

Disorders of Kidney and Urinary Tract

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RENAL ANATOMY AND PHYSIOLOGY

Each kidney is composed of approximately a million nephrons, each consisting of a glomerulus and renal tubule. The glomerulus is made of a tuft of capillaries and a central region of mesangium. The capillaries arise from the afferent arteriole and join to form the efferent arteriole, the entry and exit being at the hilum of the kidney. The capillary wall consists of fenestrated endothelium, glomerular basement membrane and foot processes (podocytes) of visceral epithelial cells. The basement membrane is made of type IV collagen, laminin and heparan sulfate proteoglycan. The Bowman space leads into the proximal tubule that has an initial convoluted portion, then the straight segment, descending and ascending limbs of the loop of Henle and the distal tubule. Six to eight distal tubules join to form the collecting ducts that finally enter the renal pelvis.

The renal artery divides into segmental arteries that branch to form interlobar and arcuate arteries. The latter give rise to the intralobar arteries, which provide the afferent arterioles for the glomeruli. The efferent arterioles from the glomeruli form a meshwork of peritubular venous capillaries that empty into intralobar veins. The early part of the distal tubule on its ascent from the medulla to the cortex lies near the glomerulus of the same nephron. The cells of the tubule in contact with the afferent arteriole are denser than the rest and called macula densa. The smooth muscle cells of the afferent arteriole, in this region, contain prominent cytoplasmic granules that are the site of renin activity. The juxtaglomerular apparatus (JGA) is composed of afferent and efferent arterioles, the macula densa and lacis cells located between these structures. The JGA is involved in systemic blood pressure regulation, electrolyte homeostasis and tubuloglomerular feedback.

Renal Physiology

Glomerular filtration depends upon the higher pressure in afferent arterioles. The filtration barrier is constituted

by the endothelium with slit pores, basement membrane and podocytes of visceral epithelial cells. Filtration of solutes depends upon their molecular size, shape and electrical charge. The filtrate from the glomerular capillaries passes from the Bowman capsule into the proximal convoluted tubule, loop of Henle, distal tubule and collecting ducts. The filtrate contains all the diffusible and ultrafiltrable substances present in plasma. Small quantities of protein are usually present, but are reabsorbed in proximal tubule. Bulk of the glomerular filtrate is reabsorbed into the peritubular capillaries and only 0.5% is excreted as urine.

Tubular Reabsorption

The proximal tubules reabsorb about 80% of the glomerular filtrate. Approximately 65% of sodium is reabsorbed in the proximal tubule, through several active transport systems. Sodium transport is dependent on the parallel transport of bicarbonate, chloride, amino acids and glucose. Tubular reabsorption of sodium and other permeable solutes is promoted by the phenomenon of solvent drag during transport of water across the tubular epithelium. Figure 16.1 indicates the principal sites of reabsorption of sodium and potassium.

The glomerular filtration rate is regulated by tubuloglomerular feedback that depends upon the functional integrity of the JGA. Increased delivery of chloride to the macula densa results in local activation of renin-angiotensin mechanism. The renin-angiotensin-aldosterone system, prostaglandins and natriuretic peptides are involved in sodium handling. Potassium is completely reabsorbed in the proximal tubule; the amount seen in urine depends upon its secretion in the distal tubule.

Distal tubules and collecting ducts are responsible for urinary acidification, concentration and regulation of sodium balance. Exchange of potassium or hydrogen ions for sodium takes place in the distal tubules under the regulation of aldosterone. Antidiuretic hormone mediates

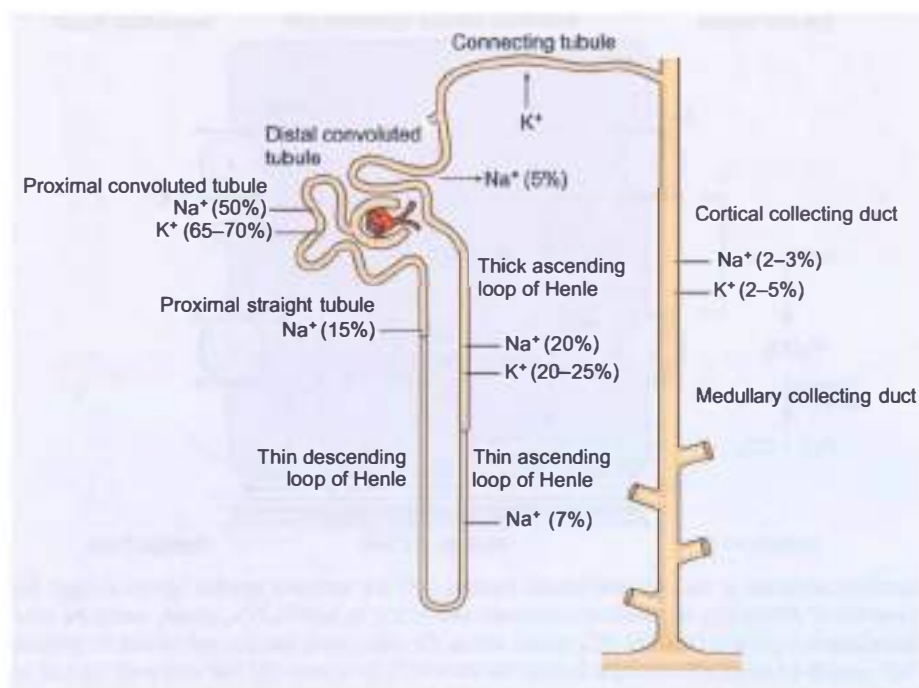


Fig. 16.1: Renal tubular handling of sodium and potassium. The major sites of reabsorption are shown, with percentage of filtered cation in parenthesis

absorption of water through insertion of 'water channels' (aquaporins) on the luminal surface of cells in the collecting tubules.

Renal acidification. The kidney helps in regulation of acid-base balance by maintaining plasma bicarbonate concentration at 24–26 mEq/l. Depending on dietary protein intake, children produce about 1–3 mEq/kg/day of nonvolatile acids. Filtered bicarbonate is almost completely reabsorbed, 85 to 90% in the proximal tubules and the rest in distal tubules and collecting ducts. Bicarbonate, consumed in the buffering of nonvolatile acids, is regenerated by the renal excretion of titratable acid and ammonia. Chronic acidosis augments the production of ammonia and thus elimination of acid. Figures 16.2 and 16.3 demonstrate the chief mechanisms involved in the reabsorption of bicarbonate and excretion of protons in the proximal and distal tubules, respectively. The reabsorption of filtered bicarbonate as well as excretion of acid is mediated by tubular secretion of hydrogen ions (H⁺).

In the proximal tubule, filtered HCO₃⁻ combines with H⁺ to form H₂CO₃ that rapidly dissociates to H₂O and CO₂ (catalyzed by carbonic anhydrase at the brush border of the tubular basement membrane) (Fig. 16.2). CO₂ diffuses along its concentration gradient into the tubular cell, combining with H₂O to generate HCO₃⁻ that is absorbed by the peritubular capillaries. The proximal tubule reabsorbs 80–90% of the filtered HCO₃⁻; the remainder is reabsorbed distally. In the distal tubule, the secreted H⁺ ions combine with the major urinary buffers, sodium hydrogen phosphate (Na₂HPO₄) and ammonia (NH₃) to

form NaH₂PO₄ and NH₄⁺ (measured in urine as titratable acidity and ammonium ion respectively) (Fig. 16.3). The distal nephron generates and maintains a steep pH gradient between the blood and urine, but its capacity to secrete H⁺ ions is small. Thus, even a slight increase in distal HCO₃⁻ delivery results in increase in urine pH. Extracellular fluid volume and potassium balance also regulate H⁺ secretion and HCO₃⁻ reabsorption.

Suggested Reading

Bernstein PL, Ellison DH. Diuretics and salt transport along the nephron. *Semin Nephrol* 2011;31:475–82

Srivastava RN, Bagga A. Renal anatomy and physiology. In: *Pediatric Nephrology*, 5th edn. Jaypee, New Delhi, 2011;1–19

Development of Structure and Function

Differentiation of the primitive kidney is stimulated by penetration of the metanephros, during the fifth week of gestation, by the ureteric bud, which is an outgrowth of the lower portion of the mesonephric duct. Division of the ureteric bud within the metanephros induces the development of nephrons. The ureteric bud gives rise to the intrarenal collecting system, renal calyces, pelvis and ureter. The most active period of nephrogenesis is from 20–36 weeks. The full number of nephrons is present around 36 weeks. Partitioning of the cloaca during the 5th week results in the formation of the urogenital sinus anteriorly and the anal canal posteriorly. The upper part of the urogenital sinus differentiates to form the fetal bladder.

The fetal kidneys are lobulated structures that ascend from the pelvis to their normal position between 6 and

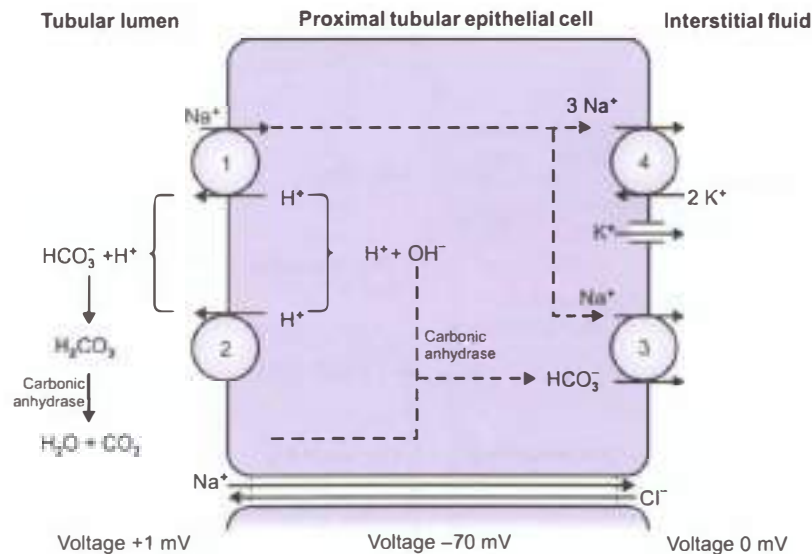
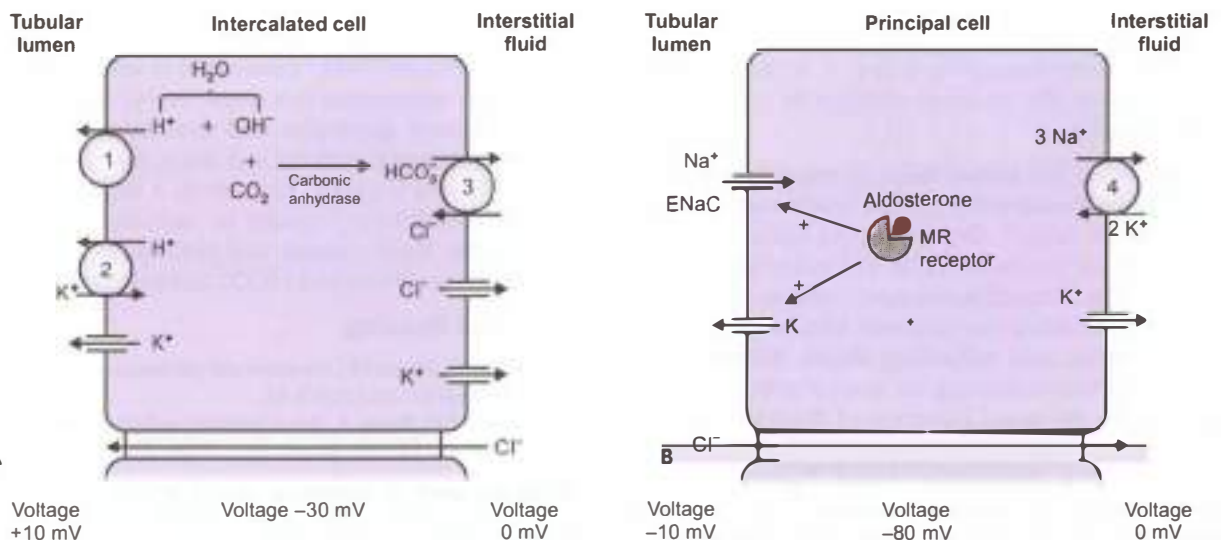


Fig. 16.2: Reabsorption of bicarbonate in the proximal tubule. Protons (H^+) are secreted into the lumen through the actions of the sodium (Na^+) H^+ antiporter (1) and the H^+ ATPase (2). Secreted H^+ combines with HCO_3^- to form H_2CO_3 , which, under the action of luminal membrane carbonic anhydrase dissociates to H_2O and CO_2 . The CO_2 travels across the membrane into the cell where it combines with OH^- to generate HCO_3^- . The HCO_3^- and Na^+ cross the basolateral membrane using the $\text{Na}^+/\text{HCO}_3^-$ symporter (3). Na^+ also exits the cell via the Na^+/K^+ ATPase (4). Electrogenic H^+ secretion generates a small lumen positive voltage, which creates current flow across the paracellular pathway



Figs 16.3A and B Mechanism of acidification and potassium excretion in the distal renal tubules. (A) The intercalated cells of the cortical collecting ducts secrete H^+ through the H^+ ATPase (1) and H^+/K^+ ATPase (2), independent of Na^+ transport. The hydroxyl (OH^-) ions generated in the cell through H^+ secretion exit the cell by the $\text{HCO}_3^-/\text{Cl}^-$ exchanger (3). The secreted H^+ is buffered by luminal ammonia forming NH_4^+ and phosphate (titrable acids), to prevent a drop in luminal pH that would prevent further H^+ secretion. (B) Principal cells mediate sodium (Na^+) absorption and potassium (K^+) transport. The apical membrane contains an amiloride sensitive Na^+ channel (epithelial sodium channel, ENaC); Na^+ exits basolaterally via Na^+/K^+ ATPase (4). Sodium transport creates a lumen negative transepithelial potential that increases the rate of H^+ secretion by intercalated cells. Aldosterone binds to the mineralocorticoid (MR) receptor and enhances Na^+ absorption and H^+ and K^+ secretion

9 weeks of gestation. These kidneys can be visualized on antenatal ultrasound by 12–13th week. The kidneys grow steadily in size between the 12th week and the 40th week, with the renal length increasing from about 1.0 cm to 2.7 cm. The fetal bladder is visualized by the 10–14th week, and its capacity increases steadily to about 50 ml at term.

Beyond the 16th week, the amniotic volume is principally dependent on urine production.

Glomerular Filtration

Glomerular filtration begins at 5–9 weeks' gestation, initiating urine formation. The fetal kidney receives about

2–4% of cardiac output, which increases in neonates to 15–18%. Serum creatinine level is high at birth, reflecting maternal values, but falls rapidly to 0.3–0.5 mg/dl by the end of first week. Most (92%) neonates pass urine within the first 48 hr. The GFR is low at birth (15–20 ml/min/1.73 m² in the first 3 days in term, 10–15 ml/min/1.73 m² in preterm) but increases to 35–45 ml/min/1.73 m² at 2 weeks and 75–80 ml/min/1.73 m² by 2 months.

Tubular Function

Tubular function contributes to urine formation around 14 weeks' gestation. Postnatal tubular maturation follows a pattern similar to GFR but its maturation is delayed. Infants have reduced sodium and bicarbonate reabsorption and limited ability for hydrogen ion excretion. The pH of urine in newborns is inappropriately high for the degree of acidemia.

Plasma Osmolality

The capacity of the kidneys to concentrate or dilute urine is limited in neonates. An infant can concentrate his urine to a maximum of 700–800 mOsm/kg whereas the older child can achieve 1200–1400 mOsm/kg. Growing babies utilize most of the protein available for growth rather than catabolize to urea. Decreased production and excretion of urea result in a relatively hyposmolar interstitium and reduced urinary concentration. The newborn can dilute urine to a minimum of 50 mOsm/kg, like an older child. However, the time taken to excrete a water load is longer. Thus, delayed feeding and overdiluted or concentrated feeds are potentially harmful.

Maturation of Renal Function

Renal function continues to improve during the first two years of life, at the end of which, various parameters of renal function approach adult values, if corrected to standard surface area. Structural growth parallels the functional maturation.

Suggested Reading

De Curtis M, Rigo J. Nutrition and kidney in preterm infant. *J Matern Fetal Neonatal Med* 2012;25 S1:55–9

Quigley R. Developmental changes in renal function. *Curr Opin Pediatr* 2012;24:184–90

Srivastava RN, Bagga A. Diseases of the newborn. In: *Pediatric Nephrology*, 5th edn. Jaypee, New Delhi, 2011;494–524

DIAGNOSTIC EVALUATION

Common manifestations of renal disorders include edema, hematuria, oligoanuria, dysuria and abnormalities of micturition, flank pain and ureteric colic. Serious renal disease may be present with subtle or no symptoms. With improvements in techniques and widespread availability of antenatal ultrasonography, several congenital anomalies of kidney and urinary tract (CAKUT) are detected. Appropriate imaging procedures are needed to confirm

and define their severity. Abnormal urinary stream or dribbling of urine suggests an anomaly of the distal urinary tract. The causes of acute kidney injury in the newborn are different from those in older children.

During infancy, unexplained fever may be the only feature of urinary tract infection (UTI). UTI may be suggested by other nonspecific symptoms such as failure to thrive, diarrhea and vomiting. It is important to diagnose these infections since urinary tract anomalies may be present. An abdominal mass at this age is likely to be Wilms' tumor, hydronephrosis or multicystic renal dysplasia. An important cause of acute kidney injury, at this age, is hemolytic uremic syndrome. About 20% patients with minimal change nephrotic syndrome have onset of the disease between 2 and 3 yr. Renal tubular disorders such as renal tubular acidosis and Fanconi syndrome are usually diagnosed at this age.

Acute poststreptococcal glomerulonephritis (GN), rare below the age of 3 yr, is usual in older children. Rickets at this age is rarely due to vitamin D deficiency, unless there is malabsorption or chronic liver disease. Nephrotic syndrome beginning in adolescence may be of the non-minimal type. Acute-on-chronic renal failure, previously undetected chronic renal failure, symptomatic hypertension and collagen vascular diseases are common.

Clinical Features of Renal Disease

Hematuria

Gross hematuria in acute GN is typically smoky brown or cola colored. Bright red blood suggests a nonglomerular cause, as in renal or vesical calculi. Gross hematuria is rare in UTI. Other conditions, which might impart a red color to urine include hemoglobinuria, myoglobinuria, porphyria and ingestion of beetroot.

Edema

Acute GN presents with facial puffiness and gross hematuria; the edema does not pit readily on pressure. If fluid intake is not restricted, the edema may increase and involve hands, feet and legs. In nephrotic syndrome, edema develops insidiously, starting with eyelid puffiness most noticeable in the morning. Over a period of several days, there is pitting edema over the feet and legs. Facial swelling is often mistaken for allergy or insect bite.

Oliguria

Oliguria, defined as urine volume less than 0.5 ml/kg per hr, commonly results from gastroenteritis and hypovolemia. Oliguria is an important feature of moderate or severe acute GN, acute tubular necrosis and conditions causing severe glomerular injury (e.g. HUS, vasculitis).

Abnormalities of Micturition

A poor urinary stream in boys, especially in presence of a full bladder, suggests obstruction, most commonly due

to posterior urethral valves. Persistent dribbling indicates abnormal ureteric insertion distal to bladder neck. Infants with meningomyelocele should be evaluated for bladder dysfunction. Dysuria, flank pain or ureteric colic suggest UTI or urinary tract calculi.

Polyuria, Polydipsia

Impaired urinary concentration is a feature of obstructive uropathy and primary or secondary tubulointerstitial disorders. Polyuria is also present in conditions associated with deficiency or resistance to antidiuretic hormone, diabetes mellitus, hypokalemia (e.g. distal renal tubular acidosis) and hypercalcemia.

Enuresis

Primary monosymptomatic enuresis needs to be distinguished from patients with dysfunctional voiding. Most children with nocturnal enuresis have no evidence of renal disease. Urinalysis and culture are recommended in patients with secondary enuresis.

Hypertension

Assessment of blood pressure is necessary in all children, and especially those with disorders of the kidneys or urinary tract. Symptomatic hypertension is chiefly due to a renal parenchymal or renovascular cause; endocrine conditions are uncommon.

Growth Retardation, Anemia

Physical retardation is a feature of chronic kidney disease (stage 3–5) and tubular disorders. Normocytic normochromic anemia is striking in patients with chronic kidney disease (stage 3–5). Patients with unexplained anemia should be evaluated for a renal disease.

Abdominal Mass

Multicystic renal dysplasia, polycystic kidneys, renal vein thrombosis, hydronephrosis (due to pelviureteric or lower urinary tract obstruction) and Wilms' tumor may result in palpable masses.

Examination of Urine

Urinalysis is an important step for diagnosis of renal disease. Evaluation includes microscopic examination of the uncentrifuged as well as centrifuged specimen and semiquantitative or quantitative detection of different substances.

Collection of Specimen

The first morning specimen is preferred since it is relatively concentrated. While a clean container is sufficient, specimens for culture should be collected in a sterile container. After cleaning the perineum with soap and water, a 'clean catch' sample is collected. If facilities for immediate processing are not available, the specimen is stored at 4°C for 12–14 hr.

It is difficult to obtain satisfactory specimens in children below 2-yr-old. Urine may be collected using a sterile bag that is applied after local cleaning and removed soon after the void. These specimens should not be used for culture. Other reliable ways for obtaining urine specimens in infants include percutaneous suprapubic aspiration or transurethral catheterization.

Specific Gravity

Specific gravity is measured using either refractometer or hydrometer; the former is convenient, requires less volume of urine and gives accurate values. The early morning urine specific gravity should exceed 1015.

pH

Urine is collected in a capped syringe if pH can be measured promptly. If measurement is likely to be delayed, urine should be collected under paraffin. Urine pH is lowest in the fasting, early morning specimen and increases following meals.

Protein

Proteinuria is an important marker of renal injury. Detection of 3–4+ albuminuria suggests glomerular disease. Low molecular weight proteinuria, including lysozyme, β_2 microglobulin, neutrophil gelatinase associated lipocalin and retinol binding protein, suggest tubular injury. Dipstick methods (Uristix) for proteinuria are convenient and reliable. Composite strips for pH, glucose, hematuria, leukocyte esterase and nitrite are also available. Proteinuria can also be semiquantitatively tested using the boiling and the sulfosalicylic acid tests.

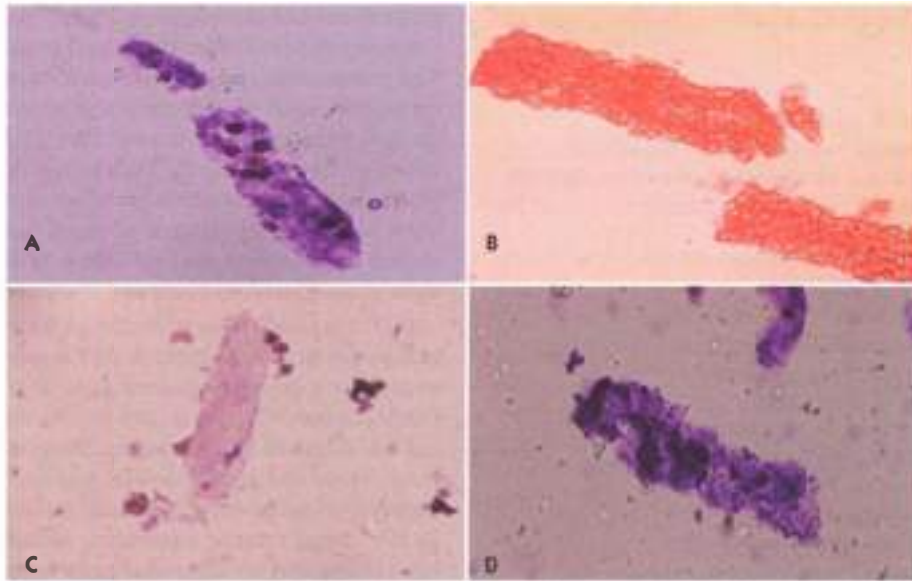
Reducing Substances

Reducing substances can be estimated by Benedict test or dipsticks based on the glucose oxidase method, both of which produce a graded color change.

Microscopic Examination

A fresh, well-mixed specimen is examined for cellular elements, crystals and casts. Alternatively, urine is centrifuged at 1500 rpm for 10 min; urine is decanted and the cell pellet resuspended in 0.3–0.5 ml urine. Evaluation for hematuria, defined as more than 5 red cells/hpf in a centrifuged specimen is abnormal. Red cell casts indicate glomerular inflammation. Leukocytes may occasionally be absent despite significant bacteriuria. On the other hand, isolated presence of leukocytes is not specific for UTI, and may be noted in interstitial nephritis, stones and high fever. The detection of bacteriuria in fresh, uncentrifuged urine is significant. Figure 16.4 shows common abnormalities picked up on urine microscopic examination.





Figs 16.4A to D: Appearance of casts on urine microscopic examination. (A) White blood cell casts; (B) red blood cells casts, (C) hyaline cast; (D) Granular cast

Blood Tests

Blood levels of creatinine and urea are used to assess renal function. The normal levels of serum creatinine are 0.2–0.5 mg/dl in children below 6 yr and 0.4–0.8 mg/dl in older children. Blood urea ranges between 20–35 mg/dl during childhood. However, it is important to realize the limitations of these investigations. Normal values of blood urea or creatinine do not increase even when glomerular filtration rate is reduced by 50%. The level of serum creatinine is dependent on muscle mass and is, therefore low in malnutrition. Bilirubin may interfere with creatinine measurements. Blood urea levels are low on a protein deficient diet and high with tissue breakdown, trauma, gastrointestinal bleeding and use of corticosteroids. Estimation of blood levels of cystatin C, which does not depend on the nutritional status, is considered a sensitive indicator of glomerular function.

Other specific investigations include albumin, cholesterol, antistreptococcal antibody titers, complement, immunoglobulins and autoantibodies. Estimation of blood pH, bicarbonate, electrolytes and osmolality are important in patients with tubular disorders and/or renal failure.

Glomerular Filtration Rate (GFR)

While clearance of inulin is regarded as the reference for estimating GFR, the test involves its accurate IV infusion followed by measurement of levels in timed urine and blood samples. Measurement of the creatinine clearance is adequate for assessing GFR in most cases.

