Answers and Explanations

1. Answer C: Repeat the urinalysis to assess for persistent hematuria.

After an initial positive urine screening test, the majority of children with an abnormal finding will have spontaneous resolution of the problem within 3 months. This is the rationale for recommending observation and repeat urinalysis testing rather than referral to a pediatric nephrologist or commencing an evaluation for specific glomerular diseases such as IgA nephropathy. Moreover, in the absence of gross hematuria or a defined anatomic abnormality, cystoscopy is not indicated in children with asymptomatic urinary findings.


2. Answer C: 24-hour ambulatory blood pressure monitoring.

The ESCAPE trial demonstrated that in children (n=385) with chronic kidney disease (GFR 15-80 mL/min/1.73 m²), the rate of progression to end stage kidney disease was significantly lower in those patients whose mean arterial BP is below the 50th percentile. This was accomplished by the combined administration of an angiotensin converting enzyme inhibitor with other antihypertensive drugs. However, this determination was based on the use of a 24-hour recording of BP and that is why choice C is the correct response. The findings of the ESCAPE trial justify prompt further action rather than leaving the BP regimen unchanged or deferring the evaluation for 3-6 months. Moreover, it has placed greater emphasis on continuous out-patient home recordings using 24-hour devices rather than reliance solely on the measurements of BP obtained in a clinic setting.

3. **Answer E: Polysomnogram.**

Pediatric patients with essential hypertension have a high prevalence of snoring and disordered sleep pattern. In part, this may reflect the rising incidence of metabolic syndrome and obesity as the cause of high BP in children and adolescents. This can be manifest as increased somnolence during the day and declining school performance. Polysomnography is the optimal test to detect abnormal sleep and can be performed in specialized centers. There is no evidence of increased risk of seizures or anatomic abnormalities in the brain of children with hypertension. High or low serum glucose levels do not cause persistent sleepiness. Serum cortical levels drawn at random times are difficult to interpret in children and diseases with elevated or depressed levels have generalized findings throughout the body.


4. **Answer D: Waist to height ratio.**

The incidence of prevalence of essential hypertension in pediatrics has been rising over the last 10-20 years because of the epidemic of obesity and overweight in children and adolescents. The elevated BP reflects the occurrence of central or visceral obesity and this index is best determined by the waist-to-height ratio. The BMI is too variable and can be impacted by variables that are not indicative of obesity per se. Trifold skin thickness and midarm muscle circumference are used as markers of overall nutrition and the upper-to-lower ratio is most helpful in the assessment of children with growth disorders and hypogonadism.


5. **Answer D: CD80.**

In a pre-school age child with new-onset primary nephrotic syndrome, the differential diagnosis consists of two diseases – minimal change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS). MCNS is nearly always responsive to steroids and while it usually follows a relapsing course, it generally resolves spontaneously without permanent kidney damage. FSGS is less responsive to immunosuppressive therapy and approximately 50-60% of patient’s progress to end stage kidney disease (ESKD) over 5-10 years of follow-up. It would be helpful to identify a biomarker that could discriminate between these two entities and potentially avoid administration of ineffective medications to patients with FSGS. Urinary excretion of CD80 is consistently higher in patients with MCNS compared to those with FSGS. KIM-1 and α2-microglobulin are tubular proteins that have not been linked to specific glomerular diseases. Similarly, NGAL and IL-18 are useful markers of acute kidney injury and the need for acute dialysis therapy but have not be utilized to distinguish between different glomerular disorders.


Urinary CD80 is elevated in minimal change disease but not in focal segmental glomerulosclerosis. *Kidney Int* 78: 296-302, 2010


6. **Answer C: Rituximab.**

In children with MCNS, nearly 90% of patients will have relapsing disease. A third of those with relapses will have frequent relapses (≥2 in 6 months or ≥4 in 12 months) or steroid dependent disease (relapse on alternate day steroids or within 2 weeks of stopping the drug). These children are at high risk of developing disabling side effects from repeated and cumulative exposure to steroids and are candidates for second-line therapy. Cyclophosphamide was the first agent that that was used successfully for this purpose. Mycophenolate mofetil and calcineurin inhibitors are newer options that are useful in this cohort of patients with MCN. In those who continue to relapse after a trial of the above agents, administration of rituximab is successful in inducing a disease free-interval in 80-90% of patients. Plasmapheresis is not a routine procedure in this clinical context. Levamisole and deflazacort are similar to steroids and have a low-likelihood of inducing an extended relapse-free interval. Bortezomib is a proteosome inhibitor and it is being tested for efficacy in patients with SLE nephritis. It has not been evaluated in children with primary nephrotic syndrome or MCNS.


