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Management of Hematuria in Children

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Abstract

Purpose of Review—This paper provides a review of the diagnostic evaluation of both microscopic and gross hematuria, as well as an update on the pathogenesis, clinical features, and treatment strategies for several diseases of the kidneys and urinary tract in which hematuria is a prominent finding. The goal is to provide pediatric providers with a framework through which appropriate and expeditious referral to subspecialty care may be made for definitive treatment.

Recent Findings—Although there has been great heterogeneity in published treatment strategies for many causes of hematuria, the Kidney Diseases Improving Global Outcomes (KDIGO) initiative has recently set forth guidelines for glomerular diseases in particular to provide evidence-based strategies for treatment. In addition, recent advances in the understanding of molecular pathogenesis and long-term clinical outcomes for other non-glomerular diseases has led to updates in treatment strategies summarized in this review.

Summary—As the pediatric primary care provider is often the first point of contact for children with microscopic or gross hematuria, updated knowledge as to the epidemiology and management of several of the various causes of hematuria will improve the care of children by both avoiding extraneous testing and interventions and implementing definitive care (either by expectant management and reassurance or by subspecialty referral) in a timely manner.

Keywords

Microscopic Hematuria; Gross Hematuria; Glomerular Diseases; Structural Renal Disease

II. Introduction

Hematuria – the presence of red blood cells (RBCs) in the urine – is alarming to pediatric patients, parents, and providers alike. The presence of hematuria is indicative of a wide range of etiologies of varying pathogenic significance. The pediatric provider must be able to both identify the presence of hematuria; initiate the proper diagnostic workup; and know how and when to promptly refer affected patients for subspecialty care.

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Conflict of Interest

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Human and Animal Rights and Informed Consent

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Though varying definitions have been proposed, hematuria is most commonly defined by the presence of more than 5 RBCs per high power field collected in an un-centrifuged mid-stream urine collection [1, 2]. Hematuria can be characterized as macroscopic (gross) or microscopic (i.e. detectable only following centrifugation, on direct testing via urine dipstick, or following direct visualization via urine microscopy). Gross hematuria may be "red" or "pink" in color due to lower tract pathology, or "brown" or "tea" colored owing to the oxidation of urinary heme pigments [3, 4].

Hematuria is rare in normal physiology, where the tightly knit structure of the glomerular basement membrane prevents blood from entering the urinary collecting system. When this barrier is disrupted, the RBCs' flexible cell membrane allows them to squeeze through the glomerular basement membrane and enter the urinary collecting system [4]. Many factors lead to hematuria, including exercise, inflammation, structural disruption, malignancy, and trauma. This brief review will highlight the important role of the pediatric provider to identify hematuria, order the initial workup, and if necessary coordinate the integration of subspecialty partners in the treatment of hematuria.

III. Epidemiology and Diagnostic Approaches

Our understanding of the epidemiology of pediatric hematuria is based largely on population studies undertaken nearly 50 years ago. These studies suggest the prevalence of asymptomatic hematuria detected on screening urinalyses in school-aged children to be about 4% [1, 2, 5]. Hematuria predominates in girls versus boys.

The American Academy of Pediatrics no longer recommends routine screening urinalyses [3]. The diagnostic approach to hematuria necessarily begins with a thorough history and physical exam. A helpful diagnostic starting point is the determination of whether the hematuria is macroscopic or microscopic. Generally, macroscopic hematuria suggests a lower urinary tract lesion (e.g. bladder, urethra), while microscopic hematuria is suggestive of upper urinary tract lesion (e.g. glomerulus or tubulointerstitium). A family history can shed light on hereditary causes of hematuria. Common co-occurring features should be explored: proteinuria; urinary casts; elevated blood pressure; the presence, localization, and character of pain; or evidence of trauma. Physical exam findings such as flank masses or costovertebral angle tenderness, or serum and urine biomarkers of infection, inflammation, or renal function can suggest the etiology of hematuria.

Clinical concern for hematuria may be confirmed by the presence of blood on screening urinalysis or direct visualization by urine microscopy. Commercially available, urine "dipstick" screening tests are very sensitive for the presence of heme protein in urine: generally, only those results that are greater than "trace" on normally concentrated, serial samples need be investigated further. Due in part to the highly sensitivity of urine dipstick screening tests, pediatric providers should be aware of the many common causes of urinalyses which falsely result positive for blood. Structurally similar pigment proteins, such as myoglobin seen in the urine of patients with rhabdomyolysis, can register a positive dipstick screen for blood without true hematuria. Heme positive urinalyses negative for blood on microscopy can be caused by intravascular hemolysis; the semen-contaminated

urine of post-coital men; contamination with menstrual blood in young women; and contamination with povidone-iodine or other oxidizing substances [4, 6–8]. In addition, excluding discoloration of the urine from the ingestion of culprit foods (e.g. beets, rhubarb, and blackberries) or medications (e.g. rifampicin, nitrofurantoin, and metronidazole) is important [9, 10, 4]. On the contrary, dilute urine specimens, highly acidic urine pH (<5), and the presence of reducing substances (like ascorbic acid) are common causes of false-negative urine dipstick hematuria screens with which pediatricians should be familiar [4].

A. Gross hematuria

A retrospective review of 342 children who presented for gross hematuria evaluation in a urological setting demonstrated that the largest etiologic categories were urethrorrhagia (15%), urinary tract infection (14%), trauma (14%), congenital urinary tract anomalies (13%), and stones (6%) [11]. During a thorough history, a pediatric provider should ask about the onset and duration of symptoms; as well as the co-occurrence of pain, dysuria, fever, or other symptoms. A history of gross hematuria and abdominal trauma may indicate emergent pathology, for which radiographic and/or surgical evaluation is immediately necessary [10]. Fever, dysuria, urgency, or frequency in the setting of gross hematuria suggests urinary tract infection (UTI). If this presentation is accompanied by flank pain, pyelonephritis should be considered [12]. Intermittent, unilateral sharp flank pain and gross hematuria makes urolithiasis a consideration, along with vascular pathology such as Nutcracker Syndrome or renal vein thrombosis [13–15]. Gross hematuria that accompanies bilateral flank pain and renal enlargement on sonography may suggest interstitial nephritis; though rare, presence of gross hematuria, a palpable mass, and sonographic abnormalities, with or without flank pain, could indicate renal malignancy [4, 16]. The timing of gross hematuria can also provide important clues regarding the etiology. For instance, bleeding noted before or at the beginning of the urine stream is likely urethral in origin, whereas mid-stream or late-stream gross hematuria likely originates from higher in the genitourinary tract. In moderately to significantly physically active children, transient, asymptomatic gross hematuria can be noted following vigorous exercise [17]. When accompanied by upper respiratory symptoms, a proximate (within 1 week) or remote (within 2 to 3 weeks) history of gross hematuria could suggest IgA nephropathy (IgAN) or post-infectious glomerulonephritis (PIGN), respectively [18].