Creatinine Clearance

Creatinine clearance depends on the body size; the values are normalized to surface area. The normal creatinine

clearance is 80–120 ml/minute per 1.73 m². GFR can be estimated from serum creatinine (mg/dl) and patient height (cm). The value of the constant *k* ranges between 0.41–0.43.

$$\text{GFR (ml/minute per 1.73 m}^2\text{)} = \frac{k \times \text{height}}{\text{Serum creatinine}}$$

Radionuclide Clearance

Disappearance curves of the radionuclides, ¹²⁵I-iothalamate, ^{99m}Tc-DTPA or ⁵¹Cr-EDTA following its IV injection can be used to accurately compute GFR.

Tests of Tubular Function

Table 16.1 lists some important evaluations useful in diagnosing disorders of tubular function.

Water Deprivation Test

Following a few hours of fluid deprivation, desamino-8-D-arginine vasopressin (DDAVP) is administered nasally (5–10 µg neonates and infants, 20 µg children) or by IM injection (0.4–1.0 µg infants and young children, 2 µg older children). Urine is collected every hr for the next 2–3 hr. Following administration of DDAVP, patients with nephrogenic diabetes insipidus fail to show a rise of urine osmolality that remains below 300 mOsm/kg (normal >800 mOsm/kg). Those with deficiency of the antidiuretic hormone concentrate urine appropriately following DDAVP administration.

Imaging of the Urinary Tract

Plain X-Ray

A plain film of abdomen provides information on renal size, shape and outline and radiopaque calculi. The length

Table 16.1: Investigations for evaluation of suspected tubular diseases

Substrate	Test
Phosphate	Blood parathormone Tubular reabsorption of phosphate Tubular maximum for reabsorption/GFR
Glucose	Renal threshold and tubular maximum for glucose reabsorption
Amino acids	Clearance of amino acid
Bicarbonate	Blood anion gap Fractional excretion of bicarbonate
H ⁺	Minimum urinary pH Urine anion gap; urine osmolal gap U-B CO ₂ gradient
Water	Maximum urine osmolality Water deprivation test Plasma ADH
Sodium	Urinary sodium excretion Plasma renin, aldosterone

ADH antidiuretic hormone; GFR glomerular filtration rate

of normal kidney approximates the height of first four lumbar vertebrae. A small kidney may indicate hypoplasia or chronic damage. The opposite kidney, unless diseased, shows compensatory hypertrophy.

Ultrasonography

Ultrasonography is the initial modality for imaging kidneys and urinary tract in renal diseases. This investigation is readily available, noninvasive and performed even in uncooperative patients, infants and those with renal failure. Anatomic details of the kidneys, ureters and bladder are examined. Doppler ultrasonography is useful for studying renal blood flow.

Intravenous Pyelogram (IVP)

The patient is prepared as for plain X-ray. The radiocontrast is injected and films taken at 2, 5, 10 and 30 min. IVP provides satisfactory details on renal size, shape, cortical outlines and calyceal pattern. The use of IVP has declined following the availability of radionuclide imaging.

Micturating Cystourethrogram (MCU)

MCU is necessary for studying the lower urinary tract. A sterile catheter is introduced into the bladder, which is filled with contrast medium; films are taken during and end-micturition. MCU provides precise details of the anatomy of the bladder and urethra, presence of vesicoureteric reflux and obstruction in the lower urinary tract (e.g. posterior urethral valves, urethral stenosis).

Radionuclide Imaging

Imaging of the kidney and urinary tract has been simplified by radionuclide methods, which have replaced conventional radiocontrast studies. Radionuclide

procedures are noninvasive, highly sensitive and expose patients to less radiation compared to radiocontrast studies. The compounds, labeled with radioactive ^{99m}technetium, commonly used include dimercaptosuccinic acid (DMSA), diethylenetriaminepentaacetic acid (DTPA) and mercaptotriacetyl glycine (MAG-3). Following IV injection, DMSA attains high concentration in the renal cortex and provides very high quality images of renal morphology. This is useful in detection and followup of renal parenchymal defects associated with urinary tract infections (Fig. 16.5A).

DTPA is freely filtered by the glomeruli with no tubular reabsorption or excretion. A DTPA renogram is useful for evaluating perfusion and function of each kidney. Obstruction to the urine flow can be diagnosed by studying the effect of IV furosemide. Normally there is prompt washout of the radionuclide, but this clearing may not occur in subjects with upper urinary tract obstruction (Fig. 16.5B). Renal arterial narrowing results in reduced renal blood flow and an abnormal pattern on DTPA renogram. This effect is accentuated by administration of angiotensin converting enzyme inhibitors, thus increasing its sensitivity in diagnosis of renal artery stenosis. MAG-3 provides highly satisfactory information on renal structure and function.

^{99m}Tc-labeled radionuclide scan can be used instead of the radiocontrast MCU. Radionuclide cystography is sensitive for detecting vesicoureteric reflux with minimal radiation exposure. However, this procedure does not provide sufficient anatomic details of bladder and urethra to recommend its use for initial evaluation of patients with suspected urinary tract obstruction, nor grading of vesicoureteric reflux.

Suggested Reading

de Bruyn R, Marks SD. Postnatal investigation of fetal renal disease. *Semin Fetal Neonatal Med* 2008;13:133–41

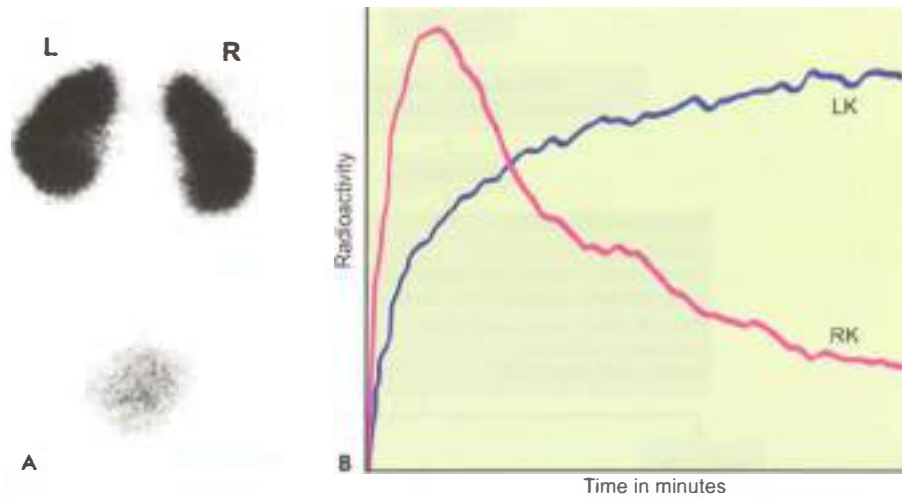
Gupta AK, Jana M. Imaging of the urinary tract. In: *Pediatric Nephrology*, 5th edn. Eds. Srivastava RN, Bagga A. Jaypee, New Delhi, 2011; 48–65

Schwartz GJ, Munoz A, Michael F, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009;20:629–37

Simoneaux SF, Greenbaum LA. Diagnostic imaging. In: *Pediatric Nephrology*, 6th edn. Avner ED, Harmon WE, Niaudet P. Lippincott Williams and Wilkins, Philadelphia 2009; 535–64

HEMATURIA

The presence of blood in urine imparts it a color, which includes various shades of deep red, smoky brown, cola-color and faint pink. Parents may mistake very concentrated urine for that containing blood. Microscopic examination of urine will show red blood cells. Reagent coated dipsticks detect free hemoglobin and myoglobin. Red urine may be present in porphyria and following beetroot ingestion. Urine appears orange-colored after administration of rifampicin or pyridium. Uric acid crystals may also impart a pink tinge to the nappy.



Figs 16.5A and B: (A) ^{99m}Tc -DMSA scintigraphy showing multiple scars and loss of volume in the right kidney. The left kidney is normal; (B) renal dynamic scan with diuretic was performed in a 6-wk-old newborn with isolated left hydronephrosis. The excretion of the tracer on the left side is sluggish and unchanged with administration of diuretic, suggesting an obstructive pattern of excretion, as seen with pelviureteric junction obstruction

In children, the commonest cause of gross hematuria is postinfectious GN. Urinary tract stones are not infrequent (Table 16.2). Gross hematuria is rare in acute pyelonephritis. Conditions that cause persistent microscopic hematuria include idiopathic hypercalciuria, benign familial hematuria, Alport syndrome, IgA nephropathy and membranoproliferative GN.

Diagnostic Evaluation

A history of pain in the flank or suprapubic region, dysuria and edema should be obtained. Physical examination includes assessment of growth and features of acute or chronic kidney disease such as edema, hypertension, unexplained pallor, bony abnormalities and abdominal mass. An audiogram and a detailed eye examination may be needed. Figure 16.6 shows an algorithm for evaluation of patients with hematuria.

A fresh specimen is examined for red cells, red cell casts and protein. Absence of large number of red cells in bloody urine suggests hemoglobinuria (intravascular hemolysis)

or myoglobinuria. In glomerular disease, urine shows dysmorphic red cells, of different shapes, whereas in bleeding from renal pelvis or the lower urinary tract, the red cells maintain normal morphology (Fig. 16.7 and Table 16.3). Presence of significant proteinuria (2+ or more) and/or red cell casts suggests glomerular disease. Hypercalciuria should be excluded by determination of urinary calcium to creatinine ratio on one or more random samples.

A plain X-ray film of the abdomen and abdominal ultrasound is done to exclude major renal and urinary tract anomalies and calculi. Blood levels of creatinine are measured; other specialized blood tests depend on the likely clinical etiology. Surgical conditions that cause hematuria can be diagnosed by appropriate imaging. Invasive procedures such as cystoscopy are rarely indicated.

In a significant proportion, mild microscopic hematuria spontaneously disappears over a period of several years. Other family members may have similar urinary abnormalities. If there is no family history, a renal biopsy

Table 16.2: Causes of hematuria

Glomerular	Non-glomerular
Postinfectious glomerulonephritis (GN)	Hypercalciuria
IgA nephropathy	Renal calculi
Henoch-Schönlein nephritis	Urinary tract infection
Membranoproliferative GN	Hemorrhagic cystitis
Rapidly progressive GN	Trauma, exercise
	Cystic renal disease
	Interstitial nephritis
Uncommon	Uncommon
Lupus nephritis	Vascular malformations
Other vasculitides, e.g. microscopic polyangiitis	Coagulation disorders
Membranous nephropathy	Thrombocytopenia
Familial benign hematuria	Nutcracker syndrome
Alport syndrome	Renal or bladder malignancy

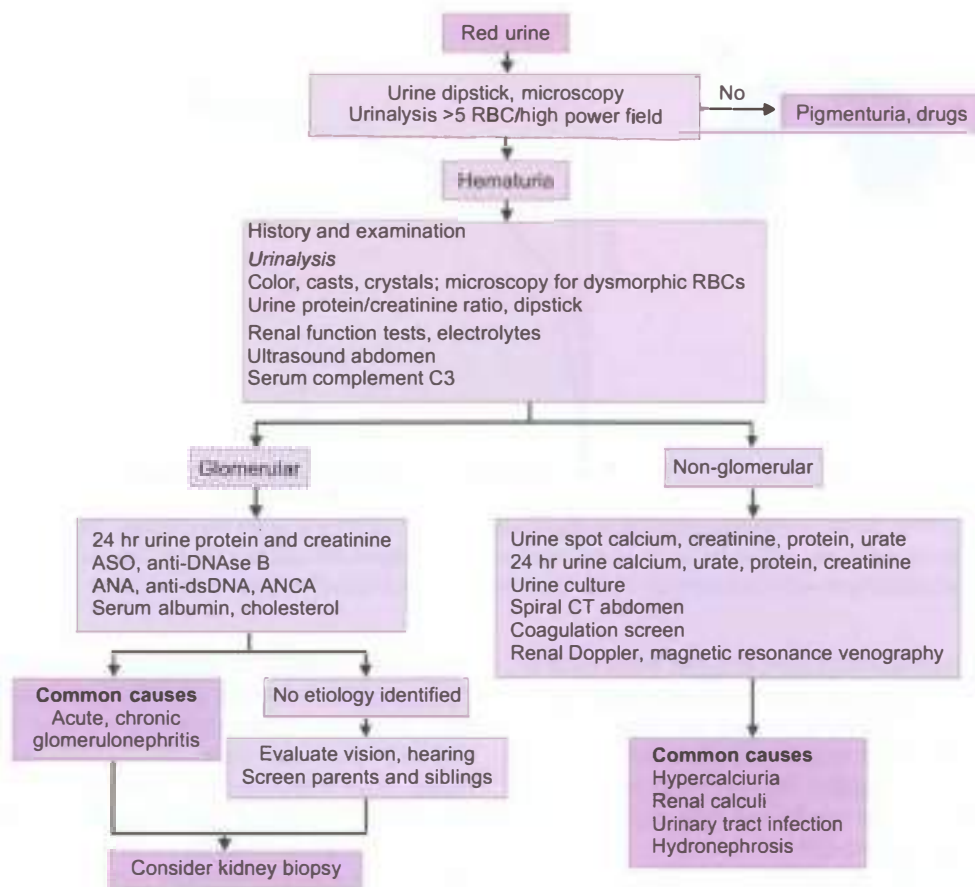


Fig. 16.6: Approach to evaluation of a patient with hematuria. The initial step in evaluation attempts to distinguish glomerular from nonglomerular causes of hematuria (see Table 16.3). Estimation of complement C3 is an important screening test for postinfectious glomerulonephritis. Patients with persistent glomerular hematuria might require kidney biopsy and/or screening for familial causes. ASO antistreptolysin O, ANA antinuclear antibody, anti dsDNA anti-double stranded DNA antibody, ANCA antineutrophil cytoplasmic antibody

Table 16.3: Features that distinguish glomerular from non-glomerular hematuria

Features	Glomerular causes	Non-glomerular causes
Dysuria	-	Suggests urethritis or cystitis
Systemic complaints	Edema, pharyngitis, rash, arthralgia (postinfectious glomerulonephritis, lupus, Henoch-Schönlein purpura)	Fever (UTI), loin pain (calculi)
Family history	Deafness, renal failure (Alport syndrome)	Calculi (hypercalciuria)
Hypertension, edema	Common	Rare
Abdominal mass	Absent	Wilms tumor, obstructive uropathy
Urine color	Brown, tea, cola	Bright red, clots
Proteinuria	2+ or more	Trace, 1+
Dysmorphic RBC	>20%	<15%
RBC casts	Common	Absent
Crystals	Absent	May suggest calculi

RBC red blood cells; UTI urinary tract infection

is not urgently indicated and the patient kept under observation.

Renal Biopsy

Renal biopsy should be done if hematuria is associated with persistent or heavy (3+ or more) proteinuria, history

of renal disease in the family or evidence of chronic kidney disease in the patient, or if renal impairment or hypertension are seen on followup. A biopsy is also considered in children showing persistent microscopic hematuria for two or more years even in the absence of the above features. This procedure is necessary to diagnose IgA

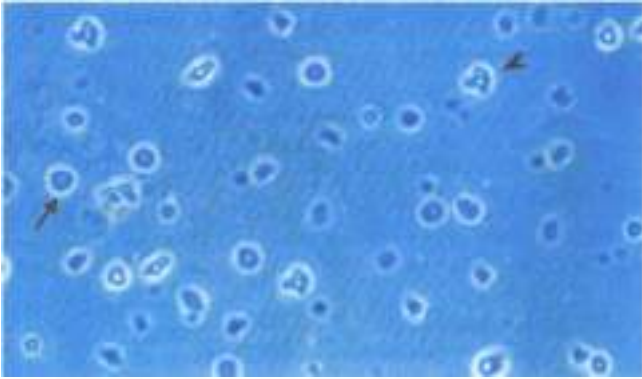


Fig. 16.7: Phase contrast microscopy showing dysmorphic red cells (arrowhead). Normal red cells are also seen (arrow)

nephropathy, Alport syndrome, thin basement membrane disease (typically presents as familial, benign hematuria) and chronic GN. The biopsy is evaluated by light, immunofluorescence and electron microscopy.

Alport Syndrome

This condition is inherited in an X-linked manner, although autosomal transmission is known. Mutations in the gene encoding alpha subunit of collagen IV (*COL4A5*) result in persistent microscopic hematuria, moderate proteinuria and progressive kidney failure. A significant proportion show high frequency sensorineural deafness; ocular defects (lenticonus, cataract, macular changes) are often associated. Ultrastructural examination of renal biopsy shows variable thickness of glomerular basement membrane with lengths of marked attenuation to areas of lamination. Therapy is supportive, including the use of angiotensin converting enzyme inhibitors. The majority of male patients show progression to end stage kidney disease.

Suggested Reading

Higashihara E, Nishiyama T, Horie S, et al; Working group for the creation of hematuria guidelines. Hematuria: definition and screening test methods. *Int J Urol* 2008;15:281–4

Indian Pediatric Nephrology Group. Consensus statement on evaluation of hematuria. *Indian Pediatr* 2006;43:965–73

Quigley R. Evaluation of hematuria and proteinuria: how should a pediatrician proceed? *Curr Opin Pediatr* 2008;20:140–4

PROTEINURIA

The glomerular capillaries provide an effective barrier to filtration of proteins. Small amounts of protein are filtered but almost completely reabsorbed by the proximal tubule. Detection of more than trace amounts of protein in the urine is abnormal. However, the degree of proteinuria does not always reflect the severity of glomerular abnormality. Massive proteinuria occurs in minimal change nephrotic syndrome, in which glomeruli are normal or show mild changes. Persistent and heavy

proteinuria, especially if associated with hematuria, should be promptly evaluated.

Quantitation of Proteinuria

Protein concentration of 100–1000 mg/m²/day indicates mild to moderate proteinuria; more than that is heavy (nephrotic range) proteinuria. Accurate quantitative measurements of 24 hr urinary protein are not needed, if semiquantitative tests are done on a concentrated (first morning) specimen. Normally the protein to creatinine ratio, in the first morning urine specimen, is below 0.1 (mg/mg); a ratio of 0.1–2 indicates mild to moderate and >2 heavy proteinuria. The latter usually corresponds to 3+ or 4+ reaction on boiling or dipstick test.

Fever, dehydration and heavy exercise may cause transient and mild proteinuria. Mild proteinuria may occur in UTI, hydronephrosis and renal tuberculosis. Mild proteinuria in proximal tubular defects (e.g. Fanconi syndrome) is composed of low molecular weight proteins, while heavy proteinuria (predominantly albumin) indicates glomerular disease.

Important causes of asymptomatic proteinuria include orthostatic proteinuria, chronic glomerular diseases, reflux nephropathy, renal hypoplasia and rarely renal tubular disorders (Table 16.4). In orthostatic (postural) proteinuria, protein is absent in urine specimen collected after overnight recumbence. The pathogenesis of this condition is not clear but longterm outcome is good. Continued followup is necessary until proteinuria disappears. Chronic renal damage from vesicoureteric reflux and UTI may manifest with proteinuria. Several forms of glomerular diseases, especially focal segmental glomerulosclerosis, may cause persistent asymptomatic proteinuria; micro-

Table 16.4: Conditions presenting with proteinuria

Glomerular proteinuria

Nephrotic syndrome (minimal change disease, focal segmental glomerulosclerosis, congenital nephrotic syndrome)
 Membranoproliferative glomerulonephritis, membranous nephropathy
 Hepatitis B and C nephropathy, HIV nephropathy
 Reflux nephropathy
 Amyloidosis
Associated hematuria: Postinfectious glomerulonephritis, IgA nephropathy, Henoch-Schönlein nephritis, lupus nephritis, Alport syndrome

Tubular proteinuria

Drug induced nephropathy (analgesics)
 Heavy metal nephropathy (e.g. gold, lead, cadmium)
 Renal tubular acidosis
 Interstitial nephritis, pyelonephritis
 Intermittent or transient proteinuria
 Postural (orthostatic)
 Fever
 Exercise

scopic hematuria is often associated. A renal biopsy is indicated in presence of persistent or heavy proteinuria. Longterm observation is necessary to monitor clinical course and renal function. Low salt diet and prolonged treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blockers are effective in reducing glomerular proteinuria.

Suggested Reading

Rademacher ER, Sinaiko AR. Albuminuria in children. *Curr Opin Nephrol Hyperten* 2009;18:246–51

Srivastava RN. Isolated asymptomatic proteinuria. *Indian J Pediatr* 2002;69:1055–8

ACUTE GLOMERULONEPHRITIS

Acute glomerulonephritis (GN) is characterized by abrupt onset of hematuria, oliguria, edema and hypertension. The clinical severity varies, depending on histological involvement, salt and water retention and glomerular filtration rate. Mild disease may go undetected; severe cases have anuria, hypertensive encephalopathy and heart failure. The most common cause of acute GN is that following streptococcal infection (Table 16.5). Key investigations include renal function tests, urinalysis, serum complement C3 and titers of antistreptolysin. Renal biopsy is required if the presentation or course suggest a diagnosis other than poststreptococcal GN (Table 16.6).

Poststreptococcal Glomerulonephritis

Acute GN following infection by group A beta-hemolytic streptococci is a common disorder. Streptococcal infection of the throat or skin precedes the onset of nephritis by 1 to 4 weeks. Only a few strains of streptococci are nephritogenic, e.g. types 4 and 12 causing pharyngitis and type 49 causing pyoderma.

Table 16.5: Etiology of the acute nephritic syndrome

Postinfectious

Streptococci, staphylococci, pneumococci, meningococci, *Treponema pallidum*, *Salmonella*, leptospira
Plasmodium malariae, *P. falciparum*, toxoplasma, filaria
Hepatitis B and C, cytomegalovirus, parvovirus, Epstein-Barr virus, coxsackievirus, echovirus, varicella
Associated with severe infections; infection of shunts, prostheses, bacterial endocarditis

Systemic vasculitis

Henoch-Schönlein purpura
Microscopic polyarteritis, Wegener granulomatosis

Others

Membranoproliferative glomerulonephritis
IgA nephropathy
Hereditary nephropathy
Systemic lupus erythematosus

Table 16.6: Indications for renal biopsy in acute glomerulonephritis

Systemic features. Fever, rash, joint pain, heart disease
Absence of serologic evidence of streptococcal infection; normal levels of C3 in the acute stage of illness
Mixed features of glomerulonephritis and nephrotic syndrome
High blood levels of urea or presence of anuria requiring dialysis (rapidly progressive GN)

Delayed resolution

Oliguria, hypertension and/or azotemia persisting past 7–10 days
Gross hematuria persisting past 3–4 weeks
Nephrotic range proteinuria beyond 2 weeks
Low C3 levels beyond 12 weeks
Persistent proteinuria beyond 6 months

Pathology

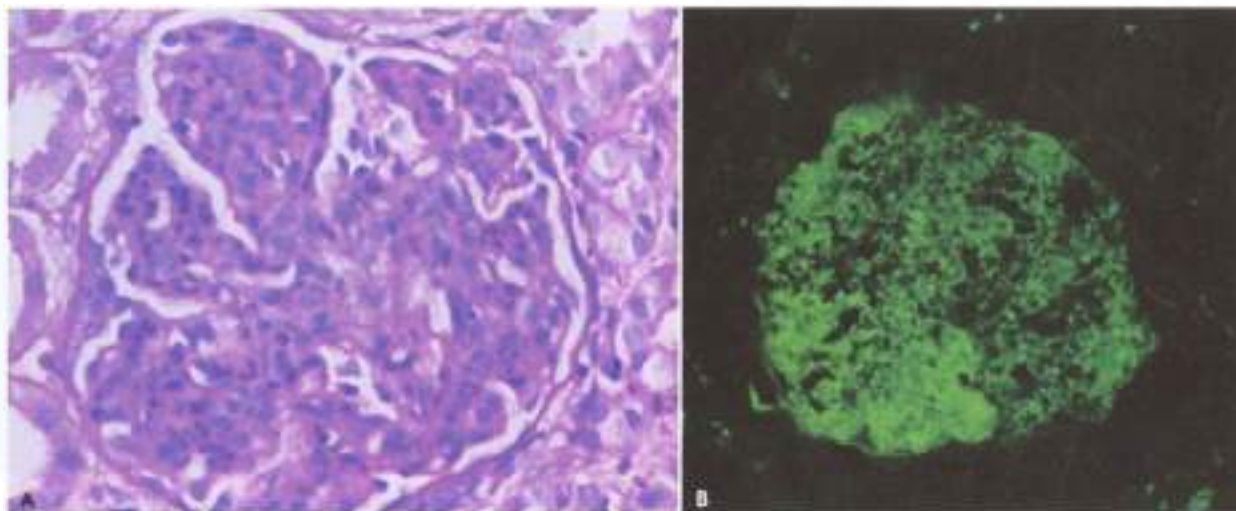
On light microscopy, glomeruli are enlarged and ischemic and capillary loops narrowed, making glomeruli appear bloodless (Fig. 16.8A); there is proliferation of mesangial cells and neutrophil infiltration. Immunofluorescence shows granular deposits of IgG and complement (C3) along capillary walls (Fig. 16.8B). Electron microscopy shows deposits (humps) on the subepithelial side of the glomerular basement membrane.

Clinical Features

Poststreptococcal GN involves school-age children, more commonly boys and is uncommon below 3 yr. Subclinical episodes are more common than overt disease, especially during epidemics. Patients may have mild proteinuria and microscopic hematuria. The onset is rapid, with puffiness around the eyes and pedal edema. Urine is cola-colored; hematuria is brief, often lasting only a few hours and does not persist beyond 1–2 weeks. While the degree of oliguria usually correlates with the disease severity, anuria is uncommon. Hypertension, present in over half the patients, resolves with loss of edema. Atypical presentations include (i) convulsions due to hypertensive encephalopathy; (ii) left ventricular failure and pulmonary edema, due to malignant hypertension and hypervolemia; (iii) acute kidney injury; and (iv) nephrotic syndrome.

