Abnormal Urinalysis/Hematuria and Medical Renal Disease

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1. Section Summary

Pediatric hematuria can be alarming to families and results from both benign and malignant etiologies. This section will detail the definition, workup, and management of common causes of pediatric microscopic and gross hematuria. This section will also include discussion on management of pediatric chronic kidney disease and renal transplant.

2. Key Words

Hematuria, Pediatric Renal Disease, Nephrolithiasis, Cystitis, Trauma, Pediatric Genitourinary Malignancy, Chronic kidney disease, Transplant

3. Introduction and Epidemiology

Causes of pediatric hematuria vary widely and include intrinsic renal anomalies, infectious/inflammatory causes, nephrolithiasis, trauma, and malignancy. Detailed histories and physical exams are necessary to help elucidate the underlying etiology. Hematuria can be classified as microscopic or macroscopic. In cases of microscopic hematuria, red blood cells are detected in the urine on a formal urinalysis but no urinary discoloration is noted. In cases of macroscopic or gross hematuria, the urine may appear pink or red; if the heme pigments are oxidized, the urine appears brown or tea colored.[1]

Our understanding of the prevalence of hematuria is based on large population studies conducted decades ago when screening urinalyses were regularly performed in school-aged children. Based on these studies, 4% of children had evidence of microscopic hematuria on one urinalysis, and 1.1% of children had two or more urine samples with microscopic hematuria.[2] While screening urinalyses are no longer recommended by the American Academy of Pediatrics, studies in countries where this remains common practice continue to confirm this prevalence rate of approximately 4%.[3]

Pediatric gross hematuria has been reported to account for 1.3/1000 emergency room visits over a two-year period.[4] The most common causes of pediatric gross hematuria include benign

urethrorrhagia (15%), urinary tract infections (14%), trauma (14%), congenital urinary tract abnormalities (13%), and stones (6%). Low grade bladder transitional cell carcinoma was found in three patients, and one was diagnosed with a Wilms tumor. The overall rarity of these cases suggests that causes of gross hematuria in children and adolescents is mostly benign.[5]

4. Diagnosis and Evaluation

4.1 Evaluation

Urinalysis: The urine dipstick is a convenient method to detect the presence of blood in the urine. The urine should ideally be a fresh sample and tested within 2 hours of collection. Urine should be kept at room temperature or allowed to return to room temperature if the sample was previously refrigerated.[6,7] Hematuria is detected on the urine dipstick via the pseudo-peroxidase activity of hemoglobin which catalyzes an oxidation reaction between hydrogen peroxide and a chromogen on the test pad. Intact red blood cells (RBCs) in the urine will hemolyze on the test pad. The freed hemoglobin from intact RBC causes a spotted green appearance whereas free hemoglobin will give a uniform green to dark blue appearance.[6]

There are several reagents that cause a false positive result for hematuria on the dipstick. These can include myoglobin, oxidizing contaminants, contamination from bacterial peroxidases, povidone-iodine, menstrual blood, and semen.[6] With the high sensitivity of the urine dipstick, transient hematuria may also be detected which warrants collecting other urine samples to determine if hematuria is persistent. Causes of transient hematuria include mild trauma, heavy exercise, and recent sexual intercourse. [8]

Definition: Gross hematuria is defined as discolored urine due the presence of large amounts of RBCs. The definition of microscopic hematuria varies between the presence of 1-10 RBC per high powered field.[8] In large pediatric cohort studies conducted in school age children, microscopic hematuria has been defined as greater than 5 RBC/mm3 in an uncentrifuged urine or greater than 5 RBCs per high powered field in a centrifuged urine across 2 to 3 different occasions.[3,7,9] The American Urological Association defines microscopic hematuria as greater than or equal to 3 RBC per high powered field.[10]

Urine microscopy: Once there is concern for hematuria, the presence of either microscopic blood or confirmation that the visible urine discoloration is secondary to the presence of blood must be obtained with urine microscopy.

There are causes of discoloration of urine which can be misdiagnosed as gross hematuria prior to confirmatory urine microscopy. These include myoglobinuria in the setting of rhabdomyolysis and hemoglobinuria from intravascular hemolysis. Urine can also appear brown in the setting of liver disease with jaundice and elevated conjugated hyperbilirubinemia. In this case, urobilinogen would turn positive on the dipstick. The urine can also become discolored by food pigments contained in beet and beet root, rhubarb, and black berries. The color change in the urine is benign.[11] Several medications can also change the urine color which include sulfonamides, nitrofurantoin, salicylates,

phenazopyridine, phenytoin, rifampin, chloroquine, defuroxamine, iron sorbitol.[7] Urate crystal precipitation in the diapers of infants is a common finding that may appear like a reddish-brown stain in the diaper triggering concerns for possible hematuria.[7,12]

Automated or manual urine microscopy can be performed. Urine is centrifuged with the supernatant discarded. The remaining urinary sediment is resuspended and placed on a microscope slide for review. For a discolored urine specimen secondary to gross hematuria, the supernatant will turn to yellow and the urinary pellet may appear visibly red or brown. In the setting of myoglobinuria or hemoglobinuria, the supernatant will remain discolored and will remain positive for heme on the urine dipstick. RBCs would not be observed on microscopy.[13,14]

Observation of the morphology of the RBCs under the microscope can help determine if the source of the RBC is secondary to glomerular hematuria. In glomerular hematuria, the RBCs appear misshapen and dysmorphic. The RBCs can become encased in Tamms Horsfall protein which is secreted by the renal tubules and thus create RBC casts. RBC casts are always pathological.[6]

4.2 History and Physical Exam

Careful history when there is concern for microscopic hematuria or gross hematuria must be obtained. Blood that is visible only at the beginning or end of the urinary stream, or if there is presence of blood clots, increases the clinical suspicion of a non-glomerular source of the blood.[6] Symptoms of flank pain, dysuria or urinary frequency could suggest urinary tract infection or nephrolithiasis. Recurrent episodes of gross hematuria could suggest glomerular diseases such as thin basement membranes disease, Alport syndrome or IgA nephropathy. Prior or concurrent infection can also help determine the etiology. Post-streptococcus glomerulonephritis would be expected 1-2 weeks after group A streptococcal pharyngitis and 6 weeks following skin infection. Gross hematuria that occurs concurrently with illness could suggest IgA nephropathy. [15,16] Family history is also essential. In thin basement membrane disease, one of the parents may reveal that they also have a history of microscopic hematuria. History of autosomal dominant polycystic kidney disease can suggest hematuria secondary to burst cyst or due to the increased risk of nephrolithiasis. [17] Concerning family history of kidney failure with dialysis or renal transplant by the 3rd decade, hearing loss or vision loss raises suspicion for Alport syndrome.[18]

Vital signs of blood pressure and weight should be obtained as edema and hypertension can occur with glomerulonephritis whereas low blood pressure can occur following trauma and blood loss. Physical exam should include assessment of edema of the face, periorbital region, and dependent areas of the lower extremities, labia, scrotum and sacrum. Abdominal exam is needed to assess for tenderness, ascites, mass or signs of trauma. A genitourinary examination should include an assessment for costovertebral angle tenderness as well as examination of the urethral meatus in males or the vaginal introitus in females for any findings of irritation or visible blood. Skin and joint examination can help determine if there are signs of a systemic process such as in systemic lupus erythematous (SLE) or vasculitis. [2]

4.3 Labs

Lab evaluation can be tailored depending on the history and associated symptoms. Serum creatinine, complete blood count, complement component 3 (C3), complement component 4 (C4), and serum albumin can be obtained. Other testing to consider can include antistreptolysin O (ASO) titer if there was a preceding infection, ANA to assess for SLE. If there is concern for an infectious etiology, a complete blood count can also be useful. Additional evaluation for the urine sample can include urine culture, urine protein to creatinine ratio to assess for concurrent proteinuria or urine calcium to creatinine ratio to assess for hypercalciuria.

4.4 Imaging

Renal ultrasound is the first line imaging modality for the urinary tract in children. Ultrasound can quickly assess the size and shape of the kidneys, the presence of hydronephrosis, obstructing renal calculi, cysts or masses of the kidneys or bladder. Calculi in the renal pelvis and in the ureter can be missed on renal ultrasound.[19] In order to minimize radiation exposure in pediatrics, low dose and ultra-low dose CT can be effective in determining burden of renal calculi. The 99mTc-MAG3 is used to assess for radiotracer uptake and excretion when there is concern for ureteropelvic junction obstruction. Doppler evaluation with renal ultrasound can assess for vascular causes of hematuria including renal vein thrombosis and left renal vein compression in Nutcracker syndrome. Imaging in renal trauma is discussed elsewhere in **the AUA curriculum**.