B. Microscopic hematuria

Microscopic hematuria, by contrast, often has a more subtle presentation, and a wider array of etiologies, each with varying degrees of pathologic significance. The prevalence of isolated asymptomatic microscopic hematuria in children is most commonly reported to be between 0.5% and 1% [19, 20]. Of this group, as many as 1 in 4 will have a normalization of urinalysis in 5 years. Since microscopic hematuria is often incidentally noted, it may be difficult to pinpoint the precise time of onset or duration of hematuria. Therefore, a thorough history and physical exam serve as the foundation for a comprehensive initial workup. As with gross hematuria, episodic microscopic hematuria that is accompanied by fever or other infectious symptoms could be indicative of IgA nephropathy or UTI. The presence and distribution of a rash with microscopic hematuria could indicate vasculitides such as systemic lupus erythematosus (SLE) or Henoch-Schönlien Purpura (HSP) nephritis [21, 22].

A family history that includes asymptomatic hematuria, or clinical features such as deafness may be indicative of pathology of the glomerular basement membrane, like Alport syndrome or thin basement membrane disease [23, 24]. A history of hematuria that accompanies painful crises in patients of African descent should raise suspicions for sickle cell nephropathy [25]. While microscopic hematuria is often incidentally noted on screening dipstick urinalysis, when microscopic hematuria is accompanied by proteinuria, the likelihood of renal parenchymal pathology is increased [3].

IV. Physical Examination

Not surprisingly, the initial physical examination of a patient with gross hematuria requires a visual examination of the urine. Urine that demonstrates the presence of bright red blood suggests a lower urinary tract lesion, while darker, tea-colored urine suggests the presence of blood which has undergone oxidization in the bladder [4]. In the setting of microscopic hematuria, evaluation of a centrifuged urine sample is key to determining whether or not the source of bleeding is glomerular or non-glomerular, a distinction that can offer clues to the etiology. The presence of RBC casts is pathognomonic for glomerular bleeding (upper-genitourinary tract bleeding). Dysmorphic RBCs may suggest glomerular bleeding as well [26]. A general physical examination also includes an evaluation for elevated blood pressure or recent weight change. An abdominal examination should note evidence of ascites, trauma, masses, or tenderness to palpation. Assessing for edema in the face, extremities, or dependent regions of the groin (e.g. scrotum or labial folds) is key. A genitourinary examination should include an assessment for costovertebral angle tenderness; and a chaperoned examination of the urethral meatus in males or the vaginal introitus in females for evidence of frank blood or irritation.

V. Management of Hematuria in Kidney Disease in Children

The management of hematuria in children is grounded in the care of the underlying etiology. An exhaustive list of the causes of gross and microscopic hematuria, and the management of each etiology, is beyond the scope of this brief review. For the general pediatrician, an understanding of the broad diagnostic categories into which the diseases that cause hematuria can be divided may aid in the proper initial work up and, if necessary, sub-specialty referral. There are many ways in which kidney disease with hematuria can be categorized. For the purposes of this review, we have organized a handful of common etiologies according to a mechanistic classification scheme. Broadly speaking, hematuria can result from structural-genetic, structural-acquired, inflammatory-immune, and inflammatory-infectious causes. Below, we overview the clinical presentation, pathogenesis, and work up of hematuria for each selected etiology.

A. Structural-Acquired Causes of Hematuria

Hematuria may be the result of structural genitourinary tract lesions that are secondary to the regional or systemic effects of other pathogenic processes. The kidney receives 25% of the circulating blood volume, and the anatomic peculiarities and physiologic demands of the kidney leave the organ uniquely susceptible to injury. In many cases, this injury results in

hematuria: regional hypoxemia, nephrotoxins, kidney stones, and tumors can all lead to direct tissue damage which results in hematuria.

1. Kidney stones and crystalluria

Clinical manifestations: Consider urolithiasis (i.e. macroscopic urinary stones) or crystalluria (microscopic urinary stones) in the setting of gross or microscopic hematuria, with or without co-occurring flank pain, abdominal pain, or vomiting. Dysuria, frequency, urgency, or recurrent UTI can be associated with the presentation as well [27]. Age at presentation varies widely, though the incidence generally increases as a child gets older [28, 29]. The majority of urolithiases are calcium-based (e.g. calcium oxalate, calcium phosphate), though others, like uric acid and cysteine stones, may be present [30, 31].

Pathogenesis of hematuria: Urinary stones mostly originate in free solution, or at the renal papilla (often at the inner-most tip of the medullary pyramids on structures known as Randall's plaques) [32]. A favorable urinary milieu leads to the formation of crystals: calcium oxalate and uric acid crystalizes within an acidic environment, calcium phosphate crystalizes within an alkaline environment. Crystals irritate the urothelial lining, resulting in micro- or macroscopic hematuria.

Diagnostic considerations: The cornerstone of diagnosis is direct pathologic evaluation of a passed stone: patients should be counseled to strain their urine if urolithiasis is suspected. A centrifuged, random spot urine sample can be analyzed microscopically for characteristic crystalline patterns associated with specific stones. Notably, calcium stones are radio-opaque, while uric acid stones are radio-lucent and will only appear on non-contrast computed tomography (CT) [33]. A 24-hour urine collection should be analyzed for urine volume, pH, and metabolic composition (e.g. calcium, oxalate, and phosphorus excretion). Adequate urinary citrate concentration is necessary to prevent the formation of calcium oxalate stones.

Initial management: The management of hematuria associated with urolithiasis and crystalluria begins with prevention. Adequate fluid intake must be maintained to mitigate against urine saturation and crystal development. The etiology directs further management: calcium oxalate and uric acid stones require urine alkalinization, while calcium phosphate stones require urine acidification [32]. Paradoxically, data shows that dietary calcium restriction leads to increased urolithiasis: sodium restriction is the recommended dietary intervention to prevent stone formation [34].

