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Pediatric Nephrology

Editors

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Contents

CHAPTER 7

Hematuria and Proteinuria

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Asymptomatic, isolated hematuria, and proteinuria are commonly observed in apparently healthy children. A careful clinical and laboratory evaluation is required. The presence of both hematuria and proteinuria indicates significant glomerular disease and requires detailed investigation.

HEMATURIA

Epidemiology and Definition

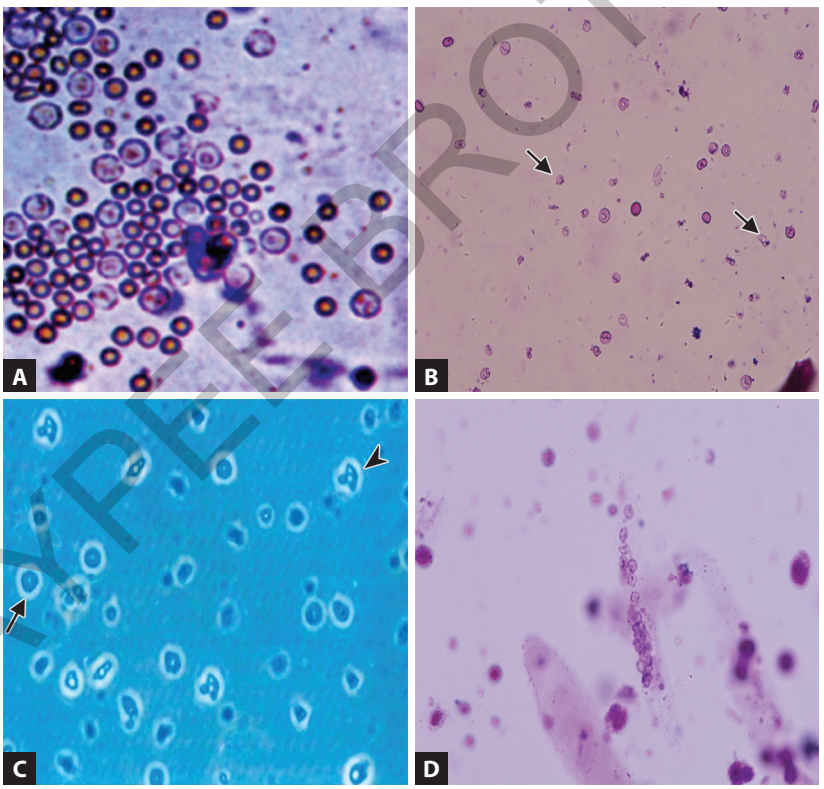
Urine dipsticks are very sensitive and detect even small numbers of red blood cells (RBCs), especially if the specimen is concentrated. The urine dipstick relies on peroxidation of a reagent (tetramethylbenzidine) incorporated into the dipstick, by hemoglobin peroxidase. Since small numbers of RBCs (<5 RBCs/high-power field on microscopic examination) in the urine are physiologic and do not signify hematuria, the urine dipstick cannot be used to diagnose "true" hematuria. Occasionally, the presence of substances other than RBCs, such as hemoglobin and myoglobin, can cause discoloration of the urine dipstick. Thus, for the diagnosis of hematuria, a microscopic examination of the urine sediment is essential. Other false positives on the dipstick include the presence of nonheme oxidizing agents and contaminants in urine, such as bleach. Microbial peroxidases, such as in urinary tract infection, may also be responsible for a false positive test. False negatives may be seen, if the urine is very dilute or if reducing substances such as ascorbic acid are present.

Microscopic hematuria is defined as the presence of >5 RBCs/high-power field on a centrifuged urine specimen (or >5 RBCs/mm^3 on unspun specimen) and is found in 4–5% of all urine specimens in American school children (8–12 years of age), more so in girls and increases with age. It is generally benign when present in isolation, without concomitant proteinuria. Persistent microscopic hematuria, defined as microscopic hematuria on two to three occasions, occurs in <1% of children. Large school-screening programs, chiefly from Japan, China, and South Korea, report isolated microscopic hematuria in 0.4–0.5% cases, while 0.03–0.7% have both hematuria

and proteinuria. Gross hematuria (visible discoloration of the urine due to the presence of RBCs) occurs is <0.1% cases. There is increasing evidence that persistent hematuria, especially if associated with proteinuria, is a risk factor for chronic kidney disease.

Microscopic Hematuria

Since isolated microscopic hematuria most often resolves spontaneously, it is prudent to repeat urinalysis on multiple occasions on fresh urine specimens. The urine specimen is examined for RBC morphology **(Figs. 7.1A to D)** and for other formed elements. If the child is otherwise healthy and hematuria resolves, no further evaluation is needed. Detailed evaluation may be warranted if microscopic hematuria persists.



Figs. 7.1A to D: Urinalysis for hematuria. (A) Red cells in a patient with idiopathic hypercalciuria. Note the normal morphology (400 x); (B) Glomerular hematuria. The variation in morphology of red cells is obvious even under bright light; arrows indicate dysmorphic red cells. (C) Phase contrast microscopy showing dysmorphic red cells (arrowhead) as well as normal red cells (arrow). There is marked variation in the size and shape of cells. (D) Red cell casts confirm glomerular origin of hematuria.