Laboratory Findings

Urine shows 1–2+ protein with red cells, and red cell and granular casts. White cells indicate glomerular inflammation and should not be regarded as evidence of UTI. Hemodilution may result in normocytic anemia; ESR is raised. Blood levels of urea and creatinine are elevated reflecting renal impairment; hyponatremia and hyperkalemia occur with continuing oliguria. Chest X-ray may show prominent vascular markings suggesting hypervolemia. Serologic evidence for streptococcal infection is present in most patients with pharyngitis, though antibiotic therapy may blunt this response. ASO titer is increased in more than 80% patients; anti-DNase B is



Figs 16.8A and B: (A) Poststreptococcal GN. Moderately severe proliferation and exudative changes with infiltration of neutrophils. Few open capillary lumina are seen; (B) Immunofluorescence examination showing extensive fine granular deposition of IgG along the capillary wall and in mesangium with a starry sky appearance

elevated in cases of streptococcal skin infection. The titers decrease to low levels within 4–6 weeks. The level of serum C3 is low in 90% patients but normalizes by 8–12 weeks. Persistent low C3 levels indicate other forms of GN.

Management

Patients with mild oliguria and normal blood pressure can be managed at home. Close attention to blood pressure and dietary intake is essential. Once acute GN has occurred, treatment with penicillin has no effect on the course of the disease, but may be given if active pharyngitis or pyoderma is present. The principles of management of patients with severe oliguria and acute kidney injury are discussed later.

Diet. The intake of sodium, potassium and fluids should be restricted until blood levels of urea reduce and urine output increases. Overhydration is a dangerous complication as it may increase hypertension and precipitate left ventricular failure. Patients with azotemia require accurate measurement of urine output and daily weight, and restriction of fluid intake to an amount equal to insensible losses and 24 hr urine output.

Diuretics. Patients showing modest edema are treated with oral frusemide at a dose of 1–3 mg/kg; the edema disappears with the return of renal function. Therapy with IV frusemide (2–4 mg/kg) is necessary in subjects with pulmonary edema.

Hypertension. Mild hypertension may be controlled by restriction of salt and water intake. Effective anti-hypertensive agents include amlodipine, nifedipine or diuretics. Beta-blockers and angiotensin converting enzyme inhibitors carry risk of hyperkalemia. Patients with hypertensive emergencies need prompt treatment with IV nitroprusside or labetalol.

Left ventricular failure. Hypertension should be controlled and IV frusemide given to induce diuresis, leading to improvement in heart failure. If diuresis is not noted, dialysis is initiated. Respiratory support with positive end-expiratory pressure may be needed.

Prolonged oliguria. Treatment, as outlined above, should be continued and levels of blood urea and electrolytes monitored. *Dialysis is required in children with severe renal failure and prolonged oligoanuria, fluid overload and life-threatening electrolyte disturbances.* Occurrence of secondary infections should be avoided.

Outcome and Prognosis

Acute poststreptococcal GN has an excellent prognosis in childhood. The symptoms begin to resolve in the first week with loss of edema and fall in blood pressure. Gross hematuria and significant proteinuria disappear within 2-weeks, although microscopic hematuria and slight proteinuria may persist for several months. Hypertension subsides within 2–3 weeks, but rarely may persist for several weeks. Patients with acute GN of nonstreptococcal etiology have variable and unpredictable outcome. These cases need close followup over several years with periodic urinalyses and measurements of blood pressure.

Renal biopsy. A biopsy is rarely indicated in those suspected to have poststreptococcal GN except when renal function is severely impaired beyond 7–10 days or serum C3 remains depressed beyond 6–8 weeks. Patients with unresolving acute GN (persistent oliguria or azotemia past 7–10 days, hypertension or gross hematuria past 2–3 weeks) or those with features of a systemic illness (e.g. systemic lupus) require a kidney biopsy (Table 16.6).

Crescentic Glomerulonephritis

Rapidly progressive GN (RPGN) is defined as an acute nephritic illness accompanied by rapid loss of renal function over days to weeks. The histopathological correlate is the presence of crescents (crescentic GN) involving 50% or more glomeruli (Fig. 16.9) suggesting severe glomerular injury. The chief forms of RPGN are: (i) immune complex crescentic GN (immunofluorescence showing immunoglobulin and C3 deposits; normal or low C3), (ii) pauci-immune crescentic GN (related to small vessel vasculitis; positive antineutrophil cytoplasmic antibodies; scant immune deposits) and (iii) anti-glomerular basement membrane GN (with anti-GBM antibodies; linear IgG deposits). The severity of clinical and histological features often correlates. Patients with circumferential crescents involving more than 80% glomeruli show advanced renal failure; those with noncircumferential crescents in fewer glomeruli have an indolent course. Renal biopsy should be performed in all patients with severe nephritic features, which do not resolve within 1–2 weeks.

The outcome is related to histological severity and prompt institution of therapy. Without appropriate treatment, patients are at risk for progressive renal failure. Satisfactory results have been obtained with initial administration of IV and oral corticosteroids and IV cyclophosphamide, followed by maintenance immunosuppression. Plasmapheresis is recommended in patients with pauci-immune crescentic GN and Goodpasture syndrome.

Nephritis in Henoch-Schönlein Purpura

Henoch-Schönlein purpura (HSP) is the most common vasculitis in children (Fig. 16.10). Mild renal involvement indicated by microscopic hematuria and mild proteinuria is common. Serum IgA levels may be elevated. Renal

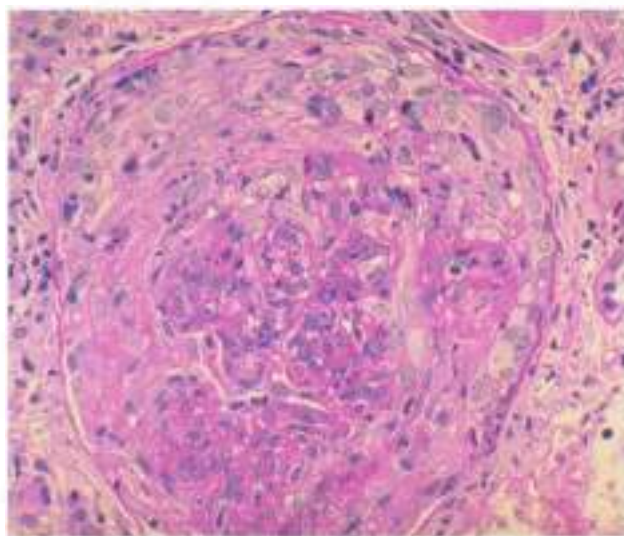


Fig. 16.9: Large cellular crescent with compression of glomerular tuft (Masson trichrome X 200)



Fig. 16.10: Henoch-Schönlein purpura in a 6-yr-old girl admitted with severe abdominal pain. Note purpuric rash over the lower limbs

biopsy shows mesangial proliferation with mesangial deposition of IgA. Most patients recover without any specific treatment. However, longterm observation is necessary to detect insidious renal damage. Rarely a patient may present with nephritic or nephrotic syndrome, hypertension, azotemia and crescentic GN. Therapy with a combination of oral/IV corticosteroids and cyclophosphamide initially, followed by maintenance steroids and azathioprine is recommended. Longterm outcome depends on the severity of renal manifestations.

Immunoglobulin A Nephropathy

Predominant deposition of IgA in the glomeruli, chiefly in the mesangium and occasionally in capillary walls is characteristic. The usual clinical manifestation is recurrent episodes of gross hematuria following upper respiratory infections; each episode lasts for 2–5 days. In between these episodes, microscopic hematuria and mild proteinuria may persist. An acute nephritic or nephrotic syndrome is rarely the initial manifestation. Renal histology shows mesangial proliferation of varying severity. Patients with hematuria and non-nephrotic proteinuria are treated using angiotensin converting enzyme inhibitors. Therapy with corticosteroids and alkylating agents is indicated in patients with nephrotic range proteinuria or deranged renal function.

Lupus Nephritis

Variable clinical and renal histological patterns are observed in patients with systemic lupus erythematosus. Asymptomatic proteinuria and/or hematuria, acute nephritic syndrome and nephrotic syndrome are most common. Rarely renal involvement may be manifested as rapidly progressive GN. Renal biopsy may show almost normal glomeruli, focal or diffuse proliferative GN or membranous nephropathy. Immunofluorescence studies show mesangial and capillary wall deposits of IgG and

C3 and usually C1q and IgA. Antinuclear and double-stranded DNA autoantibodies are present in most cases with lupus nephritis; C3 levels are reduced.

Remissions and relapses and progressive renal damage are characteristic. Infections and end stage renal disease are the chief cause of mortality. Judicious use of corticosteroids, cytotoxic agents (cyclophosphamide, mycophenolate mofetil and azathioprine), calcineurin inhibitors (cyclosporine, tacrolimus) and monoclonal antibodies and prompt treatment of infections has improved outcomes.

Suggested Reading

Brogan P, Bagga A. Leukocytoclastic vasculitis. In: Cassidy JT, Petty RE, Laxer RM, Lindsay CB, eds. *Textbook of Pediatric Rheumatology*, 6th ed. Philadelphia, Saunders Elsevier 2011;483–97

Brogan P, Eleftheriou D, Dillon M. Small vessel vasculitis. *Pediatr Nephrol* 2010;25:1025–35

Gulati A, Bagga A. Management of lupus nephritis. *Indian J Rheumatol* 2012; 7(Suppl 1):69–79

Hogg RJ. Idiopathic immunoglobulin A nephropathy in children and adolescents. *Pediatr Nephrol* 2010;25:823–9

NEPHROTIC SYNDROME

Nephrotic syndrome is characterized by massive proteinuria, hypoalbuminemia and edema; hyperlipidemia is often associated. Some patients show hematuria and hypertension. Heavy proteinuria (more than 1 g/m² per day) is the underlying abnormality, leading to hypoalbuminemia (serum albumin below 2.5 g/dl). The resultant fall in plasma oncotic pressure leads to interstitial edema and hypovolemia. This stimulates the renin-angiotensin-aldosterone axis and antidiuretic hormone secretion that enhances sodium and water retention. The pathogenesis of edema may however be different in patients with significant glomerular lesions, who show primary sodium retention and expanded intravascular volume. Hypoalbuminemia also induces hepatic synthesis of β -lipoproteins resulting in hypercholesterolemia.

More than 90% of childhood nephrotic syndrome is primary (or idiopathic). Other causes such as amyloidosis, vasculitis, systemic lupus erythematosus, postinfectious GN and hepatitis B nephropathy are infrequent. Nephrotic syndrome in children can be divided into two groups based on renal histological characteristics: (i) minimal change nephrotic syndrome (MCNS); and (ii) nephrotic syndrome with significant lesions (Table 16.7).

Steroid sensitive nephrotic syndrome (which is usually MCNS) has a satisfactory longterm outcome. In contrast, the steroid resistant form (usually associated with significant glomerular lesions) has less satisfactory course and a significant proportion progress to chronic renal failure.

STEROID SENSITIVE NEPHROTIC SYNDROME

MCNS accounts for 80% cases of nephrotic syndrome in children. Renal biopsy does not show significant

Table 16.7: Features of idiopathic nephrotic syndrome

Features	Minimal lesion	Significant lesions
Age at onset	2–6 yr	Older children
Sex incidence	Higher in boys	Equal
Hematuria	Rare	Usual
Blood pressure	Normal	Normal or increased
GFR	Normal	Normal or decreased
Renal biopsy	Normal glomeruli; mild mesangial proliferation; often IgM deposits	Changes of varying severity; C3, immunoglobulin deposits
Serum C3	Normal	Low in MPGN
Selectivity of proteinuria	High	Low
Response to steroids	Remission in >95%	Unsatisfactory
Prognosis	Good; relapses stop by second decade	Variable progression of renal damage

MPGN membranoproliferative glomerulonephritis

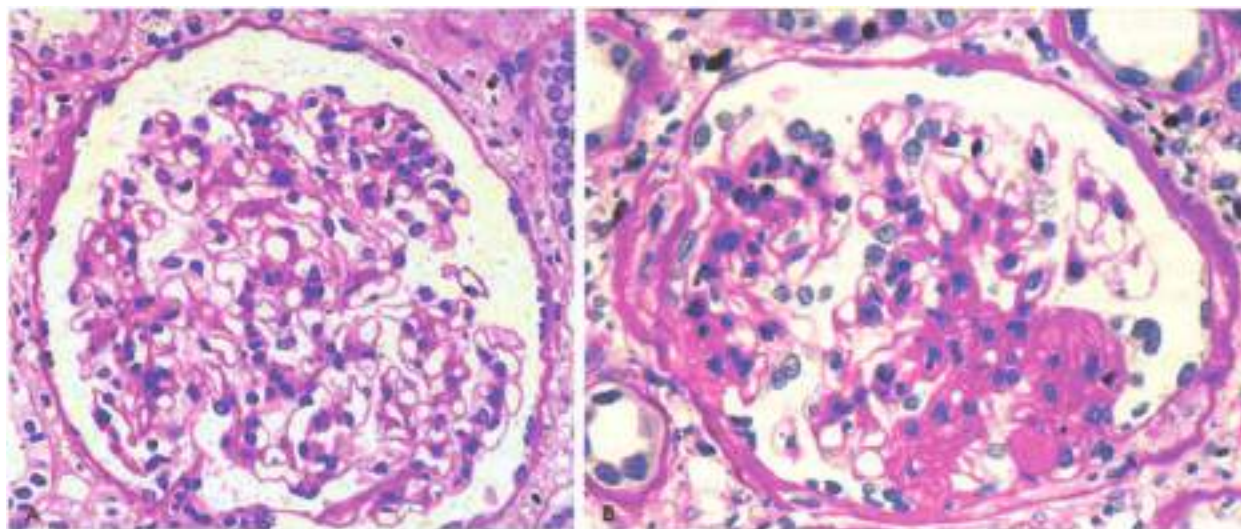
abnormalities on light microscopy (Fig. 16.11A). Electron microscopy shows nonspecific obliteration of epithelial foot processes. Immunofluorescence studies do not demonstrate deposition of immune reactants except occasional mesangial IgM. On the other hand, patients with focal segmental glomerulosclerosis (FSGS) show evidence of sclerosis involving a segment of the glomerular tuft (Fig. 16.11B). The pathogenesis of MCNS is obscure. There is evidence to suggest perturbation of cell mediated immunity, which through yet undefined mechanisms alters the permselectivity of the glomerular filter, resulting in massive proteinuria. A proportion of patients have a primary abnormality of the epithelial foot processes (podocytes).

Clinical Features

The onset is insidious with edema first noticed around the eyes and subsequently on legs. It is soft and pits easily on pressure. Gradually edema becomes generalized, with ascites, hydrothorax and hydrocele (Fig. 16.12). With increasing edema, urine output may fall. The blood pressure is usually normal; sustained elevation suggests the possibility of significant glomerular lesions. The bloated appearance and relative well-being of the child is misleading and after the loss of edema, severe muscle wasting is revealed. Infections may be present at the onset and during relapses.

Laboratory Findings

Urine examination shows heavy (3–4+) proteinuria. Gross hematuria or persistent microscopic hematuria suggests the likelihood of significant glomerular lesions; hyaline and granular casts are present. Serum albumin is low and values below 1 g/dl are often obtained. Hypercholesterolemia may impart a milky appearance to the plasma. Blood



Figs 16.11A and B: (A) Renal histology in a 4-yr-old boy with steroid dependent nephrotic syndrome. There is normal morphology of glomerular capillary loops, mesangial matrix and cells suggestive of minimal change disease; (B) histological features in a 6-yr-old girl with steroid resistant nephrotic syndrome secondary to focal segmental glomerulosclerosis. Note the hilar sclerosis involving large areas of the glomerulus and adhesions to the Bowman's capsule



Fig. 16.12: An 8-yr-old boy with steroid dependent nephrotic syndrome. Anasarca is seen affecting upper limbs (including dorsa of hands), trunk and ascites. Note the cushingoid features and striae on lower abdominal wall and upper legs

urea and creatinine values are within the normal range except when there is hypovolemia and fall in renal perfusion.

Blood levels of IgG are low and those of IgM elevated; C3 level is normal. The severity of glomerular damage is reflected in the passage of proteins of large molecular weight, chiefly globulin. Protein selectivity is the ratio of clearance of high molecular weight (e.g. IgG) to low molecular weight proteins (e.g. transferrin, albumin). A low ratio indicates highly selective proteinuria, as in MCNS. However, this information does not offer diagnostic help.

Evaluations considered at onset of nephrotic syndrome include: (i) urinalysis for proteinuria, red cells, casts; (ii) blood levels of urea, creatinine, albumin, cholesterol; (iii) complete blood counts and (iv) tuberculin test. Depending on clinical and laboratory findings, the following additional tests may be required: (i) C3 and antistreptolysin O (gross or persistent microscopic hematuria); (ii) chest X-ray (positive tuberculin test; history of contact with tuberculosis); (iii) hepatitis B surface antigen (recent jaundice, raised levels of transaminases); (iv) antinuclear antibodies (suspected systemic lupus erythematosus); and (v) urine culture (suspected urinary tract infection). A renal biopsy is not required to confirm the diagnosis of MCNS prior to starting treatment. A biopsy is recommended in children with atypical features at the onset (age below 12 months, gross or persistent microscopic hematuria, low blood C3, hypertension or impaired renal function). Patients who continue to show nephrotic range proteinuria despite appropriate steroid therapy require a biopsy to determine the underlying disorder.

Management of Initial Episode

The child should receive a high protein diet. Salt is restricted to the amount in usual cooking with no extra salt given. Any associated infection is treated. The presence of tuberculosis should be looked for. Diuretics are administered only if edema is significant. Frusemide (1–4 mg/kg/day in 2 divided doses) alone or with an aldosterone antagonist, spironolactone (2–3 mg/kg/day in 2 divided doses) is adequate. Diuretics should be used cautiously and overzealous fluid loss avoided. Therapy with corticosteroids results in abolition of proteinuria (remission) usually by 10–14 days, diuresis and loss of edema.

The first episode of nephrotic syndrome should be treated adequately, both in terms of dose and duration of corticosteroids, since this is considered an important determinant of longterm course. Only prednisolone and prednisone are of proven benefit in the treatment of proteinuria. Either of these agents is given at a dose of 2 mg/kg per day (maximum 60 mg) in single or divided doses for 6 weeks, followed by 1.5 mg/kg (maximum 40 mg) as a single morning dose on alternate days for the next 6 weeks. Therapy with corticosteroids is then stopped. While some experts propose that therapy with corticosteroids should not be stopped abruptly and tapered over the next 8–12 weeks, the benefits of prolonged therapy need to be balanced by the risk of steroid adverse effects.

Parent Education

The parents should be explained about the disease and the usual outcome and their cooperation ensured. They are taught how to examine urine for protein, which should be done periodically to detect a relapse early. During the periods of remission, no dietary restrictions are imposed.

Subsequent Course

A small proportion of patients have only a single episode of the illness, while the majority shows relapses. Some patients have three or less relapses in a year (infrequent relapsers), while others have four or more relapses (frequent relapsers) (Table 16.8). About 15% remain in remission while on prednisolone therapy and relapse whenever the dose is reduced or within 2 weeks of its discontinuation (steroid dependent). About 10–15% patients either do not respond to the initial treatment with prednisolone, or do so transiently and later cease to respond (steroid resistant).

Management of Relapse

Relapses are often triggered by minor infections. Symptomatic therapy of infectious illness might result in remission of low grade (1–2+) proteinuria. However, persistence of 3–4+ proteinuria requires treatment for

relapse. Prednisolone is given at a dose of 2 mg/kg/day until protein is negative/trace for three consecutive days, and then on alternate days at a dose of 1.5 mg/kg for 4 weeks. Thus, treatment for a relapse usually lasts for 5–6 weeks and there is no evidence that its prolongation affects the outcome.

The first 2–3 relapses are treated in the manner described above. Once the pattern of relapses is known, therapy is individualized. Patients with infrequent relapses continue to receive treatment for individual relapses as outlined above.

Frequent Relapses and Steroid Dependence

Patients with frequent relapses or steroid dependence require prolonged treatment in order to maintain disease remission.

Longterm Alternate Day Prednisolone

Following treatment of a relapse, the dose of prednisolone is tapered to maintain the patient in remission; usually a small dose is given on alternate days for 9–18 months. This strategy is effective in maintaining remission in many patients. Since infections precipitate relapses, administering the same small dose daily for 5–7 days starting at onset of infections may prevent relapses. However, relapses, while on this therapy, are treated with daily prednisolone at 2 mg/kg/day until remission, after which alternate day therapy is resumed at 1.5 mg/kg. Patients with repeated relapses, while on longterm therapy, should be considered for treatment with a steroid sparing agent.

Steroid Sparing Agents

The additional use of an alternative agent should be considered in patients with: (i) prednisolone threshold (for maintaining remission) higher than 0.5–0.7 mg/kg on alternate days, or (ii) features of corticosteroid toxicity (growth failure, hypertension and cataract). The agents used, usually in successive order, are listed below and in Table 16.9.

Levamisole. This immunomodulator is effective in reducing relapses in a proportion of patients with frequent relapsing or steroid dependent nephrotic syndrome. After inducing remission, levamisole is administered at a dose of 2–2.5 mg/kg on alternate days. Alternate day prednisolone is given in decreasing doses, until a dose of 0.3–0.5 mg/kg is reached, for 3–6 months; it is occasionally possible to discontinue steroids altogether. Treatment with levamisole is given for 1–2 yr or longer. The chief side effect is leukopenia, which should be monitored every 2 months; others include flu like symptoms and rash.

Cyclophosphamide. Treatment with alkylating agents and alternate day prednisolone is effective in many patients with frequent relapsing or steroid dependent nephrotic syndrome. A 12-week course of treatment may induce long-lasting remission in 30–40% cases. Side effects include

Table 16.8: Important definitions to clarify course of nephrotic syndrome

<i>Remission:</i> Urine albumin nil or trace (or proteinuria <4 mg/m ² /hr) for 3 consecutive early morning specimens
<i>Relapse:</i> Urine albumin 3+ or 4+ (or proteinuria >40 mg/m ² /hr) for 3 consecutive early morning specimens, having been in remission previously
<i>Frequent relapses:</i> Two or more relapses in initial six months or four or more relapses in any twelve months
<i>Steroid dependence:</i> Two consecutive relapses when on alternate day steroids or within 14 days of its discontinuation
<i>Steroid resistance:</i> Absence of remission despite therapy with daily prednisolone at a dose of 2 mg/kg per day for 4 weeks and alternate day for next 4 weeks.

Table 16.9: Therapy for steroid sensitive nephrotic syndrome

Agent	Dose	Duration	Adverse effects
Prednisolone	Maintain on 0.3–0.7 mg/kg on alternate days	9–18 mo	Cushingoid body habitus, hypertension, short stature, cataract, hirsutism
Levamisole	2–2.5 mg/kg on alternate days	1–2 yr	Leukopenia, rash, flu-like symptoms
Cyclophosphamide*	2–2.5 mg/kg/day	12 weeks	Leukopenia; alopecia; gonadal toxicity; nail discoloration (hemorrhagic cystitis; nausea and vomiting are more common with IV administration)
Mycophenolate mofetil	600–1000 mg/m ² /day or 20–25 mg/kg/day	1–3 yr	Gastrointestinal discomfort, diarrhea; leukopenia
Cyclosporine (CyA)* or Tacrolimus (Tac)*	CyA: 4–5 mg/kg/day Tac: 0.1–0.2 mg/kg/day	12–36 mo	Acute and chronic nephrotoxicity, elevated transaminases (both agents); hirsutism, gum hyperplasia, hypertension or hyperlipidemia (CsA > Tac); hyperglycemia, neurotoxicity with headache and seizures (Tac > CsA)
Rituximab*	375 mg/m ² IV once a week	2–3 doses	Infusion reactions (fever, rash, bronchospasm); hypogammaglobulinemia, neutropenia

* Preferred earlier if relapses are life threatening (associated with peritonitis, other serious infections or thrombosis) or in presence of significant steroid toxicity

leukopenia, nausea and vomiting; a high fluid intake is ensured to prevent hemorrhagic cystitis. Alkylating agents are associated with a risk of gonadal toxicity and malignancies, although at the doses and duration used these risks are minimal. Another alkylating agent, chlorambucil has significant additional toxicities and a low margin of safety, and is not recommended.

Mycophenolate mofetil. Prolonged treatment with this agent is useful in reducing relapse rates and corticosteroid sparing. The lack of renal, hemodynamic and metabolic toxicity makes it an alternative to calcineurin inhibitors. Chief side effects include gastrointestinal discomfort, diarrhea and leukopenia. The dose of the medication is 600–1000 mg/m²/day or 20–25 mg/kg/day in two divided doses for 12–36 months. Tapering doses of prednisolone are given for 6–12 months.

Cyclosporine and tacrolimus. Therapy with either of these agents is indicated in patients that fail to benefit with levamisole, cyclophosphamide and/or mycophenolate mofetil. Treatment may be associated with significant adverse effects. Cyclosporine A (4–5 mg/kg/day) or tacrolimus (0.1–0.2 mg/kg/day) are administered, in two divided doses, for 12–24 months aiming for respective trough levels of 80–120 ng/ml and 3–7 ng/ml. Both agents have strong steroid sparing potential, with steroid discontinuation achieved in most patients over 6–9 months.

Adverse effects are common and include acute and chronic nephrotoxicity. A renal biopsy is done after 2–3 yr of continuous therapy. Patients receiving cyclosporine have cosmetic side effects (hirsutism, gum hyperplasia), hypertension and hypercholesterolemia. Treatment with tacrolimus is associated with risk of hyperglycemia, elevated transaminases, diarrhea, tremors, headache and seizures.

Rituximab. This monoclonal anti-CD20 antibody has been used with success in patients with steroid dependent nephrotic syndrome, with remission lasting 6–18 months. This agent appears to be useful in patients who fail to respond or show toxicity with other therapies.

Complications in Nephrotic Syndrome

The patient should be maintained in remission, as far as possible. Relapses should be promptly treated so that the child does not develop more than minimal edema. Several complications that are associated with massive edema and ascites.

Edema

Edema is controlled with salt restriction and oral hydrochlorothiazide or furosemide for a few days. Salt must not be totally stopped and the usual amounts used in cooking should be allowed. For massive edema, higher doses of furosemide along with spironolactone are needed. Infusion of albumin may be necessary in intractable cases where serum albumin levels are extremely low causing poor renal perfusion and oliguria.