2. Renal mass lesions

Clinical manifestations: Renal masses can be benign or malignant lesions. Hematuria (often macroscopic) is a shared clinical feature of many of these lesions, though the pathogenic significance can vary as widely as the etiologies. The enlarged kidneys of patients with autosomal dominant polycystic kidney disease (ADPKD) are often asymptomatic, however gross hematuria may be seen along with flank pain and hypertension [35]. Similarly, a kidney with moderate or severe hydronephrosis may present as a renal mass, particularly in neonates, and may result in gross hematuria due to vulnerability of the

dilated collecting system to minor trauma [36]. While perhaps the most feared etiology, renal malignancies are relatively rare in children, accounting for 6–7% of all childhood malignancies [37]. Renal malignancies may be associated with genetic cancer syndromes. Wilms tumor, the most common childhood renal malignancy, is often associated with WAGR or Denys-Drash syndromes [38, 36]. Renal cell carcinoma is often seen in von Hippel Lindau disease and other hereditary cancer syndromes [39].

Pathogenesis of hematuria: Hematuria that arises from renal mass lesions can develop in a variety of ways. Often this bleeding is related to “fragile” blood vessels due to impaired angiogenesis and tissue friability, but it can also occur when renal tumors or cysts invade or interpose a native vascular supply, respectively [40]. In addition, secondary effects of malignancy – such as myelosuppression and disseminated intravascular coagulation (DIC) – can result in thrombocytopenia which can contribute to hematuria [41].

Diagnostic considerations: A thorough history of the timing of bleeding, presence of flank pain or dysuria, family history of hematuria, and other associated symptoms (e.g. urinary urgency, recurrence with concomitant illness, etc.) can all provide clues as to the etiology. The physical exam provides important clues as well: for example, hydronephrosis and renal tumors are classically discovered when flank masses are palpated after bathing or diapering an infant, and cystic kidney disease may be diagnosed following evaluation for elevated blood pressure. CT or ultrasound imaging of the abdomen and pelvis can pinpoint the location of renal mass or cystic lesions associated with hematuria, and biopsies of solid renal masses can confirm malignancy [42]. Genetic testing may prove useful if a renal tumor syndrome (e.g. WAGR or Denys-Drash) is suspected [38, 36].

Initial management: The management of renal masses associated with hematuria varies with etiology. The management of cystic kidney disease is aimed at limiting CKD progression and secondary organ damage with strict blood pressure control. For children with kidney cancers, prompt diagnostic imaging and referral to a pediatric cancer center is warranted; the role of the pediatric medical home in providing care coordination for childhood cancer survivors is indispensable [43].

B. Structural-Genetic Causes of Hematuria

Embryonic development and maintenance throughout life of the architecture of the nephron, both the glomerular filtration apparatus and tubule, is critically dependent on hundreds if not thousands of different proteins working in concert. Disruption of one or more genes important for the complex formation of renal parenchyma may have profound effects on the structure and function of the kidney, with hematuria being a common finding in many of such disorders.

1. Sickle cell nephropathy

Clinical manifestation: Consider sickle cell nephropathy (SCN) in a patient of African descent with a history of sickle cell disease and co-occurring hematuria during painful crises. Sickle cell disease’s most severe form – sickle cell anemia – results from a homozygous mutation of the gene encoding β-globin, and causes a conformational change in

the protein's structure that leaves RBCs rigid, sickle-shaped, and causes vaso-occlusive ischemia and hemolytic disease [25]. It is particularly prevalent amongst individuals of African descent. There are a wide array of renal manifestations that can present as SCN, including glomerulosclerosis, impaired concentrating ability, renal papillary necrosis, and hematuria [44].

Pathogenesis of hematuria: Hematuria is among the most common features in patients with sickle cell disease, prevalent among patients with both sickle cell trait and anemia. As blood travels through the renal medullary vasa recta, the hypertonic, hyperviscous, low-oxygen tension environment promotes RBC sickling and vaso-occlusion. This in turn leads to RBC extravasation, ischemic kidney injury and thrombotic microangiopathy (TMA), and suggest a mechanism of nephron damage responsible for presentations of hematuria [45]. Renal papillary necrosis can also present with asymptomatic hematuria, and urinary obstruction in patients with SCN [25].

Diagnostic considerations: In SCN, hematuria can be either gross or microscopic: physical and microscopic examination of the urine is essential. Additionally, in a patient with sickle cell disease, urinalysis with urine protein quantitation (e.g. urine protein to creatinine ratio); assessment of glomerular filtration rate (GFR) and electrolyte status; and assessment for elevated blood pressure is necessary. If flank mass is present, renal ultrasound or computed tomography (CT) imaging should be performed to assess for the presence of renal medullary carcinoma [44].

Initial management: There is no accepted therapy for the treatment of SCN-associated hematuria. Adequate hydration and therapies which increase the predominance of fetal hemoglobin, such as hydroxyurea, are currently the chief elements of prevention of hematuria in SCN. In patients with SCN-associated proteinuria, angiotensin-converting enzyme (ACE)-inhibitor therapy has been shown to reduce urinary albumin excretion [46]. In most cases, unless concern for associated malignancy exists or confirmation of TMA is necessary, additional imaging and/or renal biopsy is/are not indicated.

2. Alport Syndrome and Thin Basement Membrane Nephropathy

Clinical manifestations: An uncommon cause of hematuria in children, occurring in 1:5000 to 1:10,000 individuals [47, 23], Alport syndrome is an inherited disorder of the basement membrane, exhibiting microscopic hematuria and occasionally recurrent gross hematuria, and eventually progressing to proteinuria and chronic kidney disease, as well as extrarenal manifestations of sensorineural hearing loss and ocular abnormalities (e.g. anterior lenticonus, dot-and-fleck retinopathy) [23]. X-linked recessive, autosomal recessive (AR), and rarely autosomal dominant (AD) inheritance patterns have been described. Thin basement membrane nephropathy (TBMN), also known as familial hematuria, occurs in ~1% of the population [48] and was initially thought to be a separate disease entity from Alport syndrome but is now recognized as within the same disease spectrum.