5. Etiology and Management

5.1 Medical Renal Causes

5.1.1 Glomerulonephritis

1. IgA nephropathy

   IgA nephropathy is the most common cause of chronic glomerulonephritis worldwide. The clinical manifestations of IgA nephropathy are broad and range from asymptomatic microscopic hematuria to crescentic rapidly progressive glomerulonephritis. Gross hematuria around the time of pharangitis or tonsillitis can occur in 10-15% of patients and can often be the presenting symptom. Labs are notable for normal serum complement levels with either microscopic or gross hematuria. Renal biopsy is indicated if there is persistent or worsening proteinuria or progressive worsening of renal function. Management is aimed at controlling hypertension, minimizing proteinuria with renin angiotensin system blockade and lipid lowering medications. The use of corticosteroids and other immunosuppressive medications have not been well defined with most studies on their use limited by small sample sizes. Corticosteroids are used in the setting of significant proteinuria, progressively declining kidney function or evidence of proliferative lesions on kidney biopsy. [16]

2. HSP nephritis

Henoch-Schönlein purpura (HSP) is a small-vessel, leukocytoclastic vasculitis and one of the most common systemic vasculitis in childhood. Henoch-Schönlein purpura nephritis and IgA nephropathy are considered to be related diseases with HSP showing systemic symptoms including purpuric rash, abdominal pain, intussusception, arthritis or arthralgia.[20] HSP nephritis may develop up to 6 months after a child initially presents with HSP. Therefore, urinalyses need to be monitored for 6 months after initial onset in all HSP patients. HSP nephritis is mostly mild and self-limited but may lead to chronic kidney disease.[21]

3. Lupus nephritis

   SLE is a chronic, inflammatory disease that can affect any organ. Lupus nephritis occurs in 50% of patients with SLE with 10% of patients progressing to end stage renal disease.[22] The most common clinical manifestations include proteinuria and microscopic hematuria in setting of known SLE. Lupus nephritis can be diagnosed and classified based on kidney biopsy. Treatment includes corticosteroids and other immunosuppressant medications such as cyclophosphamide or mycophenolate mofetil. Lupus nephritis patients require close monitoring with both a pediatric nephrologist and a pediatric rheumatologist.

4. Post-infectious glomerulonephritis

   Post-infectious GN (PIGN) is a non-infectious, type III hypersensitivity reaction that can occur following infection.[15] It is the most common cause of acute nephritis in children.[8] Typical clinical presentation is a school aged child between the ages of 5 to 14 years with sudden development of gross hematuria, edema and hypertension. In the developed world, a quarter of acute PIGN is due to Streptococcus infection and another quarter is caused by Staphylococcus. Other less common culprit bacteria could include Pseudomonas, Pneumococcus, Enterococcus, Propionibacterium acnes, and Candida. In some cases, an infectious agent will not be found. [23] Lab evaluation will be notable for low C3 level, elevated ASO and anti-DNase B. Management is focused on control of hypertension with furosemide, low sodium diet and monitoring for acute kidney injury and electrolyte derangements. The nephritis is generally self-limited with resolution in 1-2 weeks. Microscopic hematuria can persist up to 6 months following the episode.[7]

5.1.2 Glomerular basement membrane (GBM) disorders

Alport syndrome and thin basement membrane nephropathy are genetic disorders of the glomerular basement membrane caused by mutations in type IV collagen. The earliest histologic lesion in both conditions is diffuse thinning of the GBM.[24] The course in thin basement membrane disease is generally benign (also known as benign familial hematuria), but may require initiation of RAS blockade if there is concurrent proteinuria.[24] However, Alport syndrome causes progressive nephritis with progressing thickening of the GBM, proteinuria, extrarenal manifestations of senisoneural hearing loss, vision abnormalities and progressive renal disease.[24] Alport syndrome can be x-linked, autosomal dominant or autosomal recessive in inheritance. Fifty percent of untreated males with

XLAS reach ESRD by age 25 and 90% by age 40.[24] Female carriers of XLAS have variable phenotype due to X-chromosome lyonization. Treatment of Alport syndrome is focused on reduction of proteinuria, control of hypertension and medical management of chronic kidney disease.

5.1.3 Autosomal Dominant Polycystic Kidney Disease

In ADPKD there is progressive growth of cysts that replace healthy renal parenchyma caused by gene mutations at either *PKD1* or *PKD2*. *PDK1* is more common mutation accounting for 60%–78% of cases whereas 15%–26% are affected by *PKD2* which is associated with a less severe phenotype of cyst burden.[25] ESRD occurs around a mean age of 74 in *PKD2* versus 54 years in *PKD1*.[26] The cysts can grow large and cause symptoms of flank pain and gross hematuria. Cyst hemorrhage is the most frequent cause of hematuria in ADPKD. However, there is also an increased risk of cyst infection, urinary tract infection, nephrolithiasis and renal malignancy.[17,27] Medical management in children with ADPKD includes early detection and treatment of proteinuria and hypertension, low sodium diet and high water intake.[28] For additional information regarding PKD, please refer to the AUA Core Curriculum **Congenital Anomalies of the Kidney and Urinary Tract**.

5.1.4 Ureteropelvic junction obstruction

Hematuria, whether microscopic or gross, is now rarely the first sign of congenital ureteropelvic junction obstruction as widespread use of prenatal ultrasounds have led to early detection of fetal hydronephrosis.[29] However, hematuria may be found on workup of patients who present with renal colic or Dietl's crisis, characterized by severe abdominal pain, nausea, and vomiting. These symptoms along with hematuria may suggest intermittent ureteropelvic junction obstruction due to a crossing renal vessel. For these patients, renal ultrasound is typically normal or only demonstrates mild hydronephrosis when the patient is asymptomatic but reveals severe hydronephrosis during an acute exacerbation. In a study of patients who underwent pyeloplasty for intermittent ureteropelvic junction obstruction, 11% were noted to have gross hematuria.[30] As such, intermittent ureteropelvic junction obstruction should be considered in patients who present with severe abdominal pain, nausea, vomiting, and evidence of hematuria. For management of patients with ureteropelvic junction obstruction, please refer to the **Hydronephrosis AUA core curriculum**.

5.1.5 Nutcracker syndrome

Nutcracker syndrome is a less frequent cause of gross hematuria which occurs due to left renal vein entrapment between the abdominal aorta and superior mesenteric artery. Patients have symptoms of left flank pain with radiation to the groin due to congestion of the left gonadal vein. Management ranges from supportive measures such as change in physical activity to options such as left renal vein stenting and autotransplantation in severe cases.[31,32,33]

5.2 Infectious/Inflammatory causes

5.2.1 Pyelonephritis and Bacterial cystitis

Bacterial urinary tract infection is a common cause of pediatric hematuria, accounting for 14% of

cases of pediatric gross hematuria evaluated in the emergency room.[5] Common symptoms of cystitis include hematuria, dysuria, urgency, frequency, or abdominal pain. If the infection progresses upstream to the kidneys and results in pyelonephritis, fevers and flank pain may be present. Constipation, dysfunctional voiding, uncircumcised status in boys, and underlying urologic anomalies such as vesicoureteral reflux increase risk of urinary tract infection in children. [1]

Method of urinary collection is especially important in diagnosing pediatric urinary tract infections. In toilet trained children, a clean catch specimen is preferred. In infants or pre-toilet trained children, catheterized specimens or suprapubic aspirates have lower risk of contamination than a bagged specimen. Diagnosis and management of common bacterial cystitis are discussed in detail in the **AUA core curriculum on pediatric urinary tract infections**.

5.2.2 Viral cystitis

Viral cystitis is less common than bacterial cystitis, but symptoms are similar and include hematuria, lower abdominal pain, urgency, frequency, and dysuria.[34] While self-limited in immunocompetent children, viral cystitis may result in hemorrhagic cystitis in immunocompromised individuals, such as those who have undergone bone marrow or solid organ transplants. In an evaluation of 100 children who underwent bone marrow transplant, hemorrhagic cystitis occurred in a quarter of the patients. In 95% of these cases, viral cystitis was the primary etiology. Common viruses include BK virus, adenovirus, and JC virus. [35] In high-risk children or children with lower urinary tract symptoms without a bacterial cause, urine viral culture or urine viral PCR analysis should be considered to evaluate for viral cystitis.

