

PEDIATRIC NEPHROLOGY: HIGHLIGHTS FOR THE GENERAL PRACTITIONER

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Pediatric Nephrology: Highlights for the General Practitioner

Pediatric Nephrology: Highlights for the General Practitioner

Guest Editors: Mouin Seikaly, Sabeen Habib, Amin J. Barakat,
Jyothsna Gattineni, Raymond Quigley, and Dev Desi



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Editorial

Pediatric Nephrology: Highlights for the General Practitioner

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The current special issue is written as a practical guide for the health care providers managing children with kidney diseases. In this issue, the guest editors have emphasized clinical skills, diagnostic procedures, treatment, long-term followup as well as underlying pathophysiology with the general practitioner in mind. Since the call for manuscripts by the journal, we received 27 excellent submissions. We selected 9 papers to include in this special issue. We chose only those that we deemed appropriate to the scope that we outlined for this special issue.

The guest editors who are leading experts in the field of pediatric nephrology did a terrific job writing their designated sections. A. J. Barakat's excellent perspective on presentation of children with renal disease is a practical guideline for referral to the specialist. S. Habib reviews controversies in the management of urinary tract infection. R. Quigley provides a comprehensive yet concrete review about children with chronic kidney disease. J. Gattineni discusses thoroughly the management of children presenting with proteinuria and hematuria. In my section on hypertension, I tried to provide a comprehensive practical guide that can be used in the management of a child with elevated blood pressure.

The nine papers that we selected for publication were outstanding. Y. R. Bhat et al. discuss the antenatal Bartter syndrome in a succinct fashion. D. Morin et al. provide a detailed review on nephrogenic SIADH, and kidney disease and type 2 diabetes mellitus are very well discussed by A. B. Dart et al. The approach to a patient with acute glomerulonephritis is also well covered by T. R. Welch.

On behalf of the contributing authors, we hope that the readership will use our contribution to help them manage children with kidney disease.

Acknowledgment

Mouin Seikaly, MD, is the Lead Guest Editor for this issue.

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Review Article

Highlights for the Management of a Child with Hypertension

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Over the past several decades, childhood hypertension has undergone a considerable conceptual change, as hypertension is a predictor of future development of cardiovascular disease in adults. Childhood hypertension has distinctive features that distinguish it from hypertension in adults. Pediatric hypertension is often secondary. It is widely believed that therapeutic intervention at an early age favorably modifies the long-term outcome of hypertension. Despite its significance as a cause for morbidity, childhood hypertension is underdiagnosed and less studied with many basic issues remaining contentious.

1. Overview

It is widely accepted among pediatric health care providers that the risks of developing coronary artery disease (CAD) start in early life. Hypertension (HT) is a major modifiable risk factor in the development of CAD. Identification of HT at an early age may allow early intervention to prevent future end organ damage. Despite ample literature studying HT in animals and humans, our understanding of pediatric HT is still modest at best. Many questions regarding the long-term effects of antihypertensive therapy on growth and development remain unanswered. Until recently, normal blood pressure (BP) values have been scarce especially in the very young due to the relative difficulty of measuring BP in this age group [1]. The wide availability of oscillometric BP devices have made BP measurement more feasible especially in young children. Furthermore, several normative BP values are now available. Thus, the measurement of BP in infants and children at the office and hospital should now be easier and more reproducible.

1.1. Pathophysiology. The pathogenesis of systemic arterial hypertension is multifactorial. Hypertension is a hemodynamic manifestation of total vascular resistance (TVR), and cardiac output (CO) [2] TVR is a function blood vessel wall elasticity, myocardial contractility, and cardiac afterload. Cardiac output is the product of cardiac stroke volume (SV)

and rate (HR). Both myocardial contractility and HR are regulated by sympathetic nerve activity. SV depends on myocardial contractility and preload. During the early stages of hypertension, CO is often increased. As hypertension progresses, TVR increases and CO normalizes. In a certain group of patients, hypertension develops primarily due to a decrease in the cross-sectional area of peripheral arterioles leading to an increase in resistance to flow. TVR is controlled by the interaction of vasodilators such as prostaglandins and bradykinins and vasoconstrictors such as platelet-derived growth factor (PDGF), thromboxane, and angiotensin II. Another group of patients develop hypertension due to volume over load and sodium retention. This group includes patients with renal disease, African American children, and certain genetic forms of hypertension.

1.2. Definition. A prevalent operational designation of hypertension is BP elevation above the 95% percentile for either age, height, or tanner stage and gender, using standardized measurement techniques on at least three separate occasions [1]. Prehypertension is defined as BP elevation between 90 and 95%. The normative sporadic BP values were updated in 2004 by The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents from the United States of America (US) [3]. This task force has incorporated previous data from US children and added new data from the 1999 to 2000 National Health and

Nutrition Examination Survey (NHANES). Blood pressure values are based on gender, age, and height, and 50th, 90th, 95th, and 99th percentiles are provided. While this data is accepted and used worldwide normative data from other regions of the world is available. Some regional normative data significantly vary from US data, stressing the ethnic variability in BP. European data are 3–6 mmHg higher than US data [4]. In 2003 the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP (JNC7) further stratified hypertension in adults into prehypertension and 2 stages [5]. In 2004, The Fourth Report recommended childhood classification [6]. Stage 1 HTN is defined as being from the 95th to the 99th percentile plus 5 mmHg. Stage 2 HTN is 5 mmHg or more above the 100th percentile and represents a level of BP that requires prompt evaluation.

1.3. Prevalence. The prevalence of hypertension varies among certain subgroups. The definition hypertension implies that around 5% of the general population is hypertensive. Actual BP measurement among 10 19-year-old school children, shows that the prevalence of hypertension is close to the predicted rate at 4.5%. This makes hypertension one of the most common preventable disorders facing pediatricians. Risk factors associated with hypertension include gender (males), ethnicity (African Americans and Hispanics), and increased BMI can increase the prevalence of hypertension among certain high risk groups. The prevalence of hypertension among obese children is much higher estimated to be as high as 11% [7]. Children with hypertension have 2.5 times the risk of becoming adults with hypertension. From these studies one may conclude that prevention of risk factors for the development of hypertension, such as obesity, may delay or prevent adult hypertension.

2. Clinical Presentation

Symptoms of hypertension in childhood can vary depending upon the severity and duration of hypertension. Mild to moderate hypertension is often asymptomatic, while severe hypertension can present with encephalopathy and acute loss of vision (posterior reversible encephalopathy syndrome, PRES).

2.1. Past Medical History. Determining the duration of hypertension at presentation is of clinical consequence as it helps narrow down the list of differential diagnosis. Establishing the duration of hypertension starts by obtaining a comprehensive history. Such interview should focus on symptoms associated with hypertension such as poor sense of well-being, poor sleep, restlessness, poor growth, nose bleed, all with the potential to suggest chronic hypertension. Frequent headaches, blurred vision, chest pain, symptoms of congestive heart failure, and encephalopathy seizure all could point to an acute onset of hypertension.

As most clinical conditions in pediatrics, etiology of hypertension is age specific, Table 1, as we and others have previously shown [8]. As such, history taking should be focused depending on the age of the child. Neonatal period,

prematurity low birth weight, prolonged oxygen therapy, and history of umbilical artery catheters may provide clues as to the etiology of hypertension. Also history of urinary tract infection in infancy may predispose to renal scars and may suggest renal anomalies. In older children glomerulonephritis and in adolescent females, history of urinary tract infections or dysfunctional voiding may suggest a cause for hypertension. Symptoms of systemic illness also could include pallor, flushing, joint pains, rash, edema, gross hematuria, excessive weight gain or loss, or decreased height growth which may suggest vasculitis or glomerulonephritis. Triad of flushing, palpitations and, hypertension are often suggestive of pheochromocytoma, a rare cause of hypertension in this age group. In adolescents history is often nonspecific as the prevalence of idiopathic hypertension often increases. History should question the occurrence of headaches, sleep disturbance, visual symptoms, nosebleeds, palpitations, and episodic rapid pulse. Sleep disorder, snoring fatigue could be associated with obstructive sleep apnea, a condition overlooked in older children.

2.2. Dietary and Medication History. Detailed dietary history is important when deciphering the etiology of hypertension. Excessive intake of sodium or caffeinated beverages, and energy drinks is associated with hypertension. A medication history should include specific questions about over-the-counter drugs like pseudoephedrine or herbal preparations like ephedra, St. John's Wort, or licorice as well as prescription drugs. Adolescents should be questioned in private to obtain a history of substance abuse or the possibility of pregnancy. History of current or recent prescription medications such as decongestants, corticosteroids, and nonsteroidal anti-inflammatory could all suggest a cause for hypertension.

2.3. Physical Exam. BP is a variable that depends on many factors including anxiety. Office hypertension also known as white coat effect is not an uncommon cause of referral for evaluation to the specialist. Studies have shown that repeated BP measurement can lower the incidence of office hypertension. A complete physical exam should focus on signs associated with the disease process that caused hypertension and signs of end organ damage associated with hypertension.

The prevalence of secondary hypertension is high in children. An infant with hypertension abdominal mass could suggest congenital kidney disease, and pulmonary findings could suggest bronchopulmonary dysplasia. In older children, presence of edema or rash could suggest glomerulonephritis or vasculitis. Four extremities BP check is an essential part of a physical exam of a child with hypertension to evaluate for coarctation of the aorta. Café-au-lait spots could suggest neurofibromatosis often associated with hypertension either due to pheochromocytoma or renal artery stenosis. Signs of CV disease as a complication of hypertension include gallop, tachycardia, rales, decreased breath sounds, and so forth. In severe hypertension, lethargy, loss of vision (PRES), and signs of stroke are all signs of hypertension. Signs of excessive steroids such as Cushing syndrome, for example, truncal obesity, buffalo hump, round moon faces,

TABLE 1: Causes of hypertension in children by age group (percentage).

Diagnosis	Age group					Total 0–18 yrs
	0–2 m	2 m–1 yr	2–6 yrs	7–11 yrs	12–18 yrs	
Renal disease	83	56	83	70	56	67
Primary hypertension	0	11	14	30	35	23
Others	17	33	4	0	9	10

Adapted from [7].

TABLE 2: Therapeutic objectives for treating hypertension in children.

- Achieve a diastolic blood pressure <85th percentile for children of same sex, chronological age, and body mass.
- Control hypertension with nonpharmacological means when possible.
- Use the smallest number of antihypertensive drugs and the lowest dose of each drug necessary for consistent blood pressure control and minimal drug side effects.
- Design treatment programs that are consistent with maximum likelihood of patients compliance.
- Achieve long-term prevention of end-organ damage and promote normal growth and development.

and hirsutism. Height and weight to calculate BMI is an essential part of the physical exam when evaluating a child with hypertension. A high BMI points to obesity as a possible cause for hypertension.

3. Management

3.1. Work-Up. Basic laboratory tests including basic chemistries, CBC, urinalysis, and renal sonogram are what the practitioner should request in children who have stage 1 hypertension; please refer to Table 3 for details. If the child is symptomatic or show signs of end organ damage or symptoms of secondary causes of hypertension the GP should promptly refer the child to the specialist. End organ damage are often rare in children but can include concentric hypertrophy of left ventricular, proteinuria, microalbuminuria, and retinopathy. The younger was the age at presentation with hypertension, the higher are the chances that we find its secondary cause [5]. Table 4 lists some of the biochemical and imaging tests often recommended to evaluate a child with hypertension.

3.2. Treatment. Therapeutic objectives for treating hypertension in children are listed in Table 2. Pharmacological therapy when employed should aim to control elevated blood pressure with the lowest dose and minimal number of drugs, thus minimizing potential toxicity, expense and simplifying the therapeutic regimen. The level to which elevated blood pressure is to be lowered in children and adults remains an arbitrary clinical decision. In adults, the relationship between

diastolic blood pressure and the risk of cardiovascular mortality appears to be J-shaped, that is, the risk of developing cardiovascular mortality declines with lowering diastolic blood pressure up to a nadir beyond which further drop in blood pressure will increase morbidity. It is often desired to drop diastolic blood pressure to levels between 80 and 90th percentiles for age.

Current treatment recommendations are currently based on epidemiological data rather than outcome measures. There are two accepted modalities to treat hypertension in pediatrics, namely, nonpharmacological and drug therapies. The type of therapy used often depends on the age of onset, duration, and the severity of HT. It is generally accepted that borderline hypertension (90–95th percentile for age) with no evidence of end-organ damage can be treated with non-pharmacological remedies. However, Stages 1 hypertension additional drug therapy is often required. Stage 2 hypertension the other hand (above 99th percentile) often requires admission to hospital for comprehensive management.

3.2.1. Nonpharmacological Antihypertensive Therapy. The safest therapeutic intervention to manage mild HT is the use of nonpharmacological remedies. Evidence for the efficacy of this type of intervention in children is not yet established. Nonpharmacological intervention has traditionally been focused on the reduction in dietary sodium intake along with high potassium (if there is no clinical contraindication) and on weight loss when the patient is obese. Obesity in children and young adults can predispose to higher BP. While there are no strong evidence in children about the effect of avoidance of tobacco, alcohol, and stress on BP control, these are desirable practices should be promoted through pediatric counseling.

3.2.2. Drug Therapy. It should be instituted whenever HT is severe or when nonpharmacological intervention alone fails to control the BP in mild to moderate HT. Major questions with regard to the long-term effects of antihypertensive drug treatment on growth and cognitive function in children remain unresolved. In addition, the absence of adequate information regarding drug interaction, volume of distribution, protein binding, metabolic degradation, and renal and hepatic excretion introduces additional concerns when treating HT in children. As such most antihypertensive drugs, however, carry a disclaimer relating to their use in children. A large number of antihypertensive agents with various sites and mechanisms of action are commercially available. Each

TABLE 3: Drug options for initial therapy for hypertension in children.

Class of drugs	Patients' characteristics
Diuretics	Volume-overload, low plasma renin activity, black race, oral contraceptive therapy, and congestive heart failure.
Angiotensin converting inhibitors/angiotensin receptor blockers	High plasma renin activity, unilateral renovascular hypertension, renal insufficiency, glomerular proteinuria, congestive heart failure, diabetes mellitus, gout, and hyperlipidemia.
Calcium channel blockers	Emergency hypertension, black race, diabetes mellitus, chronic obstructive lung disease, bronchopulmonary dysplasia, gout, hyperlipidemia, and peripheral vascular disease.
Beta-adrenergic antagonists	Contracted intravascular volume, high plasma renin activity, attention deficit disorder, hyperdynamic circulation, anxiety, migraine, steroid intake, hyperthyroidism, and neuroadrenergic tumors.

TABLE 4: Suggested work-up for stages 1 and 2 hypertension.

Test	To evaluate for
(A) Complete blood count; blood urea nitrogen, electrolytes, calcium phosphorous, and albumin	(A) Renal function
(B) Plasma Renin	(B) Renovascular HT
(C) Complements 3 and 4; ANA, antinuclear antibody; anti-DNA and antidiouble-stranded desoxyribonucleic acid antibody	(C) Glomerulonephritis
(D) Antineutrophil cytoplasmic antibody (ANCA); anti-GBM and antiglomerular basement membrane antibody	(D) Vasculitis
(E) Thyroxine, T4; thyroid stimulating hormone, TSH; adrenocorticotropic hormone, ACTH; OH, hydroxy; deoxycorticosterone, DOC; parathyroid hormone, PTH	(E) Hormonal
(F) Serum and urinary catecholamine and metanephhrines	(F) Neurogenic tumors
(A) Renal ultrasound	(A) Renal malformation, medical renal disease, and renal scars
(B) Mercaptoacetyl triglycine and MAG 3 scan with or without furosemide. With or without Captopril	(B) Obstructive uropathy, renovascular HT, and differential renal function
(C) Dimercaptosuccinic acid, DMSA	(C) Vesicoureteral reflux and reflux nephropathy; differential renal function
(D) Voiding cystourethrogram, VCUG; digital subtraction angiography, DSA	(D) Vesicoureteral reflux and structural bladder abnormalities
(E) Magnetic resonance angiography, MRA; digital subtraction angiography, DSA; computed tomographic angiography, CTA; magnetic resonance angiography, MRA	(E) Renovascular
(F) MIBG, metaiodobenzylguanidine	(F) Pheochromocytoma
(A) Echocardiogram, CXR ECG	(A) Cardiovascular morbidity
(B) Urinalysis	(B) Proteinuria
(C) Microalbuminuria	(C) Glomerular hyperfiltration
(D) Ambulatory BP monitoring	(D) Absence of diurnal rhythm and white coat effect

drug has undergone extensive evaluation in adult volunteers in pre- and postmarketing clinical trials.

3.2.3. Individualized Therapeutic Regimen. The availability of newer drugs allows us to make a rational choice of antihypertensive therapy. The first step in the treatment of hypertension involves a small dose of a single drug, usually a diuretic, the dose is increased until BP goals are achieved, side effects appear, or a maximum dosage is reached. If the BP is not controlled, in spite of adequate compliance,

a second and even a third drug is then added. Recently, a different approach to antihypertensive treatment has become increasingly popular where therapy is "individualized." While vasodilators can lower high BP of almost any etiology, understanding pathophysiologic mechanisms leading to the BP elevation helps in selecting targeted therapy aimed at better control of HT. Table 3 provides guidelines for the selection of antihypertensive drugs based on our knowledge of the pathogenesis of HT in an individual child. Using these guidelines, we often initiate therapy with a calcium channel

blocker agent, an ACE-I or a beta-adrenergic antagonist. These drugs are available in once-a-day dosage and have few side effects, both features reflecting positively on adherence. If monotherapy with angiotensin converting enzyme inhibitors, beta-blockers or calcium channel blockers fail to correct BP within two weeks, a diuretic or a mild vasodilator like hydralazine or prazosin are often second line therapy. A final step is to use a potent vasodilator like minoxidil or a centrally acting agent like clonidine. Often, combination therapy from different antihypertensive classes is required to achieve control of BP. Treatment of severe HT, on the other hand, requires admission to the hospital for frequent BP monitoring. For more detailed review of medications used for treatment of hypertension, the reader is referred to [4].

4. Long-Term Followup

While treatment's potential to alter long-term outcome of hypertension in children sounds intuitive, clear evidence is lacking. Furthermore, persistence of hypertension into adulthood (tracking) is unknown. What is certain is that children with hypertension require frequent monitoring for end-organ damage from hypertension as well as the potential complication of antihypertensive therapy.

5. Summary from a General Practitioner's Perspective

Hypertension is one of the most common preventable disorders facing pediatricians. Risk factors associated with hypertension include gender, ethnicity, and BMI. Adult hypertension correlates with childhood BP. It is then rather instinctive that prevention of risk factors associated with hypertension in childhood, such as obesity, may delay or prevent adult hypertension. Furthermore, the development of cardiovascular disease and renal disease later in life is also suspected to be associated with childhood hypertension. Hence, it cannot be overemphasized that early detection of hypertension by routine measurement of BP is an essential part of any office visit.