Pathogenesis: Abnormal type IV collagen formation due to mutations in the *COL4A5* (X-linked), *COL4A3* (AD, AR), and *COL4A4* genes (AD, AR) is the principle pathogenic

process that leads to an abnormally thin lamina densa of the glomerular basement membrane (GBM) [23]. In patients with Alport syndrome, this abnormal thinning of the GBM gives way to splitting, lamellation, and disruption causing worsening nephropathy, whereas in TBMN, the abnormally thin GBM does not undergo these changes. Patients with X-linked Alport syndrome (85%), specifically hemizygous males, generally have earlier and more severe disease than those with AR (15%) or AD (<1%) of disease. The majority of patients with TBMN have been found to have heterozygous mutations in the *COL4A3* or *COL4A4* genes, effectively genetic carriers of Alport syndrome. Women who are heterozygous for mutations in the X-linked *COL4A5* gene will generally also have microscopic hematuria, but may also develop progressive disease later in life due to skewed inactivation of the X chromosome [49]. Similarly, up to 25% of patients with TBMN may progressively develop proteinuria, CKD, and end stage renal disease over their lifetime.

Diagnostic Considerations: A careful family history is key in establishing the diagnosis of Alport syndrome and TBMN, although many individuals with TBMN may escape diagnosis as they only have microscopic hematuria that does not come to clinical attention. These entities may come to light by renal biopsy performed in patients with microscopic hematuria and proteinuria, or recurrent gross hematuria, with pathognomonic GBM changes. Ultimately, a definitive diagnosis is made by genetic testing of the *COL4A3*, *COL4A4*, and *COL4A5* genes.

Initial Management: As Alport syndrome and TBMN are diseases of genetic origin, there is no cure and treatment is primarily supportive. Management strategies include surveillance for hypertension and proteinuria as sequelae of the disease; therapeutic blockade of the renin-angiotensin-aldosterone system with ACE inhibitors or angiotensin receptor blockers (ARB); and implementation of treatments for the complications of chronic kidney disease with progression.

C. Inflammatory-Infectious Causes of Hematuria

Hematuria may also be the result of local inflammation secondary to underlying infectious etiology. Local inflammatory responses, mounted in an effort to eliminate a pathogen, lead to the expression of cytokines which increase glomerular capillary permeability, and can in turn result in both gross and microscopic hematuria.

1. Infection-associated hemolytic uremic syndrome

Clinical manifestations: Hemolytic uremic syndrome refers to the classically seen clinical triad of hemolytic anemia, thrombocytopenia, and AKI at presentation. It is the most common cause of AKI in children, and carries a significant risk for adverse renal sequelae [50]. Roughly 1 in 4 patients will have significant long-term renal involvement (e.g. CKD, hypertension), and 3% will develop ESRD [51]. While the classic triad is consistent, the etiology varies widely; the classic presentation is a diarrheal illness associated with Shiga toxin-producing *Escherichia coli* O157:H7 (STEC), often acquired via undercooked or contaminated meat. Other associated infections include S. pneumoniae, influenza, and Human Immunodeficiency Virus (HIV) [50]. Rarely, hemolytic uremic syndrome may be

due to an inherited defect in complement regulation (atypical HUS), or due to a defect in cobalamin C metabolism.

Pathogenesis of hematuria: Shiga-toxin mediated disruption of protein synthesis in the endothelial cell leads to endothelial cell injury and necrosis [52]. This further leads to a pro-inflammatory milieu, aggregation of platelets and activation of the coagulation system in the microvasculature, leading to further injury to a myriad of renal tissue types (e.g. endothelium, mesangium, and tubular epithelium) and ultimately hematuria. The intravascular hemolysis associated with HUS may also cause hemoglobinuria, causing a positive urinalysis for blood.

Diagnostic considerations: The diagnosis of HUS is recognition of the clinical triad of hemolytic anemia, thrombocytopenia, and AKI. Though STEC is the most common infectious cause, a variety of infectious etiologies can be responsible, including Streptococcus pneumoniae, influenza, and Human Immunodeficiency Virus (HIV). A positive Coombs test may be seen in the setting of pneumococcal HUS. Stool culture analysis for E. coli O157:H7, enzyme immunoassay for Shiga toxin protein, or polymerase chain reaction (PCR) for the Shiga toxin gene can confirm STEC.

Initial management: HUS is supportively managed. When a patient's anemia results in cardiorespiratory compromise, a red cell transfusion may be administered. Platelet transfusions are avoided unless the patient is actively bleeding while thrombocytopenic [52]. In the setting of AKI, fluid and electrolyte balance is managed both enterally and parenterally, with special care given to maintain adequate hydration without inducing fluid overload; in the event of oliguric AKI or electrolytic instability, renal replacement therapy (e.g. hemodialysis) may be necessary [50].

2. Urinary tract infection

Clinical manifestations: A common pediatric concern and one of the most common bacterial infections in children, urinary tract infection (UTI) accounts for approximately 1% of ambulatory childhood health care encounters. When a UTI affects the renal parenchyma, it is known as pyelonephritis [12]. In fact, the most common cause of gross hematuria in children is acute bacterial urinary tract infection (UTI) [5]. The overwhelming majority of UTIs in children are caused by monomicrobial bacterial infections – most commonly E. coli – however immunocompromised or catheterized children are at increased risk of acquiring Candida and adenovirus infections as well [53]. In addition to hematuria, symptoms often include fever, dysuria, urgency, or frequency. Dysfunctional voiding, constipation, or bladder and bowel dysfunction place children – especially girls – at high risk for UTI [12]. Particularly in some immunosuppressed populations, viral cystitis with adenovirus or polyomavirus can also result in hematuria [54]. In UTI, gross hematuria is usually gone within a week, with microscopic hematuria lasting a few days longer [55].

Pathogenesis of hematuria: The urinary tract's principal defense against infection is the antegrade flow of urine from the kidneys to the bladder, and most bacteria that enter the urinary tract are thus washed away without causing disease [53]. Pathogenic bacteria cause

UTI by adhering to the urothelium and bypassing host defenses, often in ways specific to the pathogen [56]. UTI causes a localized inflammatory response that results in hematuria, pyuria, and the presence of leukocyte esterase in urinalysis [57].