Management of viral cystitis is dependent on symptom severity and immune status. In immunocompetent children, supportive care is typically sufficient. In the immunocompromised population, management depends on the severity of hematuria. BK virus is the most common culprit in children undergoing hematopoietic stem cell transplantation. Those with acute graft versus host disease, concurrent CMV infection, and cord blood transplantation are at increased risk for hemorrhagic cystitis. [36] Initial management includes pain control, hyper-hydration, transfusions for thrombocytopenia and anemia, and ensuring adequate bladder emptying. In cases of severe hemorrhagic cystitis with clot retention, surgical intervention and continuous bladder irrigation may be necessary. Antivirals such as Cidofovir and quinolone antibiotics have been used to decrease BK viral load. [34,36] As viral hemorrhagic cystitis may cause significant morbidity, early urologic involvement may be prudent. [37]

5.2.3 Eosinophilic cystitis

Eosinophilic cystitis is a rare inflammatory condition with fewer than 100 cases reported in the pediatric literature.[38] Patients present with irritative voiding symptoms including urinary frequency, dysuria, hematuria, suprapubic pain, and retention.[39] Ultrasound evaluation may reveal a bladder mass raising suspicion for malignancy and prompting surgical biopsy. Histologic evaluations of these biopsies show heavy eosinophilic infiltrate. Urine cultures can be positive in these cases.

Management involves use of antibiotics, antihistamines, and steroids. While most children respond to these therapies with resolution of the bladder mass, severe cases may require transurethral resection or urinary diversion.

5.2.4 Urethritis

Terminal gross hematuria with possible dysuria with blood spotting in the underwear is a typical presentation of urethritis or benign childhood urethrorrhagia in male children and adolescents. While potential etiologies include infection, trauma, or voiding dysfunction, as many as 20-50% of cases have no defined etiology. Bowel and bladder dysfunction should be assessed and treated. Evaluation for other causes of terminal hematuria including urethral calculus, tumor, urethral polyps, stricture, or arteriovenous malformations should be performed prior to establishing a diagnosis of idiopathic urethritis or benign childhood urethrorrhagia. Initial workup includes renal and bladder ultrasound as well as urinary flow studies. Cystoscopy may be considered in cases of persistent symptoms after management of bladder and bowel dysfunction. [40]

5.3 Nephrolithiasis and hypercalciuria

Kidney stone passage can present with gross hematuria and symptoms of renal colic including flank pain and vomiting from partial or complete obstruction of the urinary tract. Similar to adults, calcium-based stones of calcium oxalate and calcium phosphate are the most common stone types.[41] Assessment of the metabolic risk factors of nephrolithiasis with 24-hour urine testing can help determine causes including idiopathic hypercalciuria, need for further evaluation for rare, genetic causes of kidney stones, initiation of therapies for stone risk reduction and further optimization of dietary modification. Management of nephrolithiasis is discussed elsewhere in the **AUA curriculum**.

5.4 Trauma

Blunt or penetrating trauma to the kidney, ureter, bladder, or urethra can result in microscopic or gross hematuria. This section will provide a brief overview of the role of hematuria in pediatric trauma workup. For further details regarding staging, workup, and management of pediatric urologic trauma, please refer to the **AUA core curriculum on Pediatric Trauma**.

5.4.1 Renal Trauma

Children are more prone to renal injury in the setting of blunt trauma as they have less perirenal fat than adults. Pediatric rib cages are also more pliable and offer less protection.[42] Of 2213 pediatric renal injuries identified from the National Trauma Database, blunt trauma accounted for 90% of cases while penetrating trauma accounted for 10% of cases. [43] Indications to evaluate children for renal trauma include the presence of gross hematuria, microscopic hematuria with hemodynamic instability, and mechanism of injury and exam concerning for renal trauma.[44,45,46] It is important to note that the presence and degree of hematuria do not necessarily correlate with degree of renal injury, and the patient's clinical status and associated injuries should be considered in the decision to pursue additional workup.

5.4.2 Ureteral Trauma

Hematuria is present in 74% of cases of ureteral injuries with gross hematuria accounting for 46% of cases. The absence of hematuria, however, does not indicate the absence of ureteral injury.[47] In patients whose mechanism of injury and clinical picture are suggestive of ureteral injury, ureteral evaluation with CT urogram, intravenous pyelogram, or retrograde pyelogram is necessary for more definitive evaluation. While ureteral stenting may be sufficient in most cases, ureteropelvic junction injuries may present with medial urinomas and require prompt surgical intervention and reconstruction if the patient is otherwise stable.[48]

5.4.3 Bladder Trauma

Bladder injuries in children secondary to blunt trauma are often associated with pelvic fractures. A distended pediatric bladder rises above the pelvic inlet and is thus more prone to injury than adult bladders. Suspicion of bladder injury should be high in a child with pelvic fractures, gross hematuria, and inability to void despite a full bladder. Diagnosis can be made via a cystogram. Isolated extraperitoneal bladder ruptures are contained by the peritoneum and can be managed conservatively with catheter drainage. Intraperitoneal bladder injuries should be managed surgically. Other indications for surgical intervention include concomitant vaginal or rectal injury or bladder neck involvement.[48]

5.4.4 Urethral Trauma

Urethral injuries typically present with blood at the meatus with inability to void and can be associated with blunt trauma with pelvic fractures or perineal straddle injuries. This injury is more common in boys due to the relatively short length of the female urethra. In cases of complete urethral disruption, urinary diversion with suprapubic catheters or primary re-anastomosis at time of injury are options but depend on the stability of the patient. Series reporting urethroplasty outcomes in boys have noted high success rates.[49,50] While female urethral injuries are rare, they can confer high morbidity with risk for incontinence. Management is not standardized but case series have reported surgical options with fair success.[51,52,53,54]

5.5 Malignancy

Albeit rare, pediatric malignancy of the urinary tract may present with hematuria. Wilms tumor is the most common renal tumor in childhood, presenting at a median age of 3.5 years.[55] Renal cell carcinoma is rare in children but typically presents with more advanced disease.[56] Urothelial carcinoma occurs in 0.1-0.4% of those younger than 20 years of age and may present with painless gross hematuria.[57] Rhabdomyosarcoma of the lower urinary tract may also present with gross hematuria and irritative bladder symptoms.[58] Due to the low index of suspicion for these conditions in children, diagnoses in these cases can be delayed. In cases of persistent hematuria without other causes, malignancy should be considered. For detailed discussions on pediatric Wilm's tumor and Rhabdomyosarcoma, please refer to the **AUA Curriculum on Pediatric Genitourinary Oncology**.

6. CKD Management Renal Transplantation

6.1 CKD

Chronic kidney disease has multiple implications to a pediatric patient's health, growth and development. CKD is defined as a gradual loss of kidney function over time or to the state of irreversible kidney damage. CKD is further described by the Improving Global Outcomes (KDIGO) guidelines as abnormalities of kidney structure or function, present for more than 3 months, with implications to health. [59]

6.1.1 Determining estimated glomerular filtration rate

The stage of CKD is determined by the estimated glomerular filtration rate (eGFR). In pediatrics, the most used eGFR equation is based on the serum creatinine via the Bedside Schwartz equation. In this equation, eGFR is equal to length in centimeters (L) divided by sCr which is multiplied by a coefficient of 0.413 or (L/sCr) x 0.413. This equation does allow for simplicity in calculating eGFR but does have limitations as the study group age range was mainly children aged 8 to 15 years and follow-up studies have shown that there is an under-estimation of eGFR in young adults.

The use of serum creatinine also has limitations in estimating GFR. Creatinine is freely filtered at the glomerulus, approximately 10-40% of creatinine is secreted by the tubules. Tubular secretion increases with progression of CKD which can result in an unpredictable impact on eGFR. [60] Creatinine is a by-product of the muscle catabolism of creatine and therefore it's measurement is influenced by muscle mass. Caution is recommended for the use of sCr based eGFR equations in elite athletes. [61] Muscle mass also increases with a child's age which makes growth a confounding factor to estimating GFR. [62] Conversely, in chronic disease settings where muscle mass is significantly affected such as in Duchenne's muscular dystrophy and spina bifida, the sCr can over-estimate eGFR making it unreliable to detect acute kidney injury or to note a progressive loss of renal function over time. [63]

Cystatin C is an endogenous biomarker used to estimate GFR and has been incorporated into eGFR equations. It is a strong predictor of renal function. [64] The Chronic Kidney Disease in Children (CKiD) Study internally validated new eGFR equations (known as CKiD U25 equations). The equations are based on age, sex, height, sCr and cystatin C with improvement in estimation of eGFR in adolescences and young adults with CKD. [65] Pediatric eGFR equations do not use race as a variable, and race has been removed from the adult eGFR equations.