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Review Article

Highlights for Management of a Child with a Urinary Tract Infection

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Urinary tract infections remain the most common bacterial infection in childhood. *Escherichia coli* is responsible for over 80% of Pediatric UTIs. Other common gram negative organisms include Klebsiella, Proteus, Enterobacter and occasionally Pseudomonas. Signs and symptoms vary greatly by age of the patient becoming more specific as the child grows older. Even in the absence of specific signs a UTI should be included in the differential diagnosis of high grade fever. In younger children, presence of upper respiratory infections, otitis media or gastroenteritis does not eliminate the possibility of a UTI. Culture of the urine remains the gold standard for diagnosing UTIs. All males and females with well documented UTIs should be imaged for the presence of urological anomalies associated with UTI. Depending on patient's clinical symptoms and tolerance, therapy can be oral or parenteral as they have both been found equally efficacious. Healthcare professionals should ensure that when a child or young person has been identified as having a suspected UTI, they and their parents are given information about the need for treatment, the importance of completing any course of treatment and advice about prevention and possible long-term management.

1. Overview

Urinary tract infections (UTIs) remain the most common bacterial infection in childhood [1]. The cumulative incidence of UTI in children by 6 years of age is 3%–7% in girls and 1%–2% in boys. This amounts to between 70 000 and 180 000 children in the United States developing UTI annually [1]. While most UTI is caused by bacteria, other infectious agents can cause UTI. These include viruses, fungi, and mycobacterial infections. Frequent urinary tract infections can result in chronic kidney disease and hypertension [2, 3].

2. Pathophysiology

In healthy children, urine in the collecting system and urinary bladder is sterile. The urethra on the other hand is colonized with bacteria. Urinary malformation, urine stasis, and adherence of bacteria to the uroepithelial mucosa are the main predisposing factors for the development of UTI. Congenital obstructive uropathy is often associated with UTI. The pathogenesis of UTI in detrusor sphincter dyssy-

nergia syndrome is due to infrequent bladder emptying and stasis. This latter condition sometimes also referred to as dysfunctional voiding [4]. Most bacterial urinary tract infections are ascending. Urogenital bacteria are often the most common causative agents. When stasis of urine is present, bacteria multiply and UTI can develop.

3. Epidemiology

Most of the studies evaluating UTI in children are observational, hence conclusions from such studies are limited [5].

In males, it is more common during neonatal period and early infancy and it declines afterwards [6]. Usually associated with anatomical abnormalities and outlet obstruction. About 8% of girls (3% prepubertal), and 2% of boys (1% prepubertal) experience at least one episode of UTI up to the age of 7 [7]. It occurs in 0.1–0.4% of infant girls and increase up to 1.4% during 1–5 years and 0.7–2.3% in school age. The incidence is greater in girls in this age group and is likely due to short urethra and translocation of fecal bacteria. Close to 0.2% of circumcised and 0.7% of uncircumcised infant boys are at risk, which reaches to 0.1–0.2 during 1–5 years

and 0.04–0.2 in school age [8]. UTI may lead to transient renal damage in 40% and permanent renal scarring in 5% of patients [9].

A multicenter study in 2007 revealed that the cumulative risk of UTI in children under age 6 years is 6.2% [10]. In older children with urinary symptoms with or without fever, the prevalence of UTI was 7.8% [11].

Asymptomatic bacteriuria occurs in 1% and 3% of infants and preschool age children, in about 1% of older children [12].

4. Etiology

Escherichia coli is responsible for over 80% of pediatric UTIs [5]. Other common gram negative organisms include Klebsiella, Proteus, Enterobacter, and occasionally Pseudomonas [13]. *Proteus mirabilis* is a common pathogen in males and in children with kidney stones [8]. Gram-positive pathogens include group B Streptococcus and Enterococcus in neonates and infants, and *Staphylococcus saprophyticus* in adolescent girls [14]. Fungal infections are much less common and are usually to those who are immune-compromised or diabetic, are on long-term antibiotics, or have long-term indwelling catheter [5, 15]. Often urine is contaminated by Lactobacillus species, Corynebacterium spp., coagulase-negative staphylococci, and α hemolytic streptococci [5].

5. Clinical Presentation

5.1. History and Physical Examination. Signs and symptoms vary greatly by age of the patient becoming more specific as the child grows older. Even in the absence of specific signs, a UTI should be included in the differential diagnosis of high-grade fever. Asymptomatic bacteriuria is present in about 3% of preschool age children, as mentioned in the previous section. About a third of these patients will have some symptoms of urinary tract eventually.

In young infants, symptoms are usually nonspecific and may include lethargy, decreased feeding, increased sleep, vomiting, and decreased urinary output [16, 17]. Occult UTI in neonates can be presented with late-onset jaundice especially if conjugated fraction is elevated too [18].

In younger children, presence of upper respiratory infections, otitis media, or gastroenteritis does not eliminate the possibility of a UTI [19, 20]. In one study of febrile infants, those testing negative for RSV also had a positive urine culture 10.1% of the time, whereas those that tested positive for RSV had a positive urine culture 5.4% of the time [21]. Even the presence of varicella, herpangina, croup has been found to decrease the risk of UTI by 2.6% [5, 21]. In this age group, recurrent abdominal pain could be a symptom of recurrent UTI and should be evaluated promptly.

In older children, fever is usually the presenting symptom of UTI. A fever of greater than 38°C without a source has a positive likelihood ratio of 3.6 and with temperatures greater than 39°C have a positive likelihood ratio of 4 [11]. Besides fever, children may have vomiting, loose stools, and abdominal pain [17]. This age group could present with more specific symptoms of either cystitis or pyelonephritis. These

may include dysuria, frequency, new onset incontinence flank pain, and fever. Sometimes, however, younger children may have short periods of urgency not associated with UTI.

Adolescent girls may have urethritis from an STD. Hence, for proper diagnosis, laboratory evaluation is mandatory [5].

The recurrence rate for UTI is 12% after a first time UTI [10].

5.2. Lab Investigation

5.2.1. Urine Culture. Urine in the bladder is usually sterile; thus any bacteria growing in should be considered an infection. Pyles reviewed the existing pediatric data in 1960 defined UTI in children [22]. This definition is still valid today. He stated that urine cultures with fewer than 10^3 colony-forming units per mL were almost always contamination, those with between 10^4 and 10^5 colony-forming units per mL were suspicious and should be repeated, and those with more than 10^5 colony-forming units per mL were indicative of infection [3].

Unfortunately, oftentimes the culture will grow a bacterium that is obviously a contaminant, either from the skin or from other parts of the genital tract. Such culture often has multiple organisms and colony count less than 10^5 . Thus, most investigators define a UTI as the presence of single organism in the urine combined with signs or symptoms of UTI in the patient [3, 23, 24].

The traditional cutoff for urine obtained by noninvasive collection methods (bag or clean catch) has been 10^5 CFU/mL [5]. For suprapubic aspiration, 10^2 CFU/mL is regarded as the cut off [5, 25]. Some people have used 50,000 CFU/mL from catheterized sample [26–28].

When there are multiple organisms, or low colony count, there is a higher chance of contamination [29].

5.2.2. Obtaining a Urine Sample. Culture of the urine remains the gold standard for diagnosing UTIs [3, 15]. The significance of bacterial growth from a urine sample depends largely on the method by which urine is obtained and the number of colonies harvested. The culture results from a bagged urine specimen have are only helpful if negative [30, 31]. Hence, a positive urine culture from a bagged specimen cannot diagnose UTI. Suprapubic specimen remains the gold standard [27]. This method is difficult to exercise beyond infancy. Transurethral catheterization is preferred in older children. Catheterization of the urethra is occasionally difficult in patients with phimosis or labial adhesions. Also, the contamination chances although small are still higher than suprapubic aspiration. Significant bacterial ($>10^5$) colony count is highly suggestive of UTI.

As children get older and become toilet trained, mid-stream clean catch sample of urine is commonly used [32, 33]. The contamination rates are within limits if obtained the urethral area is cleansed with soap and water. With improper cleaning, the incidence of contamination increases by three folds [32]. Again, the value of this method is in ruling out rather than diagnosing UTI.

5.2.3. Urine Dipstick. Urine dipstick is helpful for rapid screening till the culture result comes back. The dipstick gives information about nitrites and leukocyte esterase (LE). Nitrites are generated from the breakdown of dietary nitrate by bacteria [34] and leukocyte esterase is the breakdown product of white cells.

LE alone has a positive predictive value of about 35.8% meaning that it has a false-positive rate of about 64.7% [35]. Nitrites on the other hand, when present, are highly suggestive of UTI. Their absence does not rule out an infection as not all organisms produce nitrites (e.g., Gram-positive and *Acinetobacter* spp.). Nitrites may not be of significance in infants and small children as the conversion requires 3–4 hours and these children urinate much more frequently [36, 37].

5.2.4. Urine Microscopy. Definition of pyuria is not clear in the literature. Multiple studies and a few meta-analyses [36–38] found the cutoff of 5 WBC per HPF being used, the sensitivity being 74% and specificity being 86%.

5.2.5. Blood Tests. When the child appears sick, a CBC, CRP, blood culture, and procalcitonin should be obtained to evaluate for sepsis. The first two do not have reliability in differentiating upper from lower urinary tract infection [39]. Blood culture is usually done for sick-looking children and younger infants. About a tenth of young infants have bacteremia with UTI [40]. Bacteremia usually clears within 24 hours with appropriate antibiotics, regardless, or route [5, 13]. Procalcitonin, a proinflammatory marker, is newer and promising but further studies are needed [5, 7, 41].

In infants younger than 8 weeks, lumbar puncture is still recommended as there is lack of evidence to omit this step. There is usually CSF pleocytosis, although meningitis and UTIs are rare together [42].

5.2.6. Imaging. All males and females with well-documented UTIs should be imaged for the presence of urological anomalies associated with UTI. The extent of evaluation varies depending on the age of presentation with the first UTI and severity of the episode. The younger the child, the higher the likelihood of anatomical abnormality, hence all children younger than 2 years. of age with well-documented UTI should be evaluated with a renal ultrasound. Beyond 8 yrs of age, boys with UTIs still warrant a renal ultrasound. Girls with a first time simple UTI can likely be observed [27].

5.2.7. Renal Ultrasound. Renal ultrasound is helpful in delineating anatomic abnormalities [43]. It can also be helpful in detecting renal abscesses and stones [44]. For infants younger than 6 months with first-time UTI that responds to treatment, ultrasound should be carried out within 6 weeks of the UTI. A normal ultrasound does rule out hydronephrosis which when present can suggest either vesicoureteral reflux or obstruction of the urinary tract.

5.2.8. DMSA (Dimercaptosuccinic Acid) Renal Scan. A DMSA is a nuclear scan that is often used either to diagnose

pyelonephritis or permanent renal scars [9, 45]. During an acute UTI DMSA shows photopenic areas in the kidney. These lesions are either permanent (scars) or represent focal area of infection that eventually resolve. DMSA scan may be needed in 6 months to confirm scarring [46].

5.2.9. Voiding Cystourethrogram (VCUG). All vesicoureteric reflux is diagnosed by VCUG. VCUG does not need to be performed for every febrile UTI. It should, however, be performed if renal ultrasound shows hydronephrosis or any other sign of VUR [27].

It requires catheterization. The radiation exposure can be reduced by performing a radionucleotide cystourethrogram but this study does not help detect anatomical abnormalities and only grades the reflux into mild–moderate and severe [44]. We use contrast VCUG as the first study for male. Nuclear VCUG is used in all females with UTI and for followup of positive contrast VCUG in females.

6. Management

6.1. Acute Treatment. The goal of the acute treatment is to decrease morbidity, and to prevent long-term renal damage. Depending on patient's clinical symptoms and tolerance, therapy can be oral or parenteral as they have both been found equally efficacious. If intravenous antibiotics are used, they can usually be changed to oral in 24 to 48 hours. Parenteral administration of an antimicrobial agent also should be considered when adherence to oral regimen is uncertain [27].

The usual antibiotic choices are cephalosporins, amoxicillin plus clavulanic acid, or trimethoprim sulfamethoxazole. It is also important to be aware local pathogens and antibiotic susceptibility [27]. The total duration of therapy should be 7–14 days [47]. Recurrence rate is high with antibiotic regimen administered for shorter than 7 days [48].

Asymptomatic bacteriuria in infants and children should not be treated with antibiotics [47]. Studies have shown that it disappears over time [12].

6.2. Long-Term Management

6.2.1. Bowel and Voiding Habits. Dysfunctional voiding syndromes and constipation should be considered in young children and adolescents with UTI. Symptoms include recurrent UTI, constipation, encopresis, and day-time enuresis. Dysfunctional voiding if unrecognized and not managed properly could lead to reflux nephropathy. This later syndrome is associated with renal scars, hypertension, and chronic kidney disease. Children should be encouraged to void frequently and hydrate well. Children should have ready access to clean toilets when required and should not be expected to delay voiding [47]. We often start prophylactic antibiotics for at least 6 months or until proper voiding habits are regained. There have been no trials to support this practice.

6.2.2. Antibiotic Prophylaxis. In the recent years, the rule of vesicoureteric reflux in UTIs and the role of prophylactic

antibiotics in preventing UTIs have been controversial. There have been a few trials in younger children that found no benefit of antibiotic prophylaxis [49, 50]. Antibiotic prophylaxis may be considered in infants and children with recurrent UTI [27]. If needed, the common antimicrobials used are trimethoprim sulfamethoxazole, trimethoprim, nitrofurantoin, and first generation cephalosporins in a one nightly dose. In children less than two months of age, amoxicillin is generally used as prophylaxis [44].

6.2.3. Surgical Treatment of VUR. VUR often undergoes spontaneous resolution. The time from first UTI to resolution of VUR is 6-7 yrs. Comparison of medical and surgical treatment of VUR is hard as different studies use various outcomes. Hodson et al. [51] reported decreased febrile UTIs as the only benefit of surgical management. There was no difference in renal scars or UTIs in general [51]. Surgical treatment for vesicoureteric reflux is reserved for patients with high grade and unilateral reflux, recurrent UTIs despite antibiotic prophylaxis, and noncompliance with antibiotics persistence beyond 9 yrs of age [44]. Endoscopic management involves subureteral or intraureteral injection of bulking agent with dextranomer/hyaluronic acid is suggested as first line treatment [52].

6.3. Long Term Followup. Infants and children with uncomplicated UTIs who do not undergo imaging investigations do not require follow up by a subspecialist. Infants and children who have recurrent UTI or abnormal imaging results should be assessed by a pediatric specialist. Assessment of infants and children with renal parenchymal defects should include height, weight, blood pressure, and routine testing for proteinuria. Infants and children with a minor, unilateral renal parenchymal defect do not need long-term followup unless they have recurrent UTI or family history or lifestyle risk factors for hypertension [47].

Infants and children who have bilateral renal abnormalities, impaired kidney function, raised blood pressure, and/or proteinuria should receive monitoring and appropriate management by a pediatric nephrologist to slow the progression of chronic kidney disease.

Infants and children who are asymptomatic following an episode of UTI should not routinely have their urine retested for infection. Asymptomatic bacteriuria is not an indication for followup [47].

6.4. Parent Education. Healthcare professionals should ensure that when a child or young person has been identified as having a suspected UTI, they and their parents are given information about the need for treatment, the importance of completing any course of treatment and advice about prevention and possible long-term management [47].

Parents should be made aware of the possibility of a UTI recurring and understand the need to be vigilant and to seek prompt treatment from a healthcare professional for any suspected reinfection.

Parents should be educated about healthy voiding and stooling habits as means of preventing UTIs.

7. Summary: The Disease from a GP Perspective

Urinary tract infections are common in children. If recurrent or severe, they do have the potential to cause renal scarring. All younger infants with fever of unexplained origin should have their urine tested and older children with symptoms should also be evaluated for UTIs. The gold standard for testing for UTI is suprapubic aspiration but a urinalysis and a urine culture (catheterized/clean catch depending on age) is acceptable. Once diagnosed, prompt and appropriate antibiotic treatment can prevent long-term complications and scarring. All younger infants with UTI and older children with complicated UTI should get a renal ultrasound. This should be followed by VCUG only if there is evidence of reflux on ultrasound. A DMSA scan can help evaluate renal scarring. Prophylactic antibiotics are reserved for recurrent UTIs and do not seem to benefit patients with low-grade VUR. Preventative measures include treating constipation and voiding dysfunction.

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Review Article

Highlights for the Management of a Child with Proteinuria and Hematuria

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The identification of hematuria or proteinuria in an otherwise healthy child can cause anxiety to both the family and the pediatrician. The etiology of hematuria and proteinuria includes a long list of conditions, and detailed workup can be exhaustive, expensive and not essential in most of the patients. As will be described in this paper, most of the children with proteinuria or hematuria have a benign etiology. The primary role of the pediatrician is to identify hematuria/proteinuria, recognize the common causes of hematuria/proteinuria, and more importantly identify children with serious conditions that need referral to the nephrologist in a timely manner.

1. Proteinuria

1.1. Introduction. The prevalence of isolated proteinuria detected by routine urinalysis (urine dipstick) in school age children was shown to be approximately 10% [1]. Further testing of these children revealed no evidence of significant renal disease in the absence of both hematuria and proteinuria. Similar findings were found in a study done on healthy adolescents [2]. Even though isolated proteinuria is usually benign, increased level of persistent proteinuria can be an indicator of progressive renal disease and is associated with increased cardiovascular morbidity [3–5]. Therefore, proteinuria presents a challenge to the primary care physician in regards to distinguishing benign proteinuria and proteinuria that requires workup and referral to the nephrologist. This section will discuss the different aspects of proteinuria including pathophysiology, etiology, and diagnostic workup of patients who present with proteinuria.

1.2. Pathophysiology. The glomerular filtration barrier provides the mechanical barrier between the blood and the urinary space. This barrier is comprised of the glomerular basement membrane, slit pores between the epithelial cell foot processes and the fenestrated endothelial cells. The glomerular filtration barrier is negatively charged due to the presence of glycosaminoglycans and glycocalyx [6].

Therefore, the nature of the particles that can cross this barrier is dependent not only on the molecular size of the particle but also on the charge of the particle. The vast majority of the proteins that are filtered by the filtration barrier are reabsorbed by the proximal tubule, and the remaining are degraded and excreted as low-molecular-weight proteins. About 30% of urinary proteins consist of albumin, transferrin, macroglobulin, and degraded filtered proteins. The remaining protein (70%) is the Tamm-Horsfall protein (secreted by the loop of Henle). Increased urinary protein losses can result from increased filtration across the filtration barrier (glomerular proteinuria), decreased reabsorption from the proximal tubule (tubular proteinuria) or increased secretion of protein from the tubules (secretory proteinuria).