Diagnostic considerations: While office-based urine dipstick testing which reveals hematuria, pyuria, nitrites, and leukocyte esterase is strong enough to suggest UTI, urine culture remains the cornerstone of UTI diagnosis [57]. The presence of clinical symptoms of UTI (e.g. dysuria, frequency, urgency) corroborate the diagnosis. Additionally, recognition of constipation, dysfunction voiding, or bladder dysfunction will shed light on important UTI risk factors. Though the approach is currently the topic of much debate, clinicians should evaluate children where a concern for vesicoureteral reflux (VUR) confers an increased risk of UTI [12]. In adolescents, a history of sexual activity is important to identify sexually transmitted pathogens when concurrent UTI symptoms are present [58]. Interestingly, among children in whom UTI is clinically suspected, parental report of foul-smelling urine increases the probability of diagnosing UTI, though it cannot on its own be used to rule in or out a UTI diagnosis [59].

Initial management: Appropriate antibiotic therapy is essential to the treatment of symptomatic UTI. Trimethoprim-sulfamethoxazole or first generation cephalosporin therapy is often a reasonable empiric choice, but antibiotic adjustments based on sensitivities obtained from urine culture results, or a local published antibiogram, may be required [12]. The use of prophylactic antibiotics in the management of patients with a history of at increased risk for recurrent UTIs is a topic of much debate. Generally, studies conducted over the last decade have not demonstrated a clinically significant benefit to the use of prophylactic antibiotics in the populations studied, except for in children with high grade (grade III or IV) VUR [60, 61]. Hematuria is most often self-limiting, resolving with treatment of the underlying infection. Continued hydration is beneficial in this setting.

D. Inflammatory-Immune Causes of Hematuria

Microscopic and gross hematuria may also occur in the setting of immune-mediated glomerular injury, either from the deposition of immune complexes in the mesangium and capillary loops with subsequent recruitment of inflammatory cells in the glomerular tuft, or by direct injury to the endothelial cell and podocyte making up the glomerular capillary filtration barrier.

1. Post-infectious glomerulonephritis

Clinical manifestations: Glomerular inflammation that stems from prior exposure to a non-renal infectious etiology is known as post-infectious glomerulonephritis (PIGN). Presenting symptoms often include nephrosis, hematuria, proteinuria, and hypertension, typically following pharyngeal or skin infections [62]. The archetypical PIGN is that which follows streptococcal species infection (e.g. pharyngitis), known as acute post-streptococcal glomerulonephritis (APSGN) [63]. Causes of PIGN are wide-ranging: they include staphylococcal, gram-negative bacterial, viral, fungal, and atypical (e.g. mycobacterial, rickettsial, chlamydial) pathogens [64].

Pathogenesis of hematuria: While the mechanism of initial injury is not clear, two mechanisms of pathogenesis are commonly put forward. In one model, immune complexes form in response to an as-yet unidentified nephritogenic antigen, and are deposited in the glomerulus. In the second, antibodies form in response to infection, but which inappropriately interact with host proteins (e.g. basement membrane collagen, laminin, and glomerular heparin sulfate proteoglycan). [62] The end result of either mechanism is a glomerular inflammatory response that results in hematuria, proteinuria, and the formation of RBC and white blood cell (WBC) casts [64].

Diagnostic considerations: A thorough history is necessary to obtain clues regarding the pathogenesis and disease course in each patient. Suspect PIGN in patients with evidence of edema; hematuria and proteinuria; WBC and RBC casts; and/or hypertension – with or without evidence of decreased creatinine clearance – which has been preceded by an infection between 1 and 2 weeks prior to presentation. Commonly, serum complement C3 protein levels are low, and complement C4 protein levels are normal; complement derangements often precede hematuria [65]. While mostly a result of *Streptococcal* and *Staphylococcal* species infection, infectious cultures may be negative in patients with PIGN, and sub-clinical cases often occur.

Initial management: Treatment of the underlying infectious etiology is paramount to preventing or attenuating the course of PIGN [66]. In the case of APSGN, there is evidence that patients who receive antibiotic therapy during the course of their nephritis experience a milder clinical course [67]. Inpatient care of PIGN is largely supportive, and reserved for those with acute nephritis – namely, those with evidence or complications of hypertension, fluid overload, and acute kidney injury [63]. Common approaches include salt restriction (with or without fluid restriction) and the use of loop diuretics during the disease course. The use of immunosuppressant medications is controversial, but commonly used when clinical or histological evidence of rapidly progressive glomerulonephritis (RPGN) exists [63]. Two small studies found no benefit in the use of immunosuppressant medications in PIGN [68, 69].

2. IgA Nephropathy and Henoch-Schönlein Purpura Nephritis

Clinical manifestations: IgA Nephropathy (IgAN) and the histopathologically related Henoch-Schönlein Purpura (HSP) nephritis are collectively the most common cause of glomerulonephritis worldwide, and a frequent cause of glomerulonephritis in children. The clinical presentation of IgAN can be highly variable: asymptomatic microscopic hematuria and proteinuria, recurrent episodes of gross hematuria occurring 1–2 days after an upper respiratory or gastrointestinal infection, nephrotic syndrome, or RPGN [70]. IgAN predominantly occurs in older children and adolescents, whereas HSP nephritis occurs in younger children, with an average age of 6 years [21]. Glomerulonephritis occurs in about 30% of patients with HSP, typically occurring within the first month of the onset of the other constellation of symptoms but may occur as late as 6 months to 1 year after disease onset. The majority of children with HSP nephritis present with microscopic hematuria +/− proteinuria, and only a small subset (<1%) present with gross hematuria and more

pronounced urinary abnormalities. Hypertension may accompany both IgAN and HSP nephritis, although it is uncommon in either disease in the acute setting.

Pathogenesis of hematuria: Both IgAN and HSP nephritis share the histological appearance of deposits of aberrantly glycosylated IgA in the mesangium with accompanying C3 deposition. This results in proliferation of mesangial cells and recruitment of inflammatory cells, leading to mesangial hypercellularity as seen on renal biopsy and causing hematuria.

Diagnostic considerations: Although IgAN may be suspected in the setting of a typical clinical presentation, the diagnosis is only definitively made by renal biopsy. An elevated serum IgA level may be seen in approximately 50% of patients with IgAN [71] but is neither sensitive nor specific for identifying IgAN or HSP nephritis [72]. The Oxford classification system of renal histopathology in IgAN has demonstrated the ability to predict risk to progression to chronic kidney disease, particularly by the presence of segmental glomerular lesions and tubular atrophy [73], and more recently crescentic lesions [74]. This classification system has been recently applied to HSP nephritis as well [75], with similar findings.