7. **Answer C: Coenzyme Q10 biosynthesis monooxygenae 6.**

One of the major advances in nephrology over the last decade is the discovery of genetic mutations in podocyte proteins that are associated with focal segmental glomerulosclerosis (FSGS). Some of the proteins such as podocin and nephrin are associated with the slit diaphragm between adjacent podocytes. TRPC6 is in the podocyte cell membrane and modulates calcium entry into the cell. None of these mutations are characterized by extrarenal findings. Coenzyme Q10 biosynthesis monooxygenase 6 (COQ6) is one of the most recently proteins linked to primary steroid-resistant nephrotic syndrome and it is associated with sensorineural hearing loss. Mutations in the α5 collagen gene of type IV are causative of X-linked Alport syndrome. Although Alport syndrome is associated high tone sensorineural hearing loss, the decreased hearing acuity and the onset of nephrotic syndrome are uncommon in the first decade of life.


8. Answer C: He is at low risk of recurrent disease if he receives a kidney transplant.

The discovery that genetic mutations in podocyte proteins are associated with focal segmental glomerulosclerosis (FSGS) is one of the highlights in clinical research in nephrology over the last 10 years. Nephrin, a slit diaphragm protein, was the first gene discovered and it is altered in infants with congenital nephrotic. Overall, genetic abnormalities that cause nephrotic syndrome in childhood have an autosomal recessive pattern of inheritance. Podocin mutations are the most common findings in most pediatric series accounting for up to 25% of sporadic or familial cases. In general these cases are usually unresponsive to prednisone and other immunosuppressive medications such as calcineurin inhibitors. The mutations have no impact on complications such as infections or thromboembolic events because they reflect the systemic consequences of hypoalbuminemia and edema. However, the likelihood of recurrent FSGS after transplantation is much lower than the standard figure of 20-25% that is reported in most series of patients with FSGS who receive a kidney allograft.


The most important causes of hypocomplementemic glomerulonephritis in children are post-infectious glomerulonephritis, systemic lupus erythematosus (lupus) nephritis, or membranoproliferative glomerulonephritis (MPGN). Of the three entities MPGN is the least common. It is characterized by abnormal activation of the alternative pathway of complement. This can be triggered by C3 nephritic factor (C3Nef), an autoantibody to C3 convertase, or decreased activity of factor H, the main circulating protein that modulates activation of the alternative complement cascade in the serum. Reduced ADAMTS13 levels or activity lead to thrombotic thrombocytopenic purpura and reduced expression of membrane cofactor protein is associated
with familial cases of atypical hemolytic uremic syndrome. C1 esterase inhibitor deficiency causes hereditary angioedema. Cathepsin L activity may be implicated in the pathogenesis of proteinuria in patients with focal segmental glomerulosclerosis but not in those with MPGN.


10. **Answer A: Bovine serum albumin.**

Idiopathic membranous nephropathy (IMN) is a rare condition in pediatric, accounting for 2-3% of all kidney biopsies that are done for the evaluation of proteinuria or nephrotic syndrome. In the last 2 years, exciting discoveries have been made in understanding the cause of IMN across the entire age spectrum. In adults, nearly 70% of cases are linked to autoantibodies to M-type phospholipase A₂ receptor. The levels of this antibody may correlate with response to therapy and increases in the titer may precede clinical relapses and recurrence of proteinuria. and children. Studies in children of IMN have found that approximately 40% have antibodies to bovine serum albumin. This finding suggests that early exposure to dietary antigens may play a key role in the pathogenesis of this glomerular disease in pediatric patients. Antibodies to double stranded DNA are specific for SLE, a secondary cause of membranous nephropathy. The trans-placental passage of antibodies to neutral endopeptidase has been described in one neonate with proteinuria. Anti-gliadin antibodies are more common in IgA nephropathy and antibodies to the plasmin receptor may be linked to post-streptococcal acute glomerulonephritis.