1.3. Transient and Intermittent Proteinuria. Transient proteinuria is associated with fever, exercise, or stress and is not suggestive of underlying renal disease. When the underlying predisposing condition resolves, the proteinuria resolves. Another condition of intermittent proteinuria that causes concern for the parents and the pediatrician is orthostatic proteinuria. Orthostatic proteinuria is common in older children and adolescents with a prevalence of 2–5% [7]. Orthostatic proteinuria is the most common cause of proteinuria in adolescents (75%) [2]. The etiology is

postulated as changes in glomerular hemodynamics due to postural changes, and orthostatic proteinuria rarely exceeds 1 gm/day. The first step in patients who present with persistent proteinuria is to do a spot urine protein creatinine ratio on a first morning urine specimen. Another option is to collect a split 24 hr urine collection based upon lying/supine position and upright position and not on the time of day.

1.4. Persistent Proteinuria. Persistent proteinuria ($>4 \text{ mg/m}^2/\text{hr}$ of protein in a 24 hr urine collection or spot urine protein creatinine ratio of $>0.2 \text{ mg/mg}$), as the name suggests is present on numerous occasions and needs to be evaluated further to rule out any underlying renal pathology. Glomerular causes for proteinuria are more common than tubulointerstitial causes for proteinuria, and the common causes are listed in Table 1 [8–10]. Of the glomerular causes, nephrotic syndrome is one of the important causes. Nephrotic syndrome is defined as protein excretion of $>40 \text{ mg/m}^2/\text{hr}$ or $>1 \text{ gm/m}^2/\text{day}$ in a 24 hr urine collection or a spot urine protein creatinine ratio of $>2 \text{ mg/mg}$ [10, 11]. Patients with nephrotic syndrome also have hypoalbuminemia, edema, and hyperlipidemia. Minimal change nephrotic syndrome is the most common histopathological diagnosis of nephrotic syndrome in children, and the typical age of presentation is 2–7 years and is more common in boys (2:1) [12]. Tubular proteinuria commonly consists of low-molecular-weight proteinuria. Dent's disease is an X-linked recessive disorder that presents with low molecular weight proteinuria, proximal tubulopathy, hypercalciuria, and nephrolithiasis. In the majority of patients with Dent's disease, there is an inactivating mutation of the CLCN5 gene (renal chloride channel). Lowes syndrome is also an X-linked disorder, and patients present with low molecular weight proteinuria, bilateral cataracts, proximal tubulopathy, and hypotonia. To diagnose tubular proteinuria, urinary studies looking for the excretion of low-molecular-weight proteins including β -2 microglobulin, retinol-binding protein, and α -1 microglobulin are necessary. Detailed discussion of these disorders is beyond the scope of this paper.

1.5. Approach to a Patient with Proteinuria

History. As with any medical problem, a thorough history is critical in evaluating a patient. History should include symptoms of swelling, headaches, hematuria, joint pains, rashes, elevated blood pressure, urinary tract infections, recent throat or skin infections, loss of appetite, decreased energy, weight loss, and intake of medications (please see Table 1 for examples). Family history is also important which should include cystic kidney disease, deafness, visual disturbances, or renal disease/renal failure/dialysis.

Physical Examination. Growth is an important clue for chronic diseases and needs to be measured. Blood pressure needs to be obtained and cross-referenced with normative published data [13]. Signs of flank pain, fluid overload, edema, organomegaly, rashes, joint swelling, anemia, and evidence of osteodystrophy should be examined. Please refer to Table 1 for the common conditions associated with

persistent proteinuria to guide your physical exam for rare medical conditions.

Laboratory Testing to Detect and Quantify Proteinuria. Urinary dipsticks are commonly used to detect proteinuria and hematuria in the office setting, and they are good screening tools. The urine dipstick primarily detects albumin and does not detect low-molecular-weight proteins. This is due to the fact that albumin binds better to tetrabromophenol, which is the dye used in the dipstick. The color changes from yellow to green to blue with increasing amounts of protein in the urine, for example, trace ($<20 \text{ mg/dl}$), 1+ (30 mg/dl), 2+ (100 mg/dl), 3+ (300 mg/dl), and 4+ ($>2000 \text{ mg/dl}$) [14]. False negative results can be seen in very dilute urine samples especially when the specific gravity is <1.002 and with low molecular weight proteinuria. False positive results can be seen in highly concentrated urine samples, alkaline urine ($\text{pH} > 8.0$), after iodinated contrast, and with the use of antiseptics prior to urine collection. A quick way of quantifying proteinuria is measuring a spot/random urine protein creatinine ratio (mg/mg) when the urine dipstick shows persistent proteinuria (1+ and above). Many studies have shown a good correlation between spot urine protein creatinine ratio and 24 hr urinary protein excretion, and more importantly spot protein creatinine ratio can help the physician to decide which patients need further workup of proteinuria including a 24 hr urine collection [15–18]. The normal ratio for random urine protein creatinine ratio is <0.2 , nephrotic range is >2 when both urine protein and creatinine are measured in mg/dl. When the spot protein creatinine ratio is between 0.2 and 2, it is advisable to obtain a 24 hr urine collection. Twenty-four-hour urine collection for protein quantification is the gold standard test, but it is inherent with many problems. Twenty-four-hour urine collections are not practical in children in diapers, and even if the child is toilet-trained, it is often associated with missed voids, inadequate collection, and volume errors. Normal protein excretion in children in 24 hr urine collection is $<4 \text{ mg/m}^2/\text{hr}$, nephrotic range proteinuria is $>40 \text{ mg/m}^2/\text{hr}$ [14]. Abnormal proteinuria is from $4\text{--}40 \text{ mg/m}^2/\text{hr}$ on a 24 hr adequate urine collection.

Laboratory Workup for Isolated Proteinuria. It is paramount to establish if the proteinuria is transient, orthostatic, or persistent. In a patient who is asymptomatic with isolated proteinuria, urine dipstick needs to be repeated weekly on at least two occasions to establish that proteinuria was not transient. If the proteinuria disappears on repeat testing, then it is likely transient, and the family can be reassured. Urine dipsticks can then be repeated in 6 months–1 year [14]. In a patient with persistent proteinuria, to distinguish between orthostatic and persistent proteinuria, early morning spot protein creatinine ratio or split 24 hr urine collection should be obtained. While obtaining the split 24 hr urine collection, the most important aspect is that urine is collected based on lying/supine or upright position and not based on the timing of the day. Clear instructions need to be provided to the patients in regards to urine collection; one jug for while the patient is upright and one jug for after the patient has been supine for a considerable amount of time (overnight sleep). If the early morning urine protein creatinine ratio is

TABLE 1: Causes of persistent proteinuria.

Persistent proteinuria	
Glomerular	Tubulointerstitial
Diabetes	Acquired
Hypertension	Acute tubular necrosis
Reflux nephropathy	Toxins (gold, lead, copper, and mercury)
Primary glomerulonephropathy conditions	Pyelonephritis
Minimal change nephrotic syndrome	Interstitial nephritis (penicillins and other antibiotics, NSAIDs, and penicillamine)
Focal and segmental glomerulosclerosis	Inherited
Membranous nephropathy	Proximal renal tubular acidosis
Membranoproliferative glomerulonephritis	Cystinosis
Congenital nephrotic syndrome	Galactosemia
Secondary glomerulonephropathy conditions	Lowe syndrome
IgA nephropathy	Dents disease
Infections (Hepatitis B and C, HIV, CMV, malaria, syphilis, streptococcal)	Wilson disease
Henoch-Schönlein nephritis and systemic lupus nephritis (SLE)	Tyrosinemia
Alport syndrome	
Thin basement membrane disease	
Hemolytic uremic syndrome	
Malignancies	
Toxins	

Adapted from [8, 9].

<0.2 mg/mg or the protein excretion in the urine collected from lying/supine position is <60/m²/day, this is indicative of orthostatic proteinuria [9, 19]. Orthostatic proteinuria in longitudinal studies has shown favorable outcome without progression of renal disease [20]. If the urinary studies indicate persistent proteinuria, the patient needs a detailed and systematic workup including referral to a pediatric nephrologist. While the patient is waiting to be evaluated by a pediatric nephrologist, renal function tests (BUN and creatinine), albumin, and lipid profile can be obtained. Further evaluation will include a renal sonogram to rule out any structural malformations of the kidney, complement studies, and infectious workup based on the etiologies described in Table 1. The reader is advised to refer to the workup of proteinuria that is outlined in the publication by Hogg et al. [14].

2. Hematuria

2.1. Introduction. The incidence of macroscopic hematuria in children has been estimated to be 0.13% based on the data collected from 128,395 outpatient patient visits. In 56% of these patients, the cause was readily identifiable. In 26% of the children, the urine culture was positive, and only 9% had glomerular disease [21]. The incidence/prevalence of microscopic hematuria, which is more common than gross hematuria, varies in different studies due to the different criteria used to define microscopic hematuria. Using the definition of 10 or more red blood cells (RBCs) per high-power field (HPF) in two of the three consecutive urine

samples, the point prevalence is 1-2% [22]. Using the criteria of 6 or more RBC/HPF in 4 or more urine samples, Vehaskari et al. showed the prevalence to be 0.37% [23]. The detection of hematuria results in immense anxiety for both the family and the pediatrician. In addition, detailed workup of every child with isolated hematuria results in a needless expense. However, it is important to identify children who could have serious underlying renal pathology. This section will discuss details about the pathophysiology, etiology, and workup of children who present with hematuria.

2.2. Overview and Pathophysiology. Hematuria is usually detected when the patient either presents with a change in their urine color, or when the urine is checked for other reasons. The urine dipsticks that are commonly employed to detect microscopic hematuria are very sensitive. When used correctly, urine dipsticks have a sensitivity of 100 and a specificity of 99 to detect 1–5 RBCs/HPF, which translates to 5–10 RBCs/ μ l of urine [24, 25]. False positive results can be seen with hemoglobin, myoglobin, or hypochlorite in the urine [9]. Conversely, false negative results can be seen when the urine specific gravity is high or there are reducing agents like ascorbic acid in the urine [9]. The common causes of discolored urine are shown in Table 2. Therefore, a positive urine dipstick should be followed by urine microscopy to examine for red blood cells. Hematuria does not usually result in anemia [25]. Even 1ml of blood in 1000 ml of urine can change the urine color to red [26]. Red blood cells can arise from the glomeruli, renal tubules, interstitium, renal pelvis, ureter, bladder, or urethra. In children, glomerular

TABLE 2: Causes of discolored urine.

Red-colored urine	Hematuria (RBCs)
	Myoglobinuria (myoglobin and rhabdomyolysis)
	Hemoglobinuria (free hemoglobin)
	Porphyria (porphyrin)
	Urate crystals
	Foods (food coloring, beets, and blackberries)
Dark yellow- or orange-colored urine	Drugs (phenolphthalein, chloroquine, phenazopyridine, iron sorbitol, desferrioxamine)
	Concentrated urine
Dark brown- or black-colored urine	Drugs (rifampin and pyridium)
	Bile pigments
	Methemoglobinemia (methemoglobin)
	Melanin
	Alkaptonuria (homogentisic acid)

Adapted from [9, 25, 27, 28].

hematuria is more common and is usually associated with RBC casts, deformed RBCs and/or proteinuria [25]. Ischemia of the renal papillae can be seen in sickle cell nephropathy and with certain medications/toxins. Hematuria is generally divided into two broad categories: macroscopic hematuria (visible to naked eye) and microscopic hematuria (not visible to naked eye).

2.3. Macroscopic Hematuria. Macroscopic hematuria, as the name indicates, is visible to the naked eye. The first step in the evaluation of a patient with macroscopic hematuria is the color of the urine. Tea-colored, brown-colored or colacolored urine is indicative of glomerular hematuria. The differential diagnosis includes postinfectious glomerulonephritis, membranoproliferative glomerulonephritis, rapidly progressive glomerulonephritis, IgA nephropathy, Henoch-Schönlein purpura, and hemolytic-uremic syndrome. The conditions mentioned above are usually associated with proteinuria and RBC casts and need prompt evaluation. In addition, some of the patients with these conditions can present with life-threatening hypertension or oliguria/anuria. Bright red-or pink-colored urine is indicative of bleeding from the urinary tract, past the glomerulus. The differential diagnosis includes tumor, trauma, hydronephrosis, renal calculus, cystitis, urinary tract infection, schistosomiasis (bilharziasis, Middle Eastern or African countries), tuberculosis of the urinary tract (endemic areas for tuberculosis), sickle cell trait, vascular anomalies, polyps, coagulopathy, renal artery or renal vein thrombosis, terminal hematuria (urethrorrhagia), or polycystic kidney disease [25, 26]. Nutcracker syndrome is another entity where the patient can present with intermittent gross or microscopic hematuria with orthostatic proteinuria. This phenomenon is due to compression of the left renal vein between the aorta and the superior mesenteric artery, which results in renal vein

hypertension. Terminal hematuria (urethrorrhagia) can also result in gross hematuria (bright red color) or red staining of the undergarment. It is usually seen in prepubescent boys and can be associated with dysuria. Urethrorrhagia resolves spontaneously and does not need a detailed workup [29].

2.4. Microscopic Hematuria. As discussed earlier, there is no consensus on the definition of microscopic hematuria. In general, more than 5 RBCs/hpf is considered as microscopic hematuria. Patients with microscopic hematuria can be divided into two broad categories: asymptomatic isolated microscopic hematuria and symptomatic microscopic hematuria with positive family history and other associated features [25, 30].

In a large study done by Park et al. on school-aged children (7 million) in Korea, 1044 children had abnormal urinalysis. Of the 1044 children, isolated hematuria was found in 60% (719). Renal biopsy based on strict criteria (hypertension, severe proteinuria, family history of renal disease, abnormal renal function, or persistent hematuria and/or proteinuria for more than 12 months) was performed on a total of 113 children. Of the 719 children with isolated microscopic hematuria, 52 underwent a renal biopsy. Thirty-three children had thin basement membrane disease, 8 patients had IgA nephropathy, and 5 patients had membranoproliferative glomerulonephritis. As the criteria for performing a renal biopsy were stringent, the likelihood of finding significant renal disease was relatively higher in this group of children [31]. Another study was performed by Lee et al. where 461 renal biopsy cases were retrospectively analyzed [32]. The indications for renal biopsy in this study were isolated microscopic hematuria for 6 months or significant proteinuria (>2 g/24 hr urine) or the presence of both microscopic hematuria and proteinuria (>150 mg/24 hr urine). The biopsy criteria were less stringent than those in the study by Park et al. In the group with isolated microscopic hematuria (289 children), 136 (47%) children had no histopathological abnormality found on the renal biopsy. Thin basement membrane disease was found in 97 children (34%), and IgA nephropathy was found in 46 children (16%). The reason behind the increased number of normal renal biopsies in this study was due to the use of less stringent criteria for renal biopsy. These studies have demonstrated nicely that thin basement membrane disease is the most common cause of isolated microscopic hematuria, followed by IgA nephropathy, keeping in mind that almost half of the children with isolated microscopic hematuria might not have an identifiable cause. Thin basement membrane disease can be due to mutations in collagen IV and can be inherited in an autosomal dominant fashion. The long-term prognosis for thin basement membrane disease is favorable [33, 34]. IgA nephropathy can be progressive and needs close followup. End-stage renal disease can be seen in about 25% of pediatric patients with IgA nephropathy during a 20-year followup [35]. Treatment options for IgA nephropathy include angiotensin converting enzyme inhibitors/ angiotensin receptor blockers, immunosuppressive therapy, and fish oil supplements [35]. Hypercalciuria

is another important differential for isolated microscopic hematuria. Based on different studies, hypercalciuria has been diagnosed in 10–30% of patients, who present with isolated microscopic hematuria [25, 30, 36, 37]. Dysfunctional voiding should also be considered during the evaluation of isolated microscopic hematuria. After reviewing the large population studies done on school children, it is safe to recommend that most of the children that present with isolated microscopic hematuria do not need an extensive workup at presentation, as they do not have significant underlying renal pathology [25, 30].

Another category is symptomatic microscopic hematuria, where the patient in addition to microscopic hematuria might have hypertension, proteinuria or family history of progressive renal disease, deafness or visual disturbances. This group will include patients with RBC casts, presence of proteinuria, symptoms suggestive of infectious processes, hypertension, or/and history of renal stones. The differential includes Alport syndrome, nephrocalcinosis, glomerulonephritis, or IgA nephropathy. These patients will need further evaluation including referral to a pediatric nephrologist.

2.5. Approach to a Patient with Hematuria

History. As always, obtaining a detailed history will guide the physician in the right direction and in a patient who presents with either gross or microscopic hematuria, the following questions will help formulate further workup and management. At first, it is important to ascertain the color of the urine as this will help distinguish between glomerular and nonglomerular hematuria. Bright red-colored urine usually indicates that the blood is coming from the ureter, bladder or urethra (non-glomerular). Glomerular hematuria in general is described as coca-cola-colored, tea-colored or dark-brown colored urine. However, if the urine has been in the bladder for a long period of time, even non-glomerular hematuria can present as brown colored-urine. The brown color is due to oxidation of the heme pigment [9]. Glomerular hematuria is usually painless. History of flank pain, radiating to the groin and dysuria, is suggestive of renal colic or nephrolithiasis. History of dysuria, fever with or without chills, suprapubic pain, flank pain, frequency of micturition, or recurrence of nocturnal enuresis is indicative of a urinary tract infection. History of sore throat 2–3 weeks prior to presentation or history of impetigo/rash 4–6 weeks prior to presentation is suggestive of postinfectious glomerulonephritis. Patients with Henoch-Schönlein purpura present with history of a purpuric/petechial rash, usually on the lower extremities (buttocks) but can be generalized and can also have associated symptoms of abdominal and/or joint pains. Patients with systemic lupus erythematosus present with history of facial rash across the nose and cheeks, joint pain, generalized malaise, or weight loss. Recurrent gross hematuria, especially soon after the onset of upper respiratory infection, is suggestive of IgA nephropathy or rarely thin basement membrane disease [33, 34, 38]. History of trauma, strenuous exercise, and menstruation: drugs and food history (food colorings, herbs,

and toxins) should also be elicited. History of abdominal distension and/or abdominal mass is suggestive of tumors, hydronephrosis (ureteropelvic junction obstruction), and polycystic or multicystic kidneys. In addition, history of child abuse should be considered and in adolescents, sexual activity should be inquired. The risk of urinary tract infections, cystitis, and urethritis is increased in sexually active teenagers.

Past medical history should include the presence of similar symptoms in the past, history of prior renal disease, and history of rashes or joint pains. Family history should include the presence of recurrent hematuria (thin basement membrane and nephrolithiasis), renal disease in relatives; history of deafness and chronic kidney disease/progressive renal disease is suggestive of Alport syndrome. History should also be ascertained about autosomal dominant polycystic kidney disease.