6.1.2 Etiologies of CKD in childhood

The most common etiologies of CKD in children differ from those in adults which impacts disease progression and management. In adults, the most common causes of CKD include diabetic nephropathy, hypertension and autosomal dominant polycystic kidney disease. In children, the most common cause of CKD is CAKUT at approximately 60%. CAKUT is followed by glomerular causes (10-20%) while the remaining 20-30% includes genetic causes, interstitial nephritis and

undetermined etiology. [66]

6.1.3 Management of CKD

CKD management is multifaceted and requires close, long-term follow-up with a pediatric nephrologist. In the case of CAKUT with voiding dysfunction, bladder abnormalities and/or vesicoureteral reflux, coordinated care between pediatric nephrology and urology is essential. The main tenets of CKD management include general health maintenance, treatment of the underlying disease process when possible, avoidance of CKD progression and acute kidney injury, and management of CKD complications. In the setting of progressive or late-stage CKD, the patient and family must be prepared for dialysis initiation and/or kidney transplantation.

6.1.3a General health maintenance

CKD impacts multiple facets of a child's life. Children with CKD are at increased risk for growth failure and malnutrition as CKD progresses. There are guidelines set forth by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative for monitoring of growth and nutritional recommendations for the stage of CKD. [67] Children with CKD are at risk for adverse neurodevelopmental outcomes, quality of life, and anxiety and depressive symptoms which should be assessed to refer to additional resources.

Routine monitoring for children with CKD should include laboratory monitoring, blood pressure checks, urine dipstick and urine protein to creatinine ratio to assess for proteinuria. Children with CKD are at increased risk for cardiovascular disease and dyslipidemia.[68] Therefore, healthy lifestyle modifications with low sodium diet and regular physical activity should be discussed when appropriate. Routine vaccination is an important tenet of pediatrics and children with CKD are at increased risk for vaccine-preventable infections.[69] Pediatric CKD patients qualify for the 23-valent polysaccharide pneumococcal vaccine (PPSV23) and immunity to hepatitis B is essential given the increased risk of infection from hemodialysis.

There is an increased risk of CKD progression during puberty and closer laboratory monitoring is required. The exact etiology of CKD progression during puberty has not yet been fully elucidated but increase in BMI and sex hormones are thought to be contributing factors.[70]

6.1.3b Avoidance of CKD progression

The treatment of the underlying cause of CKD is variable and dependent on etiology. Immunosuppressant therapies are tailored in the cases of glomerulonephritis and nephrotic syndrome. In CAKUT, lower urinary abnormalities can be identified in about 50% of affected patients and include vesicoureteral reflux, UPJ and lower urinary tract obstructions. [71] Management of VUR and any underlying voiding dysfunction should be aimed to reduce the risk of UTI and reflux nephropathy. Bladder dysfunction should be treated as well.

Hypertension and proteinuria increase risk of CKD progression in pediatric patients. The CKiD study group showed that hypertension was present in 54% of participants at the time of enrolment and 48% of the children had high blood pressure despite the use of antihypertensive medications.[72] Children

with CKD are also at risk for masked hypertension which is normal in-office blood pressure but hypertensive blood pressure outside of the office. The use of 24-hour ambulatory blood pressure monitor which is worn by the patient for 24 hours at home is recommended to detect hypertension regardless of in-office blood pressure reading. [73] The ESCAPE trial noted that intensified blood-pressure control corresponded with a significant benefit in preserving renal function in children. [74] The use of ACE inhibitor and angiotensin receptor blocker are recommended as first line for pediatric CKD patients unless there is an absolute contraindication. These medications also confer the benefit of proteinuria reduction. Early ACE inhibitor use for the anti-proteinuric effect has been demonstrated to preserve renal function in pediatric CKD.[75]

6.1.3c Management of CKD complications

As CKD progresses, there is increased risk for electrolyte abnormalities, metabolic acidosis, anemia and renal osteodystrophy. Monitoring for complications require serial laboratory evaluation. Hyperkalemia is a serious electrolyte abnormality that can be encountered. Prevention of severe hyperkalemia requires dietary changes with low potassium diet and medications such as sodium polystyrene can be used to increase fecal extraction of potassium. Metabolic acidosis can further impair growth and requires treatment with alkali therapy such as sodium bicarbonate or sodium citrate. Anemia in CKD is attributed to the decreased renal production of erythropoietin and impaired iron regulation. Inflammation and impaired renal clearance increase plasma hepcidin which inhibits duodenal iron absorption and causes sequestration of iron in macrophages. [76] Treatment with recombinant human erythropoietin and iron supplementation is often required as CKD progresses with the additional goal to avoid blood transfusions which can increase human leukocyte antigen sensitization for future renal transplant. Finally, there is decreased renal production of activated vitamin D (calcitriol) and decreased renal excretion of phosphate as CKD progresses which results in secondary hyperparathyroidism and renal osteodystrophy. Treatment includes low phosphorus diet, oral phosphorus binders and supplementation with both cholecalciferol and calcitriol.

6.1.3d Pediatric dialysis and kidney transplant

The goal of CKD management is to medically control CKD complications until indications for either dialysis or renal transplant occur. Indications for dialysis in pediatric patients include uremia, refractory metabolic acidosis, hyperkalemia or hyperphosphatemia, refractory volume overload and declining nutritional status. [77] There is no absolute eGFR at which dialysis should be initiated. In the adult IDEAL study of 828 patients, there was no benefits conferred for initiation of dialysis at a higher eGFR of 10 to 14cc/min versus those with eGFR of 5 to 7cc/min.[78] This has so far been mirrored in pediatrics in a study of children aged 1 to 18 showing no benefit in survival with dialysis initiation at a median eGFR of 12.8 ml/min per 1.73 m^2 compared to those with an eGFR, 6.5 ml/min per 1.73 m^2.[79] Dialysis modalities include hemodialysis and peritoneal dialysis with peritoneal dialysis being the most used modality in pediatric patients.[80] Whenever able, early referral for pre-emptive kidney transplantation should be completed.

6.2 Renal Transplantation

This section will provide an overview of pediatric renal transplantation including pre-operative workup and post-operative urologic complications. For a more in-depth overview of renal transplantation, please refer to the AUA Core Curriculum on **Renal Transplant**.

Children with CKD stages 4-5 with eGFR approaching 20 cc/min/1.73 and no chance of improvement are referred for renal transplantation. Some indications for transplant are similar to that of adults such as uremia, hypervolemia, and hyperkalemia. Additional pediatric considerations for renal transplantation include failure to thrive, delayed psychomotor development, and renal osteodystrophy resulting in metabolic bone disease. [81,82] Renal transplant has been shown to improve physical growth, cognitive and social development, quality of life, and survival of pediatric patients. As such, current kidney allocation algorithms in the United States favor pediatric recipients.

6.2.1 Pre-transplant Medical Evaluation

Pre-transplant evaluation involves a multidisciplinary team with transplant surgeons, pediatric nephrologists, transplant nurse coordinators, social workers, nutritionists, pharmacists, psychologists, anesthesiologist, and pediatric urologists. Should the patient have underlying cardiac disease or hyper coagulopathy that may increase risk of graft thrombosis, pediatric cardiologists and hematologists may also be involved.[83] Renal failure in children may be due to a variety of causes, and children with certain medical renal diseases, including focal segmental glomerulosclerosis, IgA nephropathy, and hyperoxalosis, have high risk of disease recurrence which may result in early graft failure. Understanding the underlying etiology is important to ensure control of the primary disease and graft longevity. For patients with congenital obstructive uropathy, ensuring that a suitable and safe urinary reservoir is present is critical. However, as transplantation is increasingly performed in younger children for whom reconstruction may not yet be feasible, urologic reconstruction may occur post-transplant. [81] For patients requiring transplant secondary to malignancy, a period of disease-free state is necessary prior to transplant clearance.