11. **Answer C: Glomerular volume.**

Lack of standardization of the interpretation of renal histopathology has hindered efforts to compare studies of pediatric and adult patients with IgA nephropathy. This has led to divergent scoring systems that place differing emphasis on individual findings. Moreover, some of the elements of the evaluation are highly subjective and are difficult to reproduce among different investigators. The Oxford classification is a scheme that incorporates features that are easily identified and scored to enable rapid assessment of renal histopathology. A key feature is the present of mesangial and endothelial cell hypercellularity. Other key features are tubulointerstitial fibrosis and glomerulosclerosis. The scoring system has been demonstrated to be internally valid for repeat assessment by the same pathologist and externally valid for comparison between two independent pathologists. The scores correlate well with the activity and course of the disease in pediatric and adult patients. Glomerular size, which may reflect an adaptive response to irreversible nephron loss, is not part of the assessment system because it involves separate scanning devices. The intensity of IgA deposits in the mesangium is not included because it does not correlate with clinical indices of disease severity or outcomes. Epithelial mesenchymal transformation is not a unique feature in the pathogenesis of IgA nephropathy and its role in the progression of renal disease is controversial. Reticuloendothelial inclusion bodies are characteristic of other glomerular diseases such as SLE nephritis.


ANCA-associated vasculitis is divided into categories – granulomatosis with polyangiitis (GPA) associated with cANCA antibodies to proteinase 3 (PR3) and microscopic polyangiitis associated with pANCA antibodies to myeloperoxidase (MPO). Both variants of ANCA-associated vasculitis are rare in children; however, they are generally severe and most often affect the kidney and lung. The trigger for the production of these autoantibodies may be antecedent infection by bacteria that express a fimbrial antigen that cross reacts with lysosomal associated membrane protein-2 (LAMP-2), the titer of this antibody is generally associated with overall disease activity. The ANCA antibodies can also cross react with other endogenous proteins. Reactivity to plasminogen correlates highly with fibrinoid necrosis and glomerular inflammation. Antibodies to thrombin 3 and protein C may disrupt the coagulation cascade but do reflect renal histopathology. ANCA antibodies to not cross react with von Willebrand factor.


• Salama AD, Pusey CD. Shining a LAMP on pauci-immune focal segmental glomerulonephritis. Kidney Int 76: 15-17, 2009


GPA is a disease that generally occurs in middle age adults. Although it can occur in pediatric patients, it is a distinctly rare entity. It can involve the kidney and lungs and constitutes one of the most aggressive forms of glomerulonephritis. There is an urgency to achieve remission of the disease as quickly as possible to preserve kidney function and the standard of care has been a combination or prednisone and intravenous pulses of cyclophosphamide. However, because of the serious long-term side effects of the alkylating agent including infection, gonadal toxicity, and malignancy, there has been a search for alternative agents to induce remission. Two recent studies – one in the United States and one in Europe indicate that rituximab is equivalent to cyclophosphamide, in terms of both efficacy and safety, as an agent to achieve early control of
newly diagnosed patients with GPA. Azathioprine, methotrexate, and etanercept are agents that have been used as maintenance drugs. Adalimumab has not been tested as a therapeutic agent in any form of ANCA-associated vasculitis.


14. Answer E: Central nervous system.

Diarrheal–associated HUS (D+HUS) can be more precisely defined as Shiga toxin producing *E. coli*-associated HUS (STEC-HUS) because most causes are caused by an antecedent gastroenteritis with a strain of *E. coli* that produces Shiga toxin. D+HUS is a systemic illness caused by absorption of the Shiga toxin and subsequent binding to the globotriaosylceramide (Gb3) receptor on the surface of endothelial cells. The toxin is internalized, inhibits protein synthesis, and causes cell death. The kidney is a primary target because of the disproportionately high level of renal blood flow and increase expression of Gb3 in the glomerular microcirculation. Nearly 40% of children with D+HUS experience serious extra-renal events including skin necrosis, pancreatitis, hepatitis, and myocarditis. However, involvement of the central nervous system is indicative of more severe disease. It can manifest as coma, seizures, blindness, and hemiparesis. CNS events are the most frequent cause of mortality during the acute episode of D+HUS.


15. Answer E: Angiotensin II.

CAKUT is a relatively new term that has been introduced to describe the full spectrum of abnormalities in development in the genitourinary system and is intended to foster a more comprehensive view of these defects. One of the benefits of this perspective is that it highlights the broad consequences of genetic mutations or alterations in the level of specific hormones or signaling molecules. Angiotensin II has been identified as an important modulator of renal morphogenesis. Disruption of the renin angiotensin axis due to genetic mutations in key enzymes receptors in this system or administration of drugs (angiotensin converting enzyme inhibitors or angiotensin receptor blockers) can lead to a wide range of renal anomalies. These can include severe tubular hypoplasia that can lead to fetal death in utero. Parathyroid and thyroid hormone are not critical as angiotensin II in renal development. Insulin excess can cause renal enlargement but usually does not lead to structural anomalies. Glucagon has no defined role in renal development.