Physical Examination. As mentioned earlier, a thorough physical examination is important including measuring growth and vital signs. The presence of hypertension and edema in addition to hematuria is suggestive of acute nephritic syndromes, and thorough evaluation is essential. The absence of proteinuria and hypertension does not warrant immediate and thorough workup, but observation and followup is indicated. The presence of fever and loin pain is indicative of pyelonephritis. The presence of rashes or arthritis is indicative of systemic lupus erythematosus or Henoch-Schönlein nephritis. The palpation of an abdominal mass should raise suspicion for tumor, multicystic dysplastic kidney, polycystic kidney, or hydronephrosis.

Workup of Hematuria. Gross Hematuria. If the patient presents with gross hematuria, it is critical to examine the urine microscopically to confirm the presence of RBCs. If there are no RBCs, please refer to Table 2 to look for alternate causes of discolored urine. If the RBCs are present, the next step is to look for the origin of RBCs; examine for RBC casts or dysmorphic RBCs (phase contrast microscopy). A freshly voided urine sample is necessary to examine for RBC casts. RBC casts are usually not visible in a urine sample that has been in room temperature for a long time. In the presence of RBC casts, dysmorphic RBCs, proteinuria, hypertension, edema and oliguria, the hematuria is likely glomerular. The next step in the workup will include renal function (BUN and creatinine), electrolytes, albumin, complement studies (C3 and C4), and streptozyme test {antistreptolysinO (ASO), antihyaluronidase (AH), anti-deoxyribonuclease B (anti-DNAse B), and antinicotinamide adenine dinucleotidase (anti-NADase)}, antinuclear antibody (ANA), and possibly antineutrophil cytoplasmic antibodies (ANCA). Urgent pediatric nephrology referral should be done in patients with RBC casts, dysmorphic RBCs, proteinuria, hypertension, edema, and oliguria. In the absence of dysmorphic RBCs, RBC casts and significant proteinuria, urological conditions and malignancies should be considered. All children who present with gross hematuria should have a renal ultrasound. If ultrasound reveals a structural abnormality or malignancy, urological referral is necessary. Spiral noncontrast CT scan is advised if nephrolithiasis is suspected. Cystoscopy is recommended when bladder pathology is suspected or to

lateralize the location of the bleeding in a patient who has active recurrent hematuria. If the patient has fever, flank pain, and or dysuria, urine culture should be sent to rule out a urinary tract infection.

Microscopic Hematuria. When the microscopic hematuria is isolated, asymptomatic and not associated proteinuria or hypertension, a step-wise and non-urgent workup is indicated. Repeat urine dipstick and microscopy can be repeated in 2-3 weeks. If microscopic hematuria resolves, no further workup is necessary. If isolated microscopic hematuria persists, spot urine calcium creatinine ratio and urinalysis on parents/siblings can be performed. The benefits of renal sonogram in this situation are not proven [30] but can relieve tremendous anxiety for the parents. If the above tests are normal, it is important to reassure the family that there are no life-threatening conditions, and the pediatrician can monitor the child with yearly urinalysis and blood pressure measurement. If the parents are insistent upon knowing the exact etiology of isolated microscopic hematuria, referral to a pediatric nephrologist should be considered. Patients with microscopic hematuria with symptoms or positive family history of renal disease and/or the presence of proteinuria warrant a referral to the pediatric nephrologist. Algorithms for workup of hematuria have been well described previously in, and the reader is advised to refer to the review articles [25, 26].

3. Summary

As described in this paper, minority of patients who present with isolated microscopic hematuria or proteinuria have significant renal disease. This is based on mass urine screening studies on school-aged children. Basic screening tests can be employed to delineate transient urinary abnormalities from significant renal pathology. If the patient presents with proteinuria and hematuria, the likelihood of significant renal disease increases, and the pediatrician can initiate some of the workup as described above and refer the patient to a pediatric nephrologist. If the patient presents with hypertension, proteinuria, hematuria, and oliguria, an emergent referral to the pediatric nephrologist is recommended.

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Review Article

Chronic Kidney Disease: Highlights for the General Pediatrician

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Chronic kidney disease in the pediatric population has been increasing. Early detection and treatment can slow down the progression of kidney disease and help prevent the development of end stage renal disease. In addition, as the kidney function declines, there are many pathophysiologic interactions with other organ systems that need to be monitored and treated. In particular, because of impaired vitamin D metabolism, calcium and phosphorus homeostasis is dysregulated and results in secondary bone disease. Anemia is common due to a number of factors including impaired erythropoietin production. Growth is often impacted by chronic kidney disease but can be improved by proper treatment. Complications of chronic kidney disease can be minimized by proper monitoring and treatment of these parameters. The general pediatrician plays a critical role in this process.

1. Introduction

Chronic kidney disease (CKD) had originally been defined as a glomerular filtration rate less than 60 mL/minute/ 1.73 m^2 for a duration of 3 months or longer. This distinguished chronic kidney disease from episodes of acute kidney injury. For purposes of classification and treatment, the National Kidney Foundation developed a staging system for CKD based upon the patient's glomerular filtration rate (Table 1) [1]. Most of the data regarding the epidemiology and etiology of chronic kidney disease is based upon the adult population. However, there have been some studies recently that have begun to examine the epidemiology and etiology of chronic kidney disease in the pediatric population [2, 3]. This paper will examine the pathophysiology and epidemiology of chronic kidney disease in pediatrics. We will discuss the workup and management of these children from the perspective of a general pediatrician.

2. Pathophysiology

As the kidney function in the patient deteriorates, there are a number of pathophysiologic problems that develop in the patient. These will be reviewed according to the various organ systems that are affected. It will be important to

consider the stage of chronic kidney disease that patient is in when thinking about these disorders.

One of the first problems that develop is related to bone disease [4]. The kidney plays a crucial role in activating vitamin D. The liver performs the 25-hydroxylation function, and the kidney performs the 1-alpha hydroxylation step. The 1,25-dihydroxy vitamin D that is formed is the most active form of vitamin D and will maintain healthy bones and prevent rickets in the growing child. Depending on the form of kidney disease the 1-alpha-hydroxylase function can begin to deteriorate at stage II or stage III chronic kidney disease. The patient can then develop hypocalcemia because of the decreased absorption of calcium in the gut. This will then lead to secondary hyperparathyroidism which will cause calcium to be mobilized from the bone. Some patients will actually present with pathologic fractures or other forms of bone disease as the presenting feature of chronic kidney disease.

In addition to the problems with calcium metabolism, as the glomerular filtration rate declines, the patients will also retain phosphorus and become hyperphosphatemic. This has been shown to stimulate fibroblast growth factor 23 which can lead to additional problems. A number of studies have demonstrated that early control of the patient's phosphate can alleviate many of the problems seen with chronic kidney

TABLE 1: Stages of CKD as related to the GFR of the patient.

Chronic kidney disease stage	GFR (mL/min/1.73 m ²)	
I	>90	Mild
II	60–90	Moderate
III	30–60	Moderate
IV	15–30	Severe
V	<15	ESRD

disease. However, this can be very difficult to accomplish because the patient's dietary habits are beyond our control.

The interdependence of vitamin D, calcium, phosphorus and PTH is very complex [4]. The primary stimuli for PTH secretion are low ionized calcium and high serum phosphorus concentration. One of the actions of PTH is to stimulate the 1-alpha-hydroxylase enzyme in the renal cortex to activate more vitamin D. Vitamin D will then feed back to the parathyroid gland to decrease secretion of PTH. Vitamin D will also promote absorption of calcium and phosphorus from the intestines to help with mineralization of new bone. If the parathyroid gland is stimulated for a prolonged period of time by low calcium and high phosphorus, it will become autonomous and no longer be controlled by vitamin D. This is known as tertiary hyperparathyroidism.

Another area that is affected by chronic kidney disease is the patient's hemoglobin concentration [5]. As the patient's kidney function deteriorates, its ability to produce and secrete erythropoietin becomes impaired. In addition, as the patient becomes more uremic, the red cell half-life will decrease and so that turnover of the red cells will become increased. This can be corrected by treating the patients with exogenous erythropoietin. It is also crucial to make sure that patients do not become iron deficient. Prior to the availability of the erythropoietin, many of the chronic kidney disease patients would become iron overloaded because of the need for chronic transfusions. Now that these patients are treated with erythropoietin, many will become iron deficient.

The development of anemia is also linked with the problem of bone disease. If the patient's bone disease becomes advanced, they can develop a condition known as osteitis fibrosis cystica. In this condition the bone marrow becomes replaced with fibrous tissue and thus will not be able to respond to erythropoietin and cannot increase red cell production. Thus it becomes imperative to view the patient as a whole and treat both bone disease and anemia concomitantly.

A number of other electrolyte abnormalities come into play as the patient develops worsening chronic kidney disease. Oftentimes the patient will retain salt and develop hypertension. Potassium is normally secreted by the kidney but will oftentimes become a problem as the patient develops worsening renal function. The kidney is also responsible for maintaining the patient's acid base status by secreting protons. As the kidney function worsens, the patients often become more and more acidotic. This can lead to a number of problems such as worsening of the bone disease because

the acidosis will enhance calcium mobilization from the bones and will worsen the bone disease.

As mentioned above, the retention of salt will cause trouble with hypertension. Also in many disease states, the kidney will be secreting renin that will also exacerbate blood pressure problems. More recently there is evidence that renal nerves play a role in the increased blood pressure in patients with chronic kidney disease. The elevated blood pressure will also cause damage to the kidneys and will accelerate the decline in renal function [6, 7]. In addition, the fluid retention could result in edema formation, both peripheral as well as pulmonary. As with adults with chronic kidney disease, hypertension causes significant cardiac problems in the pediatric population. This has become quite a focus in the treatment of these patients [6, 7]. It is imperative to maintain them at a normal blood pressure and prevent the cardiac problems that they could develop. There is also some evidence that parathyroid hormone and FGF 23 can cause some cardiac problems [4]. So as we discussed above with the bone disease and anemia, it appears that there is an interrelationship between the calcium and phosphorus metabolism and cardiac disease.

Also more recently, a problem has been described with having elevated calcium and phosphorus simultaneously. This leads to an elevation in the calcium-phosphorus cross product and causes precipitation of calcium phosphate in the soft tissues. This has been shown to cause narrowing of the coronary arteries in adults and is becoming evident that this is a problem in pediatrics.

Patients with chronic kidney disease in general do not grow well [8]. Growth in these patients is a very complex problem involving many aspects of chronic kidney disease. As can be seen above, these patients with CKD have bone disease that will limit their growth potential. The fact that they are at risk for the development of cardiac disease probably also contributes to their growth problems. More importantly, as patients have declining renal function their appetite is suppressed. So many patients do not grow well because of poor nutrition. Other contributing factors include acidosis which impacts bone growth and chronic anemia, which can impact many factors including cardiac function and appetite.

Even when nutrition and bone disease are adequately addressed, patients with renal disease still may not grow well. It has been shown that the growth hormone-IGF 1 axis is abnormal in these patients. This is probably related to the interaction of IGF 1 and its binding protein. So after these patients have been treated with adequate nutrition and their bone disease is under control, they can be treated with growth hormone to stimulate growth [8].

3. Epidemiology

The incidence of chronic kidney disease (CKD) continues to increase in the United States. Unfortunately we do not have much data on the incidence or prevalence of chronic kidney disease and pediatric patients. Recently a few studies

have initiated this, but it will take some time to get more data on this. A study that was published in 2003 reported on 4,666 pediatric patients with chronic kidney disease [3]. These patients were from North America, and the data was collected from centers specialized in pediatric nephrology. Most likely this number underrepresents the total number of chronic kidney disease patients in North America. So it remains difficult to know what the prevalence and incidence of chronic kidney disease are in the pediatric population.

4. Clinical Presentation

In pediatric patients there are a number of causes of chronic kidney disease [3]. As opposed to adults, many pediatric patients develop chronic kidney disease secondary to congenital abnormalities in the urinary system. These patients are much more likely to have been followed more carefully after birth. In addition, there is more evidence that acute kidney injury can lead to chronic kidney disease [9–11]. Thus the clinical presentation will vary greatly depending on the cause of the chronic kidney disease.

There was some concern that urinary tract infections could eventually lead to chronic kidney disease. A recent study examined this question and showed that the infections themselves probably do not lead to chronic kidney disease [12]. The patients who develop chronic kidney disease had an abnormality demonstrated on a renal ultrasound or voiding cystourethrogram that predisposed the patient to urinary tract infections. The patients who had no defect did not progress to chronic kidney disease.

As discussed above oftentimes the patients will present with signs or symptoms secondary to anemia or bone disease. Thus when these patients are diagnosed, they already have significant chronic kidney disease causing problems.

In many patients the presentation of CKD can be more subtle. Many patients do not have an easily identifiable congenital problem. They may present with signs or symptoms that are not readily seen as referring to the renal system. These patients often have poor growth or chronic hypertension. In addition, if a patient has persistent proteinuria and hematuria, they should be evaluated for CKD.

5. Management

In terms of the workup for patients with chronic kidney disease, they need a very thorough assessment of their metabolic status. One of the primary laboratory tests to do is the serum creatinine. In a steady state this is one of the more common ways of estimating the renal function. While there are some problems with using the serum creatinine to estimate the renal function, it remains the main stay of clinical medicine [13, 14].

Other laboratory tests that need to be done include serum electrolytes to assess for hyperkalemia as well as the bicarbonate to determine if the patient is acidotic. The calcium and phosphorus also need to be monitored as well

as parathyroid hormone and vitamin D level. Assessment of albumin will help monitor their nutritional status.

The need for imaging will depend upon the cause of the renal disease. Since many of the patients have obstruction as a cause of their chronic kidney disease, they may require periodic assessment with ultrasounds or possibly VCUGs. On initial evaluation, it is also important to examine a chest X-ray to evaluate the heart size. The patients might have significant left ventricular hypertrophy or they may have developed uremic pericarditis with a large pericardial effusion. If the patients complain about bone disease, they may need X-rays of their long bones and possibly bone densitometry performed.

Other testing that might need to be done includes a more accurate measure of the glomerular filtration rate. As discussed, above the serum creatinine may or may not give an accurate estimate of the patient's GFR. If a more accurate measure as needed, the patients can have their GFR measured using iothalamate or iohexol disappearance [15]. This test is performed by administering radioactive iothalamate to the patient, then measuring its disappearance from the blood stream and its appearance in the urine. This is a very accurate measure of the patient's glomerular filtration rate and is not dependent on the patient's muscle mass.

A number of chronic kidney diseases also involve the eyes and ears. So the patient might need a careful eye exam. For example patients with cystinosis will develop cystine crystals in the cornea. Many of the rheumatological diseases that cause chronic glomerulonephritis can also present with uveitis. Some other forms of nephronophthisis are associated with retinitis pigmentosa. Alport's syndrome which causes chronic kidney disease will cause lenticonus. Thus it is very important get a careful eye exam performed in patients that have chronic kidney disease. In addition Alport's will lead to high-frequency hearing loss.

6. Treatment

The treatment of patients with chronic kidney disease is focused on a number of areas [16]. Depending on the cause of the chronic kidney disease, the underlying disease might require specific treatment. For example, patients with cystinosis need to be on cysteamine to help prevent accumulation of cystine which will exacerbate the renal disease as well as cause other problems with the patient. Because many patients develop chronic kidney disease from obstructive uropathy, it will be important to make sure that their obstruction is relieved and they do not have ongoing problems with urinary tract infections.

Otherwise the treatment of these patients with chronic kidney disease will be aimed at controlling the blood pressure, the bone disease and their anemia. There are ample data now examining the effects of blood pressure and the development of cardiac disease in pediatrics [7, 17, 18]. Because many times patients have renin-mediated hypertension, it is best to control the blood pressure with an ACE inhibitor or an angiotensin receptor blocker. There is also more evidence that aldosterone may play a role in the cardiac disease in

these patients. It may be beneficial to treat them with an aldosterone receptor blocker as well.

As discussed above, the metabolic bone disease, in these patients can be very significant. These patients develop hypovitaminosis D at an early stage of chronic kidney disease. Thus one of the early treatments will be supplementing their vitamin D. In the past this was done with activated 1,25-dihydroxy vitamin D or calcitriol. However more recently it has become evident that supplementing with 25-hydroxyvitamin D may also prove beneficial.

If the patients develop hyperkalemia, they may need to be treated with Kayexalate to help remove potassium from them. In infants who are dependent on being formula fed, the Kayexalate can be added to the formula. After the kayexalate has been thoroughly mixed with the formula, it will settle out and the formula can then be decanted. This way, the patient does not actually take the Kayexalate but receives the benefit of its use. Another way to help prevent hyperkalemia is to treat the patients with Lasix. This will of course depend on how much renal function the patient has and whether or not they will respond to a diuretic.

The long-term followup of these patients will of course depend on the stage of chronic kidney disease they have and how quickly they develop end-stage renal disease. If the patient has been optimally treated for the bone disease and has not responded well to nutritional support and growth hormone, they may need to have dialysis initiated to improve their growth and development. Ultimately these patients will do best with a kidney transplant. It is interesting to note that transplantation does not alleviate all of the problems related to chronic kidney disease. For example, it is known that they can continue to have significant bone disease after transplantation.

7. The Disease from a GP's Perspective

As with many subspecialty problems and pediatrics, there needs to be good communication between the general practitioner and the pediatric nephrologist. One of the issues with this has to do with the fact that most pediatric nephrologists are in large tertiary care centers. Thus many patients may have to travel quite a distance to see the nephrologist. It will improve the patient's care if the pediatrician can provide some of the local support.

For example, monitoring the patient's blood pressure can be done in the pediatrician's office, and if changes need to be made, that could be discussed with the nephrologist. Also many times the blood chemistries can be measured at the pediatrician's office and the results can be discussed with the nephrologist. This way the patient does not have to travel extensively for minor adjustments in their care.

In terms of diagnosing patients with chronic kidney disease, there are a number of things that can be addressed. Screening urinalyses have become somewhat controversial. If the patient is found to have microscopic hematuria, this might lead to a workup that is not productive. However, the presence of proteinuria seems to carry more significance. Thus one of the early signs of chronic kidney disease is the

development of proteinuria. The pediatrician must keep in mind, however, that other common causes of proteinuria include orthostatic proteinuria and transient proteinuria that can occur during many illnesses.

As with many illnesses, the family history can be extremely important. Many patients with Alport's syndrome can be suspected from their family history. Autosomal dominant polycystic kidney disease is another very common cause of chronic disease in the adult population. This is also seen in many pediatric centers.

In addition to the family history and the urinalysis, it is important to monitor the blood pressure of patients. Oftentimes one of the first signs of serious kidney disease is the development of hypertension. So it would be very helpful if general pediatricians can measure the blood pressure and follow the guidelines set up in published in the 4th report [19].