Infections

Nephrotic syndrome and steroid therapy render children susceptible to infections. Infection with *S. pneumoniae*, gram-negative organisms and varicella are common. Children present with serious infections, e.g. peritonitis, cellulitis, pneumonia and meningitis. Peritonitis may manifest with low grade fever, diarrhea and abdominal discomfort. Patients with varicella should receive oral acyclovir for 7 days; severe illness requires administration of IV acyclovir. Immunization with pneumococcal and varicella vaccines is advised once the patient is off steroids for 4 weeks.

Thrombotic Complications

Patients with nephrotic syndrome are at risk for thrombosis involving renal, pulmonary and cerebral veins. Aggressive use of diuretics, venepuncture of deep veins and hypovolemia increase the risk of this complication. Treatment with low molecular weight heparin followed by oral anticoagulants is recommended.

Hypovolemia and Acute Renal Failure

Hypovolemia may occur during a severe disease relapse or following administration of diuretics, particularly in children with poor oral intake, diarrhea and vomiting. Features include abdominal pain, lethargy, dizziness and leg cramps, tachycardia, hypotension, delayed capillary refill, low volume pulses and clammy distal extremities. Elevated ratio of blood urea to creatinine, high hematocrit, urine sodium <20 mEq/l, fractional excretion of sodium $0.2\text{--}0.4\%$ and urinary potassium index $[\text{urine K}^+ / (\text{urine K}^+ + \text{urine Na}^+)] >0.6$ suggest the presence of hypovolemia. Therapy with diuretics should be discontinued. Patients require admission and rapid infusion of normal saline (10–20 ml/kg) over 20–30 min. Those who do not respond to two boluses of saline should receive infusion of 5% albumin (10–15 ml/kg) or 20% albumin (0.5–1 g/kg).

Steroid Toxicity

Repeated and prolonged courses of steroids often result in significant toxicity, characterized by cushingoid features, short stature, hypertension, osteoporosis and subcapsular cataract. Timely use of steroid sparing agents (levamisole, alkylating agents, cyclosporin) are recommended.

Longterm Outcome

Children with MCNS usually have an excellent prognosis. The frequency of relapses decreases with time and a majority of patients outgrow the condition by adulthood. It is unfortunately not possible to predict when a particular patient will stop getting relapses. The mortality rate of 1–4% is associated with infections and hypovolemia that should be preventable.

STERIOD RESISTANT NEPHROTIC SYNDROME

The management of patients with steroid resistant nephrotic syndrome is difficult, with patients showing a variable response to immunosuppression, adverse effects of prolonged therapy and risk of progressive renal damage. Steroid resistance is diagnosed if there is lack of remission despite treatment with prednisolone, at a dose of 2 mg/kg/day (60 mg/m²/day) for 4 weeks. Care is taken to exclude systemic infections (e.g. peritonitis, cellulitis, respiratory tract infections), which might result in persistent proteinuria.

Baseline assessment of renal function, blood levels of albumin and cholesterol, and estimation of proteinuria (24 hr quantitation) guides evaluation. Patients should be

evaluated for secondary causes. Children with steroid resistance should undergo renal biopsy before instituting specific treatment. While patients with minimal change disease show satisfactory response to therapy, the presence of FSGS with chronic tubulointerstitial changes is associated with less satisfactory outcomes. Before start of immunosuppressive therapy, patients with steroid resistant nephrotic syndrome should undergo testing for hepatitis B surface antigen, anti-HCV IgG and HIV.

About 10–20% patients with familial and sporadic steroid resistant nephrotic syndrome have homozygous or compound heterozygous mutations in genes encoding podocyte proteins, including podocin (*NPHS2*), nephrin (*NPHS1*) and Wilm's tumor (*WT1*) genes. These patients are unresponsive to immunosuppressive medications, progresses rapidly to end stage renal disease and unlike nongenetic FSGS (which recurs after transplantation in 30%), does not recur. Where facilities exist, mutational analysis should be offered to patients with (i) congenital nephrotic syndrome (onset below 3 months of age), (ii) family history of SRNS, (iii) sporadic initial steroid resistance that does not respond to therapy with cyclophosphamide or calcineurin inhibitors, and (iv) girls with steroid resistant FSGS.

Management

Patients with steroid resistant nephrotic syndrome secondary to minimal change disease, FSGS or mesangio-proliferative GN are treated similarly. *The chief factor predicting renal outcome is the response of proteinuria to therapy, rather than the renal histology.* The aim of therapy in patients is thus to induce and maintain remission of proteinuria, while avoiding medication related adverse effects. Most regimens use a combination of an immunosuppressive agent with prednisolone (given on alternate days) and an angiotensin converting enzyme inhibitor (Table 16.10). The best results are obtained with regimens combining calcineurin inhibitors (cyclosporine or tacrolimus) and tapering doses of corticosteroids. The aim of treatment is the achievement of complete remission, but occurrence of partial remission is also satisfactory. Patients who respond to treatment do so within 3–6 months; those that fail therapy with one regimen may show response to different agents.

Adjunctive therapy with angiotensin converting enzyme inhibitors (e.g. enalapril 0.3–0.6 mg/kg/day, ramipril 6 mg/m²/day) is associated with decrease in proteinuria and control of hypertension. Adverse effects include dry cough, hyperkalemia and decline in renal function. Angiotensin receptor blockers (e.g. losartan, valsartan) may be used in case of persistent dry cough with ACE inhibitors, or as add-on therapy for better antiproteinuric effect. Therapy with HMG coenzyme-A reductase inhibitors is useful in lowering blood levels of cholesterol in subjects with persistent hypercholesterolemia.



Table 16.10: Agents for management of steroid resistant nephrotic syndrome

Agent	Dose	Duration	Efficacy	Adverse effects
Calcineurin inhibitors				
Cyclosporine (CsA)	4–5 mg/kg/day	12–36 months	50–80%	Acute and chronic nephrotoxicity (both agents); hirsutism and gum hyperplasia (CsA > Tac); hypertension, high cholesterol (CsA > Tac); hyperglycemia (Tac); elevated transaminases, neurotoxicity, headache and seizures (Tac > CsA)
Tacrolimus (Tac)	0.1–0.2 mg/kg/day	12–36 months	70–85%	
Cyclophosphamide				
Intravenous	500–750 mg/m ²	6 pulses	40–50%	Leukopenia; alopecia; nausea and vomiting; gonadal toxicity; hemorrhagic cystitis
Oral	2–2.5 mg/kg/day	12 weeks	20–25%	
High dose corticosteroids with cyclophosphamide				
Methylprednisolone	20–30 mg/kg IV	'Pulses' on alternate days × 6; once weekly × 8; fortnightly × 4	30–50%	Hypertension, hypokalemia, hyperglycemia, steroid psychosis, systemic infections
Prednisolone	Tapering doses*	18 mo	Side effects of cyclophosphamide therapy and prolonged steroid therapy	
Cyclophosphamide	2–2.5 mg/kg/day**	12 weeks		

*Prednisolone 1.5 mg/kg on alternate days × 4 weeks; 1.25 mg/kg × 4 weeks; 1 mg/kg × 4 mo; 0.5–0.75 mg/kg × 12–18 mo

**Cyclophosphamide is administered during 3–15 weeks

Hypertension must be controlled and infections managed appropriately. Edema is minimized with judicious use of diuretics. The use of intravenous albumin should be limited to cases with (i) symptomatic hypovolemia, (ii) symptomatic edema or (iii) marked ascites that is causing respiratory compromise. In cases with hypovolemia, 10–20 ml/kg of 4.5–5% albumin should be infused. Severe symptomatic edema or ascites may be treated with 0.75–1 g/kg of 20% albumin, infused over 2 hr, to expand the circulating volume followed by furosemide 1 mg/kg. Close monitoring is essential to avoid fluid overload and pulmonary edema. Albumin infusion augments diuresis when co-administered with furosemide in severely hypoalbuminemic patients with refractory edema.

Congenital Nephrotic Syndrome

Congenital nephrotic syndrome present in the first 3 months of life with anasarca, hypoalbuminemia and oliguria. The etiology of congenital nephrotic syndrome is heterogeneous. The 'Finnish' form of the disease is inherited in an autosomal recessive manner, with mutations in the gene encoding nephrin (*NPHS1*). The characteristic renal histology with microcystic dilation of proximal tubules is seen after a few months of life, although ultrastructural abnormalities of the glomerular basement membrane are present at birth. Elevated levels of alpha-fetoprotein (AFP) in maternal serum and amniotic fluid enable antenatal screening. The clinical course is complicated by failure to thrive, recurrent

infections, hypothyroidism and progression to renal failure by 2–3 yr.

Patients with Denys Drash syndrome show mutations in the *WT1* gene, congenital nephrotic syndrome, male pseudohermaphroditism and high risk of bilateral Wilms' tumor. Renal histology is characterized by diffuse mesangial sclerosis and there is progressive renal failure.

Other causes of congenital nephrotic syndrome include infections (congenital syphilis, cytomegalovirus disease, toxoplasmosis) and mutations in *PLCE1* or *NPHS2* genes; rarely renal histology may be normal (minimal change nephrotic syndrome) or show focal segmental glomerulosclerosis. Therapy of patients with congenital nephrotic syndrome is supportive with appropriate nutrition, control of edema, thyroxine supplements and reduction of proteinuria through ACE inhibitors and/or indomethacin.

Suggested Reading

- D'Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. *N Engl J Med* 2011;365:2398–411.
- Greenbaum LA, Benndorf R, Smoyer WE. Childhood nephrotic syndrome: Current and future therapies. *Nat Rev Nephrol* 2012;8:445–58
- Gulati A, Bagga A, Gulati S, on behalf of the Indian Society of Pediatric Nephrology. Guidelines for management of children with steroid resistant nephrotic syndrome. *Indian Pediatr* 2009;46:35–47
- Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. *Cochrane Database Syst Rev* 2007; (4):CD001533
- Indian Pediatric Nephrology Group. Indian Academy of Pediatrics. Management of steroid sensitive nephrotic syndrome. Revised guidelines. *Indian Pediatr* 2008;45:203–14
- Sinha A, Bagga A. Nephrotic syndrome. *Indian J Pediatr* 2012;79: 1045–55

CHRONIC GLOMERULONEPHRITIS

Chronic GN is not a single disease entity, but comprises advanced stages of several forms of GN. In most cases, the glomerular disease is primary and not part of a systemic disorder. However, chronic GN may occur in systemic lupus erythematosus, microscopic polyarteritis, familial nephropathies and nephropathies due to drugs and toxins. Variable glomerular deposition of immunoglobulin, complement and fibrin is found on immunofluorescence studies. Renal biopsy examination in early stages shows several patterns, while later the histologic changes are nonspecific. Most glomeruli are sclerosed with corresponding tubular, interstitial and vascular changes. Poststreptococcal GN seldom leads to chronic GN.

Clinical Features

The patient may be asymptomatic and the disease detected on routine urine examination. Others may show failure to thrive, persistent anemia, moderate to severe hypertension, edema, nocturia, microscopic or gross hematuria, bone pains and deformities.

Differential Diagnosis

It might be difficult to distinguish chronic from acute GN. The presence of anemia, growth retardation, evidence of long-standing hypertension (hypertensive retinopathy, left ventricular hypertrophy) and radiological skeletal changes indicate impaired renal function of long duration. Examination of the renal biopsy is valuable in confirming the diagnosis.

Urinalysis shows proteinuria, hematuria, white cells and casts. Urine specific gravity is fixed and low (around 1010). Blood urea and creatinine levels are raised and the glomerular filtration rate less than 30 ml/min/1.73 m². Ultrasonography shows small kidneys with regular outline.

Management

There is no specific treatment for chronic GN. Treatment with steroids and immunosuppressive drugs does not offer any benefit. The blood pressure should be controlled and infections treated. If renal function is compromised, the treatment is that of advanced chronic kidney disease.

INTERSTITIAL NEPHRITIS

This is focal or diffuse inflammatory reaction of renal interstitium with secondary involvement of tubules and rarely, glomeruli. Acute interstitial nephritis is usually due to infections or drugs (e.g. ampicillin, cephalosporins). Common causes of chronic interstitial nephritis include urinary tract obstruction and vesicoureteric reflux. Interstitial nephritis may be a feature of a systemic disorder (e.g. systemic lupus, vasculitis, associated with uveitis); autoantibodies to tubular basement membrane are found in some cases. In many instances, no cause is determined.

The clinical features are nonspecific and include abdominal pain, anorexia, pallor, headache and edema. Hypertension is absent. The presence of progressive renal insufficiency associated with satisfactory urine output, and urinary abnormalities such as hyposthenuria and mild proteinuria suggest the diagnosis. Leukocytes and eosinophils are frequently seen in the urine, the latter a feature of drug-associated disease.

A renal biopsy establishes the diagnosis and helps assess severity. Drug-related interstitial nephritis is treated with stoppage of the offending drug; treatment with corticosteroids is beneficial. Systemic illness, if any, should be appropriately managed. The treatment of chronic interstitial nephritis is symptomatic.

Suggested Reading

Ulinski T, Sellier-Leclerc AL, Tudorache E, et al. Acute tubulointerstitial nephritis. *Pediatr Nephrol* 2012;27:1051–7

URINARY TRACT INFECTIONS

Urinary tract infection (UTI) is a common medical problem in children, affecting 3–10% girls and 1–3% boys. They are an important cause of morbidity and might result in renal damage, often in association with vesicoureteric reflux (VUR). Beyond infancy, the incidence of UTI is higher in girls. During infancy, UTI are equally common in boys and girls because the route of infection is often hematogenous and boys have a higher incidence of urinary tract anomalies.

Microbiology

In most cases, UTI are caused by *E. coli* that forms the predominant periurethral flora, and uncommonly by *Klebsiella*, *Enterobacter* and *Staphylococci epidermidis*. *Proteus* and *Pseudomonas* infections occur following obstruction or instrumentation, while *Candida* infection occurs in immunocompromised children or after prolonged antimicrobial therapy.

Predisposing Factors

Recurrent UTI are observed in 30–50% children, usually within 3 months of the first episode. Predisposing factors for recurrent UTI include female sex, age below 6 months, obstructive uropathy, severe vesicoureteric reflux (VUR), habitual postponement of voiding (voiding dysfunction), constipation and repeated catheterization, e.g. for neurogenic bladder. Children with malnutrition and those receiving immunosuppressive therapy are also susceptible.

Clinical Features

The clinical features depend upon the age and the severity of UTI. Neonates show features of sepsis with fever, vomiting, diarrhea, jaundice, poor weight gain and lethargy. The older infant has unexplained fever, frequent micturition and occasionally convulsions. Gross hematuria

is uncommon. The presence of crying or straining during voiding, dribbling, weak or abnormal urine stream and palpable bladder suggest urinary obstruction.

It is difficult to distinguish between infection localized to the bladder (cystitis) and upper tracts (pyelonephritis). The distinction is not necessary since radionuclide studies show that most UTI in children below 5 yr of age involve the upper tracts. Hence, all children should be managed as if they have pyelonephritis. Patients with high fever ($>39^{\circ}\text{C}$), systemic toxicity, persistent vomiting, dehydration, renal angle tenderness or raised creatinine are considered as having *complicated UTI*. Patients with low grade fever, dysuria, frequency and urgency and absence of symptoms of complicated UTI are considered to have *simple UTI*. This distinction is important for purposes of therapy.

Important features on evaluation include history of straining at micturition, incontinence or poor urinary stream, voiding postponement and surgery for meningo-myelocele or anorectal malformation. Finding of palpable kidney(s), distended bladder, tight phimosis or vulval synechiae and neurological deficit in lower limbs suggest a predisposing cause.

Diagnosis

The diagnosis of UTI is based on growth of significant number of organisms of a single species in the urine. Significant bacteriuria is defined as a colony count of $>10^5$ /ml of a single species in a clean catch sample. Urine is obtained by suprapubic bladder aspiration or urethral catheterization in children below 2 yr. Any colonies on suprapubic aspiration and $>50,000$ /ml on urethral catheterization are considered significant. The occurrence of significant bacteriuria in absence of symptoms is termed *asymptomatic bacteriuria*.

The presence of >10 leukocytes per mm^3 in fresh uncentrifuged sample, or >5 leukocytes per high power field in centrifuged sample is useful for screening. Dipstick examination, combining leukocyte esterase and nitrite, has moderate sensitivity and specificity for detecting UTI.

Treatment

Once UTI is suspected, a urine specimen is sent for culture and treatment started. *Infants below 3 months of age and children with complicated UTI should initially receive parenteral antibiotics*. The initial choice of antibiotics is empiric and is modified once culture result is available. While a third generation cephalosporin is preferred, therapy with a single daily dose of aminoglycoside is also safe and effective (Table 16.11). Once oral intake improves and symptoms abate, usually after 48–72 hr, therapy is switched to an oral antibiotic. The duration of treatment for complicated UTI should be 10–14 days. Older infants and patients with simple UTI should receive treatment with an oral antibiotic for 7–10 days. Adolescents with cystitis may receive shorter duration of antibiotics, lasting 72 hr. Patients with asymptomatic bacteriuria do not require treatment.

Table 16.11: Antimicrobials for treatment of UTI

Medication	Dose (mg/kg/day)
Parenteral	
Ceftriaxone	75–100, in 1–2 divided doses IV
Cefotaxime	100–150, in 2–3 divided doses IV
Amikacin	10–15, single dose IV or IM
Gentamicin	5–6, single dose IV or IM
Coamoxiclav	30–35 of amoxicillin, in 2 divided doses IV
Oral	
Cefixime	8–10, in 2 divided doses
Coamoxiclav	30–35 of amoxicillin, in 2 divided doses
Ciprofloxacin	10–20, in 2 divided doses
Ofloxacin	15–20, in 2 divided doses
Cephalexin	50–70, in 2–3 divided doses

All children with UTI are encouraged to take enough fluids and empty the bladder frequently to prevent stasis of urine. Routine alkalization of the urine is not necessary. With appropriate therapy, fever and systemic toxicity reduce and urine culture is sterile within 24–36 hr. Failure to obtain such a result suggests either lack of bacterial sensitivity to the medication or presence of an underlying anomaly of the urinary tract. A repeat urine culture is not required during or following treatment, unless symptoms fail to resolve despite 72 hr of therapy; symptoms recur, suggesting recurrent UTI, or contamination of the initial urine culture is suspected.

Imaging Studies

Following treatment of the first episode of UTI, plans are made for evaluation of the urinary tract. The aim of imaging studies is to identify urologic anomalies that predispose to pyelonephritis, such as obstruction or vesicoureteric reflux, and detect evidence of renal scarring. Renal ultrasonography is useful in detecting hydronephrosis or anomalies of the urinary bladder and may be performed even during therapy for UTI. Micturating cystourethrogram is necessary for the diagnosis and grading of VUR (Fig. 16.13) and defines urethral and bladder anatomy. This procedure may be performed 2–4 weeks after treatment of the UTI. DMSA scintigraphy detects cortical scars, which are regions of decreased uptake with loss of renal contours or presence of cortical thinning with decreased volume (Fig. 16.5A). In order to differentiate between scars and reversible changes of pyelonephritis, this procedure is done 3–4 months after therapy for UTI.

These investigations should be performed judiciously, such that sufficient evaluation is done but at minimum risks of complications, such as radiation exposure and iatrogenic infections. The recommendations of the Indian Society of Pediatric Nephrology on evaluation following the first UTI are summarized in Table 16.12. All infants (<1 yr) require evaluation using ultrasonography, MCU and DMSA scan, since they are at the highest risk of UTI

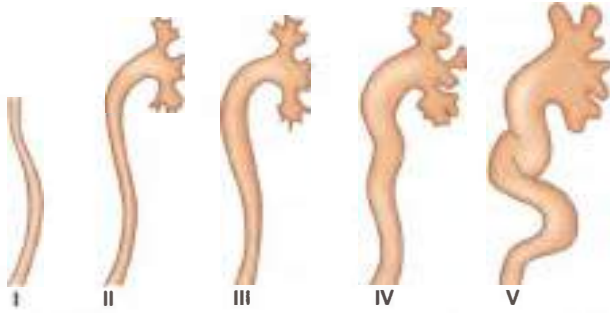


Fig. 16.13: Grading of vesicoureteric reflux (VUR) on micturating cystourethrogram. *Grade I:* VUR does not reach the renal pelvis; *Grade II:* VUR extending up to the renal pelvis without dilatation of pelvis or calyceal fornices; *Grade III:* VUR extending up to the kidney, with mild dilatation or tortuosity of the ureter and renal pelvis, and no or minor blunting of the calyceal fornices; *Grade IV:* Moderate dilatation or tortuosity of the ureter, renal pelvis and fornices, with complete obliteration of the sharp angles of the calyceal fornices, but normal appearance of the papillary impressions; *Grade V:* Gross dilatation and tortuosity of the ureter, renal pelvis and calyces, with loss of papillary impressions on calyces

recurrence and scarring. Early detection of high grade VUR or obstructive uropathy allows interventions to prevent progressive kidney damage. Imaging is less aggressive in older children, but patients with recurrent UTI require complete evaluation for anomalies.

Preventing Recurrent UTI

Prophylactic antibiotics are administered to young infants until results of imaging are available. The medication used should be effective, nontoxic with few side effects and not alter the gut flora or induce bacterial resistance (Table 16.13). The medication is given as a single bedtime dose. Longterm antibiotic prophylaxis is also recommended in patients with VUR and in those with frequent febrile UTI (3 or more episodes in a year) even if the urinary tract is normal.

Circumcision reduces the risk of recurrent UTI in infant boys, and might have benefits in patients with high grade VUR. Children with recurrent UTI and/or VUR might have dysfunctional voiding and require appropriate advice. Constipation should be managed with dietary modifications and medications as required. Some patients

Table 16.12: Evaluation following the first episode of urinary tract infection

Age	Evaluation*
Below 1 yr	Ultrasound Micturating cystourethrogram (MCU) Dimercaptosuccinic acid (DMSA) renal scan
1–5 yr	Ultrasound DMSA scan MCU, if ultrasound or DMSA scan is abnormal
Above 5 yr	Ultrasound If ultrasound abnormal: MCU and DMSA scan

*Patients with recurrent UTI need detailed evaluation with ultrasonography, DMSA scan and MCU

Table 16.13: Antimicrobials for prophylaxis of urinary tract infections

Medication	Dose (mg/kg/day)	Remarks
Cotrimoxazole	1–2 of trimethoprim	Avoid in infants <3-mo-old, glucose-6-phosphate dehydrogenase (G6PD) deficiency
Nitrofurantoin	1–2	May cause vomiting and nausea; avoid in infants <3-mo-old, G6PD deficiency, renal insufficiency
Cephalexin	10	Drug of choice in first 3–6 months of life
Cefadroxil	5	An alternative agent in early infancy

Usually given as single bedtime dose

may require bladder retraining, anticholinergic medications and/or clean intermittent catheterization.

Suggested Reading

American Academy of Pediatrics, Subcommittee on Urinary tract infections, Steering committee on Quality Improvement and Management, Roberts KB. Urinary tract infection: Clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and young children 2 to 24 months. *Pediatrics* 2011;128:593–610

Indian Society of Pediatric Nephrology. Revised statement on management of urinary tract infections. *Indian Pediatr* 2011;48:709–17

National Collaborating Centre for Women's and Children's Health. Urinary tract infection in children diagnosis, treatment and longterm management. RCOG Press, London 2007; <http://www.rcpch.ac.uk/Research/ce/Clinical-Audit/Urinary-Tract-Infection>

VESICoureTERIC REFLUX

Vesicoureteric reflux (VUR) refers to the retrograde flow of urine from bladder to ureters and pelvis at rest or during micturition. Pathogenic organisms that might be present in the bladder can gain access to the renal parenchyma, initiate inflammation and renal scarring (*reflux nephropathy*). VUR may be an isolated anomaly (primary) or associated with other anomalies of the urinary tract (secondary).

VUR is present in 30–35% of children with febrile UTI and is a major risk factor for acute pyelonephritis and reflux nephropathy. The latter may result in hypertension, renal insufficiency and cause morbidity during pregnancy.

Two techniques are commonly used to detect VUR. The radiocontrast MCU is commonly used since in addition to showing VUR it provides excellent anatomical details (Fig. 16.14). The severity of VUR is graded from I to V (Fig. 16.13). Isotope radionuclide cystography is more sensitive for detecting VUR and causes less radiation exposure but provides less anatomical details.

Management

The proposed guidelines for management of VUR are outlined in Fig. 16.15. It is recommended that patients



Fig. 16.14: Bilateral grade V vesicoureteric reflux in a girl with recurrent UTI. Note the dilatation, tortuosity of ureters and cupping of the calyces

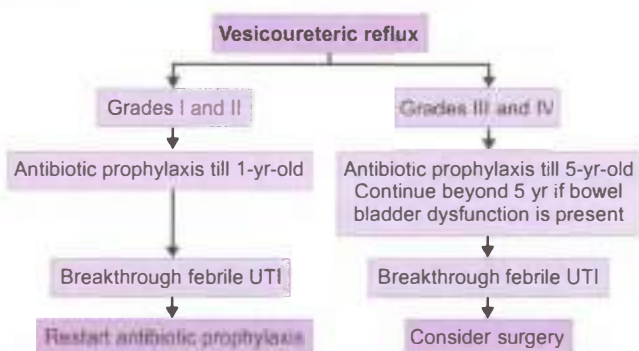


Fig. 16.15: Management of vesicoureteric reflux. Medical therapy of VUR is based on the principle that VUR resolves over time, and prophylactic antibiotics maintain urine sterility and prevent infections while awaiting spontaneous resolution. Reflux takes longer to resolve if associated with bowel bladder dysfunction or if high grade reflux is present; such patients require prolonged prophylaxis. Surgical correction of VUR is indicated if breakthrough infections occur, since significant parenchymal injury may occur with pyelonephritis

should initially receive antibiotic prophylaxis while awaiting spontaneous resolution of VUR. Continuous antibiotic prophylaxis is recommended as the initial treatment for all children with VUR since it reduces periurethral colonization and, thereby, the risk of recurrent UTI in patients with VUR. Cotrimoxazole or nitrofurantoin is given as a bedtime dose. Since the risk of recurrent UTI and renal scarring is low after 4–5 yr of age, prophylaxis may be discontinued in children older than 5 yr with normal bowel and voiding habits, even if mild to moderate reflux persists. While evidence from a few studies suggests that the strategy of prompt diagnosis and treatment of UTI might be as effective as antibiotic prophylaxis, this approach requires validation.