Initial management: Current treatment recommendations based on the Kidney Diseases Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis [76] are dependent on the degree of proteinuria present. Urinary protein excretion of > 0.5–1g/1.73m^2/d warrants consideration of treatment with antiproteinuric therapy (ACE inhibitor/ARB), and >1g/1.73m^2/d warrants consideration of immunosuppressive therapy (specifically corticosteroids) and consideration of adjunctive immunomodulatory therapy with fish oil.

VI. When to Refer for Hematuria

Referral to a pediatric nephrologist for evaluation of hematuria is warranted when accompanying factors are present that increase the risk for renal parenchymal disease or significant resulting morbidity. This includes the presence of hypertension, which may signify the presence of glomerulonephritis, and may require treatment with antihypertensive agents to avoid both acute (i.e. hypertensive encephalopathy) and chronic (i.e. left ventricular hypertrophy, dilated cardiomyopathy) sequelae. The presence of proteinuria, particularly nephrotic range proteinuria, and certainly renal dysfunction may herald a sufficiently destructive lesion (i.e. crescentic or rapidly progressive glomerulonephritis due to PIGN, IgAN, HSP Nephritis or other less common lesions [i.e. membranoproliferative glomerulonephritis, pauci-immune vasculitis such as granulomatosis with polyangiitis]). With such cases, prompt referral to a pediatric nephrologist is indicated for diagnostic renal biopsy and definitive management with immunosuppressive therapy. Identification of renal cysts in the context of hematuria may benefit from referral to nephrology, largely to provide guidance to the family as to the most likely etiology among the array of cystic kidney diseases, the risk of any associated extra-renal manifestations, and expectations of long-term outcome. Finally, if nephrolithiasis is identified through the workup of microscopic or gross hematuria, once acute management has been completed by a pediatric urologist, referral to

nephrology is appropriate to initiate a metabolic workup and then devise a comprehensive stone risk mitigation plan with dietary and pharmacological interventions.

Referral to a pediatric urologist is warranted particularly if there is evidence of structural pathology causing microscopic or gross hematuria and if the identified pathology has a surgical treatment (i.e. hydronephrosis, renal mass, obstruction or renal colic from urolithiasis). In addition, the pediatric urologist may also offer additional diagnostic tools such as cystoscopy if the clinical features are consistent with lower-tract bleeding.

VII. Conclusions

In summary, the breadth of kidney and urinary tract pathology that leads to either gross or microscopic hematuria is vast, and a careful history and physical examination as well as focused laboratory investigation may provide sufficient insight as to the likely culprit of hematuria, either reassuring the clinician as to the suitability of expectant management, or spurring them on to facilitate referral to subspecialty care. As such, the crux of management of many causes of hematuria may be to determine when it is time to refer, more than what treatments to initiate one's self. To this end, the patient's primary care provider is often an integral team member in ensuring that renal and urological pathology with significant morbidity is addressed in a timely fashion.

References

1. Dodge WF, West EF, Smith EH, Bunce H. Proteinuria and hematuria in schoolchildren: epidemiology and early natural history. The Journal of pediatrics. 1976; 88(2):327–47. [PubMed: 1249701]
2. Vehaskari VM, Rapola J, Koskimies O, Savilahti E, Vilska J, Hallman N. Microscopic hematuria in schoolchildren: epidemiology and clinicopathologic evaluation. The Journal of pediatrics. 1979; 95(5):676–84. [PubMed: 490233]
3. Massengill SF. Hematuria. Pediatrics in Review. 2008; 29(10):342. [PubMed: 18829770]
4. Yap H, Lau P. Pediatric Kidney Disease. 2. Springer; 2016. Hematuria and Proteinuria.
5. Ingelfinger JR, Davis AE, Grupe WE. Frequency and etiology of gross hematuria in a general pediatric setting. Pediatrics. 1977; 59(4):557–61. [PubMed: 850596]
6. Mazouz B, Almagor M. False-positive microhematuria in dipsticks urinalysis caused by the presence of semen in urine. Clinical biochemistry. 2003; 36(3):229–31. [PubMed: 12726934]
7. Grossfeld GD, Litwin MS, Wolf JS Jr, Hricak H, Shuler CL, Agerter DC, et al. Evaluation of asymptomatic microscopic hematuria in adults: the American Urological Association best practice policy—part I: definition, detection, prevalence, and etiology1. Urology. 2001; 57(4):599–603. [PubMed: 11306356]
8. Simerville JA, Maxted WC, Pahira JJ. Urinalysis: a comprehensive review. Am Fam Physician. 2005; 71(6):1153–62. [PubMed: 15791892]
9. PEARCY RM, MITCHELL SC, SMITH RL. Beetroot and red urine. Portland Press Limited; 1992.
10. Patel HP, Bissler JJ. Hematuria in children. Pediatric Clinics. 2001; 48(6):1519–37. [PubMed: 11732128]
11. Greenfield SP, Williot P, Kaplan D. Gross hematuria in children: a ten-year review. Urology. 2007; 69(1):166–9. [PubMed: 17270642]
12. Jackson EC. Urinary tract infections in children: knowledge updates and a salute to the future. Pediatrics in Review. 2015; 36(4):153–64. quiz 65–6. [PubMed: 25834219]
13. Asghar M, Ahmed K, Shah S, Siddique M, Dasgupta P, Khan M. Renal vein thrombosis. European journal of vascular and endovascular surgery. 2007; 34(2):217–23. [PubMed: 17543556]