8. Conclusion

The role of the general pediatrician in patients with chronic kidney disease can be very important. The general pediatrician can help identify patients at risk for chronic kidney disease early in the course of their disease. They can also participate in their ongoing care by being a resource. It is also important to remember that many subspecialists may not be adequately prepared to care for the other significant problems the patient might develop. So the general pediatrician can serve as a great resource to coordinate all of the care for the patient.

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Review Article

Presentation of the Child with Renal Disease and Guidelines for Referral to the Pediatric Nephrologist

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Renal disease is a major cause of morbidity and mortality. Pediatric patients with renal disease, especially younger ones may present with nonspecific signs and symptoms unrelated to the urinary tract. Pediatricians, therefore, should be familiar with the modes of presentation of renal disease and should have a high index of suspicion of these conditions. Affected patients may present with signs and symptoms of the disease, abnormal urinalysis, urinary tract infection, electrolyte and acid-base abnormalities, decreased renal function, renal involvement in systemic disease, glomerular and renal tubular diseases, congenital abnormalities, and hypertension. Pediatricians may initiate evaluation of renal disease to the extent that they feel comfortable with. The role of the pediatrician in the management of the child with renal disease and guidelines for patient referral to the pediatric nephrologist are presented.

1. Introduction

Renal disease is a major cause of morbidity and mortality [1–3]. Pediatric patients especially younger ones with renal disease may present with nonspecific signs and symptoms unrelated to the urinary tract. Pediatricians, therefore, should be familiar with the modes of presentation of different renal conditions and should have a high index of suspicion of renal disease. Early diagnosis and treatment of renal disease in children is important in the prevention of renal failure and end-stage renal disease (ESRD). I will discuss here the presentation of the child with these diseases and outline guidelines for patient referral to the pediatric nephrologist.

2. Presentation of the Child with Renal Disease

Patients with renal disease may present with (1) signs and symptoms of renal disease, (2) abnormal urinalysis, (3) urinary tract infection (UTI), (4) electrolyte and acid-base abnormalities, (5) decreased renal function, (6) renal involvement in systemic disease, (7) glomerular disease, (8) renal tubular disease, (9) congenital abnormalities of the kidney or urinary tract, and (10) hypertension (HT). Often, renal disease may be asymptomatic; therefore, a blood

pressure determination, a thorough abdominal examination, and a urinalysis should be an integral part of a routine medical examination in children.

3. Signs and Symptoms of Renal Disease

Renal disease, particularly in children, may present in a subtle manner such as failure to thrive, unexplained fevers, vague pains, gastrointestinal symptoms, anemia, abdominal mass, edema, HT, and metabolic acidosis. Failure to thrive may suggest chronic kidney disease or renal tubular disease. Anemia, growth failure, HT, and abnormal retinal changes may be the first signs of chronic kidney disease. Frequency, urgency, dysuria, hesitancy, and urinary retention suggest UTI, obstructive uropathy, or urinary calculi.

Physicians should be familiar with the normal voiding pattern of children at various ages. *Frequency* is frequent urination suggesting UTI, while *polyuria* is the passage of a larger amount of urine than normal. It indicates decrease in concentrating ability which occurs in diabetes mellitus, diabetes insipidus, chronic pyelonephritis, or chronic kidney disease. *Pollakiuria* (Greek pollakis, meaning often) is a common symptom affecting toilet-trained school children

especially boys. It refers to daytime isolated urinary frequency which has a sudden onset and lasts from a few days to a few weeks. Affected children have a normal physical examination, urinalysis and urine culture, and do not require further investigation.

Enuresis (nocturnal incontinence) is bedwetting beyond the age when the child should be able to control urination. It is usually idiopathic and associated with a positive family history. It initially requires no other investigation than a urinalysis and urine culture. Secondary and diurnal forms of enuresis, as well as enuresis beyond the age of 12 years, may require urologic evaluation. *Nocturia* in older children is defined as awakening at night to pass urine. This may be normal, or may suggest a decrease in urine concentrating ability and may also be an early sign of chronic kidney disease.

It is important to keep in mind that renal disease including UTI in children may present in a subtle manner. Physicians, therefore, should have a high index of suspicion and should perform urinalyses and urine cultures on any child with unexplained fevers.

Most renal diseases are painless. Acute pyelonephritis, renal calculi, and trauma to the kidney or bladder may present with abdominal or flank pain. *Dysuria*, or pain on urination, is a symptom of UTI or urethritis. The pain of cystitis or prostatitis is usually suprapubic and gradual in onset.

Abdominal masses of renal origin may represent hydronephrosis, multicystic, dysplastic or polycystic kidney disease, renal vein thrombosis, and Wilms tumor or neuroblastoma.

4. Abnormal Urinalysis

Patients with kidney disease may present with abnormal urinary findings. A carefully performed urinalysis using physical, chemical, and microscopic examination is an easy and informative tool to the practicing physician [4]. The American Academy of Pediatrics recommends a urinalysis as a part of preventive pediatric health care at age 5 years and mid-adolescence [5]. An abnormal urinalysis may be the only presenting sign of chronic GN.

The most common urinary abnormalities are hematuria and proteinuria. *Hematuria* may be gross or microscopic, discovered during a routine urinalysis. Evaluation of the child with hematuria may be easily initiated by the primary care physician. Urinalysis and, when indicated, an audiogram on immediate family members should be performed, since recurrent benign hematuria, Alport syndrome, IgA nephropathy, and other forms of glomerular disease may be familial. In general, the presence of persistent and recurrent gross hematuria should prompt referral to a pediatric nephrologist.

Persistent *proteinuria* should be investigated. The primary care physician may quantitate the proteinuria and exclude the orthostatic type. Significant proteinuria ($>1\text{ g}/1.73\text{ m}^2/\text{day}$), or proteinuria associated with abnormal RBC

morphology, decreased renal function, HT, low serum complement, or manifestations of systemic disease are suggestive of glomerular disease and are indications for renal biopsy.

Pyuria may originate from any part of the urinary tract and usually suggests UTI, but it may be seen also with any inflammatory process of the kidney and urinary tract, renal calculi and abnormalities of the urinary tract. *Casts* are of diagnostic importance. Red blood cell casts, for example indicate glomerular bleeding.

5. Urinary Tract Infection

Urinary tract infection (UTI) is the most common bacterial disease responsible for long term morbidity in children [6]. Accurate and prompt diagnosis and treatment are crucial and may prevent renal scarring. Diagnosis of UTI requires a high degree of suspicion because of the nonspecific nature of symptoms in younger children such as unexplained fevers, gastrointestinal symptoms, and irritability. The diagnosis is established by a quantitative urine culture. Because of the high association of UTI with vesicoureteral reflux and other urinary tract abnormalities, imaging studies should be considered.

6. Electrolyte and Acid-Base Abnormalities

Electrolyte and acid-base abnormalities are commonly seen in pediatric practice. Patients may present with nausea, vomiting, diarrhea, decreased intake of fluids, irritability, lethargy, weight loss, dry skin and mucus membranes, elevated pulse, seizures and coma. The most common cause of acid-base disorder in children is metabolic acidosis secondary to diarrheal dehydration; however, affected children may present with a very complex clinical picture, and treating physicians should be familiar with the intricacies of their diagnosis and management. Severely affected patients should be referred immediately to a hospital where expert care can be delivered.

7. Decreased Renal Function

Azotemia is elevated serum urea nitrogen, *renal failure* is reduction in renal function, and *uremia* is the syndrome that encompasses the overt consequences of chronic kidney disease such as anemia, osteodystrophy, and central nervous system, gastrointestinal and other manifestations. *Acute kidney injury* is an abrupt severe reduction in glomerular filtration and is characterized by oliguria (urine $<0.5\text{ mL/kg/hr}$) or anuria. The etiology of acute kidney injury should be identified promptly because many causes are reversible, and because management and prognosis of this condition vary with the specific etiology. Affected patients should be referred to a pediatric nephrologist immediately.

The presence of growth retardation, anemia, history of underlying renal disease, renal osteodystrophy or small, contracted kidneys suggests the presence of *chronic kidney disease*, which is defined as the stage at which the kidneys are irreversibly damaged and unable to maintain the body

homeostasis. Congenital renal abnormalities of the urinary tract are the most prevalent cause of chronic kidney disease in young children, whereas GN is more prevalent in adolescents [7]. These patients should also be referred to the pediatric nephrologist, since they frequently progress to ESRD, requiring chronic dialysis and renal transplantation. Since many causes of ESRD in children are potentially preventable (hereditary and congenital abnormalities of the kidney and UTI), early diagnosis and treatment of these conditions is of utmost importance.

8. Renal Involvement in Systemic Diseases

Various systemic diseases (systemic vasculitis-systemic lupus erythematosus, Henoch-Schönlein purpura, hemolytic uremic syndrome, sickle cell disease, and malignancy) and syndromes (chromosomal aberrations, Rubinstein-Taybi, Cornelia de Lange, and many others) may affect the kidney in childhood [1]. Renal involvement should be excluded in any individual with multisystem disease (collagen disease, diabetes mellitus, and storage diseases). Systemic diseases associated with glomerular abnormalities may present with arthritis, rash, hypertension, hematuria, or proteinuria. The diagnosis of renal involvement in systemic disease is based on clinical findings (hematuria, proteinuria, hypertension, and decreased serum complement levels, decreased renal function) as well as renal histology.

9. Glomerular Disease

The majority of children with glomerulonephritis (GN) present with proteinuria, hematuria, hypertension, edema, reduced renal function, or the nephrotic syndrome. Post-streptococcal acute GN is familiar to the practicing pediatrician. Most affected children have a benign course and can be easily treated by the primary care physician on an ambulatory basis. Obviously, a nephrology consultation should be obtained on patients with oliguria, hyperkalemia, nephrotic syndrome, cardiac overload, and renal insufficiency. Patients with prolonged oligoanuria, a persistently low serum complement for more than 8 weeks, or associated nephrotic syndrome may require a kidney biopsy.

Nephrotic syndrome is characterized by proteinuria $\geq 40 \text{ mg/m}^2/\text{hr}$ (or 50 mg/kg/day), serum albumin $< 2.5 \text{ g/dL}$ and variable degrees of edema. The most common form of nephrotic syndrome in children is *minimal change nephrotic syndrome*, which is characterized by response to corticosteroids and good prognosis, although most patients have one or more relapses. Patients with this type of nephrosis may be treated by the primary care physician, while those who are steroid-resistant or -dependent, those with a suspected structural glomerular abnormality, and those associated with systemic disease should be referred to the pediatric nephrologist, since they usually require a kidney biopsy, knowledge of the current therapeutic regimens, and a close followup.

10. Renal Tubular Disease

Renal tubular diseases (renal glucosuria, Fanconi syndrome with or without cystinosis, aminoacidurias, renal tubular acidosis, nephrogenic diabetes insipidus, and others) are rare and complex, and their management usually requires the help of a pediatric nephrologist [8]. Affected patients may present with failure to thrive, acidosis, glucosuria, aminoaciduria, phosphaturia, rickets, and inability to concentrate the urine. Renal tubular acidosis should be considered in patients with metabolic acidosis and persistently alkaline urine. A positive family history may suggest the presence of these conditions.

11. Congenital Abnormalities of the Kidney and Urinary Tract

Congenital abnormalities of the kidney and urinary tract are reported to occur in 5 to 10% of the population [9]. They represent 25% of the total ultrasonographically diagnosed malformations that occur in 0.25–0.7% of fetuses. About 1/3 to 2/3 of ESRD in children are due to congenital abnormalities of the kidney and urinary tract. In addition, these abnormalities occur in 23% of patients with chromosomal aberrations, and 2/3 of patients with abnormalities of other organ systems. Some of these abnormalities are minor and are discovered incidentally; others are major, leading to obstruction, renal scarring, pyelonephritis, and ESRD. Urinary tract abnormalities should be suspected in any child with UTI, congenital anomalies of other organ systems (cardiovascular, gastrointestinal, central nervous system, and others), chromosomal aberrations, various malformation syndromes, and those with single umbilical artery or supernumerary nipples. Prenatal diagnosis of these conditions by ultrasonography as early as 12–16 weeks gestation will reduce the occurrence of renal damage and ESRD.

12. Hypertension

The prevalence of hypertension in children ranges from less than 1% to 5.1% [10]. While pediatric hypertension was previously assumed to be secondary to renal, cardiovascular or endocrine causes, there is now increased evidence that it could be a part of a spectrum of essential hypertension, mainly linked to the obesity epidemic. The three most common symptoms of hypertension in children are headache, difficulty sleeping, and tiredness, all of which improve with treatment. Pediatricians can play a pivotal role in the early diagnosis and treatment of HT to reduce long-term cardiovascular morbidity and mortality. Blood pressure should be measured routinely in every child starting at age three years and in children with comorbid conditions such as the presence of heart or kidney disease, obesity, history of umbilical line, or UTI [11]. Referral to a specialist depends on the level of comfort of the pediatrician and the degree of the etiological complexity.

TABLE 1: Role of the pediatrician in the management of the child with renal disease [1].

- (1) keep a high index of suspicion for UTI and renal disease
- (2) take patient/family history, perform a complete physical exam with BP, and exclude the presence of systemic diseases
- (3) perform a urinalysis on patient, and, when indicated, on family members, urine culture, antibiogram, and other laboratory tests: BUN, creatinine, electrolytes, serum complement, quantitative proteinuria, and creatinine clearance
- (4) order imaging studies: renal ultrasound, VCUG, renal scan and others on patients with UTI, and suspected congenital abnormalities and calculi
- (5) screen for orthostatic proteinuria and tubular disorders
- (6) treat UTI, uncomplicated acute GN, conditions not associated with acute or progressive deterioration of renal function: minimal change nephrotic syndrome, mild abnormalities and others that the physician is comfortable with
- (7) follow-up patients that the physician is comfortable with
- (8) discuss and refer children with renal and urinary tract abnormalities diagnosed on routine prenatal ultrasound

UTI: urinary tract infection; BP: blood pressure; BUN: blood urea nitrogen; VCUG: voiding cystourethrogram; GN: glomerulonephritis.

TABLE 2: Guidelines for patient referral to the pediatric nephrologist [1].

- (1) persistent unexplained hematuria, nonorthostatic proteinuria and HT
- (2) decreased renal function (acute, chronic, and ESRD)
- (3) renal tubular disease
- (4) nephrotic syndrome, particularly steroid-dependent or -resistant
- (5) atypical or persistent GN
- (6) unexplained and severe acid-base and electrolyte abnormalities
- (7) systemic diseases associated with progressive renal involvement—systemic SLE and diabetes mellitus
- (8) genetic and congenital abnormalities likely to produce progressive renal damage
- (9) when invasive studies, for example, kidney biopsy, are indicated
- (10) major renal/urinary tract abnormalities found on routine prenatal ultrasound
- (11) renal disease that is likely to progress—FSGN and IgA nephropathy
- (12) conditions associated with acute complications—HT, calculi, and HUS
- (13) when teamwork is needed—urologist, geneticist, dietician, and social worker
- (14) parental anxiety

HT: hypertension; ESRD: end-stage renal disease; GN: glomerulonephritis; SLE: systemic lupus erythematosus; FGS: focal glomerulosclerosis; HUS: hemolytic uremic syndrome.

13. Guidelines for Patient Referral

In the present era of managed care, primary care physicians find themselves performing some duties that have traditionally been performed by the specialist. It is difficult to clearly delineate indications for referral of patients to the pediatric nephrologist. In general, pediatricians may initiate evaluation to the extent that they feel comfortable with. The most common reasons for referral to a pediatric nephrologist include fluid and electrolyte disorders and

hematuria/proteinuria, followed by chronic GN, nephrotic syndrome, UTI, hypertension, acute GN, and ESRD [12].

The role of the pediatrician in the management of the child with renal disease is outlined in Table 1. Guidelines for patient referral to the pediatric nephrologist are listed in Table 2.

Abbreviations

- ESRD: End-stage renal disease
 GN: Glomerulonephritis
 HT: Hypertension
 UTI: Urinary tract infection.

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Review Article

Nephrogenic Syndrome of Inappropriate Antidiuresis

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Mutations in the vasopressin V2 receptor gene are responsible for two human tubular disorders: X-linked congenital nephrogenic diabetes insipidus, due to a loss of function of the mutant V2 receptor, and the nephrogenic syndrome of inappropriate antidiuresis, due to a constitutive activation of the mutant V2 receptor. This latter recently described disease may be diagnosed from infancy to adulthood, as some carriers remain asymptomatic for many years. Symptomatic children, however, typically present with clinical and biological features suggesting inappropriate antidiuretic hormone secretion with severe hyponatremia and high urine osmolality, but a low plasma arginine vasopressin level. To date, only two missense mutations in the vasopressin V2 receptor gene have been found in the reported patients. The pathophysiology of the disease requires fuller elucidation as the phenotypic variability observed in patients bearing the same mutations remains unexplained. The treatment is mainly preventive with fluid restriction, but urea may also be proposed.

1. Introduction

Since 1992, when the vasopressin V2 receptor gene (*AVPR2*) sequence that codes for the V2 receptor (V2R) was first described [1], more than 200 mutations in the *AVPR2* have been found in patients presenting with X-linked congenital nephrogenic diabetes insipidus (cNDI) [2, 3]. Functional studies of these mutant receptors have demonstrated a loss of function in the mutated protein that results in the insensitivity of the renal collecting duct to the action of the arginine vasopressin hormone (AVP). This in turn leads to a defect in water reabsorption with polyuria, polydipsia, and hypernatremic dehydration.

Recently, it was demonstrated that the V2R may be affected by gain of function mutations that cause a new syndrome: the nephrogenic syndrome of inappropriate antidiuresis (NSIAD) [4]. This phenomenon has been observed for other G-protein-coupled receptors, for example, TSH (thyrotoxicosis), LH (familial male-limited precocious puberty), PTH-rp (Bloom syndrome), and the calcium sensing receptors (hypercalcemic hypocalcemia). NSIAD

was subsequently described in two infant boys presenting with seizures due to severe hyponatremia and high urinary osmolality, but low plasma AVP levels. *AVPR2* sequencing demonstrated that these two children harbored the arginine-137-cysteine (R137C) and arginine-137-leucine (R137L) mutations in their respective V2 receptors. Since 2005, when the disease was first described, all the NSAID patients presented in the literature have had one of these two *AVPR2* mutations [4–10]. Functional studies have shown that both mutations are responsible for a constitutive activation of the mutant V2R, leading to inadequate water reabsorption in spite of low AVP levels [4, 11]. Nevertheless, the clinical presentations of these NSIAD patients have been highly variable, with one of them showing severe neurological consequences, while others were fully asymptomatic with only a urine dilution defect revealed during water-load testing [5, 6]. Thus, patients may be diagnosed early in life or in adulthood, or they may remain asymptomatic. The diagnosis of NSIAD thus should be systematically considered in cases of childhood hyponatremia, especially when associated with high urine osmolality.