Other measures to be instituted include a liberal fluid intake, regular and complete bladder emptying and local toilet. Constipation should be avoided. A close followup is required for occurrence of breakthrough UTI.

The indications for surgical correction of primary VUR are limited and include poor compliance or intolerance to

medical treatment. Patients with grade III to V reflux may be offered surgical repair if they have breakthrough febrile UTI, if parents prefer surgical intervention to prophylaxis, or in patients who show deterioration of renal function. Ureteric reimplantation has cure rates of 95–97%.

The precise indication for endoscopic submucosal injection of dextranomer/hyaluronic acid copolymer (Deflux) at ureteric orifices is not defined. While results are satisfactory in centers with expertise, a significant proportion of patients, particularly those with bowel bladder dysfunction, may show persistence and/or recurrence of reflux and progressive renal damage.

Followup

Repeat imaging is required after 18–36 months in patients with grade III–V VUR. Radionuclide cystogram, with lower radiation exposure and higher sensitivity, is preferred for followup evaluation. Urinalysis and measurement of height, weight and blood pressure are done annually. Urine cultures are obtained if patient has symptoms of UTI.

Screening of Siblings and Offspring

VUR is inherited in an autosomal dominant manner with incomplete penetrance; almost one-third siblings and offspring of patients show VUR. Ultrasonography is recommended to screen for presence of reflux; further imaging is performed if ultrasonography is abnormal.

Outcome

Primary VUR tends to resolve by 6–10 yr of age. Factors favoring resolution are younger age and low grade and unilateral VUR. The rate of resolution is 70–90% for grades I–III and 10–35% for higher grades.

Reflux Nephropathy

This is characterized by renal cortical scarring, predominantly at the poles. The underlying calyces lose their normal concave shape and show clubbing. Such scarring occurs early in life when the kidneys are still growing. Reflux nephropathy is an important cause of hypertension and end stage renal disease in children.

Suggested Reading

Nevés T, von Gontard A, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the standardization committee of the International Children Continence Society. *J Urol* 2006;176:314–24

Peters CA, Skoog SJ, Arant BS, Copp HL, Elder JS, Hudson RG, et al; American Urological Association Education and Research, Inc. Summary of the AUA Guideline on management of primary vesicoureteral reflux in children. *J Urol* 2010;184:1134–44

Skoog SJ, Peters CA, Arant BS, et al. American Urological Association Education and Research. Pediatric vesicoureteral reflux guidelines panel summary report: clinical practice guidelines for screening siblings of children with vesicoureteral reflux and neonates/infants with prenatal hydronephrosis *J Urol* 2010;184:1145–51

ACUTE KIDNEY INJURY

Acute kidney injury (AKI) or acute renal failure (ARF) denotes an acute impairment of renal function resulting in retention of nitrogenous wastes and other metabolic derangements. Oliguria or anuria is a prominent feature, though rarely urine output may be normal.

Definition and Classification

In the absence of a standard definition of ARF, the term **acute kidney injury (AKI)** is proposed to reflect the entire spectrum of the disorder. Patients are diagnosed to have AKI if there is abrupt (within 48 hr) reduction in kidney function, defined as either (i) absolute increase in serum creatinine of more than or equal to 0.3 mg/dl, or a percentage increase of more than or equal to 50% from baseline, or (ii) reduction in urine output (less than 0.5 ml/kg/hr for >6 hr). The inclusion of both an absolute and a percentage change in creatinine allows for variations related to age, gender and body mass index. Table 16.14 shows a proposed method for classifying the severity of AKI.

Incidence and Etiology

The etiology of AKI is classified as prerenal, intrinsic renal or postrenal (Table 16.15). The chief causes of AKI include acute tubular necrosis (ATN) secondary to hypovolemia, sepsis and nephrotoxic agents, acute glomerulonephritis and hemolytic uremic syndrome (HUS). Postrenal failure is consequent to mechanical obstruction in the collecting system. In developing countries, common causes include septicemia with multiorgan failure, HUS, gastroenteritis with dehydration, postinfectious and crescentic GN and intravascular hemolysis. In developed countries, AKI follows major surgical procedures, HUS and severe systemic infections.

Pathophysiology

Prerenal failure is secondary to systemic hypovolemia or renal hypoperfusion, where renal tubular injury leads to marked decline in glomerular filtration and renal blood flow, often by 50 to 75%. Leakage of glomerular filtrate back into the circulation across the damaged tubular epithelium and tubular obstruction from impaction of

Table 16.15: Important causes of acute kidney injury

Prerenal failure

Hypovolemia (dehydration, blood loss, diabetic ketoacidosis)
Third space losses (septicemia, nephrotic syndrome)
Congestive heart failure
Perinatal asphyxia
Drugs (ACE inhibitors, diuretics)

Intrinsic renal failure

Acute tubular necrosis
Prolonged prerenal insult (*see above*)
Medications: aminoglycosides, radiocontrast, NSAIDs
Exogenous toxins: diethylene glycol, methanol
Intravascular hemolysis, hemoglobinuria
Tumor lysis syndrome
Hemolytic uremic syndrome: diarrhea associated (D+) and atypical (D-) forms
Glomerulonephritis (GN)
Postinfectious GN
Systemic disorders: SLE, Henoch-Schönlein syndrome, microscopic polyangiitis
Membranoproliferative GN
Interstitial nephritis (drug-induced, idiopathic)
Bilateral renal vessel occlusion (arterial, venous)

Postrenal failure

Posterior urethral valves, urethral stricture
Bilateral pelviureteric junction obstruction
Ureteral obstruction (stenosis, stone, ureterocele)
Neurogenic bladder

NSAIDs nonsteroidal anti-inflammatory drugs; SLE systemic lupus erythematosus

casts and cellular debris results in oliguria. While early stages are rapidly reversible by infusion of fluids, prolonged or severe ischemia may lead to acute tubular necrosis. Nephrotoxic agents cause uniform epithelial damage, especially in the proximal tubules, without disruption of tubular basement membrane.

Clinical Features

In acute tubular necrosis, examination may be normal except for dehydration. The oliguric phase lasts about 3–10 days, during which period the biochemical and clinical abnormalities gradually worsen, more rapidly if infection, trauma and bleeding are associated. Subse-

Table 16.14: Staging of acute kidney injury (AKI), based on criteria proposed by the AKI network (AKIN)*

AKIN Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of ≥ 0.3 mg/dl or $\geq 150\%$ to 200% (1.5- to 2-fold) from baseline	Less than 0.5 ml/kg per hour for >6 hr
2	Increase in serum creatinine to more than 200% to 300% (>2- to 3-fold) from baseline	Less than 0.5 ml/kg per hour for >12 hr
3**	Increase in serum creatinine to more than 300% (>3-fold) from baseline (or serum creatinine ≥ 4.0 mg/dl with acute increase of ≥ 0.5 mg/dl)	Less than 0.3 ml/kg per hour for 24 hr, or anuria for 12 hr

*Only one criterion (creatinine or urine output) should be fulfilled to qualify for a stage

**Patients receiving renal replacement therapy (RRT) are considered in stage 3 or F

quently urine output increases steadily. A diuretic phase may be observed, usually lasting for a week, during which large amounts of water and electrolytes, particularly potassium may be lost.

Approach to Evaluation

History provides clues to the underlying cause of AKI. It is important to examine for prerenal factors that lead to renal hypoperfusion. A history of diarrhea, vomiting, fluid or blood loss is taken and assessment of fluid intake in the previous 24 hr made. In patients with nephrotoxicity or intravascular hemolysis, urine output is often not diminished (nonoliguric renal failure).

Laboratory evaluation (Table 16.16) includes complete blood counts and estimation of blood levels of urea, creatinine, electrolytes, pH and bicarbonate and urinalysis. In prerenal azotemia, the renal tubular function is intact and reabsorption of water and sodium is increased. The urine is concentrated with low sodium content. Impaired tubular function in intrinsic renal failure results in increased sodium excretion and failure to concentrate urine. Determination of urine sodium and osmolality and fractional excretion of sodium help in differentiating functional oliguria (prerenal) from established (intrinsic) renal failure. Ultrasonography is a useful imaging tool in renal failure since it allows visualization of the pelvicalyceal system and assessment of the renal size, structural anomalies and calculi, does not depend on renal function.

Most patients with AKI do not require a renal biopsy. Indications for biopsy are: (i) rapidly progressive or nonresolving glomerulonephritis; (ii) AKI associated with underlying systemic disorder, e.g. lupus erythematosus, Henoch-Schönlein purpura; (iii) suspected interstitial nephritis; (iv) clinical diagnosis of acute tubular necrosis

Table 16.16: Investigations in patients with acute kidney injury

Blood

Complete blood counts

Urea, creatinine, sodium, potassium, calcium, phosphate, pH, bicarbonate

Urine

Urinalysis; culture

Sodium, osmolality, fractional excretion of sodium

Chest X-ray (for fluid overload, cardiomegaly)

Abdominal ultrasonography

Investigations to determine cause

Peripheral smear examination, platelet and reticulocyte count, complement (C3), LDH levels; stool shigatoxin (suspected hemolytic uremic syndrome)

Blood ASO, C3, antinuclear antibody, antineutrophil cytoplasmic antibody (suspected acute or rapidly progressive GN)

Doppler ultrasonography (suspected arterial or venous thrombosis)

Renal biopsy (specific diagnosis feasible)

or HUS, if significant dysfunction persists beyond 2–3 weeks; (v) underlying cause of AKI not apparent on clinical features and investigations. Patients with severe azotemia might require dialysis prior to biopsy to reduce the risk of bleeding.

Occasionally a patient with undetected chronic kidney disease may present for the first time with acute onset of oliguria. History of previous renal disease may be present. The presence of the following suggests the possibility of chronic kidney disease: (i) retarded physical growth, (ii) severe anemia, (iii) hypertensive retinopathy, (iv) hypocalcemia, hyperphosphatemia and high parathormone, (v) radiologic features of mineral bone disease and (vi) small kidneys on imaging.

Management

Prompt clinical and laboratory evaluation is necessary. Management includes treatment of life-threatening complications, maintenance of fluid and electrolyte balance and nutritional support. Evaluation for complications includes measurement of blood pressure, search for signs of congestive heart failure, fluid overload, acidosis and anemia. Complications such as dehydration or fluid overload, hypertension, heart failure, severe anemia, hyperkalemia and acidosis require urgent treatment.

Fluid Repletion

Prerenal ARF responds to fluid replacement with improved renal perfusion and increased urine output. Dehydration is corrected by infusion of 20–30 ml/kg of normal saline or Ringer's lactate over 45–60 min. If hemorrhage accounts for vascular collapse, blood transfusion should be given. Potassium should not be administered until urine flow is established; care is taken to avoid overhydration. Patients with renal hypoperfusion, in whom the only reason for oliguria is intravascular volume depletion, respond to fluids with increase in urine output (2–4 ml/kg over 2–3 hr). Appropriate fluid therapy should be continued. However, if no diuresis occurs despite correction of dehydration, frusemide (2–3 mg/kg IV) may be given. If these measures fail to induce diuresis, a diagnosis of AKI is made.

Fluid Restriction

In patients with established AKI, fluid retention may result from excessive oral or parenteral fluids, and leads to edema, hypertension and heart failure. The daily fluid requirement is restricted to insensible water losses (300–400 ml/m²), urinary output and extrarenal fluid losses. This is usually given orally; intravenous fluids are not required.

Intake-output monitoring, daily weight, physical examination and serum sodium guide fluid management. Hyponatremia usually reflects overhydration. If fluid in an appropriate volume and composition is given, the patient

should lose 0.5–1% of weight every day because of tissue breakdown. The serum sodium concentration should stay within normal range. A rapid weight loss and rising sodium suggest inadequate fluid replacement, while absence of weight loss and low serum sodium indicate fluid excess.

Diet

Patients with AKI have increased metabolic needs and are usually catabolic. Adequate nutritional support with maximization of caloric intake should be achieved as early as possible. A diet containing 1.0–1.2 g/kg of protein in infants and 0.8–1.2 g/kg in older children and a minimum of 60–80 Cal/kg is recommended. Energy requirements are met by addition of carbohydrates and fat in the diet. Vitamin and micronutrient supplements are provided. In patients with oligoanuria and fluid overload, daily caloric requirement cannot be met due to fluid restriction. Once dialysis is initiated, dietary protein, fluid and electrolyte intake should be increased.

General Measures

Patients with ARF are managed under intensive care conditions. Accurate records of intake and output and daily weight should be maintained. Urine should be collected by condom drainage; bladder should preferably not be catheterized. The risk of infection is high and appropriate preventive measures are necessary. Prophylactic antibiotics are not recommended, but infections should be promptly managed.

Drugs that increase severity of renal damage, delay recovery of renal function or reduce renal perfusion, e.g. aminoglycosides, radiocontrast media, NSAIDs, amphotericin B, ACE inhibitors and indomethacin should be avoided. Standard charts are used for modifying the dose and dosing interval of antibiotics, depending on the severity of renal injury. While diuretics may transiently improve urine output, they do not affect renal function. Their utility is limited to settings where high urine flow is required to prevent intratubular precipitation, such as with intravascular hemolysis, hyperuricemia and myoglobinuria.

Dopamine at low doses causes renal vasodilatation and may induce a modest natriuresis and diuresis. However, it has no beneficial effect on the outcome of AKI, and may be associated with transient tachyarrhythmia or tissue ischemia. Hence, its use for prevention or treatment of acute tubular necrosis is not recommended. The role of other medications, including fenoldopam, atrial natriuretic peptide, calcium channel blockers and other medications is investigational. Mannitol is not recommended for children.

Treatment of Complications

In a child with ARF, immediate attention is directed towards detection and management of life-threatening complications. Table 16.17 lists important complications and measures for their management. Children with pulmonary edema and congestive cardiac failure may

Table 16.17: Management of complications

Complication	Treatment	Remarks
Fluid overload	Fluid restriction. Insensible losses (400 ml/m ² /day); add urine output and other losses; 5% dextrose for insensible losses; N/5 saline for urine output	Monitor other losses and replace as appropriate, consider dialysis
Pulmonary edema	Oxygen; frusemide 2–4 mg/kg IV	Monitor using CVP; consider dialysis
Hypertension	<i>Symptomatic.</i> Sodium nitroprusside 0.5–8 µg/kg/minute infusion; frusemide 2–4 mg/kg iv; nifedipine 0.3–0.5 mg/kg oral/sublingual <i>Asymptomatic.</i> Nifedipine, amlodipine, prazosin, labetalol, clonidine	In emergency, reduce blood pressure by one-third of the desired reduction during first 6–8 hr, one-third over next 12–24 hr and the final one-third slowly over 2–3 days
Metabolic acidosis	Sodium bicarbonate (IV or oral) if bicarbonate levels <18 mEq/l	Watch for fluid overload, hypernatremia, hypocalcemia; consider dialysis
Hyperkalemia	Calcium gluconate (10%) 0.5–1 ml/kg over 5–10 minutes IV Salbutamol 5–10 mg nebulized Sodium bicarbonate (7.5%) 1–2 ml/kg over 15 min Dextrose (10%) 0.5–1 g/kg and insulin 0.1–0.2 U/kg IV Calcium or sodium resonium (Kayexalate) 1 g/kg per day	Stabilizes cell membranes; prevents arrhythmias Shifts potassium into cells Shifts potassium into cells Requires monitoring of blood glucose Given orally or rectally, can be repeated every 4 hr
Hyponatremia	Fluid restriction; if sensorial alteration or seizures 3% saline 6–12 ml/kg over 30–90 min	Hyponatremia is usually dilutional; 12 ml/kg of 3% saline raises sodium by 10 mEq/l
Severe anemia	Packed red cells 3–5 ml/kg; consider exchange transfusion	Monitor blood pressure, fluid overload
Hyperphosphatemia	Phosphate binders (calcium carbonate, acetate; aluminum hydroxide)	Avoid high phosphate products: milk products, high protein diets

require endotracheal intubation and assisted ventilation. Severe acidosis is treated by administration of sodium bicarbonate, and, if persistent, dialysis. Patients should be monitored for fluid retention and hypertension; correction of acidosis may precipitate hypocalcemic seizures.

Factors that aggravate hyperkalemia are acidosis, which causes potassium to shift from the intracellular compartment, infection, hemolysis and tissue damage. Urgent treatment is instituted, depending on blood potassium levels and EKG changes. The benefit following medical therapy is transient and most patients with hyperkalemia secondary to ARF require dialysis.

Severe hypertension may occur with acute GN and HUS, leading to encephalopathy and heart failure. Symptoms of hypertensive encephalopathy are related to the rapidity of rise rather than the absolute value of blood pressure. Infusion of nitroprusside causes a predictable reduction in blood pressure; the rate of infusion is titrated depending on the response. Since the half-life of this drug is in minutes, it may be stopped if there is a precipitous fall in blood pressure. Furosemide is given if there are features of fluid excess. IV infusion of labetalol is as effective as sodium nitroprusside. Maintenance oral therapy is instituted using a calcium channel blocker (nifedipine, amlodipine), beta-adrenergic blocker (atenolol), or vasodilator (prazosin) alone or in combination.

Hyponatremia (sodium <130 mEq/l) usually is the result of excessive fluid administration rather than salt loss. Plasma sodium concentration >125 mEq/l is rarely symptomatic. Sodium concentration between 120–125 mEq/l may be associated with encephalopathy, lethargy and seizures. Fluid restriction is the primary mode of therapy. Treatment with hypertonic saline is reserved for those with symptomatic hyponatremia or level <115 –120 mEq/l. A dose of 6 ml/kg of 3% saline (given over 30–60 min) raises serum sodium by 5 mEq/l. Hypertonic saline must be used cautiously because of complications of fluid overload and hypertension.

Infections, including respiratory and urinary tract, peritonitis and septicemia, are important causes of death. Procedures should be performed with aseptic techniques, IV lines carefully watched, skin puncture sites cleaned, and longterm catheterization of the bladder avoided.

Dialysis

AKI requiring dialysis can be managed with multiple modalities, including peritoneal dialysis, intermittent hemodialysis and continuous hemofiltration or hemodiafiltration. The purpose of dialysis is to remove endogenous and exogenous toxins and maintain fluid, electrolyte and acid base balance until renal function recovers. Indications for dialysis include persistent hyperkalemia (>6.5 mEq/l), fluid overload (pulmonary edema, severe hypertension), uremic encephalopathy, severe metabolic acidosis (total CO_2 <10 –12 mEq/l) and hyponatremia (<120 mEq/l) or

hypernatremia. The decision to institute dialysis should be based on assessment of the patient keeping in view the likely course of ARF. *Dialysis should begin early to prevent these complications, especially in hypercatabolic states (e.g. extensive trauma, infections).*

The choice of dialysis modality is influenced by several factors, including goals of dialysis, the advantages and disadvantages of each modality and institutional resources. It is important to assess the clinical situation and anticipate the course of ARF, depending on type and severity of renal injury.

Peritoneal dialysis. Peritoneal dialysis does not require vascular access and sophisticated equipment and is easy to perform even in neonates. It is often the initial renal replacement therapy of choice in sick and unstable infants. Peritoneal access is obtained using a stiff catheter and trocar, or a soft silastic catheter. The abdominal skin is prepared as for a surgical procedure. Dialysis fluid is infused 30–50 ml/kg, left in the peritoneal cavity for 30–60 min and then drained using siphon effect. Initially 30–40 cycles are carried out. Commercially available dialysates are lactate based and with a dextrose concentration of 1.7%. In patients with fluid overload, the concentration of dextrose is increased to 2.5–3% to facilitate ultrafiltration. The initial dialysis cycles are of short duration (20–30 min). Potassium is not added in the first 5–10 cycles, to enable correction of hyperkalemia. Later, 3–4 mEq/l potassium chloride is added to the dialysate. Patients who are sick and have severe lactic acidosis are dialyzed using a bicarbonate dialysate. The results of peritoneal dialysis are gratifying. In acute tubular necrosis, often a single dialysis is adequate. The procedure can be repeated if necessary.

The most important complication is peritonitis. Meticulous aseptic precautions will minimize its incidence. The dialysate should be examined for white cells and bacteria and cultured. Stiff catheters should be removed after 48–72 hr, beyond which the risk of infection is very high. The risk of injury to viscera and infections is considerably less with soft silastic (Tenckhoff or Cook) catheters, which therefore can be used for prolonged periods. While the standard (double-cuff) Tenckhoff catheter needs to be placed surgically, a temporary (peel away) catheter is inserted bedside. The use of an automated cyclor is preferred to manual peritoneal dialysis.

Hemodialysis. Hemodialysis is efficient for correction of fluid and electrolyte abnormalities. It is expensive to institute, and requires expertise and skilled nursing. The procedure might not be suited for patients with hemodynamic instability, bleeding tendency and in young children with difficult vascular access.

The equipment required is the hemodialysis machine, pediatric dialyzer with tubings and dialysate fluid. These dialyzers are available in different sizes (0.5–1.5 m²) and selection depends upon patient size and ultrafiltrate



properties. Vascular access is necessary for removing and returning large quantities of blood required for the procedure. This is usually achieved using a double lumen catheter inserted into the internal jugular, femoral vein or subclavian vein. Most children are maintained on a hemodialysis regimen of 3–4 hr, three times a week. Sick patients with fluid overload benefit from daily dialysis initially.

Continuous renal replacement therapies (CRRT). CRRT is any extracorporeal blood purification therapy intended to substitute for impaired renal function over an extended period of time and applied for, or aimed at being applied for, 24 hr a day. Continuous hemofiltration provides smoother control of ultrafiltered volume and gradual correction of metabolic abnormalities in unstable patients. Special equipment and trained staff is necessary to provide CRRT in children. Various modalities include CAVH (continuous arteriovenous hemofiltration), CVVH (continuous venovenous hemofiltration), continuous venovenous hemodiafiltration (CVVHD) and slow continuous ultrafiltration (SCUF). These therapies are useful when large amount of fluids have to be removed in sick and unstable patients. CVVH is preferred modality in AKI secondary to major surgical procedures, burns, heart failure and septic shock, especially when conventional hemodialysis or intermittent peritoneal dialysis is not possible. Hemodialysis is less expensive than CRRT and is often preferred in limited resources.

Slow long extended daily dialysis (SLEDD). Sick patients often benefit from hybrid treatments that combine the advantages of CRRT and feasibility of hemodialysis. SLEDD is done daily for an extended but limited period (8–10 hr) using low dialysate flow rates and at the same time minimizing the cost and technical complexities of CRRT.

Specific Therapy

Patients with atypical HUS benefit from plasma exchanges. Immunosuppressive medications and plasma exchange are useful in dialysis dependent patients with vasculitis, crescentic GN or systemic lupus erythematosus. If interstitial nephritis is suspected, the offending agent should be withdrawn and oral corticosteroids given.

Outcome

ARF carries a mortality of 20–40%, chiefly related to the underlying etiology and duration of renal failure. Patients with septicemia and HUS with prolonged anuria are associated with poor prognosis. The outcome in crescentic GN and vasculitis depends on the severity of the renal injury and promptness in initiation of specific therapy. The outlook is satisfactory in acute tubular necrosis without complicating factors. Other factors associated with poor outcome include delayed referral, presence of complicating infections and cardiac, hepatic or respiratory failure. Maintenance of nutrition and prevention of infections is extremely crucial in improving outcome.

Suggested Reading

- Andreoli SP. Acute kidney injury in children. *Pediatr Nephrol* 2009; 24:253–63
- Askenazi D. Evaluation and management of critically ill children with acute kidney injury. *Curr Opin Pediatr* 2011;23:201–7
- Cerda J, Bagga A, Kher V, Chakravarthi RM. The contrasting characteristics of acute kidney injury in developed and developing countries. *Nature Clin Pract Nephrol* 2008;4:138–53
- Goldstein SL. Advances in pediatric renal replacement therapy for acute kidney injury. *Semin Dial* 2011;24:187–91

Acute Renal Failure in the Newborn

Newborns are at high risk of AKI. Important causes of renal failure include: (i) perinatal hypoxemia, associated with birth asphyxia or respiratory distress syndrome; (ii) hypovolemia secondary to dehydration, intraventricular hemorrhage, heart disease and postoperatively, (iii) sepsis with hypoperfusion; (iv) delayed initiation and inadequacy of feeding in early neonatal period; (v) increased insensible losses (due to phototherapy, radiant warmers, summer heat), twin-to-twin transfusions and placental hemorrhage; (vi) nephrotoxic medications, e.g. aminoglycosides, indomethacin; maternal intake of ACE inhibitors, nimesulide; and (vii) renal vein thrombosis, e.g. in infants of diabetic mothers, severe birth asphyxia, dehydration, polycythemia and catheterization of umbilical veins. Renal failure may occasionally be the first manifestation of a congenital anomaly of the urinary tract.

Symptoms of renal failure may be insidious, including lethargy, puffiness and some decline in urine output. Oliguria may not be present. Renal vein thrombosis is suspected in at-risk neonates with hematuria, enlarging flank mass, thrombocytopenia and azotemia. Features suggestive of urinary tract obstruction include an abdominal mass, hypertension and oligoanuria.

Levels of serum creatinine and urea should be monitored in sick neonates. Renal failure is suspected in the presence of oliguria (urine output <0.5 ml/kg/hr) or blood creatinine >1.2 mg/dl. Serum creatinine levels are high at birth (reflecting maternal levels) and decrease to below 0.5 mg/dl by 5–7 days of age. Failure of reduction or rise of serum creatinine indicates impaired renal function. Urinary indices should be interpreted with caution (Table 16.18).