14. Siddiqui WJ, Bakar A, Aslam M, Arif H, Bianco BA, Trebelev AE, et al. Left Renal Vein Compression Syndrome: Cracking the Nut of Clinical Dilemmas–Three Cases and Review of Literature. The American journal of case reports. 2017; 18:754. [PubMed: 28680033]
15. Ananthan K, Onida S, Davies A. Nutcracker Syndrome: An Update on Current Diagnostic Criteria and Management Guidelines. European journal of vascular and endovascular surgery. 2017
16. Raghavan R, Eknoyan G. Acute interstitial nephritis–a reappraisal and update. Clinical nephrology. 2014; 82(3):149. [PubMed: 25079860]
17. West CD. Asymptomatic hematuria and proteinuria in children: Causes and appropriate diagnostic studies. The Journal of pediatrics. 1976; 89(2):173–82. [PubMed: 940012]
18. Meyers KE. Evaluation of hematuria in children. Urologic Clinics of North America. 2004; 31(3): 559–73. [PubMed: 15313065]
19. Yap H, Quek C, Shen Q, Joshi V, Chia K. Role of urinary screening programmes in children in the prevention of chronic kidney disease. Ann Acad Med Singapore. 2005; 34(1):3–7. [PubMed: 15726213]
20. Murakami M, Yamamoto H, Ueda Y, Murakami K, Yamauchi K. Urinary screening of elementary and junior high-school children over a 13-year period in Tokyo. Pediatric nephrology. 1991; 5(1): 50–3. [PubMed: 2025538]
21. Davin J-C, Coppo R. Henoch–Schönlein purpura nephritis in children. Nature Reviews Nephrology. 2014; 10(10):563. [PubMed: 25072122]
22. Lehman TJ. A practical guide to systemic lupus erythematosus. Pediatric clinics of North America. 1995; 42(5):1223–38. [PubMed: 7567193]
23. Kruegel J, Rubel D, Gross O. Alport syndrome—insights from basic and clinical research. Nature Reviews Nephrology. 2013; 9(3):170. [PubMed: 23165304]
24. Kashtan CE. Alport syndrome and thin glomerular basement membrane disease. Journal of the American Society of Nephrology. 1998; 9(9):1736–50. [PubMed: 9727383]
25. Nath KA, Hebbel RP. Sickle cell disease: renal manifestations and mechanisms. Nature Reviews Nephrology. 2015; 11(3):161. [PubMed: 25668001]
26. Fogazzi GB, Edefonti A, Garigali G, Giani M, Zolin A, Raimondi S, et al. Urine erythrocyte morphology in patients with microscopic haematuria caused by a glomerulopathy. Pediatric nephrology. 2008; 23(7):1093–100. [PubMed: 18324420]
27. Omoloja AA, Patel H, Ey E, Jackson E. Common renal problems in pediatric medicine. Current problems in pediatric and adolescent health care. 2007; 37(5):153–94. [PubMed: 17485041]
28**. Hernandez JD, Ellison JS, Lendvay TS. Current trends, evaluation, and management of pediatric nephrolithiasis. JAMA pediatrics. 2015; 169(10):964–70. This recent review provides a comprehensive update on the epidemiology, metabolic evaluation, and management of nephrolithasis in children. [PubMed: 26302045]
29. Tasian GE, Ross ME, Song L, Sas DJ, Keren R, Denburg MR, et al. Annual incidence of nephrolithiasis among children and adults in South Carolina from 1997 to 2012. Clinical Journal of the American Society of Nephrology. 2016; 11(3):488–96. [PubMed: 26769765]
30. Claes DJ, Jackson E. Cystinuria: mechanisms and management. Pediatric nephrology. 2012; 27(11):2031–8. [PubMed: 22281707]
31. Copelovitch L. Urolithiasis in children: medical approach. Pediatric Clinics. 2012; 59(4):881–96. [PubMed: 22857835]
32. Evan AP. Physiopathology and etiology of stone formation in the kidney and the urinary tract. Pediatric nephrology. 2010; 25(5):831–41. [PubMed: 19198886]
33. Teichman JM. Acute renal colic from ureteral calculus. New England Journal of Medicine. 2004; 350(7):684–93. [PubMed: 14960744]
34. Borghi L, Schianchi T, Meschi T, Guerra A, Allegri F, Maggiore U, et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. New England Journal of Medicine. 2002; 346(2):77–84. [PubMed: 11784873]
35. Srivastava A, Patel N. Autosomal dominant polycystic kidney disease. American family physician. 2014; 90(5)

36. Malkan AD, Loh A, Bahrami A, Navid F, Coleman J, Green DM, et al. An approach to renal masses in pediatrics. Pediatrics. 2015; 135(1):142–58. [PubMed: 25452658]
37. Howlader NNA, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA, editorsSEER Cancer Statistics Review, 1975–2010. National Cancer Institute; Bethesda, MD: Apr, 2013 http://seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER data submission, posted to the SEER web site
38. Fischbach BV, Trout KL, Lewis J, Luis CA, Sika M. WAGR syndrome: a clinical review of 54 cases. Pediatrics. 2005; 116(4):984–8. [PubMed: 16199712]
39. Castellino SM, McLean TW. Pediatric genitourinary tumors. Current opinion in oncology. 2007; 19(3):248–53. [PubMed: 17414644]
40. Weis SM, Cheresh DA. Tumor angiogenesis: molecular pathways and therapeutic targets. Nature medicine. 2011; 17(11):1359.
41. Escobar MA. Bleeding in the patient with a malignancy. Cancer. 2012; 118(2):312–20. [PubMed: 21720995]
42. O'Connor OJ, McSweeney SE, Maher MM. Imaging of hematuria. Radiologic Clinics. 2008; 46(1):113–32. [PubMed: 18328883]
43. Fallat M, Hutter J. American Academy of Pediatrics Section on Hematology Oncology, American Academy of Pediatrics Section on Surgery. Preservation of fertility in pediatric and adolescent patients with cancer. Pediatrics. 2008; 121(5):e1461–9. [PubMed: 18450888]
44. Becker AM. Sickle cell nephropathy: challenging the conventional wisdom. Pediatric nephrology. 2011; 26(12):2099–109. [PubMed: 21203778]
45. Pham P-TT, Pham P-CT, Wilkinson AH, Lew SQ. Renal abnormalities in sickle cell disease. Kidney International. 2000; 57(1):1–8.
46. Naik RP, Derebail VK. The spectrum of sickle hemoglobin-related nephropathy: from sickle cell disease to sickle trait. Expert review of hematology. 2017; 10(12):1087–94. [PubMed: 29048948]
47. Alves FR, Ribeiro FdAQ. Revision about hearing loss in the Alport's syndrome, analyzing the clinical, genetic and bio-molecular aspects. Revista Brasileira de Otorrinolaringologia. 2005; 71(6):813–9. [PubMed: 16878253]
48. Kashtan CE. Alport Syndrome and Thin Basement Membrane Nephropathy. In: Adam MPAH, Pagon RA. , et al., editorsGeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 2001. Aug 28, 1993–2018. [Updated 2015 Nov 25]Available from: https://www.ncbi.nlm.nih.gov/books/NBK1207/
49. Mehta L, Jim B, editorsSeminars in nephrology. Elsevier; 2017. Hereditary Renal Diseases.
50. Tarr PI, Gordon CA, Chandler WL. Shiga-toxin-producing Escherichia coli and haemolytic uraemic syndrome. The Lancet. 2005; 365(9464):1073–86.
51. Garg AX, Suri RS, Barrowman N, Rehman F, Matsell D, Rosas-Arellano MP, et al. Long-term renal prognosis of diarrhea-associated hemolytic uremic syndrome: a systematic review, meta-analysis, and meta-regression. Jama. 2003; 290(10):1360–70. [PubMed: 12966129]
52. Scheiring J, Andreoli SP, Zimmerhackl LB. Treatment and outcome of Shiga-toxin-associated hemolytic uremic syndrome (HUS). Pediatric nephrology. 2008; 23(10):1749. [PubMed: 18704506]
53. Chang SL, Shortliffe LD. Pediatric urinary tract infections. Pediatric clinics of North America. 2006; 53(3):379–400. [PubMed: 16716786]
54. Boeckh M, Erard V, Zerr D, Englund J. Emerging viral infections after hematopoietic cell transplantation. Pediatric transplantation. 2005; 9(s7):48–54. [PubMed: 16305617]
55. Mufson MA, Belshe RB, Horrigan TJ, Zollar LM. Cause of acute hemorrhagic cystitis in children. American Journal of Diseases of Children. 1973; 126(5):605–9. [PubMed: 4355446]
56. Mulvey MA. Adhesion and entry of uropathogenic Escherichia coli. Cellular microbiology. 2002; 4(5):257–71. [PubMed: 12027955]
57. Semeniuk H, Church D. Evaluation of the leukocyte esterase and nitrite urine dipstick screening tests for detection of bacteriuria in women with suspected uncomplicated urinary tract infections. Journal of clinical microbiology. 1999; 37(9):3051–2. [PubMed: 10449505]