In infants with a febrile UTI, it has been the standard of care to perform a VCU to detect vesicoureteral reflux (VUR). This practice is being challenged and has led to major modification in clinical practice guidelines that were published recently by the American Academy of Pediatrics for the management of an initial febrile UTI in infants age 2 to 24 months. Because prophylactic antibiotics do not prevent UTIs and the infection can occur in the absence of VUR, it is no longer recommended to perform a VCU in all infants with a febrile UTI. Instead, the test should be reserved for infants who have an abnormal renal ultrasound. This change in practice will increase the importance of developing non-invasive markers of high grade VUR to ensure thoughtful application of VCU. Serum procalcitonin levels have been demonstrated to be higher in children with a febrile UTI and high grade VUR. NGAL and IL-18 are useful markers of acute kidney injury and may be high in children with UTI but are not the levels are predictive of the specific grade of VUR. Prorenin levels have been used to define patients with diabetic nephropathy but have not been tested in children with UTI and VUR. Serum PTH levels are not useful as a sign of renal inflammation or an anatomic anomaly.


Subcommittee on urinary tract infection, steering committee on quality improvement and management. Urinary tract infection: Clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 128:595-610, 2011

17. Answer A: Within 1 week.

It has been considered standard of care to perform a VCU in any child age 2 to 24 months who presents with a febrile UTI. There are some clinicians who will defer the test if the mother had adequate prenatal care including fetal sonography that demonstrated two normal kidneys. More importantly, revised clinical guidelines for the management of an initial febrile UTI in infants, age 2-24 months, concluded that a VCU should not be performed routinely unless the child has an abnormal renal sonogram, i.e. reduced renal parenchyma or hydronephrosis. It is likely that that this recommendation will lead to a reduction in the number of VCU that are done for evaluation of febrile UTIs. Thus, in the next issue of NephSAP on Pediatric Nephrology, the correct answer may be D. However, with the situation in flux, when the test is done,
the question of timing will remain clinically relevant. Clinical studies indicate that a VCUG can be safely done within 1 week of the diagnosis of a febrile UTI, provided the child is clinically improving. There is no need for a 2-4 week waiting period.


- Subcommittee on urinary tract infection, steering committee on quality improvement and management. Urinary tract infection: Clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics* 128:595-610, 2011

18. Answer D: Bilateral ureteroceles.

The clinical value of anti-reflux procedures in children with vesicoureteral reflux (VUR) is primarily to reduce the frequency of recurrent UTIs. There is no proven benefit in terms of reducing the likelihood of developing reflux nephropathy. The standard procedure in the past had been an open surgical procedure with reimplantation of the ureter. Over the last decade, non-surgical procedures have been developed that involve injection of non-toxic material at the ureterovesical junction to correct the VUR. The procedure is done with cystoscopic guidance and avoids the necessity of a surgical procedure. Anatomic abnormalities at the ureterovesical junction such as a ureterocele decrease the likelihood that the non-surgical approach will successfully restore competency of the junction. Age and lack of toilet training have no adverse impact on the outcome of the procedure. In addition, it is effective even in children with a family history of VUR or new renal scars.


19. Answer C: 24-hour urine collection for calcium and citrate.

Numerous reports have documented an increased incidence of kidney stones in pediatric patients over the last 10-15 years. The rising number of cases is especially prominent in adolescent girls. There is no apparent explanation for this secular trend and obesity does not appear to be a factor in this epidemiological change. The etiology of kidney stones in pediatric patients is most often a metabolic abnormality that leads to an increased supersaturation of the urine and heightened propensity for crystal formation. Thus, a 24-hour urine collection is the most useful test in the initial evaluation of a pediatric patient with a newly-detected kidney stone and hypercalciuria and hypocitraturia are the two most common metabolic abnormalities. Hyperparathyroidism, renal tubular acidosis, or abnormalities in vitamin B metabolism are infrequent causes of stones. Changes in bone density are not observed in children with kidney stones.


