA, Streubel B, Steiss JO, Hahn A, Csaicsich D, Castro C, et al. WDR73 Mutations Cause Infantile Neurodegeneration and Variable Glomerular Kidney Disease. *Hum Mutat.* 2015; 36:1021–1028. [PubMed: 26123727]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Key points

- Congenital nephrotic syndrome typically presents with in the first three months of life with anasarca, hypoalbuminemia and nephrotic range proteinuria.
- Genetic mutations involving the various components of the glomerular filtration barrier proteins account for majority of the causes of congenital nephrotic syndrome and immunosuppressive therapy has no role.
- Renal vein thrombosis should be diagnosed in a timely fashion to avoid detrimental consequences.
- The classic triad of gross hematuria, abdominal mass and thrombocytopenia is not present in all patients with renal vein thrombosis.

Table 1

Common inherited causes of nephrotic syndrome [9,10,55].

GENE	Protein	Mode of inheritance	Phenotype	Extra-renal manifestations
NPHS1	Nephrin	AR	Congenital nephrotic syndrome (CNS)	None
NPHS2	Podocin	AR	Recessive familial nephrotic syndrome	None
PLEC1	1-phosphatidylinositol 4,5 bisphosphate phosphodiesterase epsilon-1	AR	Nephrotic syndrome	None
WT1	Wilms tumor protein	AD/AR	Denys-Drash syndrome, Frasier syndrome	Pseudohermaphroditism, gonadoblastoma, Wilms tumor
LAMB2	Laminin Beta-2	AR	Pierson syndrome	Microcoria, cornea or lens abnormality, severe hypotonia, psychomotor retardation
WDR73	WD repeat containing protein 73	AR	Galloway Mowat syndrome	Microcephaly, cerebellar and cerebral atrophy, optic atrophy, hiatal hernia, severe mental retardation
LMX1B	Lim Homeobox transcription factor 1-beta	AD	Nail-Patella syndrome	Hypoplastic nails, hypoplastic or dysplastic patellae, iliac horns, dysplastic elbows, glaucoma and/or hearing impairment