58. Meglič A, Čavić M, Hren-Vencelj H, Tršinar B, Ravnik M, Kenda R. Chlamydial infection of the urinary tract in children and adolescents with hematuria. Pediatric nephrology. 2000; 15(1–2):132–3. [PubMed: 11095030]

59. Gauthier M, Gouin S, Phan V, Gravel J. Association of malodorous urine with urinary tract infection in children aged 1 to 36 months. Pediatrics. 2012; 129(5):885–90. [PubMed: 22473364]

60. Brandström P, Esbjörner E, Herthelius M, Swerkersson S, Jodal U, Hansson S. The Swedish reflux trial in children: III. Urinary tract infection pattern. The Journal of urology. 2010; 184(1):286–91. [PubMed: 20488494]

61. Investigators RT. Antimicrobial prophylaxis for children with vesicoureteral reflux. New England Journal of Medicine. 2014; 370(25):2367–76. [PubMed: 24795142]

62. Ahn S-Y, Ingulli E. Acute poststreptococcal glomerulonephritis: an update. Current opinion in pediatrics. 2008; 20(2):157–62. [PubMed: 18332711]

63. Eison TM, Ault BH, Jones DP, Chesney RW, Wyatt RJ. Post-streptococcal acute glomerulonephritis in children: clinical features and pathogenesis. Pediatric nephrology. 2011; 26(2):165–80. [PubMed: 20652330]

64. Kanjanabuch T, Kittikowit W, Eiam-Ong S. An update on acute postinfectious glomerulonephritis worldwide. Nature Reviews Nephrology. 2009; 5(5):259. [PubMed: 19384327]

65. Sjöholm AG. Complement components and complement activation in acute poststreptococcal glomerulonephritis. International Archives of Allergy and Immunology. 1979; 58(3):274–84.

66. Rodriguez-Iturbe B, Musser JM. The current state of poststreptococcal glomerulonephritis. Journal of the American Society of Nephrology. 2008; 19(10):1855–64. [PubMed: 18667731]

67. Zoch-Zwierz W, Wasilewska A, Biernacka A, Tomaszewska B, Winiecka W, Wierciński R, et al. The course of post-streptococcal glomerulonephritis depending on methods of treatment for the preceding respiratory tract infection. Wiadomosci lekarskie (Warsaw, Poland: 1960). 2001; 54(1–2):56–63.

68. Roy S, Murphy WM, Arant BS. Poststreptococcal crescenteric glomerulonephritis in children: comparison of quintuple therapy versus supportive care. The Journal of pediatrics. 1981; 98(3): 403–10. [PubMed: 7205449]

69. Wong W, Morris MC, Zwi J. Outcome of severe acute post-streptococcal glomerulonephritis in New Zealand children. Pediatric nephrology. 2009; 24(5):1021–6. [PubMed: 19096879]

70. Coppo R, editorSeminars in nephrology. Elsevier; 2008. Pediatric IgA nephropathy: clinical and therapeutic perspectives.

71. Yuzawa Y, Yamamoto R, Takahashi K, Katafuchi R, Tomita M, Fujigaki Y, et al. Evidence-based clinical practice guidelines for IgA nephropathy 2014. Clinical and experimental nephrology. 2016; 20(4):511–35. [PubMed: 27095365]

72. Tomino Y, Suzuki S, Imai H, Saito T, Kawamura T, Yorioka N, et al. Measurement of serum IgA and C3 may predict the diagnosis of patients with IgA nephropathy prior to renal biopsy. Journal of clinical laboratory analysis. 2000; 14(5):220–3. [PubMed: 11018800]

73. Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney International. 2009; 76(5):534–45. [PubMed: 19571791]

74*. Trimarchi H, Barratt J, Cattran DC, Cook HT, Coppo R, Haas M, et al. Oxford classification of IgA nephropathy 2016: an update from the IgA nephropathy classification working group. Kidney International. 2017; 91(5):1014–21. This article adds new understanding as to the implications of histopathological characteristics in IgA Nephropathy, specifially the prognostic significance of crescentic disease. [PubMed: 28341274]

75. Xu K, Zhang L, Ding J, Wang S, Su B, Xiao H, et al. Value of the Oxford classification of IgA nephropathy in children with Henoch–Schönlein purpura nephritis. Journal of nephrology. 2017:1–8.

76**. Cattran DC, Feehally J, Cook HT, Liu ZH, Fervenza FC, Mezzano SA, et al. Kidney disease: improving global outcomes (KDIGO) glomerulonephritis work group. KDIGO clinical practice guideline for glomerulonephritis. Kidney International Supplements. 2012; 2(2):139–274. This set of practice guidelines describes the evidence-based consensus guidelines for diagnostic

evaluation and treatment of several forms of glomerulonephritis with additional pediatric-focused recommendations.