Nutrition optimization and vaccination status are important in pediatric renal transplant. Children with CKD often have poor oral intake which may be multifactorial and secondary to underlying disease as well as behavioral feeding problems.[84] Patients may need to be supported with tube feeds as they await transplant as transplant can be more challenging in children <10 kg. As children will be immunosuppressed following transplant, they must also be as up to date as possible on their vaccines.[82] It is noteworthy that transplant is a major life event for the recipients and their families. Adequate psychosocial support is necessary prior to and following renal transplant.[85]

As in adult transplant, a detailed history and physical is necessary as a part of pre-transplant evaluation with optimization of underlying disease processes. Laboratory evaluations include complete metabolic panel, complete blood count, urinalysis, coagulation studies, infectious screening studies, tuberculosis screening, ABO blood type, and HLA testing. Abdominal ultrasounds are used to evaluate intraabdominal organs and patency of vital vasculature including the aorta, inferior vena cava, and iliac vessels. When ultrasound imaging is inadequate, MR angiogram may be useful. Some surgeons may also elect for additional cross-sectional imaging to better characterize vascular

anatomy, and decision for this must be balanced with radiation exposure to the young child. For patients with underlying urologic conditions, additional workup with voiding cystourethrogram or urodynamics studies may be necessary. [86]

6.2.2 Pre-transplant Urologic Evaluation

The goals of pre-transplant urologic evaluation are to ensure that the recipient has a safe urinary reservoir that can be effectively emptied, determine whether native nephrectomy is necessary, and mitigate foreseeable urologic complications. This is especially important for children with known anomalies of the urinary tract. For children who are toilet trained with no known urologic anomalies, urologic workup need not be extensive. Bladder/voiding diaries, uroflowmetry, and pre-and post-void residuals may be sufficient to provide insight into the patient's bladder volume, ability to effectively empty, and risk of urinary obstruction. A renal ultrasound can also help determine whether hydronephrosis is present and additional workup is necessary. [87] For children with known bladder anomalies including neurogenic bladder or posterior urethral valves, further workup with urodynamics should be pursued prior to transplant. Video urodynamic studies allow the urologist to assess the patient's bladder capacity, bladder compliance, presence of reflux, and sphincter activity with emptying. The study helps identify high-risk bladders that require further optimization. [83,87] The role of a voiding cystourethrogram is less defined but may be useful to ensure adequate valve ablation in cases of posterior urethra valves prior to transplant clearance. Patients with lower urinary tract disease, if properly managed, have equal rates of graft survival as those with end stage renal disease secondary to other causes. [88]

1. Lower urinary tract optimization and reconstruction
   Having a low-compliance urinary reservoir of adequate capacity to ensure social continence is important for a child pending transplant. In cases of neurogenic bladder secondary to spina bifida, this may be achieved with conservative measures such as clean intermittent catheterization and anticholinergic medications. Should these measures prove ineffective, bladder augmentation may be necessary to improve compliance and increase bladder capacity. Bladder outlet procedures may be considered concomitantly in patients with incontinence. For a more in-depth discussion of the various reconstruction techniques, please refer to the AUA Core Curriculum on **Spina Bifida and Neurogenic Bladder**. For patients with bladder agenesis or urethral sphincters incapable of facilitating continence, continent urinary diversion with a catheterizeable channel or incontinent diversion in the form of an ileal conduit may be offered. In young infants for whom reconstruction is not yet feasible, a temporizing vesicostomy or ureterostomy may be considered, though risks of stenosis exist. [87,89]
   Besides safe bladder storage, effective bladder emptying is also important. Bladder emptying may be facilitated with timed voiding or catheterization. Use of alpha blockers may be effective in some patients with high post-void residuals. Many patients with abnormal bladders will require catheterization to ensure adequate emptying. This may be performed per the urethra or via a catheterizeable channel such as an appendicovesicostomy or a Monti. For

non-ambulatory patients or those who are sensate, such as patients with posterior urethral valves, use of a catheterizeable channel is often preferable.[83]

Bladder cycling has been considered in patients with anuria and small bladders. However, if the bladder is normal without concern for neurogenic bladder, studies have shown that these bladders will regain function following transplant without need for pre-transplant cycling.[90]

2. Native nephrectomies

Approximately 10-20% of pediatric patients undergo native nephrectomies prior to transplant. Advantage of retaining the native kidneys include volume management which limits need for strict fluid restrictions, production of native erythropoietin, calcium homeostasis, and urine production for bladder cycling. Indications for native unilateral or bilateral nephrectomies include significant proteinuria, non-functional kidneys with significant renal stone burden, hypertension refractory to medical management, recurrent pyelonephritis with or without associated high grade vesicoureteral reflux, symptomatic polycystic kidneys, malignancy, or persistent antiglomerular basement membrane antibody levels. In cases of polycystic kidneys, native nephrectomies may be necessary to provide room to accommodate the transplant kidney.

As most children are on peritoneal dialysis, approach to and timing of native nephrectomies must be considered judiciously. Laparoscopic retroperitoneal approaches preclude the need to convert to hemodialysis as the peritoneum is not violated. Native nephrectomies may be performed at time of transplant or 6 weeks prior based on surgeon preference. [83]

6.2.3 Technical Concerns in Pediatric Renal Transplant

The renal allograft is typically placed in the retroperitoneal space in the iliac fossa via a Gibson incision which provides easy access to the iliac vessels and bladder. For pediatric patients, however, patient size and thereby vessel size can affect choice in allograft placement.[81] It may be challenging to fit an adult sized kidney in the retroperitoneal space of a child or infant and significant size mismatch may result in graft loss due to increased compartment pressures. For many small children weighing less than 10-20 kg, transplant surgeons may elect to place the allograft intraperitoneally with anastomosis of the artery and vein to the aorta and inferior vena cava, respectively. This is typically accomplished through a midline incision. Some centers, however, have elected to approach this retroperitoneally in select patients with placement of the allograft in the iliac fossa but anastomosing the vasculature to the aorta and vena cava as the iliac vessels of young children are of small caliber and at high risk for thrombosis. A retroperitoneal approach reduces risk of ileus and intraabdominal adhesions as well as risk of the kidney twisting or kinking. Ultimately, location of allograft placement depends on patient size and surgeon preference. [91,92]

The transplant ureter is reimplanted via an extravesical approach. While refluxing anastomoses can be performed in adults, non-refluxing anastomoses are typically preferable in children, especially those with baseline bladder pathology. Ureteral complications following transplant are higher in children with bladder pathology, and collaboration between transplant surgery and urology at time of reimplant may help mitigate risk of these complications, especially that of transplant vesicoureteral

reflux.[93] Ureteral stenting is recommended to help decrease risk of urinary leak and obstruction. The stent is removed cystoscopically under a short anesthetic a few weeks after transplant.

6.2.4 Post-transplant Complications

Risks of transplant include surgical complications, rejection, infection, recurrence of primary disease, and side effects of immunosuppression. Risk of readmission within 6 months of transplant is as high as 40%. [83] Acute graft thrombosis may require emergent exploration. Lymphoceles may occur and may be managed conservatively if asymptomatic or with drain placement if necessary.

Urologic complications after transplant include urine leaks, ureteral stricture, vesicoureteral reflux with associated transplant pyelonephritis, and nephrolithiasis. Urine leak and urinomas present in the immediate post-surgical period. Should a ureteral stent be in place, foley catheter placement for urinary decompression can help the leak seal. Long term urologic complications include ureteral stricture disease which can be secondary to infection or ischemia at the ureterovesical junction. Endoscopic management may be pursued initially but if recurrence occurs, surgical revision may be necessary. The most common long-term complication is vesicoureteral reflux with associated recurrent transplant pyelonephritis. In these cases, ensuring adequate bladder drainage and revision of the ureteral anastomosis with a longer submucosal tunnel may be necessary. [83,94] Incidence of transplant nephrolithiasis is increasing with an estimated prevalence of 2-5%. Stone disease may present atypically in this population as the kidney is denervated. As a result, the child may not experience the typical symptoms of pain and nausea. This can lead to delayed diagnosis and risk of graft loss. Depending on stone size and location, approach to management varies. Relieving the obstruction is vital in initial management. Ureteroscopic approaches may be feasible via antegrade or retrograde approaches. Renal stones may be managed with shockwave, percutaneous nephrolithotomy, or with active surveillance. For details regarding stone management, please refer to the AUA Core Curriculum on **Urolithiasis Surgical Treatment**.[95,96]

Given the patients' immunocompromised states, they are subject to infections after transplantation. Viral infections with adenovirus and BK virus may cause hemorrhagic cystitis. Please refer to the section above on viral cystitis for management of this. BK virus may also cause nephropathy and ureteral strictures, leading to graft loss in 11% of cases. [83]

Presentations

Pediatric Hematuria and Medical Renal Disease Presentation 1

References

1 Bignall, O. N. R., 2nd, & Dixon, B. P. (2018). Management of Hematuria in Children. Curr Treat Options Pediatr, 4(3), 333-349. doi:10.1007/s40746-018-0134-z

2 Vehaskari, V. M., Rapola, J., Koskimies, O., Savilahti, E., Vilska, J., & Hallman, N. (1979). Microscopic hematuria in school children: epidemiology and clinicopathologic evaluation. J Pediatr, 95(5 Pt 1), 676-684. doi:10.1016/s0022-3476(79)80710-6

3 Suthar, K. S., Vanikar, A. V., Nigam, L. A., Patel, R. D., Kanodia, K. V., Thakkar, U. G., . . . Patel, M. H. (2018). Urinary Screening for Early Detection of Kidney Diseases. Indian J Pediatr, 85(8), 607-612. doi:10.1007/s12098-017-2494-y

4 Ingelfinger, J. R., Davis, A. E., & Grupe, W. E. (1977). Frequency and etiology of gross hematuria in a general pediatric setting. Pediatrics, 59(4), 557-561. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/850596