2. Pathophysiology of NSIAD

AVP is synthesized in the supraoptic and paraventricular nuclei and acts through three types of AVP receptors: the V1a receptor (vasopressive effects of AVP), the V1b receptor found in the adenohypophysis (ACTH secretion), and the V2 receptor (V2R) localized in the distal renal collecting duct [12]. At the cellular level, AVP-V2R binding initiates a cascade of events, with adenosine 3:5-cyclic phosphate (cAMP) production through stimulated V2R coupling with the G_{αs} protein and the activation of adenylyl cyclase. Intracellular protein phosphorylation by cAMP-dependent protein kinase A therefore occurs, which leads to the exocytic insertion of aquaporin 2 (AQP2), a specific water channel, into the luminal membrane of the principal cells of the renal collecting duct, thereby increasing its water permeability.

Under normal conditions, AVP activation of the V2R also leads to phosphorylation of serine residues located in the C-terminal receptor tail with, secondarily, β-arrestin recruitment and V2R internalization [13]. This negative regulation of the V2R after stimulation by AVP prevents prolonged and excessive tubular reabsorption of water. In NSIAD, the constitutively active mutant V2R appears to lose this important property, at least partly, but by a mechanism that remains not fully understood.

Functional studies of the R137C- and R137L-V2R mutants have shown that both mutants have increased basal cAMP production compared with the Wt-V2R, confirming their constitutive activity [4, 11]. It has also been shown that their relatively low amplitude constitutive activities are only weakly sensitive to the action of a V2R-inverse agonist like the SR121463 compound [11]. These data suggest that these mutant receptors are mainly in an almost blocked conformation and are consistent with Decaux's observation that NSIAD patients are insensitive to nonpeptide V2R inverse agonists [6]. Nevertheless, it has also been shown that the relatively low AVP-induced stimulation of both mutants is completely inhibited by V2R inverse agonists. Therefore, this latter finding suggests that, although these mutant receptors are more often in a blocked conformation, they can also adopt a more flexible conformation capable of a desensitization/internalization process [11].

3. Clinical Presentation

All patients diagnosed with NSIAD to date have been boys and most diagnoses were made during the first two years of life. Most patients appeared to have a relatively clear phenotype with biological features initially suggesting a syndrome of inappropriate antidiuretic hormone secretion (SIADH) with hyponatremia, low serum osmolality, and unexpectedly high urine osmolality, but low plasma AVP levels. The main clinical features, seizure or irritability, appeared to be linked to the severe hyponatremia.

During the neonatal period, boys bearing the mutated receptor seem able to enough dilute their urine and therefore avoid the risk of severe hyponatremia. Indeed, unless peculiar clinical conditions such as neonatal asphyxia, the physiological limitation in concentration capacity during the

first weeks of life may protect them from excessive water reabsorption during this period.

Two large kindreds of patients with NSIAD have also been reported. Decaux et al. reported the first kindred and showed that the male patients in this family had been diagnosed in adulthood and were doing well, suggesting that NSIAD conditions may sometimes remain unrecognized until advanced age [6]. The late diagnosis in such patients may also be explained by the drop in water excretion naturally observed in the elderly [14].

The female carriers of this X-linked disorder were also clinically asymptomatic, but some of them demonstrated an impaired ability to dilute urine during a water-load test performed with 20 mL/kg of water.

More recently, we reported another four-generation family with NSIAD bearing the R137C-V2R mutation [5]. In this family, the clinical presentation was highly variable in the male carriers. Indeed, one of the children had two episodes of seizures related to hyponatremia with low plasma AVP level, when he was 10 months and 34 months. Both episodes occurred during the summertime when large amounts of water were given to this young boy to prevent dehydration. His older brother, also bearing the mutated V2R, lived in the same city and, as far as we know, had the same diet but remained fully asymptomatic. Unfortunately, a first cousin, also having the same AVPR2 mutation, experienced several seizure episodes due to recurrent hyponatremia between 27 months and 5 years of age and eventually developed permanent mental retardation.

A water-load test was performed in the asymptomatic male carrier (10 mL/kg water load) and the heterozygous females (20 mL/kg water load). The results showed that water loading in the hemizygous male carrier was characterized by persistent AQP2 urine excretion independently of concomitant vasopressin excretion. This finding is consistent with a constitutive activation of the V2R. Slow and incomplete water elimination with slight hyponatremia was also found. The female carriers displayed variable biological findings after water loading that can be explained by random X inactivation [5].

Among all the family members explored, only the symptomatic hemizygous male exhibited all the expected signs under basal conditions: persistent AQP2 urine excretion, low output of highly concentrated urine, and low plasma and urine AVP levels. His asymptomatic brother, bearing the same mutation, had low AQP2 excretion and normal urine output under basal conditions but displayed a total absence of downregulation of AQP2 excretion after a cautious 10 mL/kg water load.

Concerning the plasma AVP levels measured in these NSIAD patients, most levels appeared to be low or undetectable in spite of hyponatremia and high urine osmolality. Nevertheless, in at least one case, it was shown that AVP production can persist despite low plasma sodium and plasma osmolality [8]. Thus, of the four SIADH categories described, NSIAD most often belongs to the D group with a low plasma AVP levels, although it can also be grouped in category B, which is characterized by a measurable plasma AVP level [8, 15]. The explanation for this persistent AVP secretion

found in some patients despite low plasma osmolality is not clear. Nevertheless, this residual and relatively low AVP secretion should have only a weak action on the V2R mutants given their low affinity for AVP and, mainly, the reduced cAMP production level observed after stimulation by AVP. [11].

4. Diagnosis of NSIAD Patients

When NSIAD is suspected, the plasma sodium level, plasma and urine osmolalities, and plasma AVP level should all be measured at the same time during the hyponatremic episode. The association of hyponatremia with relatively high urine osmolality and a low or undetectable plasma AVP level is an indication for sequencing the AVPR2. In siblings, a water-load test can be performed in an asymptomatic boy but cautiously: for example, with only 10 mL/kg of water [5]. In girls, a 20 mL/kg water-load test can help to determine their ability to dilute their urine, as this is variable in heterozygous females due to random X inactivation and will help in providing them with recommendations for water intake.

Assessment of the concentration of the plasma von Willebrand factor (vWF) antigen, which is known to be increased by AVP stimulation of the so-called “extrarenal V2R,” does not seem to be helpful in diagnosing NSIAD patients [4].

5. Management of Patients with NSIAD

In symptomatic NSIAD patients with hyponatremia, rapid management with fluid restriction and, if necessary, administration of 30–50% oral urea solution, is necessary to avoid persistent or increased hyponatremia, which carries the risk of brain damage [9, 16].

In addition, hemizygous boys have to avoid massive water intake, as shown by the results observed during water-load testing. In these patients, caution is particularly important when environmental factors may encourage sharp rises in water intake (sports activities, during heat waves, in the summertime, etc.). However, boys bearing the mutation are mainly at risk of developing severe hyponatremia during infancy when their water intake is mostly under parental control. In heterozygous females, the advice will depend on the results of the water-load test and will range from normal to cautious water or fluid intake.

6. Conclusion

The prevalence of this recently recognized disease is difficult to determine in children, and adults. Although NSIAD does not seem to have an early neonatal expression, the diagnosis should systematically be considered in infants, children and adults presenting with hyponatremia associated with high urine osmolality. In males, the diagnosis will be easily made by sequencing the AVPR2. In siblings, a water-load test can be helpful in studying and advising female carriers. The treatment of symptomatic patients is based on fluid restriction and, if necessary, administration of an oral urea

solution. Otherwise, treatment is mainly preventive and aims to avoid poorly adapted fluid intake.

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Review Article

Antenatal Bartter Syndrome: A Review

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Antenatal Bartter syndrome (ABS) is a rare autosomal recessive renal tubular disorder. The defective chloride transport in the loop of Henle leads to fetal polyuria resulting in severe hydramnios and premature delivery. Early onset, unexplained maternal polyhydramnios often challenges the treating obstetrician. Increasing polyhydramnios without apparent fetal or placental abnormalities should lead to the suspicion of this entity. Biochemical analysis of amniotic fluid is suggested as elevated chloride level is usually diagnostic. Awareness, early recognition, maternal treatment with indomethacin, and amniocentesis allow the pregnancy to continue. Affected neonates are usually born premature, have postnatal polyuria, vomiting, failure to thrive, hypercalciuria, and subsequently nephrocalcinosis. Hypokalemia, metabolic alkalosis, secondary hyperaldosteronism and hyperreninaemia are other characteristic features. Volume depletion due to excessive salt and water loss on long term stimulates renin-angiotensin-aldosterone system resulting in juxtaglomerular hyperplasia. Clinical features and electrolyte abnormalities may also depend on the subtype of the syndrome. Prenatal diagnosis and timely indomethacin administration prevent electrolyte imbalance, reconstitute normal growth, and improve activity. In this paper, authors present classification, pathophysiology, clinical manifestations, laboratory findings, complications, and prognosis of ABS.

1. Introduction

Bartter syndrome is a rare renal tubulopathy first described by Frederic Bartter in 1962. The primary pathogenic mechanism is defective transepithelial chloride reabsorption in thick ascending limb of loop of Henle (TALH). The disease is characterized by hypokalemia, metabolic alkalosis, and secondary hyperaldosteronism with normal to low blood pressure due to renal loss of sodium and hyperplasia of juxtaglomerular apparatus [1, 2]. There are two distinct presentations of Bartter syndrome, namely; antenatal Bartter syndrome (ABS) and classical Bartter syndrome. ABS is the severe form having onset in utero. The awareness of the condition is important for early recognition. The typical features include fetal polyuria, early onset maternal polyhydramnios, intrauterine growth restriction, preterm birth, postnatal polyuria, episodes of dehydration, recurrent vomiting, and failure to thrive [3, 4]. Another syndrome, Gitelman syndrome, is often called as variant of Bartter syndrome. This is a rare autosomal recessive disorder

characterized by late onset hypokalemic metabolic alkalosis, hypocalciuria, and hypomagnesemia. History of maternal hydramnios or prematurity will be absent. They are frequently asymptomatic. Muscular weakness and tetany may be present sometimes. Polyuria and growth retardation are not major manifestations. Plasma renin and aldosterone are increased but not to the degree seen in Bartter syndrome. Urinary prostaglandins are not increased.

2. Classification and Inheritance of Bartter Syndrome

Antenatal Bartter syndrome has four variants [5, 6] with mild differences in phenotype and genotype (Table 1). Principal clinical features in most of them include early onset polyhydramnios, failure to thrive, prematurity, and nephrocalcinosis. Types I, II, and III have severe antenatal symptoms, prematurity, and failure to thrive, while type IV is a mild salt losing nephropathy with mild antenatal

TABLE 1: Pharmacological classification of Bartter syndrome with important clinical features.

Subtypes	Gene loci	Molecule affected	Molecule implicated	Site in renal tubule	Pharmacological classification	Important clinical features
Antenatal Bartter syndrome	I (601678)	<i>SLC12A1</i> /15q21.1	Na-K-2Cl cotransporter	TAL	Pure frusemide type	Severe maternal polyhydramnios, hypercalcemia, nephrocalcinosis
Antenatal Bartter syndrome	II (241200)	<i>KCNJ1</i> /11q24	Kir1.1 potassium channel	TAL	Thiazide type	Hypochloremia, hypomagnesemia, failure to thrive in infancy, EAST syndrome
Classic Bartter	III (602522)	<i>CLCNKB</i> /1p36	ClC-Kb chloride channel	DCT	Thiazide type	Hypomagnesemia, hypocalciuria, EAST syndrome
Bartter syndrome with sensorineural deafness	IV (606412)	<i>BSND</i> /1p31 or <i>CLCNKA</i> - <i>CLCNKB</i> /1p36	Barttin, ClC-Ka and ClC-Kb chloride channels	TAL+DCT	Thiazide-frusemide type	Polyuria, hypochloremia, mild hypomagnesemia, SND, CRF

TAL: thick ascending loop of Henle, TAL: thin ascending loop of Henle, DCT: distal cortical tubule, EAST syndrome: epilepsy, ataxia, sensorineural deafness, tubulopathy, SND: sensorineural deafness, and CRF: chronic renal failure.

symptoms. Type IV involves chloride channels which are present in distal nephron as well as in inner ear resulting in sensorineural hearing loss in addition. Table 1 shows the new pharmacology based classification with details of the types and molecules affected in each of them. This classification is designed on Bartter syndrome for easy understanding as students and young physicians are more familiar with pharmacologic actions of diuretics at each level of nephron [6].

3. Pathophysiology

Thick ascending loop of Henle (TAL) has channels, namely, Na-K-2Cl cotransporter, K⁺ (ROMK: rat outer medulla potassium), and chloride (CIC-Kb) channels which are responsible for electrolyte absorption. Each of these channels is coded by a specific gene (Table 1). Any mutation in gene results in impaired channel function and hence defective electrolyte reabsorption. K⁺ transport occurs through ROMK channel, whereas Na⁺ and Cl⁻ get absorbed from the luminal space. Passage of Cl⁻ from the cell into the interstitium can take place through kidney-specific chloride channels (CIC-Kb) and via K^{+/Cl⁻ cotransport system. In the apical membrane, there is also an exchange of Na⁺/H⁺. Thus, the handling of chloride ions by the thick ascending loop of Henle (TALH) is an intimate part of the normal function of Na⁺ K⁺ 2Cl⁻ electroneutral cotransport, as well as K⁺ channels (ROMK) and Cl⁻ channels (CIC-Kb). Any loss or altered function of Na⁺-K⁺-2Cl⁻ cotransporter and/or K⁺ channels as well as chloride channels results in defective Cl⁻ transport. This defect will result in malreabsorption of Na⁺, K⁺, Cl⁻, and Ca²⁺ in the TALH and delivery of large volumes of urine with a high content of Na⁺, K⁺, Cl⁻, and Ca²⁺ to the distal tubule. In the distal tubule, part of the delivered Na⁺ will be reabsorbed in exchange for intracellular K⁺. Hence, potassium wasting occurs. Impaired Na absorption in TALH will result in increased levels of prostaglandin E2. Increased PGE2 will exacerbate primary defect of chloride transport}

in TALH which will stimulate renin angiotensin-aldosterone axis causing hypokalemia (due to hyperaldosteronism), and impede water reabsorption in collecting ducts leading to hyposthenuria (Figures 1 and 2). Hyperaldosteronism increases K wasting and stimulates exchange of intracellular H ions for K ions for intraluminal K (distal tubule and collecting duct) resulting in exaggeration of metabolic alkalosis. The normal blood pressure despite high levels of renin and angiotensin is thought to be due to nonresponsive of their blood vessels to angiotensins [1–7]. Continuous loss of calcium in urine results in nephrocalcinosis [2–4].

4. Clinical Features

Mothers of fetus with Bartter syndrome often present with unexplained polyhydramnios between 24 and 30 weeks of gestation [3, 4, 7]. Intrauterine growth restriction may also be associated. Inability of the kidney tubule to retain salt and water results in fetal polyuria. Important biochemical abnormality in amniotic fluid is normal sodium and potassium but consistently elevated chloride levels [4, 8–12]. Infants are usually born preterm. After birth, important diagnostic finding is hyposthenuria and rapid weight loss. Poor feeding and lethargy are the other symptoms. Urine examination shows low specific gravity, normal potassium but high sodium and chloride levels. However, after 1–3 weeks, level of potassium considerably rises above normal with relatively less sodium than in the first week of life. Prostaglandin levels are high in blood and urine as a secondary phenomenon [5, 6, 9, 13]. Impaired sodium absorption in TALH will result in increased levels of prostaglandin E₂ [13, 14]. If the diagnosis gets delayed, infants may present with poor feeding, dehydration, and severe electrolyte imbalance. Transient hyperkalemia may be observed in type II ABS. Blood pressure is usually normal. Growth faltering, dwarfism, polydipsia, and weakness may be present in older children. Mild mental retardation is

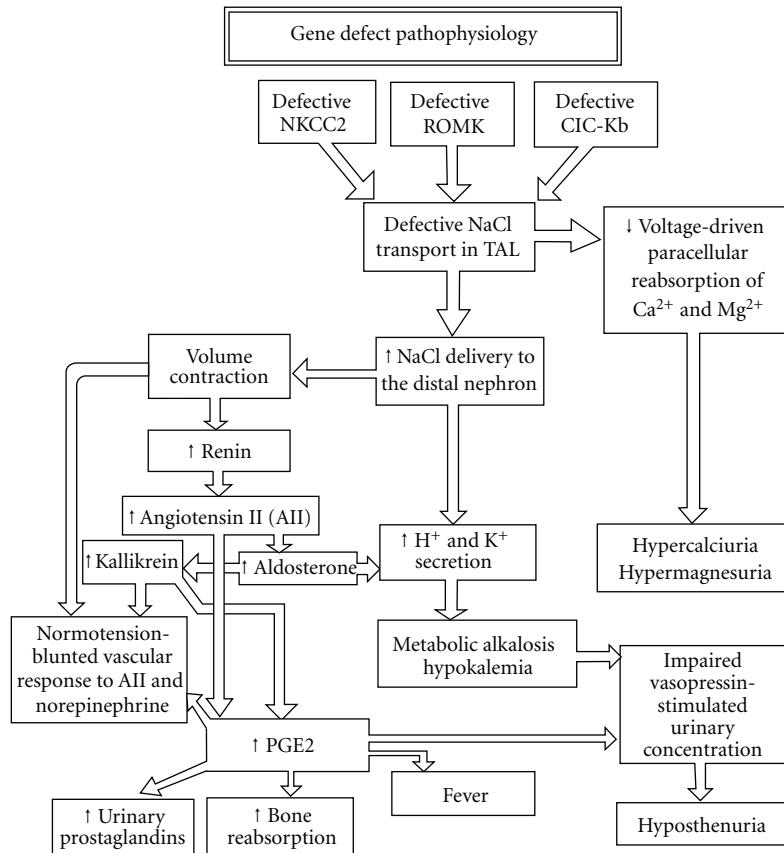


FIGURE 1: Pathophysiology of Bartter syndrome.

reported in few patients. Facial features such as triangular face, prominent forehead, large eyes, protruding ears, and drooping mouth may be present [15, 16]. Sensorineural deafness is seen in type IV Bartter syndrome. Strabismus, convulsions, and increased susceptibility to infections are also reported [15, 16]. Urinary electrolytes except potassium in second trimester are low in mother's urine in cases of Bartter syndrome [17].

5. Laboratory Investigations

When there is early onset unexplained maternal polyhydramnios, ultrasonography should be performed to confirm structurally normal fetus and placenta. If ABS is strongly suspected, one should do amniocentesis and subject amniotic fluid for biochemical analysis. High chloride in amniotic fluid is a consistent finding and diagnostic of ABS [4, 9, 17]. Other electrolytes in the amniotic fluid will be normal. In affected neonates, serum and urinary electrolyte estimation is important. Urinary electrolytes show increased sodium, potassium, and chloride levels. Hypokalemia is the usually observed serum electrolyte abnormality. Blood gas analysis detects metabolic alkalosis. Plasma renin will be usually high. Ultrasonography of the kidneys detects bilateral medullary nephrocalcinosis which is observed after several weeks of severe hypercalciuria [2, 4, 11]. Mutational analysis of the genomic DNA will identify the fundamental defect [5].