20. **Answer A: Amiloride.**

Nephrogenic diabetes insipidus (NDI) can be caused by genetic mutation in the type 2 vasopressin receptor or the aquaporin 2 channel. Acquired forms of NDI can be caused by obstructive uropathy, interstitial diseases, or various medications. Lithium, a drug that continues to be used in the treatment of bipolar disorder, is one of the commonest causes of NDI and acts by entering the collecting duct cell and antagonizing intracellular vasopressin signaling. Amiloride can prevent this complication by blocking the epithelial sodium channel and reducing lithium entry into the collecting duct cell. Furosemide acts in the medullary thick ascending limb while metolazone and acetazolamide act in the proximal tubule and do not impact on the adverse effect of lithium. Mannitol causes an osmotic diuresis but does not inhibit lithium entry into cells.


21. **Answer B: Focal segmental glomerulosclerosis (FSGS).**

Dent disease can be caused by genetic mutations in the CCL5 gene on the X-chromosome or the OCRL gene. The later abnormality causes an illness with features that overlap with Lowe’s syndrome. Most children with Dent disease have tubular proteinuria characterized by increased excretion of low molecular weight proteins. However, there are patients who can develop nephrotic-range proteinuria and albuminuria of glomerular origin. The renal histopathological lesion that has been observed under these circumstances is FSGS and has been documented in patients with both genetic causes of Dent Disease. None of the other glomerular abnormalities – DDD, membranous nephropathy, mesangial IgA nephropathy, or thinning of the GBM – has been documented in this patient cohort.


22. Answer A: Do not perform screening urinalyses.

The current recommendation of the American Academy of Pediatrics (AAP) is not to perform a screening urinalysis at any age or at all routine clinic visits. This conclusion is based on data indicating that the test is overly sensitive and yields a large number of false positive results. These abnormal urinalyses trigger the performance of costly tests that are highly unlikely to diagnose an important kidney disease. Thus, even guidelines that recommend less frequent urinalyses at specific ages or defined intervals of time are not cost effective. This later recommendation may need to be revised based on recent reports indicating a significantly higher likelihood of developing chronic kidney disease in young adults with persistent microscopic hematuria on dipstick testing.

Haysom L, Williams R, Hodson E, Lopez-Vargas P, Roy LP, Lyle D, and Craig JC. Risk of CKD in


23. Answer C: Left ventricular hypertrophy.

Essential hypertension is more prevalent in African American compared to White children even after controlling for numerous covariates such as obesity. In addition, African Americans are more likely to have left ventricular hypertrophy compared to their White counterparts. Although they also have higher plasma renin activity, this is not paralleled by significant differences in renal function such as microalbuminuria or reduced GFR. Retinopathy is unusual in pediatric patients because of the relatively short duration of the elevated blood pressure. Hyperinsulism is a common feature of the metabolic syndrome and is equally prevalent in children regardless of their racial or ethnic background.

The introduction of 24-hour ambulatory blood pressure monitoring (ABPM) into clinical practice has led to a more precise characterization of pediatric patients into one of four categories – normal based on normal measurements in clinic and ABPM, hypertensive based on high readings in clinic and ABPM, WCH based on high clinic readings but normal ABPM, and masked based on normal clinic readings but high ABPM. The prognosis of the middle categories has been controversial with some practitioners considering them to be normal and other who view them as hypertensive. Recent studies have documented target organ damage in children with WCH or masked hypertension. The most common abnormality is left ventricular hypertrophy and children and adolescents with WCH have left ventricular mass index that is midway between the values obtained in those with normal blood pressure and those with confirmed hypertension., thus, echocardiography is the most useful test to guide the therapy of pediatric patients with WCH. There are no other renal structural or metabolic abnormalities that have been consistently documented in pediatric patients with WCH. Thus, renal ultrasonography with Doppler and blood tests are not useful in this circumstance unless there are other findings to justify the test.


FSGS can be a primary or secondary abnormality. The secondary causes include genetic mutations in select podocyte proteins, surgical or traumatic reduction in renal mass, prematurity and low birth weight, reflux nephropathy, and various medications. A recent addition to the list of agents incriminated in causing FSGS is anabolic steroids. It is important to identify this association because the histological abnormality can resolve with cessation of the drug. Accutane is generally free of major renal toxicity. Dextamphetamine may cause hypertension. Creatine and taurine are often taken as part of energy supplements in young adults who would consider the use of anabolic steroids but do not cause significant proteinuria.