5 ☆ Greenfield, S. P., Williot, P., & Kaplan, D. (2007). Gross hematuria in children: a ten-year review. Urology, 69(1), 166-169. doi:10.1016/j.urology.2006.10.018

6 Avner, E. D., Harmon, W. E., Niaudet, P., Yoshikawa, N., Emma, F., Goldstein, S. L., & SpringerLink (Online service). Pediatric Nephrology(7th ed., pp. 506 illus., 240 illus. in color. eReference). Retrieved from https://yale.idm.oclc.org/login?URL=http://dx.doi.org/10.1007/978-3-662-43596-0

7 Viteri, B., & Reid-Adam, J. (2018). Hematuria and Proteinuria in Children. Pediatr Rev, 39(12), 573-587. doi:10.1542/pir.2017-0300

8 Cohen, R. A., & Brown, R. S. (2003). Clinical practice. Microscopic hematuria. N Engl J Med, 348(23), 2330-2338. doi:10.1056/NEJMcp012694

9 Dodge, W. F., West, E. F., Smith, E. H., & Bruce, H., 3rd. (1976). Proteinuria and hematuria in schoolchildren: epidemiology and early natural history. J Pediatr, 88(2), 327-347. doi:10.1016/s0022-3476(76)81012-8

10 ☆ Barocas, D. A., Boorjian, S. A., Alvarez, R. D., Downs, T. M., Gross, C. P., Hamilton, B. D., . . . Souter, L. H. (2020). Microhematuria: AUA/SUFU Guideline. J Urol, 204(4), 778-786. doi:10.1097/JU.0000000000001297

11 Sauder, H. M., & Rawla, P. (2021). Beeturia. In StatPearls. Treasure Island (FL).

12 Jeng, J. Y., & Franz, W. B., 3rd. (2014). Orange stains in a healthy neonate's diaper. Clin Pediatr (Phila), 53(9), 908-910. doi:10.1177/0009922814536777

13 Marc L Miller, M. Clinical manifestations and diagnosis of rhabdomyolysis. In M. Ira N Targoff, Jeremy M Shefner, MD, PhD (Ed.), UpToDate. UpToDate, Waltham, MA (accessed August 30, 2021).

14 Trivedi, D. J., Kulkarni, S. P., & Mudaraddi, R. (2017). Primary Myoglobinuria: Differentiate Myoglobinuria from Hemoglobinuria. Indian J Clin Biochem, 32(3), 367-369. doi:10.1007/s12291-016-0607-4

15 Rawla, P., Padala, S. A., & Ludhwani, D. (2021). Poststreptococcal Glomerulonephritis. In StatPearls. Treasure Island (FL).

16 Rodrigues, J. C., Haas, M., & Reich, H. N. (2017). IgA Nephropathy. Clin J Am Soc Nephrol, 12(4), 677-686. doi:10.2215/CJN.07420716

17 Bhasin, B., Alzubaidi, M., & Velez, J. C. Q. (2018). Evaluation and Management of Gross Hematuria in Autosomal Dominant Polycystic Kidney Disease: A Point of Care Guide for Practicing Internists. Am J Med Sci, 356(2), 177-180. doi:10.1016/j.amjms.2017.11.013

18 Watson, S., Padala, S. A., & Bush, J. S. (2021). Alport Syndrome. In StatPearls. Treasure Island (FL).

19 Brisbane, W., Bailey, M. R., & Sorensen, M. D. (2016). An overview of kidney stone imaging techniques. Nat Rev Urol, 13(11), 654-662. doi:10.1038/nrurol.2016.154

20 Davin, J. C., Ten Berge, I. J., & Weening, J. J. (2001). What is the difference between IgA nephropathy and Henoch-Schonlein purpura nephritis? Kidney Int, 59(3), 823-834. doi:10.1046/j.1523-1755.2001.059003823.x

21 Pohl, M. (2015). Henoch-Schonlein purpura nephritis. Pediatr Nephrol, 30(2), 245-252. doi:10.1007/s00467-014-2815-6

22 Almaani, S., Meara, A., & Rovin, B. H. (2017). Update on Lupus Nephritis. Clin J Am Soc Nephrol, 12(5), 825-835. doi:10.2215/CJN.05780616

23 Kambham, N. (2012). Postinfectious glomerulonephritis. Adv Anat Pathol, 19(5), 338-347. doi:10.1097/PAP.0b013e31826663d9

24 Kashtan, C. E. (2004). Familial hematuria due to type IV collagen mutations: Alport syndrome and thin basement membrane nephropathy. Curr Opin Pediatr, 16(2), 177-181. doi:10.1097/00008480-200404000-00011

25 Lanktree, M. B., Guiard, E., Akbari, P., Pourafkari, M., Iliuta, I. A., Ahmed, S., . . . Pei, Y. P. C. (2021). Patients with Protein-Truncating PKD1 Mutations and Mild ADPKD. Clin J Am Soc Nephrol, 16(3), 374-383. doi:10.2215/CJN.11100720

26 Hateboer, N., v Dijk, M. A., Bogdanova, N., Coto, E., Saggar-Malik, A. K., San Millan, J. L., . . . Ravine, D. (1999). Comparison of phenotypes of polycystic kidney disease types 1 and 2. European PKD1-PKD2 Study Group. Lancet, 353(9147), 103-107. doi:10.1016/s0140-6736(98)03495-3

27 Yu, T. M., Chuang, Y. W., Yu, M. C., Chen, C. H., Yang, C. K., Huang, S. T., . . . Kao, C. H. (2016). Risk of cancer in patients with polycystic kidney disease: a propensity-score matched analysis of a nationwide, population-based cohort study. Lancet Oncol, 17(10), 1419-1425. doi:10.1016/S1470-2045(16)30250-9

28 Gimpel, C., Bergmann, C., Bockenhauer, D., Breysem, L., Cadnapaphornchai, M. A., Cetiner, M., . . . Schaefer, F. (2019). International consensus statement on the diagnosis and management of autosomal dominant polycystic kidney disease in children and young people. Nat Rev Nephrol, 15(11), 713-726. doi:10.1038/s41581-019-0155-2

29 Ficara, A., Syngelaki, A., Hammami, A., Akolekar, R., & Nicolaides, K. H. (2020). Value of routine ultrasound examination at 35-37 weeks' gestation in diagnosis of fetal abnormalities. Ultrasound Obstet Gynecol, 55(1), 75-80. doi:10.1002/uog.20857

30 Rigas, A., Karamanolakis, D., Bogdanos, I., Stefanidis, A., & Androulakakis, P. A. (2003). Pelvi-ureteric junction obstruction by crossing renal vessels: clinical and imaging features. BJU Int, 92(1), 101-103. doi:10.1046/j.1464-410x.2003.04265.x

31 Ahmed, K., Sampath, R., & Khan, M. S. (2006). Current trends in the diagnosis and management of renal nutcracker syndrome: a review. Eur J Vasc Endovasc Surg, 31(4), 410-416. doi:10.1016/j.ejvs.2005.05.045

32 Kurklinsky, A. K., & Rooke, T. W. (2010). Nutcracker phenomenon and nutcracker syndrome. Mayo Clin Proc, 85(6), 552-559. doi:10.4065/mcp.2009.0586

33 Miro, I., Serrano, A., Perez-Ardavin, J., March, J. A., Polo, A., Conca, M. A., . . . Dominguez, C. (2020). Eighteen years of experience with pediatric nutcracker syndrome: the importance of the conservative approach. J Pediatr Urol, 16(2), 218 e211-218 e216. doi:10.1016/j.jpurol.2019.12.003

34 Paduch, D. A. (2007). Viral lower urinary tract infections. Curr Urol Rep, 8(4), 324-335. doi:10.1007/s11934-007-0080-y

35 Gorczynska, E., Turkiewicz, D., Rybka, K., Toporski, J., Kalwak, K., Dyla, A., . . . Chybicka, A. (2005). Incidence, clinical outcome, and management of virus-induced hemorrhagic cystitis in children and adolescents after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant, 11(10), 797-804. doi:10.1016/j.bbmt.2005.06.007

36 Salamonowicz-Bodzioch, M., Fraczkiewicz, J., Czyzewski, K., Zajac-Spychala, O., Gorczynska, E., Panasiuk, A., . . . Styczynski, J. (2021). Prospective analysis of BKV hemorrhagic cystitis in children and adolescents undergoing hematopoietic cell transplantation. Ann Hematol, 100(5), 1283-1293. doi:10.1007/s00277-021-04454-7

37 Hannick, J. H., & Koyle, M. A. (2019). Canadian Urological Association Best Practice Report: Pediatric hemorrhagic cystitis. Can Urol Assoc J, 13(11), E325-E334. doi:10.5489/cuaj.5993