6. Complications

The important complications of ABS include hypercalciuria leading to nephrocalcinosis [2, 4, 11, 12] and growth restriction. Sensorineural deafness is associated with Bartter syndrome IV. Defects in the barttin subunit of the ClC-Ka and ClC-Kb channels are responsible for sensorineural deafness [15]. Very rarely progressive renal disease, renal failure, and interstitial nephritis can occur. Acute renal failure from rhabdomyolysis due to hypokalemia has also been reported.

7. Treatment

Prenatal diagnosis can be made by the high chloride content of the amniotic fluid [18–20] and mutational analysis of genomic DNA extracted from cultured amniocytes obtained by amniocentesis [21]. Once ABS is confirmed, mother should be treated antenatally at the earliest with indomethacin (1 mg/kg/day) in two divided doses [22]. Indomethacin inhibits prostaglandin synthetase, decreases renal salt wasting, reduces fetal urine output, and thereby controls polyhydramnios. Indomethacin may lead to constriction of ductus arteriosus. Hence, patency of ductus arteriosus needs to be monitored in all such fetuses. Rapidly increasing hydramnios may require therapeutic amniocentesis. Indomethacin therapy and therapeutic amniocentesis usually allow the pregnancy to continue. Following birth,

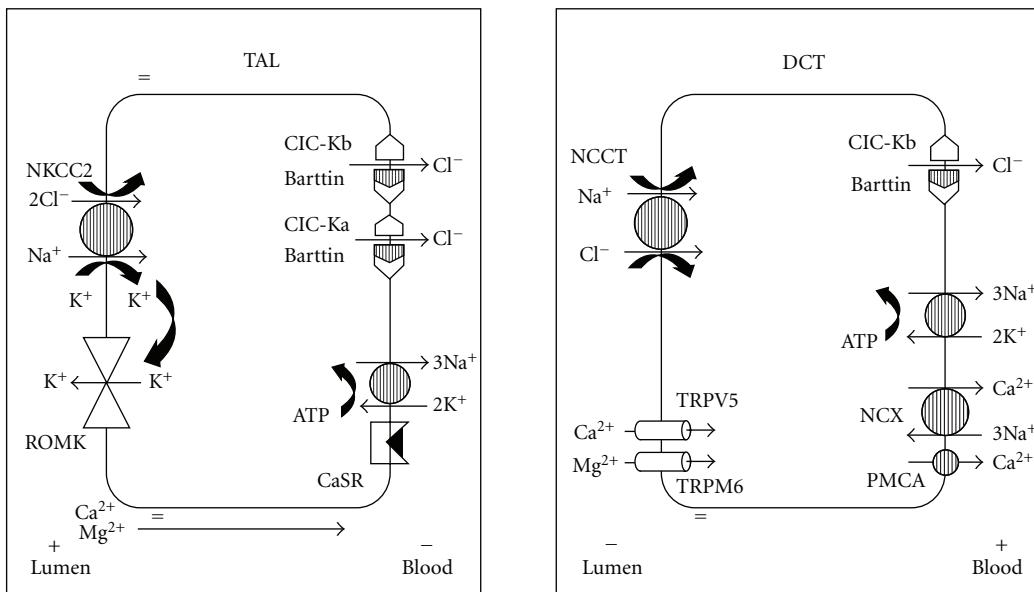


FIGURE 2: Pictorial representation of ion transporters in thick ascending limb of Loop of Henle (TAL) and distal convoluted tubule (DCT).

neonate should be monitored for urine output, hydration, weight loss, and electrolyte balance. Correction of dehydration and electrolyte imbalance are the important aspects of management. Potassium supplements are usually needed by 2–3 weeks. Prostaglandin synthetase inhibitors are usually required for the disease control. Indomethacin at a dose of 1–5 mg/kg is usually recommended and well tolerated [18, 22, 23]. Early initiation of indomethacin may be required in neonatal Bartter syndrome caused by mutations at gene coding for the NKCC2 transporter. Benefit from initiation of indomethacin therapy at 4–6 weeks and doses below 1 mg/kg/day is likely in patients with mutations at the ROMK channel gene [19]. Indomethacin has side-effects on gastrointestinal tract. Colonic perforation after indomethacin administration has been reported emphasizing the importance of careful monitoring [24]. Other drugs used are acetylsalicylic acid (100 mg/kg/day), ibuprofen (30 mg/kg/day), or ketoprofen (20 mg/kg/day). Addition of potassium sparing diuretics may be initially effective in the control of hypokalemia, but their effect is transient. Caution in such treatment is required as treatment with potassium sparing diuretics may be dangerous in situations of gross salt and water wasting and circulatory volume contraction. Long-term prognosis is guarded. Lack of satisfactory control may lead to morbidity, growth failure, and renal insufficiency [2, 18, 23].

8. Prognosis

Untreated ABS patients may succumb to dehydration, dyselectrolytemia, and intercurrent infections. Timely and appropriate therapy results in clinical improvement and catch up growth in majority of children. Long-term outcome including mental development and puberty is usually normal [2, 18, 23]. Growth retardation is a uniform feature in nearly

all patients with Bartter syndrome. Developmental delay has also been described in earlier reports. Hypokalemia, hypercalcioria, and nephrocalcinosis may lead to chronic tubulointerstitial nephropathy and progressive reduction in GFR. Renal failure is likely to occur especially in children with BSND mutations. Renal failure requiring dialysis or transplantation is fairly uncommon in Bartter syndrome. Brochard et al. [25] reported chronic renal failure in 3 out of 42 children with a median followup of 8.3 years. Satisfactory prognosis after a median followup of more than 10 years and gallstones representing a new complication of ABS has also been reported [26]. Benefits from renal transplantation have been mentioned. Spontaneous recovery of ABS following a period of treatment has been recognized [27].

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Review Article

Kidney Disease and Youth Onset Type 2 Diabetes: Considerations for the General Practitioner

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Youth onset type 2 diabetes (T2DM) continues to increase worldwide, concomitant with the rising obesity epidemic. There is evidence to suggest that youth with T2DM are affected by the same comorbidities and complications as adults diagnosed with T2DM. This review highlights specifically the kidney disease associated with youth onset T2DM, which is highly prevalent and associated with a high risk of end-stage kidney disease in early adulthood. A general understanding of this complex disease by primary care providers is critical, so that at-risk individuals are identified and managed early in the course of their disease, such that progression can be modified in this high-risk group of children and adolescents. A review of the pediatric literature will include a focus on the epidemiology, risk factors, pathology, screening, and treatment of kidney disease in youth onset T2DM.

1. Epidemiology of Youth Onset Type 2 Diabetes

Type 2 diabetes (T2DM) has been described in children and adolescents since the 1980s [1], and coincident with the rising obesity epidemic, the incidence and prevalence have continued to rise over the last thirty years [2, 3]. Youth onset T2DM has now been described around the world, including Canada, Japan, India, Australia, the United States (US), and the United Kingdom (UK) [4–9]. The highest rates have been reported in the Pima Indian population in the US, with a prevalence of 1.4% in boys and 2.88% in girls between 10 and 14 years [10]. In Canadian First Nation children 4–19 years of age, the prevalence has been reported to be as high as 1% in some communities [11]. In most other populations, although rates are increasing, the disease remains comparably rare. In the US, for example, the incidence in 10–14 years old is 8.1/100,000 person years, and 11.8 per 100,000 person years in children 15–19 years [12]. In Canada, a recent active surveillance initiative revealed a minimum incidence rate of T2DM in children less than 18 years of 1.54 per 100,000 per year. The highest rate was seen in the province of Manitoba, with a minimum incidence rate of 12.45 per 100,000 children

[13]. The lowest rates have been reported in the UK at 0.53 per 100,000 in less than 17 year olds [14].

In addition to obesity, multiple other risk factors for the development of youth onset T2DM have been identified. Firstly, most affected children belong to minority ethnic groups including Canadian First Nation, American Indian, Hispanic, African-American, and Indo-Asian [6]. T2DM represents only 6% of non-Hispanic white children in the US with diabetes [15] but accounts for 46.1% of newly diagnosed Hispanics, 57.8% of non-Hispanic blacks, 69.7% of Asian Pacific Islanders, and 86.2% of American Indians with youth onset diabetes [12].

A strong family history is almost universal, with 45–80% of children with T2DM having at least one parent and 70–100% having a first or second-degree relative affected with the disease [16, 17]. The intrauterine environment has also been shown to be important. Children at the lowest and highest extremes of birth weight are at increased risk [18], as are those exposed to pregestational or gestational diabetes in utero [19, 20]. In contrast, breastfeeding has been shown to be protective [19, 20]. Finally, specific genetic factors may play an important role. For example, a unique hepatic

nuclear factor- (HNF-)1 α is a transcription factor expressed in many tissues including the liver, intestine, pancreatic β -cell, and kidney. A polymorphism of this gene (HNF-1 α G319S) has been identified in the Oji-Cree language group of First Nation people in Manitoba and northwestern Ontario. It is associated with an insulin-secretory defect, which predisposes to early onset T2DM in this population [21, 22].

2. Nephropathy Associated with Type 2 Diabetes

In adults, T2DM is the leading cause of end-stage kidney disease (ESKD) accounting for 30–40% of cases in most countries. ESKD secondary to diabetic nephropathy typically manifests after 20 to 30 years of diabetes exposure [23]. In children and adolescents, diabetes accounts for only 0.1% of ESKD [24]. However, there is mounting evidence to suggest that renal complications in youth onset T2DM manifest themselves early in the course of disease, and that progression parallels that seen in adult onset T2DM [25]. As youth onset T2DM has only been described for twenty years, we are just now starting to see the impact of the renal complications associated with this devastating disease, as the first cohort of youth enter their third decade.

Microalbuminuria is the first manifestation of a renal complication of diabetes and is the most commonly reported complication of T2DM in youth [26–30]. Reported rates vary widely between 7 and 22% at presentation [27, 28, 31] and between 9.6 and 72% within 3–10 years after diagnosis [26–32]. Variation in rates depends mainly on the definition of albuminuria utilized in each study. Most studies report albuminuria in one random urine sample, which overestimates the prevalence of pathologic albuminuria, as urinary albumin excretion can be transient. Studies that have utilized more stringent criteria (2 out of 3 abnormal samples over a 3–6 month period) report more conservative rates, such as the TODAY study cohort, which reported a prevalence of albuminuria of 13% at a mean age of 14 years, and mean diabetes duration of 7.8 months [33]. This cohort had an average hemoglobin A1c (HbA1c) of 5.9% at enrollment and is therefore likely a low-risk group. In contrast, rates of microalbuminuria in a Manitoba, Canada, cohort with an average HbA1c of 8.9%, based on at least 2 abnormal samples, are much higher at 26.9%, at a mean age of 16.5 years and mean duration of diabetes of 3 years [34]. There has yet to be a study in youth that has reported rates of persistent albuminuria confirmed with a first morning urine sample or overnight urine collection, which are considered the gold standard tests. Nevertheless, these high rates in adolescence are concerning, as microalbuminuria is predictive of progressive diabetic nephropathy, declining glomerular filtration rate (GFR), and cardiovascular disease [35–38].

In the Pima Indian population of the US, there is a 5-fold increased risk of age-specific ESKD in those diagnosed with diabetes before the age of 20 compared to those with diabetes onset between 25 and 54 years of age [39]. However, after controlling for confounders, age at onset was no longer associated with an increased incidence of ESKD, suggesting that the longer duration of diabetes accounted for the increased

risk in middle age. These results are in keeping with a previous study by Krakoff et al. which directly compared youth with T2DM <20 years at diagnosis versus young adults 20–39 years versus older adults >40 years at diagnosis which did not show a difference in risk of nephropathy over 25 years between groups [25]. What remains especially concerning, however, is the young age at which youth with T2DM will reach ESKD, requiring dialysis or kidney transplant to sustain life. In Manitoba, ESKD has previously been reported to occur prior to the age of 30 years in young adults diagnosed with T2DM prior 18 years [40]. The same cohort has also recently been shown to have a 4-fold increased risk of ESKD compared to youth with type 1 diabetes (T1DM). In addition, the renal survival fifteen years after diagnosis is 92%, and only 55% in those individuals with 20 years of followup [34]. A higher incidence of nephropathy in young adults with T2DM compared to those with T1DM has also been reported in the Japanese population [41]. A subgroup of this population with proliferative retinopathy prior to age 35 was associated with diabetic nephropathy in 60% and renal failure in 23%, with a requirement for renal replacement therapy at 35 years of age [42].

3. Risk Factors for Progression

Kim et al. followed youth with T2DM longitudinally for a median of 3 years, and microalbuminuria identified on one initial urine assessment remained persistent in >93% of youth less than 20 years of age [45]. This study also demonstrated that microalbuminuria in adolescents with T2DM is a predictor of progression to macroalbuminuria over a median followup of 8.1 years [45]. Albuminuria detected in adolescence has also been associated with a 4-fold increased risk of renal failure in early adulthood [34]. Microalbuminuria can therefore be considered a harbinger of renal injury in youth with T2DM, consistent with adult onset T2DM.

The adult literature has identified clinical risk factors associated with the development of diabetic nephropathy. There may also be a genetic predisposition, as has been shown in the Pima Indians in the US [46] as well as in Caucasians [47]. A study of 191 normoalbuminuric adults with T2DM followed prospectively for 5 years described a risk of microalbuminuria of 5% per year and identified male sex, older age, baseline albuminuria, HbA1c, cholesterol, and presence of retinopathy as risk factors [48]. In addition, glomerular hyperfiltration (i.e., increased GFR) has been well described in adults with T2DM, hypothesized to be secondary to concomitant obesity and hyperglycemia. The GFR has been shown to progressively increase and reach a plateau once microalbuminuria develops. Once progression to macroalbuminuria occurs, the GFR begins to decline [49]. It is, however, not consistent in the literature that hyperfiltration is pathogenic, as some studies have shown no association between hyperfiltration and decreased GFR [49].

The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have shown that the intensity of glycemic control

significantly impacts the development of diabetic nephropathy in T1DM and adult onset T2DM [50–52]. The pediatric literature is scant but available data suggests that glycemic control is also an important risk factor in youth with T2DM [30, 53]. However, the ideal target for HbA1c to minimize the risk of nephropathy in youth with T2DM has not yet been determined. The clinical practice guidelines currently extrapolate from adult data to target an HbA1c $\leq 7\%$ [54]. Unfortunately, this target HbA1c is difficult to achieve in youth, due in part to adolescent behavior and nonadherence to treatment recommendations.

Youth with type 2 diabetes have a high prevalence of comorbidities such as obesity, hypertension, and dyslipidemia [55, 56]. The role of these potentially modifiable clinical risk factors in the development of diabetic nephropathy has not yet been clearly defined in youth onset T2DM. Obesity is associated with glomerular hyperfiltration and the development of glomerulosclerosis and kidney failure [57, 58]. Renal hyperfiltration and hypertrophy may develop in the setting of T2DM in response to disproportionate weight gain and declining insulin sensitivity [59]. According to this hypothesis, adolescents with T2DM may be particularly at risk for premature renal injury relative to adults who experience more gradual weight gain and insulin resistance in adulthood.

Hypertension is highly prevalent in youth with T2DM, with a reported prevalence between 10 and 73% at diagnosis [28, 55, 60–64]. In contrast to the T1DM and adult onset T2DM literature [65], which consistently demonstrates hypertension to be an important modifiable risk factor for the development and progression of diabetic nephropathy, the association between blood pressure control and microalbuminuria in adolescents with T2DM is inconsistent [32, 45, 53]. A small case-control study ($n = 23$) revealed that daytime systolic blood pressure was ~ 8 mmHg higher among youth with T2DM, relative to normoalbuminuric controls [32]. In contrast, multivariate regression analyses from a larger cross-sectional study and a prospective cohort study demonstrated that systolic blood pressure is not associated with microalbuminuria in adolescents and young adults with T2DM [30, 31, 53]. These different findings may be explained by differences in measurement techniques (casual clinic-based measures versus 24 hr blood pressure monitoring), underpowered studies, or a lack of prospective studies with adequate followup.

Dyslipidemia is a frequent finding in youth with T2DM [27, 28, 31, 55, 62, 64, 66–68]. Two small studies have shown increased LDL cholesterol and triglyceride levels in youth with T2DM and microalbuminuria compared with those with normal albumin excretion [30, 32], suggesting that modification of dyslipidemia may affect risk of nephropathy.

Smoking is reported in 7–48% of youth with diabetes [69, 70]. In T1DM, smoking has been shown to increase the risk of microalbuminuria [71]. In addition, smoking is also associated with a reduced GFR in adults with T1DM and T2DM even after controlling for multiple confounders, including microalbuminuria [72]. Strategies to help with smoking cessation are therefore very important for these high-risk youth.

TABLE 1: Definitions for albuminuria* [43].

	Albumin : Creatinine ratio (mg/mmol) [43] [†]	24 hour collection for albumin excretion (mg/day)
Normal	<2.0 (boys) <2.8 (girls)	<30
Microalbuminuria	2.0–20.0 (boys) 2.8–28.0 (girls)	30–300
Macroalbuminuria	>20.0 (boys) >28.0 (girls)	>300

[†]Must be confirmed with either first morning urine sample or overnight urine collection.

*Persistent albuminuria defined as 2/3 positive samples over a 3–6 month period, samples must be at least 1 month apart.

4. Pathology

Classic diabetic nephropathy is characterized by glomerular hypertrophy, basement membrane (GBM) thickening, and mesangial matrix expansion [73]. There is very little biopsy data available on youth with T2DM. In a cohort of ten Canadian First Nation youth with T2DM and macroalbuminuria who underwent renal biopsy, nine of ten biopsies exhibited immune complex disease or glomerulosclerosis, and none had classic diabetic nephropathy [74]. This may in part be due to the high burden of nondiabetic primary renal disease in Canadian First Nation populations [75–77]. Adults with T2DM have also been shown to have nondiabetic glomerular disease, either superimposed on diabetic nephropathy (17%) or more commonly without underlying diabetic disease (28%) [78]. Concomitant obesity is also associated with focal glomerulosclerosis and renal failure [57, 58]. Therefore, there may be early changes seen in youth with T2DM related to nondiabetic kidney disease, and obesity. The additive effects of diabetes and its associated comorbidities may alter progression of renal dysfunction over time.