The principles of management are similar to that for older children. Fluid should be limited to insensible (30 ml/kg per day for full-term, 50–100 ml/kg per day for preterm neonates), gastrointestinal and renal losses. Extremely premature neonates nursed in radiant warmers require extra fluids. Systolic blood pressure more than 95–100 mm Hg may need treatment. Extra care should be taken while dialyzing these children; peritoneal dialysis is technically easier and preferred. Sudden distention of peritoneal cavity may cause respiratory embarrassment or apnea. Hypothermia should be avoided by carefully

Table 16.18: Indices to differentiate pre-renal azotemia from intrinsic renal failure

	Pre-renal azotemia	Intrinsic renal failure
Urinary sodium (mEq/l)	<20	>40
Urinary osmolality (mOsm/kg)	>500	<300
Blood urea-creatinine ratio	>20	<20
Urine-plasma osmolality ratio	>1.5	<1.0
Fractional excretion of sodium* (%)	<1	>3

$$*FeNa (\%) = \frac{\text{urine sodium} \times \text{serum creatinine}}{\text{serum sodium} \times \text{urine creatinine}} \times 100$$

warming the dialysis fluid. A number of drugs are dialyzable and appropriate amounts should be added to supplement for their losses.

Mortality rates for oliguric renal failure are approximately 40–50%; nonoliguric patients have a better prognosis. The outcome is related to the underlying condition unless the renal failure is prolonged beyond a few days. Infants with tubular necrosis usually show complete recovery; those with cortical or medullary necrosis regain partial function and show chronic kidney disease.

Suggested Reading

Goldstein SL. Advances in pediatric renal replacement therapy for acute kidney injury. *Semin Dial* 2011;24:187–91

Jetton JG, Askenazi DJ. Update on acute kidney injury in the neonate. *Curr Opin Pediatr* 2012;24:191–6

HEMOLYTIC UREMIC SYNDROME

Hemolytic uremic syndrome is a heterogeneous group of disorders that are a common cause of acute renal failure in children. They are characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute renal insufficiency. Two broad subgroups are recognized; the first is more common, occurs in young children and is associated with shigatoxin producing enteropathogens (shigatoxin-associated HUS), whereas the second is uncommon, affects children of all ages and is associated with abnormalities of the alternative complement pathway (complement associated or atypical HUS). Atypical HUS might also be associated with pregnancy, lupus erythematosus, use of oral contraceptives and some chemotherapeutic medications, deficiency of ADAMTS13, and disorders of cobalamin metabolism.

Shigatoxin Associated HUS

Verotoxin-producing *E. coli* (in North America and Europe; most commonly with the strain O157: H7; O104:H4 in a recent epidemic) and *Shigella dysenteriae* 1 (in south Asia) cause the diarrheal prodrome preceding HUS. Cytotoxin mediated injury to endothelium in the renal microvasculature leads to localized coagulation and fibrin deposition. As red cells and platelets traverse these damaged vessels, they are injured and sequestered. Though the brunt of the microvascular injury is on the

kidney, other organs especially the brain may be affected. Since chiefly shigatoxins 1 and 2 are implicated, the illness is also called shigatoxin *E. coli*-related hemolytic uremic syndrome (STEC-HUS).

Atypical HUS

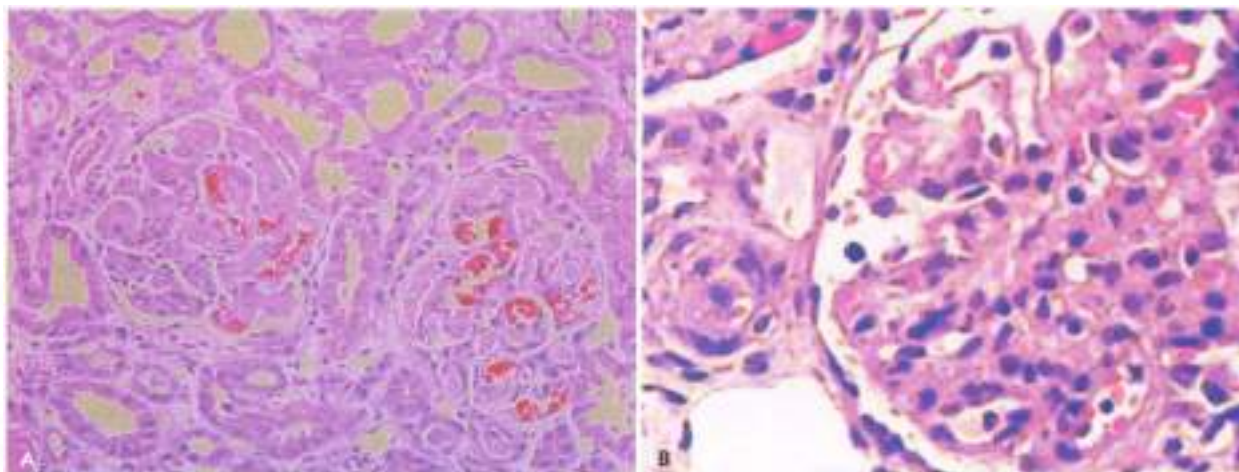
This condition, seen at any age, often lacks the prodromal history of diarrhea or dysentery, but may be triggered by minor infections. The onset may be insidious or present with a rapidly progressive illness. The microangiopathic lesions chiefly affect interlobular arteries and result in severe hypertension and progressive renal insufficiency. Predisposing factors include mutations in regulators of the complement pathway (factors H, I and B, C3, membrane cofactor protein and thrombomodulin), antibodies against complement factor H, infection with neuraminidase-producing organisms (pneumococci) or HIV, cobalamin deficiency, systemic lupus and medications (e.g. cyclosporin, mitomycin). A proportion of children with atypical HUS show presence of antibodies to factor H. Defective cobalamin metabolism leads to a severe form presenting in early infancy. Patients with thrombotic thrombocytopenic purpura (TTP) may have an inherited or acquired deficiency of a metalloproteinase with thrombospondin motifs-13 (ADAMTS13) which leads to massive platelet thrombi.

Clinical and Laboratory Features

Children less than 2–3 yr are usually affected. Following a prodrome of acute diarrhea or dysentery, patients show sudden onset of pallor and oliguria. Blood pressure may be high. Focal or generalized seizures and alteration of consciousness are common.

The blood film shows broken and distorted red cells, increased reticulocyte count and high blood levels of LDH. Coombs' test is usually negative except in *S. pneumoniae* associated HUS where the direct Coombs' test is positive. Thrombocytopenia is usually present; neutrophilic leukocytosis is seen in patients with shigellosis. Urine shows microscopic hematuria and mild proteinuria. Blood levels of urea and creatinine reflect the severity of renal failure. In patients with STEC-HUS, establishing etiology requires either stool culture or PCR for STEC or ELISA for shigatoxin. Serum complement C3 levels are low in some patients with atypical HUS and abnormalities of the complement system. Detailed analysis of components of the alternative complement pathway and its regulators is recommended in all patients with atypical HUS.

On renal biopsy, the endothelial cells are swollen and separated from the basement membrane with accumulation of foamy material in the subendothelial space (Figs 16.16A and B). The capillary lumen is narrowed by swollen endothelial cells, blood cells and fibrin thrombi. Arterioles may show similar changes. Patchy or extensive renal cortical necrosis may be present. HUS is diagnosed



Figs 16.16A and B: Features of thrombotic microangiopathy showing (A) Glomeruli showing marked endothelial swelling and capillary lumina occluded with fibrin thrombi, resulting in mesangiolysis; (B) glomerulus showing endothelial swelling and detachment, widened subendothelial space with narrowing of capillary lumina. Arteriole shows endothelial swelling and intimal hyperplasia, and platelet thrombi resulting in occlusion of the lumen

on clinical and laboratory features, and a renal biopsy is rarely required.

Treatment

Treatment includes management of complications of renal failure, treatment of hypertension and correction of anemia. Proper nutrition must be ensured. Peritoneal or hemodialysis may be necessary to prevent complications of renal insufficiency. Repeated plasma exchange with infusion of fresh frozen plasma is recommended for patients with atypical HUS. Plasma exchanges are initiated as early as possible, performed daily until hematological remission, and then less frequently. Patients with anti-factor H antibodies benefit from immunosuppression with agents that reduce antibody production. The use of eculizumab, a high affinity monoclonal antibody targeted against C5, is reported to benefit patients with HUS associated with activation of the complement cascade.

Outcome

Mortality during the acute episode of shigatoxin associated HUS is low. On followup, 20–30% patients show varying degree of residual renal damage. Factors suggestive of poor outcome include oligoanuria for more than 2 weeks, severe neurological involvement and presence of cortical necrosis. The acute and longterm outcome in atypical HUS is unsatisfactory, though the prognosis has improved with supportive measures. Recurrent episodes of HUS may occur, including in the allograft after renal transplantation.

Suggested Reading

Ariceta G, Besbas N, Johnson S, European Pediatric Study Group for HUS: Guideline for the investigation and initial therapy of diarrhea negative hemolytic uremic syndrome. *Pediatr Nephrol* 2009;24:687–96

Besbas N, Karpman D, Landau D, Loirat C. A classification of hemolytic uremic syndrome and thrombotic thrombocytopenic purpura and related disorders. *Kidney Int* 2006;70:423–31

Loirat C, Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome. *Orphanet J Rare Dis* 2011;8:6–60

CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is defined as kidney damage lasting for at least 3 months, as characterized by structural or functional abnormalities of the kidney with or without decreased glomerular filtration rate (GFR). Abnormalities may include structural malformations (e.g. hydronephrosis, single kidney), pathological conditions (e.g. focal segmental glomerulosclerosis) and markers of kidney damage such as abnormal urinalysis (hematuria, proteinuria) or biochemistry (persistently increased serum creatinine). CKD is divided into 5 stages, based on level of GFR estimated from level of serum creatinine and height using the modified Schwartz formula (Table 16.19). Since renal maturation increases from infancy to reach adult values at the age of 2 yr, CKD stages apply only to children beyond >2-yr-old. Terms such as chronic renal failure and end stage renal disease are avoided. Important conditions resulting in CKD are listed in Table 16.20.

Table 16.19: Stages of chronic kidney disease (CKD)

Stage	GFR, ml/min/1.73 m ²	Description
1	90	Kidney damage with normal or increased GFR
2	60–89	Kidney damage with mild reduction of GFR
3	30–59	Moderate reduction of GFR
4	15–29	Severe reduction of GFR
5	<15, or dialysis*	Kidney failure

* Patients on dialysis are denoted as CKD stage 5D; GFR glomerular filtration rate

Table 16.20: Common causes of chronic kidney disease

Glomerulonephritis: Idiopathic (e.g. focal segmental glomerulosclerosis); secondary (to systemic lupus erythematosus, IgA nephropathy, microscopic polyarteritis, Henoch-Schönlein purpura)

Reflux nephropathy: Primary, secondary

Obstructive uropathy: Posterior urethral valves, pelviureteric junction obstruction, renal stones

Developmental anomalies: Bilateral renal hypoplasia, dysplasia

Familial nephropathy: Nephronophthisis, Alport syndrome, polycystic kidneys

Others: Hemolytic uremic syndrome, amyloidosis, renal vein thrombosis, renal cortical necrosis

Pathophysiology and Clinical Features

The term CKD implies permanent decrease in renal function. Most children with CKD stage 1–3 (GFR more than 30 ml/min/1.73 m²) are asymptomatic; reduction of GFR below this level is associated with symptoms. Regardless of the etiology, once there is a critical loss of nephron mass, the renal failure is progressive and manifests with similar symptoms. Loss of urinary concentrating ability results in frequent passage of urine, nocturia and increased thirst. Anemia that is usually normocytic and normochromic is chiefly due to reduced renal erythropoietin production. Mild hemolysis and blood loss from gastrointestinal tract may also contribute.

Resistance to the action of growth hormone, the levels of which are increased, is considered to be responsible for growth failure. Anorexia, malnutrition and skeletal deformities contribute to growth retardation. Abnormalities in metabolism of calcium and phosphate and bone disease results from hyperphosphatemia, lack of renal formation of 1, 25-dihydroxyvitamin D₃, deficiency of calcium, chronic acidosis and secondary hyperparathyroidism.

The blood pressure may be increased and optic fundi show hypertensive retinopathy. Severe proximal muscle weakness, peripheral neuropathy, itching, purpura and pericarditis are late features. Infections are common and may acutely worsen renal function. Failure to thrive, growth retardation, anemia, hypertension and bony deformities may be the presenting features of CKD, without a previous history of renal disease.

Investigations

The patient should be investigated to find the cause of renal failure and detect reversible factors (e.g. urinary tract obstruction, UTI, severe hypertension, drug toxicity and dehydration). Appropriate imaging studies are done. Blood counts and levels of urea, creatinine, electrolytes, pH, bicarbonate, calcium, phosphate, alkaline phosphatase, parathormone, protein and albumin are obtained. Blood levels of ferritin and transferrin saturation are obtained in patients with anemia. GFR can be estimated based on serum creatinine and height; its accurate

assessment by creatinine clearance or radionuclide methods is rarely necessary.

Management

Optimal management of CKD involves a team approach involving pediatric nephrologist, trained nurse, dietitian, social worker and orthopedic surgeon. The management of CKD focuses on the following principles: (i) Treatment of reversible conditions; (ii) Retarding the progression of kidney disease, with particular attention to control of hypertension and proteinuria; (iii) Anticipation and prevention of complications of CKD; (iv) Optimal management of significant complications as and when they are detected, such as anemia, mineral bone disease, malnutrition, growth failure and metabolic acidosis; and (v) Identification of children in whom renal replacement therapy (RRT) is anticipated; adequate counseling and preparation of the family for RRT.

At the initial stages, management aims at maintaining nutrition and retarding progression of the renal failure. Later, treatment of complications and renal replacement therapy in the form of dialysis or transplantation is required.

Treatment of Reversible Renal Dysfunction

Common conditions with potentially recoverable kidney function include an obstruction in the drainage, recurrent urinary tract infections with vesicoureteric reflux and decreased renal perfusion due to renal arterial stenosis. In addition, care should be taken to avoid AKI that may potentially follow the administration of nephrotoxic drugs, herbal medications and radiocontrast agents, and occur with hypoxic injury due to inadequate hydration during or following surgery.

Retarding Progression of Renal Failure

Hypertension and proteinuria lead to increased intraglomerular perfusion, adaptive hyperfiltration and progressive renal injury. Hypertension should be adequately controlled. Longterm therapy with angiotensin converting enzyme inhibitors has been shown to reduce proteinuria and may retard progression of renal failure. Recent evidence emphasizes that strict control of blood pressure to 50th to 75th centile for age, gender and height, is useful in delaying CKD progression. Children with proteinuria should be treated with an ACE inhibitor or an angiotensin receptor blocker (ARB) because of their antiproteinuric effect. Therapy with lipid lowering agents and correction of anemia, shown to be useful in retarding progression of CKD in adults, may have utility in children, as well.

Diet

Careful attention to diet is essential. Recommended daily amounts of calories should be ensured. A diet high in polyunsaturated fats, such as corn oil and medium chain triglycerides and complex carbohydrates is preferred.

Water restriction is usually not necessary, except in ESRD or presence of fluid overload. Excessive use of diuretics, overzealous restriction of salt and gastroenteritis may lead to dehydration that should be corrected.

Proteins The protein intake should be 1–2 g/kg/day; proteins consumed should be of high biologic value. Restriction of protein intake is not required.

Sodium Since renal regulation of sodium reabsorption is impaired, its dietary intake needs to be individualized. Some infants are polyuric and lose large amounts of sodium requiring salt supplementation. Children with chronic glomerulonephritis retain sodium and water, which contributes to hypertension. These patients require salt and water restriction and may benefit from diuretics.

Potassium Renal regulation of potassium balance is maintained until very late, but the capacity to rapidly excrete a potassium load is reduced. Dietary items with large potassium content should be avoided.

Calcium and phosphorus Calcium supplements are given as calcium carbonate or acetate. Excessive consumption of dairy products should be avoided to restrict phosphate intake.

Vitamins Vitamins B1, B2, folic acid, pyridoxine and B12 are supplemented.

Hypertension

Hypertension in patients with proteinuria and glomerular filtration rate >30 ml/min/ 1.73 m² should preferably be treated with angiotensin converting enzyme inhibitors (e.g. enalapril). Beta-adrenergic blockers (atenolol) and calcium channel antagonists (nifedipine, amlodipine) are also effective agents; the latter are the preferred initial choice in CKD stage 4–5. Additional treatment with loop diuretics is beneficial in those with fluid overload. Patients with severe hypertension, uncontrolled with the above medications, may require additional treatment with clonidine or prazosin.

Anemia

Anemia due to reduced erythropoietin production generally develops when the GFR falls below 30 ml/min/ 1.73 m². Iron deficiency, indicated by low transferrin saturation ($<20\%$) and elevated serum ferritin (above 100 ng/dl), is the most common underlying contributing factor. Therapy with iron (elemental iron 4–6 mg/kg per day) should be initiated if iron deficiency is detected. Subcutaneous administration of recombinant human erythropoietin allows satisfactory increase in levels of hemoglobin. The dose of erythropoietin should be adjusted to achieve target hemoglobin of 11–12 g/dl. Patients should receive iron and micronutrient supplements concomitantly. Patients on hemodialysis should receive intravenous iron supplementation. Inadequate

response to erythropoietin may occur due to iron, folate or vitamin B12 deficiency, chronic infection, aluminum toxicity and severe hyperparathyroidism. Patients with hemoglobin level below 6 g/dl should receive leukocyte-poor, packed red cell transfusions. Blood should be transfused slowly, since it may aggravate hypertension and heart failure.

Infections

Urinary tract and other infections should be promptly treated with effective and least toxic drugs. The dosage of most drugs requires modification (reduction of dosage and/or increase in dosing interval), depending on the severity of renal failure.

Growth

Optimization of caloric and protein intake and treatment of mineral bone disease is important. Administration of recombinant human growth hormone improves growth velocity in children with chronic renal failure. Early recognition and management of malnutrition, mineral bone disease, metabolic acidosis and electrolyte disturbances should take precedence over the institution of therapy with growth hormone. The goal of therapy is to achieve the patient's genetic height potential. The high cost of this treatment, however, limits its use.

Mineral Bone Disease

Mineral bone disease is a serious problem in children as it occurs during the period of active growth (Fig. 16.17). Its prevention and adequate treatment is crucial. The proximal nephron is the chief site of synthesis of 1,25-dihydroxyvitamin D3 (calcitriol), the most potent



Fig. 16.17: Mineral bone disease associated with hyperphosphatemia and secondary hyperparathyroidism in a 12-yr-old girl on chronic hemodialysis. Note the osteopenia and bone resorption in terminal phalanges of the fingers

metabolite of vitamin D. Its decreased production is an important factor in the pathogenesis of secondary hyperparathyroidism in CKD. Recent studies have also shown a high incidence of vitamin D deficiency among children with CKD. With reduction of renal function, phosphate balance is initially maintained by its increased excretion from the normal nephrons. However, when the GFR falls below 25%, blood phosphate levels rise.

The symptoms are vague and nonspecific. Bone pain, muscle weakness, growth retardation and skeletal deformities are prominent. Blood examination shows hypocalcemia, hyperphosphatemia and raised levels of alkaline phosphatase and parathyroid hormone. X-rays reveal metaphyseal changes suggestive of rickets. Radiologic features of secondary hyperparathyroidism are initially seen in the phalanges and clavicles.

The goals of early intervention are to maintain normal bone mineralization and growth, avoid hyperphosphatemia and hypocalcemia, and prevent or reverse increased PTH secretion. Treatment is based on dietary restriction of phosphate, and administration of phosphate binders and vitamin D. Recommended values targeted in different stages of CKD are provided in Table 16.21. When serum phosphate exceeds the target range, phosphate containing dietary articles (e.g. dairy products) are restricted. Blood phosphate levels should be maintained in the normal range using oral phosphate binders. Calcium carbonate or acetate, 0.5–1 g/day with meals, reduces intestinal absorption of phosphate. The renal excretion of aluminum, in children with renal failure, is poor; its accumulation may increase the risk of bone disease and aluminum-related encephalopathy. Prolonged administration of aluminum hydroxide as a phosphate binder is therefore avoided. Sevelamer hydrochloride, a calcium and aluminum free ion-exchange resin which binds phosphorus within the intestinal lumen preventing its absorption, is a safe and effective alternative to calcium containing phosphate binders, with no risk of hypercalcemia.

The first steps in managing elevated levels of PTH in children with CKD are correction of underlying nutritional deficiency of vitamin D deficiency and management of

hyperphosphatemia. If the PTH still remains elevated after these measures, therapy with activated vitamin D should be started. Vitamin D analogs with short half-life are preferred. Medications that may be used include calcitriol (20–50 ng/kg/day) or 1 α -hydroxy D3 (25–50 ng/kg/day). Excessive vitamin D intake may cause hypercalcemia, hypercalciuria and elevation of calcium phosphorus product, which should be monitored.

Osteotomy may be required to correct bony deformities.

Immunization

Children with CKD have relatively poor immunity and hence it should be ensured that these children receive all routine immunizations. Apart from the regular immunization, children with CKD should also receive vaccines against pneumococcal, chicken pox and hepatitis A and B infections, especially if prepared for transplantation. Immunization is scheduled so as to complete live vaccinations prior to transplantation. Primary as well as booster doses of inactivated vaccines can be given 6 months after transplant.

Longterm Care

The rate of progression of chronic renal injury is variable. In some disorders (e.g. hemolytic uremic syndrome, crescentic GN), stage V CKD is present within few weeks or months. In others (e.g. reflux nephropathy and some forms of chronic GN), the decline in renal function is slow. Patients showing a rapid deterioration of renal function should be evaluated for potentially reversible complications (infection, urinary outflow obstruction, fluid loss, hypertension and use of nephrotoxic drugs).

Suggested Reading

K/DOQI Clinical Practice Guidelines for bone metabolism and disease in children with chronic kidney disease. *Am J Kidney Dis* 2005;46:S1–S123

Rees L, Shroff RC. Phosphate binders in CKD: chalking out the differences. *Pediatr Nephrol* 2010;25:385–94

Rees L, Shaw V. Nutrition in children with CRF and on dialysis. *Pediatr Nephrol* 2007;22:1689–1702

Whyte DA, Fine RN. Chronic kidney disease in children. *Pediatr Rev* 2008;29:335–41

Table 16.21: Targets for laboratory markers of mineral bone disease

	Calcium, mg/dl*	Phosphorus, mg/dl	Ca × P product	SAP, IU/dl	PTH, pg/ml
Age 1–12 yr					
CKD 2–3	9.0–10.2	4–6	100–450	<65	35–70
CKD 4	9.0–10.2	4–6	100–450	<65	70–110
CKD 5, 5D	8.8–9.7**	4–6	100–450	<65	200–300
Age >12 yr					
CKD 2–3	8.8–10.2	2.5–4.5	40–180	<55	35–70
CKD 4	8.8–10.2	2.5–4.5	40–180	<55	70–110
CKD 5, 5D	8.8–9.7**	3.5–5.5	40–180	<55	200–300

SAP serum alkaline phosphatase; PTH parathormone; CKD chronic kidney disease

*In patients with hypoalbuminemia, corrected calcium (mg/dl) = observed calcium + 0.8 × [4 – albumin g/dl]

** Hypercalcemia is defined as blood level >10.2 mg/dl

RENAL REPLACEMENT THERAPY

Preparation of a child for end stage care should be discussed in advance with the family members. The financial resources and the family support available should be addressed. Initiation of dialysis should be considered when the glomerular filtration rate (GFR) falls below 12 ml/min/1.73 m² body surface area and is strongly recommended when the GFR is <8 ml/min/1.73 m². The well-being of the patient is more important than the estimated GFR for deciding when dialysis should be started. The presence of fluid overload, hypertension, gastrointestinal symptoms, growth retardation and neurological consequences of uremia influence the decision to initiate RRT.

The different forms of renal replacement therapy are chronic peritoneal dialysis, hemodialysis and renal transplantation. In children with stage V CKD (ESRD), transplantation is the desired form of therapy. While chronic dialysis is life sustaining, it is inferior to renal transplantation in providing adequate renal replacement. Transplantation is associated with significant survival advantage, decreased risks of hospitalization and improved quality of life.

Chronic Peritoneal Dialysis (PD)

Chronic PD is done through a Tenckhoff catheter tunneled through the abdominal wall into the peritoneum. Chronic PD can be done manually (ambulatory PD) or with the help of an automatic cycler (cyclic PD). The duration of dialysis is usually 10–12 hr a day during which 4–6 cycles are performed. Chronic PD is preferred to chronic hemodialysis since it is done at home, without the need for hospital visits. Patients on chronic PD have less restriction on fluid and caloric intake; control of hypertension is better and hematocrit is maintained. The success of chronic PD, however, relies upon the motivation of families to carry out the procedure.

Chronic Hemodialysis (HD)

HD is mostly carried out in the hospital setting. These children require vascular access either an arteriovenous fistula or graft, or a double lumen indwelling catheter in a central vein (e.g. internal jugular, femoral or subclavian vein). Dialysis is done for 3–4 hr/session, with a frequency of 3 sessions/week. During a hemodialysis session, blood is circulated through an extracorporeal circuit that includes a hollow fiber dialyzer (artificial kidney) (Fig. 16.18). Anticoagulation of the circuit is achieved by systemic heparinization. The procedure requires technical expertise and need for continuous monitoring.

Renal Transplantation

The feasibility and efficacy of renal transplantation as standard therapy for ESRD in children is well established. Advances in surgical skills, availability of better immunosuppressive medications and ability to prevent and treat



Fig. 16.18: Hemodialysis in a patient with end-stage renal disease. Note the vascular access through a catheter in the internal jugular vein, hemodialysis machine and the dialyzer (solid arrow)

infections, has improved the short- and long-term outcome. The usual immunosuppressive therapy is a combination of a calcineurin inhibitor (cyclosporin or tacrolimus), purine synthesis inhibitor (azathioprine or mycophenolate mofetil) and prednisolone. Long-term allograft survival is better with live compared to deceased donors. Following successful renal transplantation the child can lead a normal life and resume physical activity and schooling. The allograft survival varies between 10 and 17 yr.