38 ☆ Zhou, A. G., Amin, A., Yates, J. K., Diamond, D. A., Tyminski, M. M., Badway, J. A., . . . Owens, C. L. (2017). Mass Forming Eosinophilic Cystitis in Pediatric Patients. Urology, 101, 139-141. doi:10.1016/j.urology.2016.11.002

39 van den Ouden, D. (2000). Diagnosis and management of eosinophilic cystitis: a pooled analysis of 135 cases. Eur Urol, 37(4), 386-394. doi:10.1159/000020183

40 Degheili, J. A., & Dickson, A. P. (2020). Childhood and adolescent idiopathic urethritis: what does the current literature say? J Pediatr Urol, 16(3), 276-283. doi:10.1016/j.jpurol.2020.02.001

41 Bowen, D. K., & Tasian, G. E. (2018). Pediatric Stone Disease. Urol Clin North Am, 45(4), 539-550. doi:10.1016/j.ucl.2018.06.002

42 Dalton, B. G. A., Dehmer, J. J., & Shah, S. R. (2015). Blunt Renal Trauma. J Pediatr Intensive Care, 4(1), 16-20. doi:10.1055/s-0035-1554984

43 ☆ Grimsby, G. M., Voelzke, B., Hotaling, J., Sorensen, M. D., Koyle, M., & Jacobs, M. A. (2014). Demographics of pediatric renal trauma. J Urol, 192(5), 1498-1502. doi:10.1016/j.juro.2014.05.103

44 ☆ Morey, A. F., Broghammer, J. A., Hollowell, C. M. P., McKibben, M. J., & Souter, L. (2021). Urotrauma Guideline 2020: AUA Guideline. J Urol, 205(1), 30-35. doi:10.1097/JU.0000000000001408

45 Brown, S. L., Haas, C., Dinchman, K. H., Elder, J. S., & Spirnak, J. P. (2001). Radiologic evaluation of pediatric blunt renal trauma in patients with microscopic hematuria. World J Surg, 25(12), 1557-1560. doi:10.1007/s00268-001-0149-6

46 Morey, A. F., Bruce, J. E., & McAninch, J. W. (1996). Efficacy of radiographic imaging in pediatric blunt renal trauma. J Urol, 156(6), 2014-2018. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/8911380

47 Elliott, S. P., & McAninch, J. W. (2006). Ureteral injuries: external and iatrogenic. Urol Clin North Am, 33(1), 55-66, vi. doi:10.1016/j.ucl.2005.11.005

48 Singer, G., Arneitz, C., Tschauner, S., Castellani, C., & Till, H. (2021). Trauma in pediatric urology. Semin Pediatr Surg, 30(4), 151085. doi:10.1016/j.sempedsurg.2021.151085

49 Waterloos, M., Verla, W., Spinoit, A. F., Oosterlinck, W., Van Laecke, E., Hoebeke, P., & Lumen, N. (2019). Urethroplasty for urethral injuries and trauma-related strictures in children and adolescents: a single-institution experience. J Pediatr Urol, 15(2), 176 e171-176 e177. doi:10.1016/j.jpurol.2018.11.014

50 Baradaran, N., McAninch, J. W., Copp, H. L., Quanstrom, K., Breyer, B. N., & Hampson, L. A. (2019). Long-term follow-up of urethral reconstruction for blunt urethral injury at a young age: urinary and sexual quality of life outcomes. J Pediatr Urol, 15(3), 224 e221-224 e226. doi:10.1016/j.jpurol.2019.02.013

51 Dorairajan, L. N., Gupta, H., & Kumar, S. (2004). Pelvic fracture-associated urethral injuries in girls: experience with primary repair. BJU Int, 94(1), 134-136. doi:10.1111/j.1464-4096.2004.04874.x

52 Hemal, A. K., Dorairajan, L. N., & Gupta, N. P. (2000). Posttraumatic complete and partial loss of urethra with pelvic fracture in girls: an appraisal of management. J Urol, 163(1), 282-287. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10604377

53 Hosseini, J., Tavakkoli Tabassi, K., & Razi, A. (2009). Delayed retropubic urethroplasty of completely transected urethra associated with pelvic fracture in girls. Urol J, 6(4), 272-275. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20027556

54 Lv, R., Jin, C., Shu, H., Wang, L., & Sa, Y. (2020). Bladder neck reconstruction in girls' pelvic fracture bladder neck avulsion and urethral rupture. BMC Urol, 20(1), 179. doi:10.1186/s12894-020-00741-z

55 Kieran, K., & Ehrlich, P. F. (2016). Current surgical standards of care in Wilms tumor. Urol Oncol, 34(1), 13-23. doi:10.1016/j.urolonc.2015.05.029

56 ☆ Akhavan, A., Richards, M., Shnorhavorian, M., Goldin, A., Gow, K., & Merguerian, P. A. (2015). Renal cell carcinoma in children, adolescents and young adults: a National Cancer Database study. J Urol, 193(4), 1336-1341. doi:10.1016/j.juro.2014.10.108

57 Abbasion, R., Jafarpisheh, A., Dehghanian, P., & Mottaghi, M. (2020). A Case of Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP) in Childhood. Case Rep Urol, 2020, 8865741. doi:10.1155/2020/8865741

58 Lopes, R. I., Mello, M. F., & Lorenzo, A. J. (2020). Recent advances in pediatric bladder malignancies. F1000Res, 9. doi:10.12688/f1000research.19396.1

59 Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International Supplements 2013 Vol. 3 Issue 1 Pages 150

60 A. S. Bargnoux, N. Simon, V. Garrigue, A. M. Dupuy, S. Badiou, G. Mourad, et al., Accuracy of GFR predictive equations using ID-MS traceable creatinine: compensated Jaffe and enzymatic. Clin Lab 2011 Vol. 57 Issue 5-6 Pages 357-6. Accession Number: 21755826

61 R. Milic, G. Banfi, M. Del Fabbro and M. Dopsaj. Serum creatinine concentrations in male and female elite swimmers. Correlation with body mass index and evaluation of estimated glomerular filtration rate. Clin Chem Lab Med 2011 Vol. 49 Issue 2 Pages 285-9. Accession Number: 21118048 DOI: 10.1515/CCLM.2011.057

62 Mian AN, Schwartz GJ. Measurement and Estimation of Glomerular Filtration Rate in Children. Adv Chronic Kidney Dis. 2017 Nov;24(6):348-356. doi: 10.1053/j.ackd.2017.09.011. PMID: 29229165; PMCID: PMC6198668.

63 Braat E, Hoste L, De Waele L, Gheysens O, Vermeersch P, Goffin K, Pottel H, Goemans N, Levtchenko E. Renal function in children and adolescents with Duchenne muscular dystrophy. Neuromuscul Disord. 2015 May;25(5):381-7. doi: 10.1016/j.nmd.2015.01.005. Epub 2015 Jan 19. PMID: 25683700.

64 Filler G, Huang SH, Yasin A. The usefulness of cystatin C and related formulae in pediatrics. Clin Chem Lab Med. 2012 Dec;50(12):2081-91. doi: 10.1515/cclm-2012-0257. PMID: 23093265.

65 Pierce CB, Muñoz A, Ng DK, Warady BA, Furth SL, Schwartz GJ. Age- and sex-dependent clinical equations to estimate glomerular filtration rates in children and young adults with chronic kidney disease. Kidney Int. 2021 Apr;99(4):948-956. doi: 10.1016/j.kint.2020.10.047. Epub 2020 Dec 8. PMID: 33301749; PMCID: PMC9083470.

66 D. K. W. Bradley A Warady. Chronic kidney disease in children: Definition, epidemiology, etiology, and course. In, edited by Tej K Mattoo. UpToDate, Waltham, MA (Accessed on August 15, 2022)

67 Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero JJ, Chan W, Fouque D, Friedman AN, Ghaddar S, Goldstein-Fuchs DJ, Kaysen GA, Kopple JD, Teta D, Yee-Moon Wang A, Cuppari L. KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update. Am J Kidney Dis. 2020 Sep;76(3 Suppl 1):S1-S107. doi: 10.1053/j.ajkd.2020.05.006. Erratum in: Am J Kidney Dis. 2021 Feb;77(2):308. PMID: 32829751.

68 Kaspar CD, Bholah R, Bunchman TE. A Review of Pediatric Chronic Kidney Disease. Blood Purif. 2016;41(1-3):211-7. doi: 10.1159/000441737. Epub 2016 Jan 15. PMID: 26766175.

69 Neu AM. Immunizations in children with chronic kidney disease. Pediatr Nephrol. 2012 Aug;27(8):1257-63. doi: 10.1007/s00467-011-2042-3. Epub 2011 Nov 3. PMID: 22048175; PMCID: PMC3382633.