5. Screening

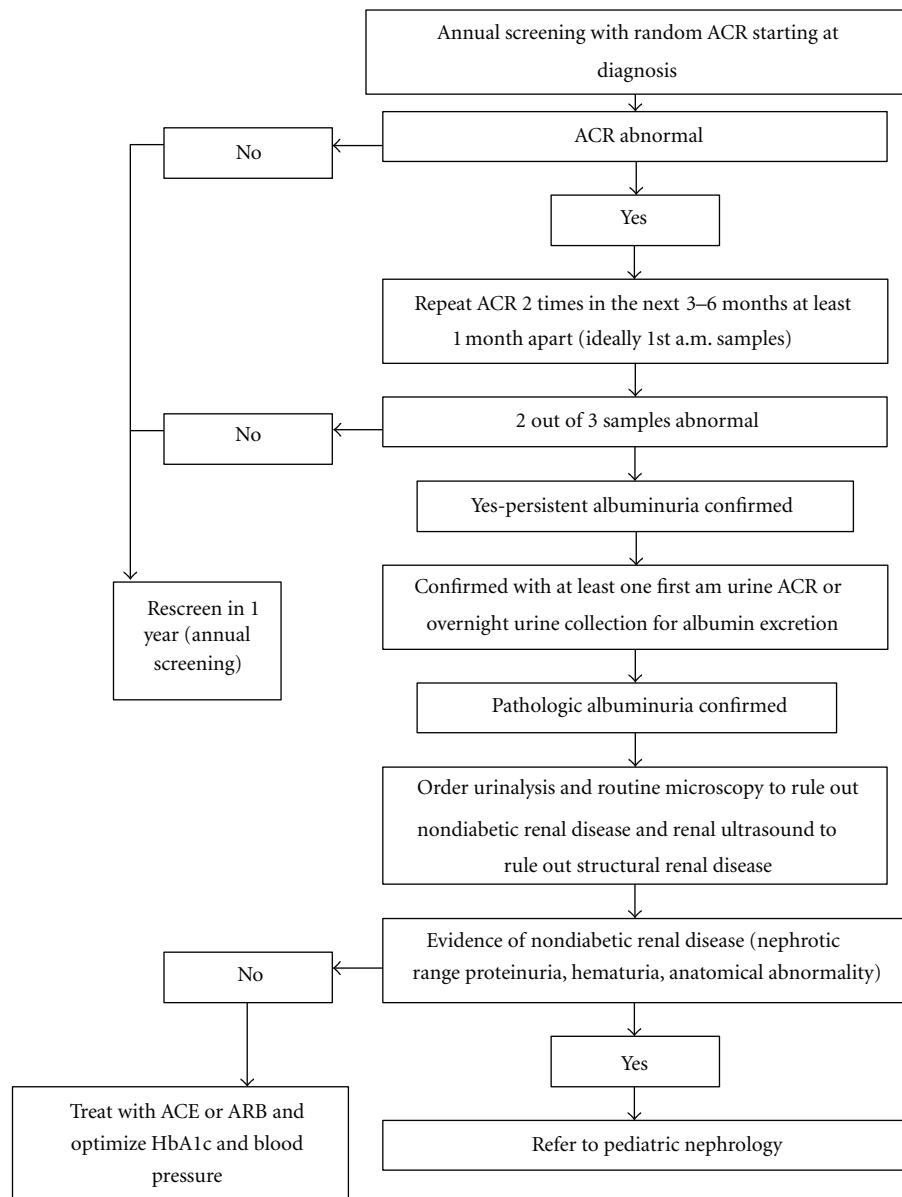
Canadian, American, and International guidelines [15, 54, 79] all recommend screening for diabetic nephropathy at first presentation of diabetes. There are no validated definitions for albuminuria in youth, therefore, the adult values are currently utilized to stage patients (Table 1).

Albumin excretion rates in adolescents are influenced by several factors including orthostatic changes, fever, infection, and physical activity. Therefore, it is necessary to have at least 2 positive samples over 3 to 6 months, separated by at least 1 month to confirm the diagnosis [43]. In addition, the diagnosis in youth should be confirmed with a first-morning urine sample or overnight urine collection, to rule out orthostatic proteinuria [80]. An algorithm for screening and treatment has been proposed (Figure 1).

In addition to screening for albuminuria, screening for concomitant comorbidities (dyslipidemia, hypertension, and smoking) is also recommended [54, 79, 81]. An assessment of renal function should also be considered in the form

TABLE 2: Recommended treatment targets that may reduce risk of nephropathy in youth with type 2 diabetes.

Clinical parameter	Intervention	Treatment target
Glycemic control	Lifestyle/Insulin/Metformin	HbA1c ≤ 7%
Prehypertension [44] (bp > 90th–95th)	Lifestyle	Bp < 90th percentile
Hypertension [44] (bp > 95th percentile)	Lifestyle ± Ace inhibitor or Angiotensin II Receptor Blocker	Bp < 90th percentile
Dyslipidemia LDL ≥2.6 mmol/L	Lifestyle	LDL < 2.6 mmol/L
Dyslipidemia LDL >4.1 mmol/L	Lifestyle + Statin	LDL < 2.6 mmol/L
Overweight and Obesity	Lifestyle	BMI < 85th percentile
Smoking	Cessation strategies	Nonsmoker



ACR = albumin to creatinine ratio

ARB = angiotensin II receptor blocker

ACE = angiotensin converting enzyme inhibitor

HbA1c = hemoglobinA1c

FIGURE 1: Screening algorithm for albuminuria in youth with type 2 diabetes (modified from CDA guidelines) [43].

of an estimated glomerular filtration rate [43, 82]. A urinalysis and a renal ultrasound should be performed. The presence of hematuria or red blood cell casts raises the possibility that a nondiabetic kidney disease could be present. In those cases, a glomerulonephritis workup should be initiated, and a renal biopsy considered. In the event of macroalbuminuria, evidence of nondiabetic kidney disease, or an atypical course, a referral to a pediatric nephrologist is recommended.

6. Treatment of Nephropathy and Associated Comorbidities (Table 2)

First line in the prevention and treatment of nephropathy associated with T2DM is lifestyle modification and behavior change, including weight reduction, low-sodium diet, and exercise [17] in order to optimize glycemic control and reduce comorbidities such as obesity, hypertension, and hypercholesterolemia. Smoking cessation strategies should be implemented. Unfortunately, this type of therapy requires significant buy in from patients, families, and health care providers. This patient population is particularly challenging to treat due to their adolescent age, as well as the very high rates of lower socioeconomic status (SES). In the TODAY study, 41.5% of participants had a household income < \$25,000 [33], and in Manitoba 59.1% of youth with T2DM are in the lowest SES quintile [34]. If lifestyle modification is not sufficient to reduce and maintain HbA1c to <9% (target HbA1c is ≤7%), then pharmacologic management is indicated, in the form of insulin and/or metformin [17, 54, 81], which is the only oral hypoglycemic agent that has been approved (in 2000) by the US Food and Drug Administration [83, 84].

In the absence of concrete blood pressure data in children with diabetes, the current guidelines recommend targeting normal blood pressures in children with T2DM (<90th percentile for age and height, or a maximum of <130/80), [17, 44] not only to potentially reduce the risk of renal injury, but to decrease the risk of cardiovascular disease [17, 54, 81]. Angiotensin II receptor blockers (ARBs) have been used most often in studies of adult onset T2DM and have been shown to consistently reduce the rate of progression from microalbuminuria to macroalbuminuria [85–87]. Angiotensin-converting enzyme (ACE) inhibitors have also been evaluated and been shown to decrease the risk of microalbuminuria in normoalbuminuric patients with T2DM [88]. No studies have evaluated these drugs in youth with T2DM. There is a small number of nonrandomized studies in youth with T1DM, all of which have shown reductions in albuminuria with ACE inhibitors [89–91]. Treatment with an ACE or ARB is therefore considered first-line therapy for both hypertension and microalbuminuria in youth with T2DM [17, 81]. If treatment targets are not achieved with one medication, then it is recommended that a second agent be added [17]. Female patients must be advised that congenital malformations, even in the first trimester, have been reported with ACE and ARB use [92]. Contraception counseling is thus very important when these drugs are being used.

Treatment of hyperlipidemia is more controversial. Lifestyle modification is considered first-line therapy, and improvement in glycemic control often results in improved lipid levels. If lifestyle fails, then pharmacologic management with HMG CoA reductase inhibitors is recommended. The Canadian Diabetes Association currently recommends targets used for familial hyperlipidemia for initiation of pharmacologic agents, as studies done in this particular group have not yet been done. A low-density lipoprotein (LDL) threshold value >4.1 mmol/L is utilized to initiate pharmacologic management if there is a family history of early cardiovascular events or ≥4.9 mmol/L in the absence of cardiovascular events [54, 93]. In contrast, the International Society for Pediatric and Adolescent Diabetes recommends a stricter target of <2.6 mmol/L, based on adult data [94].

7. Conclusions

The prevalence of type 2 diabetes in youth continues to increase and is associated with microalbuminuria early in the course of disease. The rate of progression to ESKD is in keeping with adult onset disease. Poor metabolic control and co-morbidities such as hypertension, dyslipidemia, and smoking are highly prevalent and likely hasten the progression of diabetic nephropathy and chronic kidney disease. Multifactorial-based prevention and treatment approaches focusing on lifestyle modification and incorporating pharmacologic management of hyperglycemia, hypertension, and albuminuria have been proven in adult studies. Similar strategies are also likely important to delay progression to ESKD in youth with T2DM, however, more research is required to better define the natural history of diabetic nephropathy and optimal treatment targets and therapies in this high-risk population.

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Review Article

An Approach to the Child with Acute Glomerulonephritis

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Acute glomerulonephritis (AGN) is a common condition in childhood. Many children with AGN can be managed in the primary care setting. The diagnosis is usually made on the basis of urinary findings, especially the presence of red blood cell casts. One of the most important initial investigations is determining the complement C3 level; hypocomplementemia is most characteristic of post streptococcal AGN, while normocomplementemia is most often seen with IgA nephropathy. Children whose AGN is accompanied by significant hypertension or renal insufficiency should be assessed by a specialist immediately. The presence of serious extrarenal signs or symptoms also merits urgent referral. Otherwise, serial followup in the primary care office is appropriate.

1. Introduction

Many children with acute glomerulonephritis (AGN) are first seen in their primary physicians' offices. This initial contact may be crucial in determining the child's most appropriate disposition as well as identifying any immediate threats to life.

This paper will review the office approach to AGN in children on the basis of upon a firm grounding in pathophysiology. It will begin with an overview of the pathology and pathophysiology of glomerulonephritis and then present a practical outline of the important aspects of the history and physical examination pertinent to a child with suspected AGN. It will then provide guidance in choosing and interpreting appropriate laboratory studies for the initial evaluation. Finally, some guidance will be provided on referral of children with AGN, including a discussion of some situations in which management by the primary caretaker may be appropriate.

2. Overview of AGN

AGN is a complex of findings which is marked histologically by a generalized glomerular inflammation. Frequently, renal biopsy is not available, but AGN can usually be recognized by the clinical picture of hematuria, fluid overload (edema

and hypertension), and some evidence of renal insufficiency (elevation of BUN and creatinine).

In most circumstances, glomerular inflammation begins with an antigen-antibody reaction, either direct antibody binding to an antigen expressed or trapped in the glomerulus, or the localization of a circulating complex in the kidney. This incites injury by activating one or more systems of inflammatory mediators: the complement cascade, coagulation factors, cytokines, growth factors, and others. The inflammation is marked by proliferation of resident glomerular cells and infiltration by lymphocytes or neutrophils.

The glomerular inflammation and expansion impairs the microcirculation, reducing the glomerular filtration rate (GFR) and usually resulting in an increase in BUN and creatinine. This reduction in GFR, in turn, leads to the retention of salt and water, causing fluid overload. The degree of fluid overload in AGN can vary considerably. In severe situations, it can be manifest by life-threatening hypertension and pulmonary edema. Indeed, hypertensive encephalopathy may be the presenting complaint in some children with AGN [1].

In some situations, AGN is a primary process, and virtually, all of the clinical findings are a consequence of the renal lesion. Poststreptococcal AGN is the best example of this [2]. In other cases, the AGN is but one manifestation of a systemic illness which has targeted multiple organs, each of which may be independently injured. In children, the AGN

associated with Henoch Schoenlein purpura is the prototype for this [3].

Fortunately, most cases of AGN in children are either self-limited or amenable to therapy although there may be devastating complications of the illness during the acute phase. Less commonly, what begins as an apparent AGN may presage the development of a chronic process, which ultimately may progress into irreversible end-stage renal disease (ESRD).

3. History and Physical Examination

Most typically, the child with AGN will be seen because of the sudden development of change in urine color. On occasion, however, the presenting complaint may relate to a complication of the disease: hypertensive seizures, edema, and so forth.

The history begins with obtaining more details about the change in urine. Hematuria in children with AGN is typically described as "coke," "tea," or "smoky" colored. True bright red blood in the urine is more likely a consequence of anatomic problems such as urolithiasis [4] than glomerulonephritis. Urine color in AGN is uniform throughout the stream. The gross hematuria of AGN is virtually always painless; dysuria accompanying gross hematuria points to acute hemorrhagic cystitis [5] rather than renal disease. A history of previous such episodes would point to an exacerbation of a chronic process such as IgA nephropathy [6]. Although a history of a recent documented streptococcal infection would be consistent with poststreptococcal AGN, such a history is frequently unavailable.

It is next important to ascertain any symptoms suggestive of complications of the AGN. These might include shortness of breath or exercise intolerance from fluid overload or headaches, visual disturbances, or alteration in mental status from hypertension.

Since AGN may be the presenting complaint of a multisystem illness, a complete review of systems is vital. Particular attention should be paid to rash, joint discomfort, recent weight change, fatigue, appetite changes, respiratory complaints, and recent medication exposure. The family history should address the presence of any family members with autoimmune disorders, as children with both SLE and membranoproliferative glomerulonephritis (MPGN) may have such relatives. A family history of renal failure (specifically asking about dialysis and kidney transplantation) may be the first clue to a process such as Alport syndrome, which may initially present with an AGN picture.

The physical examination begins with a careful assessment of vital signs, particularly blood pressure. Blood pressures 5 mm above the 99th percentile for the child's age, sex, and height, especially if accompanied by any alteration in mental status, demand prompt attention. Tachycardia and tachypnea point toward symptomatic fluid overload. Careful examination of the nose and throat may provide evidence of bleeding, suggesting the possibility of one of the ANCA-positive vasculitides such as Wegner's granulomatosis [7]. Cervical lymphadenopathy may be the residua of a recent

streptococcal pharyngitis. The cardiopulmonary examination will provide evidence of fluid overload or the pulmonary involvement characterizing the rare kidney-lung syndromes. The abdominal examination is particularly important. Ascites may be present if there is a nephrotic component to the AGN. Hepato- or splenomegaly may point to a systemic disorder. Significant abdominal pain may accompany HSP. Scrotal edema may occur in nephrotic syndrome as well, and orchitis is an occasional finding in HSP.

A very careful examination of the skin is important in AGN. The rash of HSP, while characteristic when florid, may initially be subtle and limited to the buttocks or the dorsa of the feet. Some peripheral edema from salt and water retention is seen in AGN, but this tends to be a more subtle "brawny" edema than the pitting edema characteristic of nephrotic syndrome.

Joint involvement occurs in some multisystem disorders with AGN. Small joint (e.g., fingers) is more typical of SLE, while or knee involvement is seen with HSP.

4. Laboratory Assessment

Obviously, a good urinalysis is the first order of business in assessing a child with suspected AGN. The presence of red blood cell casts, while not invariably seen, is diagnostic of glomerulonephritis if present [8]. AGN is an inflammatory process, so it is not at all unusual to see white blood cells in nephritic urine. Unfortunately, this occasionally leads to an inappropriate diagnosis of urinary tract infection.

Proteinuria is also nearly invariant in AGN although any cause of gross hematuria can lead to some urinary protein. If the urine is not grossly bloody, however, the combined presence of hematuria and proteinuria virtually always means glomerulonephritis.

The initial blood work required in suspected AGN is actually limited; more sophisticated immunologic investigations, for example, are really "second tier" studies after the initial results are known. Obviously, assessing renal function and electrolytes is an important first step, as is obtaining a hemogram. A mild degree of anemia is frequently seen with AGN and likely is dilutional; more significant anemia would be evidence that the process may be more chronic. There are typically no important changes in the white blood cell count or platelet count in most causes of AGN. A normal platelet count in the presence of petechiae and purpura is the usual finding in HSP.

Beyond these basic tests, only a few others are helpful in the initial evaluation. A serum albumin is usually included; a slight degree of hypoalbuminemia is typical of many inflammatory processes such as HSP, but values <2.0 gm/dL are quite unusual in straightforward AGN and point to a process with a nephrotic syndrome component. By far, the most important (and frequently forgotten) test to obtain initially is an assessment of the complement system. This generally means obtaining a serum C3 and C4; the total hemolytic complement ("CH50") is generally of only historical interest. Poststreptococcal AGN is characterized by a very low C3, sometimes with minimal decreases in C4 [9]. The latter

is very transient and likely due to activation by Type III cryoglobulins.

The importance of a timely measurement of C3 cannot be overstressed. The hypocomplementemia of poststreptococcal AGN is evanescent, typically normalizing in six to eight weeks. On the other hand, urinary abnormalities may persist much longer. Thus, if a child with a few weeks' of abnormal urine has not had a C3 measurement earlier, it may be impossible to make a diagnosis of poststreptococcal AGN with certainty without a kidney biopsy.

All of these tests should be easily obtained in the primary care setting and will usually identify the child for whom referral is going to be necessary.

5. Office Management

Some children with AGN will require immediate referral to a pediatric nephrologist. The child with severe hypertension (more than 5 mm above the 99th percentile), especially if accompanied by any neurologic complaints, must be referred immediately. Similarly, children with significant renal insufficiency should be assessed by a specialist. When AGN is accompanied by a nephrotic syndrome, the additional diagnostic and therapeutic interventions are also beyond the typical primary care practice.

Beyond these situations, however, many such children can be reasonably managed in the primary care setting. The child with AGN in the setting of HSP, for example, who is normotensive, has normal renal function, and who is not nephrotic requires little more than careful serial observation. Although the urinary abnormalities may persist for some time after the rest of the disease has resolved, these children have little if any risk of permanent kidney injury.

Many children with poststreptococcal AGN may also be followed in the primary care setting, but this will entail a commitment to serial examination. The major threat to such children is hypertension and its complications, and this may evolve over a few days. In otherwise typical poststreptococcal AGN with minimal hypertension (e.g., blood pressure between the 95th and 99th percentiles) and no renal failure, therapy with a loop diuretic is reasonable, with daily blood pressure rechecks.

The urinary abnormalities in poststreptococcal AGN may persist for a long time, even a year. The best indicator of resolution of the disease is the return of the C3 level to normal. This generally occurs within 6 to 8 weeks. Persistent decrease in C3 by this time merits referral, as this could be an indicator that the "AGN" was actually the initial presentation of a more chronic process such as MPGN [10].

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