Suggested Reading

Auron A, Brophy PD. Pediatric renal supportive therapies: the changing face of pediatric renal replacement approaches. *Curr Opin Pediatr* 2010;22:183–8

Certain conditions have a high risk of recurrence in the renal allograft, such as membranoproliferative glomerulonephritis type II, focal segmental glomerulosclerosis and atypical hemolytic uremic syndrome K/DOQI clinical practice guidelines for nutrition in children with CKD: 2008 Update. *Am J Kidney Dis* 2009;53:S11–104

<http://www.kidney.org/professionals/kdoqi/>

K/DOQI; National Kidney Foundation. Clinical practice recommendations for anemia in chronic kidney disease in children. *Am J Kidney Dis* 2006;47:S86–108

Staples A, Wong C. Risk factors for progression of chronic kidney disease. *Current Opin Pediatr* 2010;22:161–9

Transplantation offers survival advantage and improved quality of life

DISORDERS OF RENAL TUBULAR TRANSPORT

In comparison to glomerular diseases, tubular disorders are less common. Early and correct diagnosis is essential since specific management is possible in many cases. The diagnosis of a *primary* tubular disorder implies that there is no significant impairment of glomerular function or tubulointerstitial inflammation. A tubular disorder may be congenital or acquired and involve a single function of a tubule (renal glucosuria, nephrogenic diabetes insipidus) or multiple functions (Fanconi syndrome).

Initial Evaluation

Children with primary defects in tubular function usually present during infancy. Table 16.22. shows important

Table 16.22: Presenting features in tubular disorders

Growth retardation, failure to thrive
 Delayed gross motor milestones
 Polyuria, excessive thirst
 Recurrent episodes of dehydration, vomiting, fever
 Rickets, bone pains
 Episodic weakness
 Constipation
 Craving for salt and savory foods

clinical features of patients with such disorders. Most renal tubular disorders can be diagnosed following careful interpretation of urine and plasma biochemistry, and tests useful in arriving at a diagnosis are listed in Table 16.1.

Renal Tubular Acidosis (RTA)

RTA encompasses conditions characterized by a defect of renal acidification, which result in hyperchloremic metabolic acidosis and inappropriately high urine pH. Defects in tubular transport result in reduced proximal tubular reabsorption of bicarbonate (HCO_3^-), the distal secretion of protons (hydrogen ion, H^+) or both, leading to impaired capacity for net acid excretion and persistent hyperchloremic metabolic acidosis. The plasma anion gap [$\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$] is in the normal range (8–12 mEq/l). The renal function is normal or only mildly impaired. Two main forms are recognized: distal RTA (type 1) and proximal RTA (type 2). Another variety (type 4) distinguished by the presence of hypoaldosteronism and hyperkalemia is less common in children. The above conditions are either secondary to other causes or primary, with or without known genetic defects.

Distal RTA

Distal (type 1) RTA is due to defective secretion of H^+ in the distal tubule, in the absence of significant decrease in glomerular filtration rate. Patients with distal RTA are unable to excrete ammonium (NH_4^+) ions adequately, and the urine pH cannot reach maximal acidity (i.e. remains >5.5) despite acidemia, indicating low H^+ concentration in the collecting duct. Hypokalemia is caused by increased urinary losses of potassium and aldosterone stimulation by urinary Na^+ loss and volume contraction, leading to further increase in tubular K^+ secretion.

The condition is often sporadic, but may be inherited (dominant, recessive or X-linked). Important forms are listed in Table 16.23. The disease may be associated with systemic diseases (systemic lupus erythematosus, Wilson disease) or secondary to renal disease (obstructive uropathy, reflux nephropathy) or drug toxicity (lithium, analgesics, amphotericin B).

Presenting features. Children present with failure to thrive, polyuria, polydipsia, hypokalemic muscle weakness and rickets. Ultrasonography may show nephrocalcinosis (Fig. 16.19). Patients with incomplete forms of distal RTA may present with nephrolithiasis or incidentally detected nephrocalcinosis.

Diagnosis. Biochemical abnormalities include hyperchloremic metabolic acidosis, hypokalemia, increased urinary excretion of calcium and decreased urinary citrate. Urinary net acid excretion (titratable acid and ammonium) is markedly reduced. Despite moderate to severe acidosis, patients cannot lower urine pH below 5.3. Measurement of the difference between urinary and blood CO_2 , during

Table 16.23: Inherited forms of renal tubular acidosis (RTA)

Type of RTA	Associated disorders
Type 1 (distal)	Hemolytic anemia Early hearing loss Normal hearing; delayed hearing loss
Type 2 (proximal), isolated	Ocular abnormalities (band keratopathy, cataracts, glaucoma); defective dental enamel; intellectual impairment; basal ganglia calcification
Type 2, Fanconi syndrome	Dent disease Cystinosis Tyrosinemia type 1 Fanconi Bickel Wilson disease Galactosemia Hereditary fructose intolerance Lowe syndrome Glycogen storage disease type I Mitochondrial disorders
Type 3 (combined)	Osteopetrosis; blindness, deafness
Type 4 (hyperkalemic)	Congenital adrenal hyperplasia Pseudohypoaldosteronism (PHA) PHA type 2, Gordon syndrome

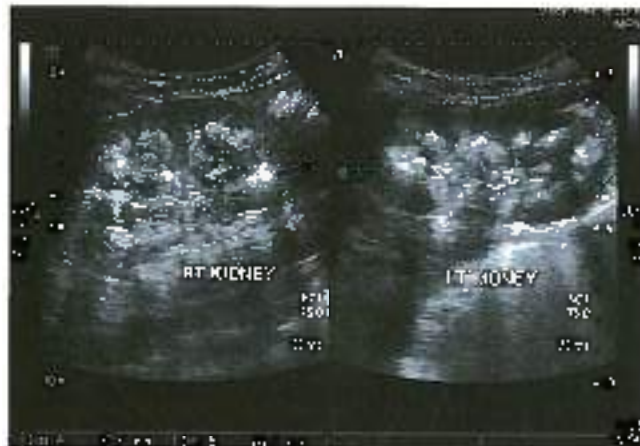


Fig. 16.19: Medullary nephrocalcinosis. Ultrasonography in a 3-year-old boy with distal renal tubular acidosis shows hyperechoic medulla.

the passage of alkaline urine, is a reliable indicator of distal tubular acidification. Normally the difference is more than 20 mm Hg, provided the urine pH is >7.5 . In children with distal RTA, the urine to blood CO_2 gradient is reduced below 10 mm Hg. Table 16.24 shows useful tests for the evaluation of patients with RTA. Hearing evaluation should be performed in all patients with idiopathic distal RTA.

Patients with incomplete forms of distal RTA show normal levels of serum pH and bicarbonate. The defect in distal acidification can be demonstrated by the fludrocortisone frusemide test. Hypercalcaemia and hypocalcaemia are associated.

Treatment. Hypokalaemia should be treated before correction of acidosis. Acidosis is treated by administration of sodium bicarbonate (initially 2 J mEq/kg in divided doses); the dose of alkali can be increased until the blood bicarbonate level is normal. Alkali requirements decrease beyond 5 yr of age. Treatment of acidosis reduces potassium losses and promotes growth and healing of rickets. Some patients require prolonged potassium replacement. Vitamin D supplements are not required. If

hypercalcaemia persists, administration of thiazides is necessary.

Proximal (Type 2) RTA and Fanconi Syndrome

Proximal RTA is due to reduced proximal tubular reabsorption of bicarbonate, so that marked bicarbonaturia is found at normal levels of plasma bicarbonate. Once the plasma bicarbonate falls below 16 mEq/L, it is mostly reabsorbed. At steady state, daily acid loads are excreted successfully and the distal acidification mechanism is intact. Thus, children with proximal RTA have less severe acidosis than distal RTA.

Pathophysiology. The primary defect in proximal RTA is reduced renal threshold for bicarbonate, resulting in bicarbonaturia. Proximal RTA may represent isolated or generalized proximal tubular dysfunction (Table 16.23). The latter, termed Fanconi syndrome, is characterized by tubular proteinuria and aminoaciduria and variable degrees of bicarbonaturia, phosphaturia, electrolyte wasting and glucosuria. Fanconi syndrome may be (i) idiopathic, or secondary to (ii) a metabolic disorder (cystinosis, galactosemia, tyrosinemia, Lowe syndrome, fructosemia, some forms of glycogen storage disease, Wilson disease and mitochondrial disorders), (iii) drugs (ifosfamide, aminoglycosides, cisplatin), (iv) toxins (cadmium, lead, mercury) and (v) tubulointerstitial nephritis.

Clinical features. Failure to thrive and physical retardation are the chief clinical features. Irritability, anorexia and listlessness may be present. Rickets is rare in isolated proximal RTA but common in Fanconi syndrome. Those with secondary Fanconi syndrome may have features of the underlying disorder. Nephrocalcinosis and urolithiasis are not seen. Symptoms related to hypokalaemia (weakness, paralysis) are uncommon.

Diagnosis. Table 16.24 shows the features that allow proximal RTA to be distinguished from other forms of RTA. The blood pH and HCO_3^- levels are low and urine

Table 16.24: Investigations to differentiate types of renal tubular acidosis (RTA)

	Proximal RTA	Classic distal RTA	Type 4 RTA
Plasma potassium	Normal or low	Normal or low	High
Urine pH	<5.5	>5.5	<5.5
Urine anion gap	Positive	Positive	Positive
Urine ammonium	Low	Low	Low
Fractional bicarbonate excretion	$>10\text{--}15\%$	$<5\%$	$>5\text{--}10\%$
U-B PCO_2 mm Hg	>20	<20	>20
Urine calcium	Normal	High	Normal or low
Other tubular defects	Often present	Absent	Absent
Nephrocalcinosis	Absent	Present	Absent
Bone disease	Common	Often present	Absent
U-B PCO_2 urine to blood PCO_2 gradient			

pH relatively alkaline. However if the blood HCO_3^- falls below 14–16 mEq/L, urine pH falls to <5.5. Urinary calcium and citrate excretion is normal. Demonstration of its high fractional excretion of bicarbonate (>15%), following bicarbonate infusion to raise the plasma bicarbonate level above 22 mEq/L, is confirmatory.

Evaluation of other proximal tubular functions is essential. This includes an assessment of phosphate excretion and evaluation for aminoaciduria, glucosuria and low molecular weight proteinuria. Estimation of calcium excretion and examination for rickets is important. Disorders that are associated with Fanconi syndrome should be screened for, including cystinosis, Lowe syndrome, galactosemia and Wilson disease.

Treatment. The correction of acidosis requires administration of 5–20 mEq/kg of alkali daily. Part of the alkali is replaced as potassium citrate. Since administration of large amounts of alkali result in bicarbonate wasting, it is prudent to give a modest amount of sodium bicarbonate (5–8 mEq/kg/day in divided doses) along with restriction of dietary sodium. The latter causes contraction of extracellular fluid volume and increased proximal bicarbonate reabsorption. Administration of hydrochlorothiazide has a similar effect. Children with Fanconi syndrome also need supplements of phosphate (neutral phosphate, Joulie solution). Treatment with vitamin D is necessary in children with rickets.

Cystinosis

This autosomal recessive disorder presents in infancy with features of severe Fanconi syndrome. The underlying defect is in the lysosomal membrane protein (cystinosin) that transports cystine from lysosomes into the cytosol. This leads to very high levels of free lysosomal cystine, which is deposited as crystals in the cornea, conjunctiva, bone marrow, leukocytes and lymph nodes. Tubular handling of cystine is normal. The most common form of cystinosis is the infantile nephropathic form in which patients present in early infancy. Later, patients may be noted to have photophobia and enlarged liver and spleen; some have blond hair.

In most patients, diagnosis is indicated by the presence of cystine crystals in cornea on slit lamp microscopy (Fig. 16.20). Confirmation depends on demonstration of elevated levels of cystine in polymorphonuclear leukocytes or cultured fibroblasts. Prenatal diagnosis is possible, and requires measurement of cystine level in chorionic villi or cultured amniotic fluid cells.

Correction of metabolic acidosis and replacement of electrolytes is an essential part of management. Early initiation of treatment with oral cysteamine may retard progression of systemic disease. Topical therapy is essential to prevent corneal deposits, since oral treatment is ineffective. Longterm complications include hypothyroidism and diabetes mellitus. If untreated, most



Fig. 16.20: Slit lamp examination of the cornea in a 4-yr-old girl with cystinosis; diffuse crystal deposition is noted

patients show progression to end stage renal failure by late childhood.

Lowe Syndrome

This X-linked condition presents within the first few months of life with Fanconi syndrome, severe rickets, ocular defects (congenital cataracts, buphthalmos, corneal degeneration, strabismus), neonatal or infantile hypotonia, rickets, seizures, developmental delay and mental impairment. Hypercalciuria may be prominent. Diagnosis is confirmed by either mutational analysis of the affected gene (OCRL) or measurement of the activity of the enzyme (phosphatidylinositol bisphosphate 5-phosphatase) in cultured fibroblasts. Chronic tubular injury leads to glomerulosclerosis and slowly progressive chronic renal insufficiency. Most children die in early childhood.

Hyperkalemic (Type 4) RTA

Hyperkalemia with distal RTA occurring due to aldosterone resistance or deficiency is termed type 4 RTA. Aldosterone directly stimulates the proton pump, increases Na^+ absorption resulting in negative intratubular potential and increases urinary K^+ losses, and stimulates basolateral Na^+/K^+ ATPase. Hence, aldosterone deficiency or resistance is expected to cause hyperkalemia and acidosis. Maximally acidic urine (<5.5) can be formed, indicating the ability to establish a maximal H^+ gradient. However, the rate of ammonium excretion is low. Aldosterone deficiency without renal disease may occur with Addison disease, or following adrenal necrosis or tuberculosis. Aldosterone resistance may occur with chronic renal insufficiency such as obstructive uropathy or interstitial nephritis or with use of certain drugs (e.g. amiloride, spironolactone, ACE inhibitors, heparin, NSAIDs, calcineurin inhibitors).

Clinical features are not distinctive. Nephrocalcinosis and urolithiasis are absent and bone lesions are rare. In

children, aldosterone unresponsiveness is more common than aldosterone deficiency and is commonly associated with obstructive uropathy. The autosomal recessive form of pseudohypoaldosteronism (PHA type 1) should be considered in infants presenting with salt loss, hypotension, hyperkalemia and metabolic acidosis. Patients with PHA type 2 have hypertension, acidosis and hyperkalemia with hyporeninemic hypoaldosteronism.

Diagnostic workup should include ultrasound to identify structural abnormalities and renal function tests for parenchymal dysfunction. Measurement of plasma renin activity and aldosterone levels are necessary. The transtubular potassium gradient (TTKG) is useful in diagnosing type 4 RTA. It is calculated as follows:

$$\text{TTKG} = \frac{\text{urine K}^+ \times \text{plasma osmolality}}{\text{plasma K}^+ \times \text{urine osmolality}}$$

In patients with hyperkalemia, inappropriately low TTKG (<8) suggests hypoaldosteronism or tubular resistance to aldosterone. Following administration of fludrocortisone, TTKG rises to above 7 in patients with hypoaldosteronism, but not in those with aldosterone resistance.

Nephrogenic Diabetes Insipidus

Congenital nephrogenic diabetes insipidus is an inherited disorder of water reabsorption, caused by resistance to the action of ADH on its receptor. Absorption of water in the distal tubules and collecting ducts is significantly impaired. The defect usually involves the arginine vasopressin V2 receptor (*AVPR2*) gene on the X chromosome. Less commonly, the disease is inherited in an autosomal recessive manner due to mutations in genes encoding the aquaporin 2 channels.

The usual history is of a boy who, within a few weeks of life, shows failure to thrive, excessive thirst, recurrent episodes of dehydration and unexplained fever. The infant continues to have increased or normal urine output even when dehydrated. Constipation is common. Polyuria, polydipsia and nocturnal enuresis are striking in older children. Recurrent episodes of dehydration and rapid rehydration may lead to neurological injury with intracranial calcification, seizures and psychomotor dehydration.

Hypernatremia (serum sodium often more than 170 mEq/l), with low urine sodium is characteristic. Correspondingly, serum chloride and osmolality are high. The urine osmolality is inappropriately low (usually below 150–200 mOsm/kg) for the elevated plasma osmolality. Further, urine osmolality does not increase despite administration of DDAVP. This allows nephrogenic diabetes insipidus to be differentiated from deficiency of the ADH (central diabetes insipidus). The latter show normal response to DDAVP with increase in urine osmolality to more than 600–800 mOsm/kg. Tubular unresponsiveness to ADH may also occur as part of

chronic pyelonephritis, obstructive uropathy, sickle cell disease, lithium toxicity, hypercalcemia, hypokalemia and tubulointerstitial disease. A DMSA scan may be useful in detecting subtle renal scars.

Treatment consists of increased fluid intake and sodium restriction to reduce the osmolar load. Administration of hydrochlorothiazide (2–3 mg/kg/day), alone or in combination with amiloride (20 mg/1.73 m²/day), reduces polyuria and leads to clinical improvement. Indomethacin may also reduce urine volume, but its use is limited beyond infancy.

Renal Glucosuria

Renal glucosuria is an autosomal recessively transmitted, isolated defect of tubular glucose transport. It is recognized by the presence of glucose in the urine, despite normal blood glucose levels. Glucose metabolism and other renal tubular transport mechanisms are normal. Several members of a family may be affected. The disorder is asymptomatic and benign, and does not require treatment.

Type A defects are characterized by generalized decrease in capacity of tubules to reabsorb glucose, and a low tubular maximum for glucose. In type B defects, the tubular maximum for glucose is normal, but the capacity of individual nephrons to reabsorb glucose is affected variably. In type O defects, there is no tubular reabsorption of glucose.

Bartter Syndrome

Bartter syndrome is an autosomal recessive disorder characterized by hypokalemia and metabolic alkalosis, resulting from excessive chloride, potassium and sodium wasting in the thick ascending limb of the loop of Henle. Clinical features include failure to thrive, polyuria, polydipsia and recurrent episodes of dehydration. Vomiting, constipation, muscle weakness and cramps are other manifestations. Patients show marked hypokalemia with high urinary potassium and hypochloremic metabolic alkalosis. Volume contraction leads to increase in levels of plasma renin and aldosterone. Elevated urinary levels of chloride (>20–30 mEq/l) are characteristic.

Several subtypes of Bartter syndrome are recognized, differing in their molecular basis and clinical severity. The condition may occasionally present in the neonatal period with history of maternal polyhydramnios and postnatal polyuria, dehydration and nephrocalcinosis; some have sensorineural deafness.

Bartter syndrome should be differentiated from other conditions with persistent hypokalemic metabolic alkalosis (e.g. cystic fibrosis, recurrent vomiting, inherited forms of hypertension and Gitelman syndrome) by the presence of normal blood pressure and high urinary chloride and calcium excretion.

Therapy is directed towards replacement of urinary losses of fluid, sodium, potassium and chloride. Most

patients require supplements of potassium chloride (1–3 mEq/kg/day). Despite supplementation, serum potassium rarely returns to normal range. Use of prostaglandin synthase inhibitors (indomethacin 2–3 mg/kg/day or ibuprofen 20–30 mg/kg/day) is beneficial. Potassium sparing diuretics and ACE inhibitors have been used with modest benefit in correcting hypokalemia.

Gitelman Syndrome

Hypokalemia, hypomagnesemia and metabolic alkalosis may be caused by Gitelman syndrome, an autosomal recessive condition characterized by a defect in the apical thiazide sensitive sodium chloride cotransporter (NCCT) in the distal tubules. Clinical and laboratory features are milder than in Bartter syndrome. Patients present in adolescence or adulthood, with episodes of muscle weakness, cramps, tetany, vomiting or fatigue. Polyuria and failure to thrive are less pronounced.

Suggested Reading

Bagga A, Bajpai A, Menon S. Approach to renal tubular disorders. *Indian J Pediatr* 2005;72:771–6

Bagga A, Sinha A. Evaluation of renal tubular acidosis. *Indian J Pediatr* 2007;74:679–86

Lin SH, Halperin ML. Hypokalemia: a practical approach to diagnosis and its genetic basis. *Curr Med Chem* 2007;14:1551–65

Seyberth HW, Schlingmann KP. Bartter- and Gitelman-like syndromes: salt-losing tubulopathies with loop or DCT defects. *Pediatr Nephrol* 2011; 26:1789–802

Soriano JR. Renal tubular acidosis, the clinical entity. *J Am Soc Nephrol* 2002;13:2160–70

NEPHROLITHIASIS AND NEPHROCALCINOSIS

Renal calculi are uncommon in children and occur usually in the setting of an underlying metabolic abnormality. Symptoms include dysuria, hypogastric pain, hematuria and occasionally urinary infections. Nephrocalcinosis refers to formation of crystalline deposits within the renal parenchyma, presenting as enhanced renal echogenicity, which may be cortical, medullary or diffuse. Table 16.25 lists common underlying metabolic causes. Urinary tract infection, particularly with urease producing organisms like *Proteus*, *Staphylococcus* and *Pseudomonas* spp. favor precipitation of magnesium ammonium phosphate and calcium phosphate (struvite stones). Progressive renal impairment may occur in patients with nephrocalcinosis, untreated obstruction or recurrent UTI.

Evaluation

Ultrasonography detects most radiopaque and radiolucent calculi and nephrocalcinosis. High resolution computerized tomography detects even minute calculi. Plain radiographs and intravenous pyelography are rarely required; the latter is useful only if suspecting radiolucent or low density stones (uric acid, xanthine), duplex system or obstruction, particularly in a young child where performing CT would necessitate sedation. However, high

Table 16.25: Underlying metabolic abnormalities in children with nephrolithiasis or nephrocalcinosis

Hypercalciuria with hypercalcemia

Vitamin D overdose
Primary hyperparathyroidism
Production of PTH related peptide (malignancy, sarcoidosis)

Hypercalciuria with normal serum calcium

Idiopathic hypercalciuria
Familial hypophosphatemia with hypercalciuria
Dent's disease
Bartter syndrome with/without sensorineural deafness
Autosomal dominant hypocalcemic with hypercalciuria
Familial hypomagnesemia, hypercalciuria and nephrocalcinosis
Lowe syndrome
Frusemide use

Miscellaneous causes

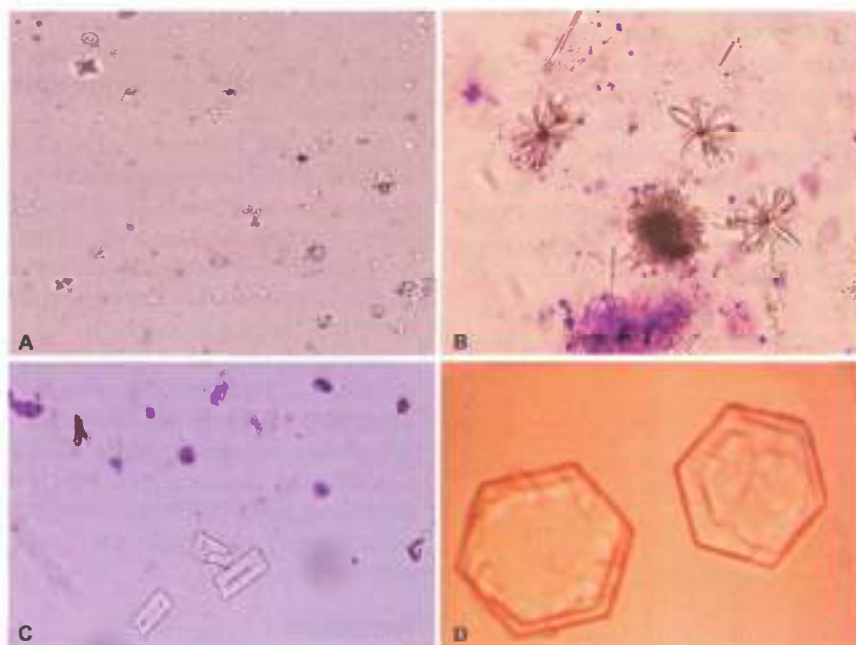
Distal renal tubular acidosis (hypocitric aciduria and hypercalciuria)
Primary hyperoxaluria, type I, type II
Cystinuria
Abnormal purine, pyrimidine metabolism: Lesch-Nyhan syndrome, glycogenosis type 1, xanthinuria
Melamine toxicity

resolution ultrasonography may overdiagnose nephrocalcinosis, particularly in newborns where physiologically increased echogenicity or deposition of Tamm-Horsfall protein is mistaken for medullary nephrocalcinosis.

Investigations aiming at detecting abnormalities show a metabolic cause in 50–75% patients. Initial investigations should include renal functions tests, blood levels of calcium, phosphorus, uric acid, pH and bicarbonate. Detection of specific crystals in the urine may suggest an etiology (Figs 16.21A to D). High (>5.5) urine pH in first morning sample suggests defective tubular acidification. Quantification of calcium, oxalate and uric acid in timed urine collections evaluates excretion of solutes as compared to normal individuals. Alternatively, solute excretion is expressed as a ratio to urinary creatinine in spot samples. Patients with hypercalciuria require evaluation for hypercalcemia (intact PTH, 25-hydroxyvitamin D) and for association with partial form of distal renal tubular acidosis, hypomagnesemia, hypophosphatemic rickets and abnormalities of the thyroid hormone. Where available, stone analysis is performed using X-ray diffraction or near red spectroscopy.

Idiopathic Hypercalciuria

This is the most common underlying cause in patients with nephrolithiasis, but may alternatively present with microscopic and gross hematuria. A family history of hematuria or nephrolithiasis is often present. Urinary calcium to creatinine ratio in the early morning 'spot' urine serves as a screening test. The upper limit of normal in children over 2 yr is 0.2 (mg/mg); higher values suggest



Figs 16.21A to D: Morphology of urine crystals may suggest etiology of renal stones. (A) Envelope shaped oxalate dihydrate crystals; (B) florets of calcium phosphate; (C) coffin lid shaped triple phosphate; (D) hexagonal cystine crystals

hypercalciuria. The diagnosis is confirmed by an accurate measurement of 24 hr urinary calcium; values greater than 4 mg/kg/day are abnormal. *Blood levels of calcium and magnesium are normal.* Idiopathic hypercalciuria should be distinguished from hypercalciuria secondary to persistent hypercalcemia (e.g. hyperparathyroidism, vitamin D toxicity) or associated with renal tubular acidosis. A high fluid intake and diet low in animal protein and salt is advised. Therapy with thiazide diuretics, which reduces urinary calcium excretion, may be required.