70 Kim HS, Ng DK, Matheson MB, Atkinson MA, Akhtar Y, Warady BA, Furth SL, Ruebner RL. Association of Puberty With Changes in GFR in Children With CKD. Am J Kidney Dis. 2022 Jan;79(1):131-134. doi: 10.1053/j.ajkd.2021.05.011. Epub 2021 Jun 24. PMID: 34171395; PMCID: PMC8958516.

71 Stonebrook E, Hoff M, Spencer JD. Congenital Anomalies of the Kidney and Urinary Tract: A Clinical Review. Curr Treat Options Pediatr. 2019;5(3):223-235. doi: 10.1007/s40746-019-00166-3. Epub 2019 Jun 11. PMID: 32864297; PMCID: PMC7451090.

72 Flynn JT, Mitsnefes M, Pierce C, Cole SR, Parekh RS, Furth SL, Warady BA; Chronic Kidney Disease in Children Study Group. Blood pressure in children with chronic kidney disease: a report from the Chronic Kidney Disease in Children study. Hypertension. 2008 Oct;52(4):631-7. doi: 10.1161/HYPERTENSIONAHA.108.110635. Epub 2008 Aug 25. PMID: 18725579; PMCID: PMC3136362.

73 Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, de Ferranti SD, Dionne JM, Falkner B, Flinn SK, Gidding SS, Goodwin C, Leu MG, Powers ME, Rea C, Samuels J, Simasek M, Thaker VV, Urbina EM; SUBCOMMITTEE ON SCREENING AND MANAGEMENT OF HIGH BLOOD PRESSURE IN CHILDREN. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics. 2017 Sep;140(3):e20171904. doi: 10.1542/peds.2017-1904. Epub 2017 Aug 21. Erratum in: Pediatrics. 2017 Nov 30;: Erratum in: Pediatrics. 2018 Sep;142(3): PMID: 28827377.

74 ESCAPE Trial Group; Wühl E, Trivelli A, Picca S, Litwin M, Peco-Antic A, Zurowska A, Testa S, Jankauskiene A, Emre S, Caldas-Afonso A, Anarat A, Niaudet P, Mir S, Bakkaloglu A, Enke B, Montini G, Wingen AM, Sallay P, Jeck N, Berg U, Caliskan S, Wygoda S, Hohbach-Hohenfellner K, Dusek J, Urasinski T, Arbeiter K, Neuhaus T, Gellermann J, Drozdz D, Fischbach M, Möller K, Wigger M, Peruzzi L, Mehls O, Schaefer F. Strict blood-pressure control and progression of renal failure in children. N Engl J Med. 2009 Oct 22;361(17):1639-50. doi: 10.1056/NEJMoa0902066. PMID: 19846849.

75 van den Belt SM, Heerspink HJL, Gracchi V, de Zeeuw D, Wühl E, Schaefer F; ESCAPE Trial Group. Early Proteinuria Lowering by Angiotensin-Converting Enzyme Inhibition Predicts Renal Survival in Children with CKD. J Am Soc Nephrol. 2018 Aug;29(8):2225-2233. doi: 10.1681/ASN.2018010036. Epub 2018 Jun 21. PMID: 29930161; PMCID: PMC6065076.

76 Ganz T, Nemeth E. Iron Balance and the Role of Hepcidin in Chronic Kidney Disease. Semin Nephrol. 2016;36(2):87-93. doi:10.1016/j.semnephrol.2016.02.001

77 M. Anthony Bleyer, MS. Indications for initiation of dialysis in chronic kidney disease. In, edited by M. Steve J Schwab, Jeffrey S Berns, MD. UpToDate, Waltham, MA (Accessed August 15, 2022)

78 Cooper BA, Branley P, Bulfone L, et al. The Initiating Dialysis Early and Late (IDEAL) study: study rationale and design. Perit Dial Int. 2004;24(2):176-181.

79 Winnicki E, Johansen KL, Cabana MD, et al. Higher eGFR at Dialysis Initiation Is Not Associated with a Survival Benefit in Children. J Am Soc Nephrol. 2019;30(8):1505-1513. doi:10.1681/ASN.2018111130

80 Warady BA, Schaefer F, Bagga A, et al. Prescribing peritoneal dialysis for high-quality care in children. Perit Dial Int. 2020;40(3):333-340. doi:10.1177/0896860819893805

81 Roach, J. P., Bock, M. E., & Goebel, J. (2017). Pediatric kidney transplantation. Seminars in pediatric surgery, 26(4), 233–240. https://doi.org/10.1053/j.sempedsurg.2017.07.006

82 Hebert, S. A., Swinford, R. D., Hall, D. R., Au, J. K., & Bynon, J. S. (2017). Special Considerations in Pediatric Kidney Transplantation. Advances in chronic kidney disease, 24(6), 398–404. https://doi.org/10.1053/j.ackd.2017.09.009

83 Palmer, B., & Kropp, B. (2018). Urologic Evaluation and Management of Pediatric Kidney Transplant Patients. The Urologic clinics of North America, 45(4), 561–569. https://doi.org/10.1016/j.ucl.2018.06.004

84 Anthony, S. J., Annunziato, R. A., Fairey, E., Kelly, V. L., So, S., & Wray, J. (2014). Waiting for transplant: physical, psychosocial, and nutritional status considerations for pediatric candidates and implications for care. Pediatric transplantation, 18(5), 423–434. https://doi.org/10.1111/petr.12305

85 Shellmer, D., Brosig, C., & Wray, J. (2014). The start of the transplant journey: referral for pediatric solid organ transplantation. Pediatric transplantation, 18(2), 125–133. https://doi.org/10.1111/petr.12215

86 Damasio, M. B., Ording Muller, L. S., Piaggio, G., Marks, S. D., & Riccabona, M. (2017). Imaging in pediatric renal transplantation. Pediatric transplantation, 21(3), 10.1111/petr.12885. https://doi.org/10.1111/petr.12885

87 Evans-Barns, H., Mushtaq, I., Michell, I., Kausman, J., Webb, N., & Taghavi, K. (2022). Paediatric kidney transplantation: Towards a framework for pretransplant urological evaluation. Pediatric transplantation, e14299. Advance online publication. https://doi.org/10.1111/petr.14299

88 ☆ Jahromi, M. S., Velasquez, M. C., Blachman-Braun, R., Gosalbez, R., Castellan, M., Labbie, A., Ciancio, G., Chandar, J., & Alam, A. (2020). Pediatric Kidney Transplantation Outcomes in Children with Primary Urological Abnormalities Versus Nonurological Abnormalities: Long-Term Results. The Journal of urology, 203(2), 406–412. https://doi.org/10.1097/JU.0000000000000528

89 Stein R, Zahn K, Huck N. Current Indications and Techniques for the Use of Bowel Segments in Pediatric Urinary Tract Reconstruction. Front Pediatr. 2019 Jun 12;7:236. doi: 10.3389/fped.2019.00236. PMID: 31245339; PMCID: PMC6581750.

90 Wu, Y. J., Veale, J. L., & Gritsch, H. A. (2008). Urological complications of renal transplant in patients with prolonged anuria. Transplantation, 86(9), 1196–1198. https://doi.org/10.1097/TP.0b013e318187bd37

91 Etesami, K., Hogen, R., & Lestz, R. (2021). Pediatric kidney transplantation, a technical update. Current opinion in organ transplantation, 26(4), 356–359. https://doi.org/10.1097/MOT.0000000000000898

92 Etesami, K., Lestz, R., & Hogen, R. (2020). Pediatric kidney transplantation in the United States. Current opinion in organ transplantation, 25(4), 343–347. https://doi.org/10.1097/MOT.0000000000000783

93 ☆ Morrison, C. D., Shannon, R., Rosoklija, I., Nettey, O. S., Superina, R., Cheng, E. Y., & Gong, E. M. (2019). Ureteral Complications of Pediatric Renal Transplantation. The Journal of urology, 201(4), 810–814. https://doi.org/10.1016/j.juro.2018.08.082

94 Alam, S., & Sheldon, C. (2008). Urological issues in pediatric renal transplantation. Current opinion in urology, 18(4), 413–418. https://doi.org/10.1097/MOU.0b013e328302ede7

95 Ma, S., Taher, A., Zhu, B., & Durkan, A. M. (2020). Post-renal transplant urolithiasis in children: an increasingly diagnosed complication: a retrospective cohort study. Archives of disease in childhood, 105(1), 69–73. https://doi.org/10.1136/archdischild-2019-317203

96 Emiliani, E., Subiela, J. D., Regis, F., Angerri, O., & Palou, J. (2018). Over 30-yr Experience on the Management of Graft Stones After Renal Transplantation. European urology focus, 4(2), 169–174. https://doi.org/10.1016/j.euf.2018.06.007