Endemic Vesical Calculi

Vesical calculi are usually single stones, detected in young boys (<5-yr-old) in some regions of the country, e.g. Rajasthan, Andhra Pradesh and North-Eastern states, and in neighboring countries, e.g. Pakistan and Afghanistan. These stones are composed of ammonium acid urate and calcium oxalate. Risk factors for formation include consumption of a predominantly cereal (wheat or jowar) based diet, which has low amounts of calcium and phosphate and high oxalate content. Recurrent diarrheal episodes contribute by causing dehydration and an acidic, concentrated urine. A high intake of dairy products and animal proteins has led to a decline in the prevalence of these stones. Treatment requires suprapubic cystolithotomy; these stones rarely recur.

Primary Hyperoxaluria

Primary hyperoxaluria type 1 is an autosomal recessive disorder of glyoxylate metabolism with deficient activity of the liver specific enzyme, alanine glyoxylate amino-

transferase causing overproduction of endogenous oxalate, manifest as renal stones and/or nephrocalcinosis. Precipitation of oxalate also affects the eyes, heart, bones and bone marrow. The diagnosis is suggested by elevated oxalate in plasma and/or urine, and confirmed by deficient activity of affected enzyme on liver biopsy and sequencing of the affected gene, *AGXT*. Treatment is supportive; some patients with partial deficiency benefit from pyridoxine supplementation. Patients presenting in childhood progress to end-stage renal disease by adolescence and require combined liver kidney transplantation.

Cystinuria

This autosomal recessive disorder is characterized by impaired proximal tubular reabsorption of cystine and dibasic amino acids (ornithine, lysine and arginine). Supersaturation of urine with cystine crystals may lead to formation of recurrent radiopaque calculi and account for 10% of cases presenting in childhood. The diagnosis is suggested by presence of hexagonal crystals in urine, urinary excretion of specific amino acids (as above) and positive urine nitroprusside cyanide test. Confirmation requires quantification of urinary cystine excretion (24 hr or cystine:creatinine ratio), stone analysis or genetic testing. A high fluid intake and urinary alkalization help, since cystine is poorly soluble at normal urinary pH but dissolves well at pH >8.0. Agents such as penicillamine and tiopronin prevent formation of calculi by cleaving disulfide bonds of cystine to form the more soluble homodimer cysteine.



Management of Renal Calculi

Stones less than 5–7 mm in size may pass spontaneously. Extracorporeal shock wave lithotripsy (ESWL) may suffice for small stones. Percutaneous nephrolithotomy may be appropriate in patients with relative contraindication for ESWL or with stones too large for lithotripsy. Ureteroscopy is useful for distal and mid ureteric calculi. Open surgery is necessary for stones more than 3 cm in size or those with associated pelviureteric junction obstruction.

UTI should be treated and an adequate fluid intake ensured. Patients with idiopathic hypercalciuria may benefit from a low salt intake; dietary calcium restriction is not necessary. Persistent hypercalciuria is treated with oral potassium citrate, an inhibitor of crystallization. Thiazide diuretics reduce urine calcium excretion, reducing the risk of stone formation; their longterm use is, however, restricted due to side effects. Prolonged alkali supplementation is necessary in patients with distal RTA.

Suggested Reading

Copelovitch L. Urolithiasis in children: medical approach. *Pediatr Clin North Am* 2012;59:881–96

Hoppe B, Kemper MJ. Diagnostic examination of the child with urolithiasis or nephrocalcinosis. *Pediatr Nephrol* 2010;25:403–13

Tanaka ST, Pope IV JC. Pediatric stone disease. *Curr Urol Rep* 2009;10:138–43

ENURESIS

Enuresis is defined as normal, nearly complete evacuation of the bladder at a wrong place and time at least twice a month after 5 yr of age. Enuresis should be differentiated from continuous or intermittent incontinence or dribbling. The bed is usually soaking wet in enuresis, compared to incontinence in which there is loss of urine without normal emptying of the bladder. Enuresis is usually functional while continuous or daytime incontinence is often organic.

More than 85% children attain complete diurnal and nocturnal control of the bladder by five years of age. The remaining 15% gain continence at approximately 15% per year, such that by adolescence only 0.5–1% children have enuresis. Up to the eleventh year, enuresis is twice as common in boys as it is in girls; thereafter, the incidence is similar or slightly higher in girls.

Enuresis is called primary when the child has never been dry and secondary when bed wetting starts after a minimum period of six months of dryness at night. It is termed monosymptomatic if it is not accompanied by any lower urinary tract symptoms and nocturnal if it occurs only during sleep. Children with *monosymptomatic nocturnal enuresis* require no further evaluation.

Etiology

Maturational delay is the most likely cause of nocturnal enuresis, suggested by high spontaneous cure rates with

increasing age. Anxiety producing episodes during the second to fifth years, the time for development of nocturnal bladder control, are associated with increased risk of enuresis.

Antidiuretic hormone (ADH) has a circadian rhythm, with increased secretion occurring during the night and peak secretion between 4 and 8 am. A lack of this circadian rhythm or impaired response of the kidneys to ADH may be a possible etiology for nocturnal enuresis. A lack of inadequate arousal is also believed to impair vasopressin secretion, leading to polyuria.

Secondary enuresis may be precipitated by acute stressful condition or traumatic experience. Bladder irritability due to urinary tract infection or severe constipation with the full rectum impinging on the bladder can cause enuresis. Conditions causing polyuria (diabetes mellitus or insipidus), spina bifida (neurological bladder dysfunction), ectopic ureter and giggle and stress incontinence are other causes.

Evaluation

Less than 5% of cases with nocturnal enuresis have an organic basis. A careful history helps determine whether the enuresis is primary or secondary, whether any daytime symptoms are present and whether any voiding difficulty is present. In cases of secondary enuresis, history should be taken to rule out acute stressful conditions, polyuria and features of bladder irritability such as frequency and urgency. Physical examination should focus on spinal anomalies.

If the child has a normal urinary stream with no daytime symptoms suggestive of a voiding disorder and normal physical examination, the child does not require extensive evaluation. Clinical and neurological examination excludes an anatomical or neurological cause for incontinence.

A voiding diary with frequency and volume charting of urine output and fluid intake for at least 2 days, with a record of daytime accidents, bladder symptoms and bowel habits for at least 7 days is useful. It helps detect children with non-monosymptomatic enuresis or polydipsia, provides information on nocturnal polyuria (such children benefit from desmopressin) and helps monitor compliance to instructions and response to therapy. A urinalysis rules out infection, proteinuria and glucosuria. Additional diagnostic and invasive procedures, ultrasonography and MCU are limited to patients with suspected neurological or urological dysfunction.

Treatment

The decision about when to start treatment should be guided by the degree of concern and motivation on the part of the child rather than the parents. General advice should be given to all enuretic children, but active treatment need not begin before the age of 6 yr. Caffeinated drinks like tea, coffee and sodas should be avoided in the evening. Adequate fluid intake during the day as 40% in

the morning, 40% in the afternoon and 20% in the evening is recommended.

The first line of treatment is usually non-pharmacological, comprising motivational therapy and use of alarm devices. *Motivational therapy* alone is successful in curing enuresis in 25% patients. The child is reassured and provided emotional support. Every attempt is made to remove any feeling of guilt. The benign nature of the disorder is explained to the child and parents using diagrams, if required, to explain the probable basis of the disorder. The child is encouraged to assume active responsibility, including keeping a dry night diary, voiding urine before going to bed and changing wet clothes and bedding. Dry nights should be credited with praise and encouraging words from the parents. Punishments and angry parental responses should be avoided.

Behavioral modification is encouraged to achieve good bladder and bowel habits. The child is encouraged both to void frequently enough to avoid urgency and daytime incontinence and to have a daily bowel movement. A stool softener such as polyethylene glycol helps children with constipation. Bladder training exercises have not been shown to be useful in improving the functional bladder capacity.

Alarm therapy involves the use of a device to elicit a conditioned response of awakening to the sensation of a full bladder. Gradually, the association with bladder distention evokes micturition. The alarm device consists of a small sensor attached to the child's underwear, or a mat under the bed-sheet and an alarm attached to the child's collar or placed at the bedside. When the child starts wetting the bed, the sensors are activated causing the alarm to ring. The child should awaken to the alarm, void in the toilet and reattach the alarm; a parent should attend the child each time to ensure the child does not merely wake to switch off the alarm. The alarm is best used after seven years of age and is successful in about two-thirds of children; a third of children may relapse afterwards. Alarm systems are now available in India; however, the ordinary alarm clock may be used to wake the child up, to void in the toilet at a critical time when the bladder is full and the child is still dry. The combination of motivational and alarm therapy is successful in up to 60–70% of children.

Pharmacotherapy is considered if enuresis persists despite institution of alarm, regular voiding habits, exclusion or treatment of constipation and exclusion of postvoid residual urine, dysfunctional voiding or low voiding frequency. Imipramine works by altering the arousal-sleep mechanism. It gives a satisfactory initial response at a dose of 1–2.5 mg/kg/day, but relapse rate after discontinuation of therapy is high. Cardiac arrhythmias are a serious adverse event effect. Anticholinergic drugs reduce uninhibited bladder contractions and are useful in children who have significant daytime urge incontinence besides nocturnal enuresis. The usual dose is 5 mg for oxybutynin, 2 mg for tolterodine or

0.4 mg/kg for propiverine at bedtime, given above 6 yr of age. Desmopressin (DDAVP, 10 µg orally or intranasally) works by reducing the volume of urine. However, its the relapse rate is high after stopping the medication. Its rapid onset of action makes it a satisfactory choice for special occasions like staying out for the night.

Suggested Reading

Lottmann HB, Alovera I. Primary monosymptomatic nocturnal enuresis in children and adolescents. *Int J Clin Pract (suppl)* 2007;155: 8–16

Weaver A, Dobson P. Nocturnal enuresis in children. *J Fam Health Care* 2007;17:159–61

CONGENITAL ABNORMALITIES OF KIDNEY AND URINARY TRACT

Congenital abnormalities of kidney and urinary tract (CAKUT) are common and account for about 25% cases of CKD in children.

Single Kidney

Unilateral renal agenesis is present when one kidney fails to form while the other kidney is normal in size, position and function. Agenesis may occur due to primary failure of formation of the ureteric bud or its inability to engage with the renal mesenchyme. The condition may occur sporadically or as part of syndromes such as branchio-otorenal, Di George, Fanconi anemia, Fraser or nail-patella syndromes. Renal agenesis is asymptomatic, usually detected incidentally on ultrasonography. Ultrasound also confirms compensatory hypertrophy of the normal single kidney. A DMSA scan helps in ruling out scarring due to associated vesicoureteric reflux or an ectopic kidney. Children with single kidney should avoid contact sports. While affected patients are expected to maintain glomerular function, they require annual monitoring for hypertension and proteinuria.

Fetuses with bilateral renal agenesis or hypoplasia rarely survive to term. Lack of fetal urine production leads to oligohydramnios and limb anomalies. Neonates show low set ears, flat nose, prominent epicanthic folds and small chin (Potter facies). Pulmonary hypoplasia is the usual cause of death.

Renal Dysplasia

Renal dysplasia implies abnormal development of renal parenchyma. Primitive ducts surrounded by connective tissue, metaplastic cartilage, poorly differentiated glomeruli and dilated tubules are present. Bilateral total renal dysplasia is fatal in the neonatal period.

Multicystic dysplastic kidney. A multicystic dysplastic kidney (MCDK) is an enlarged nonfunctioning kidney with cysts of varying sizes resulting from abnormal differentiation of the metanephros. Affecting 1 in 2400 to 4300 live births, it is the most common cystic renal malformation in children. Ultrasonography shows



characteristic findings, including multiple thin-walled noncommunicating cysts of varying size, in an enlarged kidney without identifiable parenchyma or renal pelvis (Fig. 16.22).



Fig. 16.22: Multicystic dysplastic kidney. Multiple, thin-walled and noncommunicating cysts are seen to involve the left kidney on postnatal ultrasound at one month age

Most patients with MCDK have a normal contralateral kidney showing compensatory hypertrophy. However, 20–40% cases may show associated abnormalities of the contralateral genitourinary tract, such as vesicoureteric reflux or pelviureteric junction obstruction. A DMSA scan confirms that the affected kidney is nonfunctional and rules out reflux-associated scarring of the contralateral kidney. Children with MCDK require regular monitoring by ultrasound to ensure compensatory hypertrophy of the normal kidney and progressive involution of the affected kidney, which is undetectable by 5–7 yr of age in most cases. Progressive renal impairment is seen only if other abnormalities are associated. The risk of malignant transformation (Wilms' tumor) and hypertension are negligible. Nephrectomy is not indicated except in presence of severe hypertension, suspected malignancy, or a large kidney that fails to involute.

Obstructive Uropathy

Obstructive anomalies of the urinary tract are an important cause of irreversible renal damage in childhood. The common lesions include pelviureteric junction obstruction, vesicoureteric junction obstruction and posterior urethral valves. Diagnosis is suspected on antenatal ultrasonography or following presentations with dribbling of urine, poor urinary stream, fever and/or urinary tract infections. Chronic obstruction results in dysfunction of distal tubules with impaired urinary concentration and acidification, leading to polyuria, polydipsia, failure to thrive, refractory rickets and systemic acidosis.

Pelviureteric junction (PUJ) obstruction Stenosis of the PUJ may be unilateral or bilateral. Obstruction is more

common in boys and in presence of ectopic, malrotated or horseshoe kidney. It may present as an asymptomatic flank mass, or with upper abdominal pain, UTI or hematuria. Ultrasonography shows a dilated renal pelvis without ureteric dilatation. Radionuclide (DTPA) renal scans shows impaired drainage of the affected kidney which does not improve despite administration of a diuretic. Where scintigraphy is not available, intravenous pyelography is performed, which shows renal pelvis dilatation with an abrupt cut-off at the PUJ. Mild cases are followed up with ultrasound. Surgical treatment by pyeloplasty is indicated if the relative function of the affected kidney is impaired. Nephrectomy may be required for a kidney in which extremely poor function does not improve despite temporary nephrostomy and severe hypertension or recurrent urinary infections are present.

Posterior urethral valves These constitute an important cause of distal urinary tract obstruction in boys. The usual presenting features are dribbling, abnormal urinary stream, palpable bladder and recurrent UTI. The presence of severe obstruction in the urinary tract in utero may lead to renal dysplasia, with mild to moderate renal dysfunction at birth. Antenatal ultrasound shows bilateral hydroureteronephrosis with or without a thick-walled bladder and oligohydramnios. The diagnosis is confirmed on MCU, which shows dilated posterior urethra and valves at its junction with the anterior urethra. The bladder is enlarged and may show diverticuli and trabeculations; secondary vesicoureteric reflux is common.

Endoscopic fulguration of the valves is performed as early as possible. Alternatively, temporary urinary diversion by vesicostomy or bilateral ureterostomies is necessary. Longterm followup after surgery is necessary since a significant proportion of patients may show progressive kidney disease. Additionally, bladder dysfunction is common, with delayed continence or incontinence, poor bladder sensation and a poorly compliant low capacity bladder. If pharmacotherapy fails, patients may require clean intermittent catheterization and occasionally bladder augmentation.

Meatal stenosis Significant narrowing of urethral meatus is rarely a cause of urinary tract obstruction. The treatment consists of meatal dilatation, failing which meatoplasty may be needed.

Phimosis Phimosis may predispose to recurrent UTI in infants. However, up to the age of 2 yr, the prepuce cannot be fully retracted because of its congenital adhesions with the glans. Therefore, the diagnosis of phimosis should be made with caution in young children.

VUJ obstruction This condition is caused by an aperistaltic segment of the ureter near VU junction. Primary VUJ obstruction is more common in males and on the left side, and may be associated with ureterocele or VUR.

Ureterocele This is a congenital condition in which the terminal part of the ureter distends within the bladder to form a sac, due to an abnormality of the submucosal part of the ureter and stenosis of the ureteric orifice. Ureteroceles are commonly associated with duplex systems, particularly in girls. Endoscopic deroofing is the treatment of choice.

Miscellaneous

Renal ectopia, renal fusion An ectopic kidney may lie in the pelvis or the iliac fossa. It may be structurally normal or hypoplastic. The patient may be asymptomatic, or have abdominal discomfort or dysuria. A horseshoe kidney results from fusion of identical poles of both kidneys. Patients with horseshoe kidney show vesicoureteric reflux in 30% cases.

Renal duplication A duplex (duplicated) system is a kidney with two pyelocalyceal systems. In patients with partial or incomplete duplication, either a single or bifid ureter is present; in those with complete duplication, two ureters from the affected side empty separately into the bladder. Evaluation consists of imaging of the upper tract (ultrasonography, DTPA renal scan, intravenous pyelography) to evaluate for obstruction and lower tract (MCU) for vesicoureteric reflux.

ANTENATAL HYDRONEPHROSIS

Extensive use of antenatal ultrasonography has led to increasing detection of CAKUT. On antenatal ultrasound, hydronephrosis is identified in 4–5% pregnancies. However, the majority of cases of antenatal hydronephrosis resolve without sequelae, representing transient physiological obstruction or stasis. These children require monitoring by ultrasound during the antenatal period for progressive worsening and association with oligohydramnios, which suggests severe lower urinary tract obstruction. A postnatal ultrasound is recommended during the first week of life and on day 1 in severe cases. Neonates with posterior urethral valve, solitary kidney or bilateral hydronephrosis and impaired renal function require prompt management. Neonates showing significant unilateral or bilateral dilatation should undergo a MCU at 4–6 weeks of life to detect vesicoureteric reflux; if reflux is ruled out, a diuretic renal dynamic (DTPA) scan is done to detect significant PUJ or VUJ obstruction and evaluate differential renal function. Most cases with mild to moderate hydronephrosis require only ultrasound monitoring and show spontaneous resolution by 2–5 yr of age. Surgery is indicated in presence of obstructive drainage pattern associated with low differential function, and/or recurrent UTI. Infants with vesicoureteric reflux should receive continuous antibiotic prophylaxis.

Figure 16.23 shows a proposed algorithm for postnatal evaluation and management of antenatally detected

hydronephrosis. Parents of all infants with antenatal hydronephrosis should be counseled regarding increased risk of urinary tract infections and their prompt management.

Suggested Reading

Nguyen HT, Herndon CD, Cooper C, et al. The Society for Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. *J Pediatr Urol* 2010;6:212–31

Sinha A, Bagga A, Krishna A, et al. Revised guidelines on the management of antenatally detected hydronephrosis. *Indian Pediatr* 2013;50:215–32

CYSTIC KIDNEY DISEASES

Polycystic kidney disease and nephronophthisis are relatively common and glomerulocystic kidney disease is increasingly diagnosed. Better delineation using high resolution ultrasonography or MRI and identification of genetic loci have enabled accurate diagnosis and improved management for these conditions.

Polycystic Kidneys

Polycystic kidneys are inherited in either the autosomal dominant or autosomal recessive form, with distinctive features. Autosomal recessive polycystic kidney disease (ARPKD), caused by mutations in *PKHD1* gene encoding fibrocystin or polyductin, is characterized by fusiform dilation of collecting tubules which are arranged radially from the cortex to medulla. Affected children usually present in the neonatal period with oliguria, respiratory insufficiency and palpable kidneys. ARPKD is sometimes diagnosed in young children presenting with hypertension, renal insufficiency and enlarged kidneys, or with portal hypertension due to associated congenital hepatic fibrosis. Ultrasonography shows enlarged 'bright' kidneys, usually without visible cysts (Fig. 16.24A). Contrast enhanced computerized tomography (CT) reveals a characteristic striate pattern of contrast excretion on delayed films.

The autosomal dominant form of polycystic kidneys (ADPKD) is caused by mutations in the *ADPKD1* (chromosome 16) or *ADPKD2* (chromosome 4) genes encoding polycystins 1 and 2, respectively, membrane proteins called that regulate tubular and vascular development in various tissues. This condition usually presents beyond the third decade of life with episodic hematuria, hypertension, palpable kidneys and gradual decline in renal function, but may be detected incidentally in childhood. Associated findings include cysts in the liver, spleen and pancreas, mitral valve prolapse and berry aneurysms of the cerebral arteries. Ultrasonography reveals cysts in the kidneys (Fig. 16.24B) in one affected parent unless they are younger than 30 yr, in which case grandparents should be screened; rare cases are due to *de novo* mutations. Therapy with angiotensin converting enzyme inhibitors helps control hypertension and limits



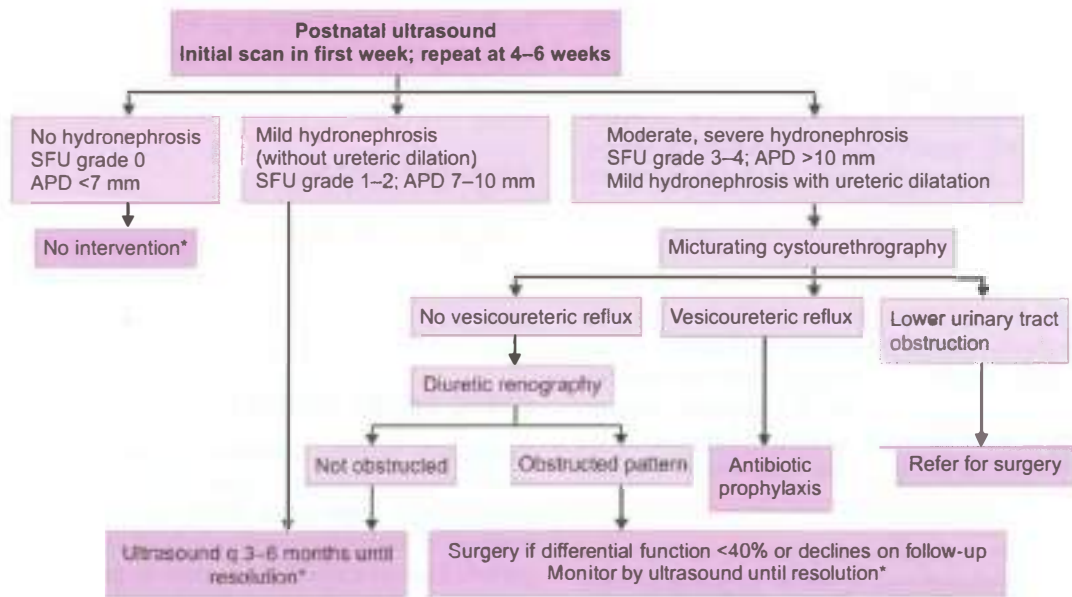


Fig. 16.23: Postnatal evaluation in patients with antenatal hydronephrosis. A postnatal ultrasound is recommended at 3–7 days except in suspected lower urinary tract obstruction, where it is done earlier. Postnatal hydronephrosis is classified using Society for Fetal Urology (SFU) grade or renal pelvic anteroposterior diameter (APD). Infants with normal findings should undergo a repeat study at 4–6 weeks. Patients with isolated mild hydronephrosis (unilateral or bilateral) should be followed with sequential ultrasounds, at 3 and 6 months, followed by 6–12 monthly until resolution; those with worsening hydronephrosis require closer evaluation. Patients with higher grades of hydronephrosis or dilated ureter(s) are screened for underlying obstruction or vesicoureteric reflux. Diuretic renography is useful in detecting pelviureteric junction or vesicoureteric junction obstruction and determining the need for surgery.

*Parents of infants with hydronephrosis should be counseled regarding the risk of urinary tract infections



Figs 16.24A and B: Findings on ultrasonography in polycystic kidney disease. (A) Note bulky enlarged kidney with increased echogenicity, loss of corticomedullary differentiation and occasional visible cyst (arrow) in a child with autosomal recessive polycystic kidney disease; (B) renal architecture is disorganized by multiple irregular cysts of varying sizes in autosomal dominant polycystic kidney disease; also note the foci of calcification

hyperfiltration and proteinuria. The role of inhibitors of the mTOR pathway such as sirolimus and everolimus is being explored.

Glomerulocystic Kidney Disease

The predominant finding in glomerulocystic kidney disease (GCKD) is cysts involving glomeruli, diagnosed most definitely on renal biopsy. Ultrasonography shows

small subcortical cysts with increased kidney echogenicity and loss of cortical medullary differentiation. The condition may occur sporadically, with autosomal dominant inheritance, as a part of known syndromes (tuberous sclerosis, trisomy 13) or in association with other renal diseases such as dysplasia, ADPKD or ARPKD. Mutations in the hepatocyte nuclear factor β gene lead to the renal cysts and diabetes syndrome, characterized by

GCKD, maturity onset diabetes and genitourinary abnormalities.

Nephronophthisis Medullary Cystic Disease Complex

This group includes recessively inherited cystic disorders caused by mutations in genes, named *NPHP 1–9*, encoding cytosolic proteins called nephrocystins. Patients with nephronophthisis present during the first decade of life with polydipsia, polyuria or enuresis, growth retardation and nonspecific signs of renal insufficiency, acidosis and anemia. Extrarenal features may include retinitis pigmentosa; ocular motor apraxia, hypotonia and cerebellar or midbrain abnormalities (Joubert syndrome); skeletal chondrodysplasia (Jeune syndrome); and hepatic fibrosis with pancreatic dysplasia.

The diagnosis of nephronophthisis is supported by the ultrasound or CT finding of small kidneys with corticomedullary cysts and poor corticomedullary differentiation. Renal histology shows cysts involving the collecting ducts, interstitial fibrosis and tubular dilatation with atrophy. While medullary cystic kidney disease is

histologically indistinguishable from nephronophthisis, the disease is inherited in an autosomal dominant manner, and presentation is delayed to adulthood.

Renal Cysts in other Syndromes

Cystic dysplastic kidneys may be seen as a part of syndromes such as Bardet Biedl, Beckwith-Wiedemann, Meckel Gruber, Zellweger and brachiootorenal syndromes. Since the affected genes are contiguous, ADPKD may be associated with tuberous sclerosis, presenting with characteristic skin lesions, periungual fibromas and seizures. The presence of retinal and central nervous system hemangioblastomas, pheochromocytoma and pancreatic cysts with cystic renal tumors suggests von Hippel-Lindau syndrome.

Suggested Reading

Avni FE, Hall M. Renal cystic diseases in children: new concepts. *Pediatr Radiol* 2010;40:939–46

Guay-Woodford LM. Renal cystic diseases: diverse phenotypes converge on the cilium/centrosome complex. *Pediatr Nephrol* 2006;21:1369–76