Epidemiologic studies suggest that in 60–80% of children with persistent microscopic hematuria, no identifiable cause can be found using noninvasive means. Common identified causes include idiopathic hypercalciuria, poststreptococcal glomerulonephritis (GN), immunoglobulin A (IgA) nephropathy, and thin basement membrane disease. A limited work up in this setting is appropriate, including a random urine calcium-to-creatinine ratio for hypercalciuria, and screening of family members for microscopic hematuria to evaluate for familial GN. However, if the patient has microscopic hematuria along with proteinuria or other associated signs or symptoms, it is necessary to rule out significant renal diseases, using a complete work-up as for gross hematuria. Idiopathic persistent microscopic hematuria resolves in the majority of children. At 1-year follow-up, only one-third of children have persistent urinary abnormalities, and by 5 years, the proportion is even lower.

Gross Hematuria

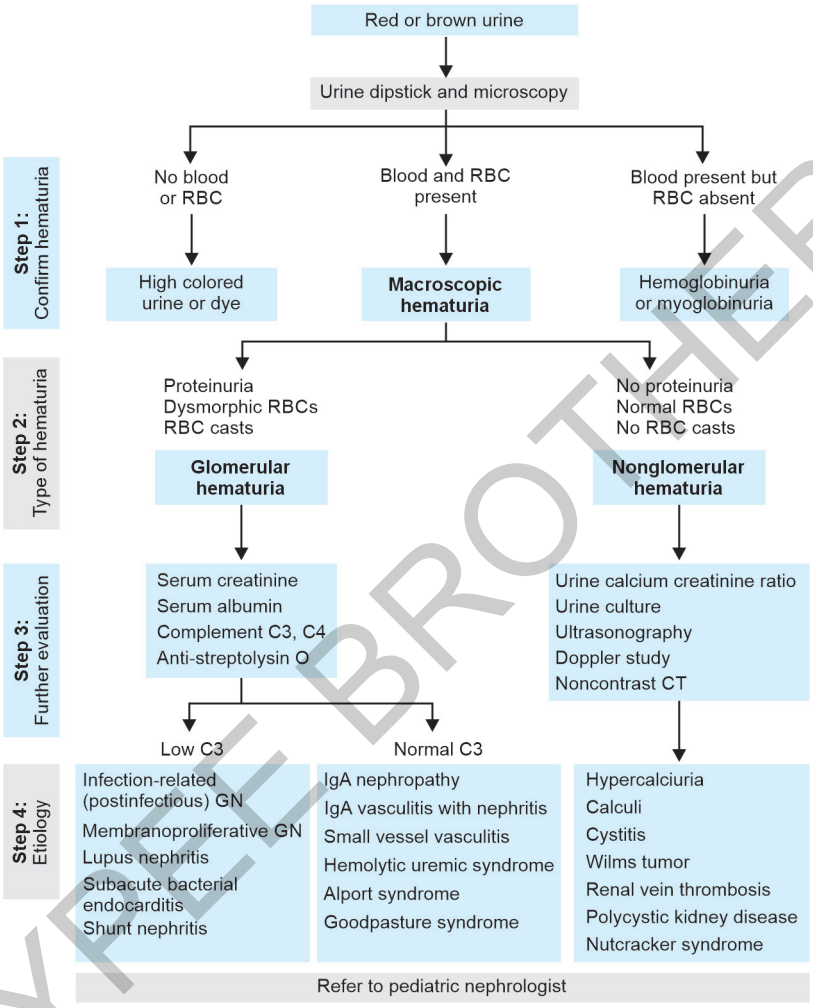
The likelihood of identifying an underlying cause is much greater in patients with gross hematuria, chief causes being hypercalciuria, renal calculi, infection-related GN, and IgA nephropathy. A complete work-up is therefore needed in patients with gross hematuria. History, physical examination, and urinalysis can identify if the source of the bleeding is the renal parenchyma (glomerular hematuria) or the collecting system (nonglomerular hematuria) **(Table 7.1 and Flowchart 7.1)**. If the source can be identified, the patient should be evaluated further for various etiologies **(Box 7.1)**. If the source of hematuria is not identified, examining the child and the urine again at time of an episode of gross hematuria may be of value. **Flowcharts 7.1 and 7.2**

TABLE 7.1: Approach to a patient with hematuria

	Parenchymal, intrarenal (glomerular hematuria)	*Collecting system, extrarenal (nonglomerular hematuria)*
Appearance of urine	Tea colored	Bright red, blood clots
Pattern of hematuria	Hematuria throughout urinary stream	Initial, terminal hematuria
Urinary symptoms	Painless	Dysuria, urgency, frequency
Associated features	Sore throat, hypertension, edema	Fever, colicky pain
Family history	Deafness, renal failure	Renal stones, urinary infection
Proteinuria	≥2+ on dipstick; PCR >1 mg/mg	Trace to 1+; PCR <1 mg/mg
Urinary findings	Red cell casts; dysmorphic red cells	Crystals, eumorphic red cells

PCR (first morning spot) urine protein to creatinine ratio

Flowchart 7.1: Approach to evaluation of gross hematuria. Also see Table 7.1.
C3: complement C3; GN: glomerulonephritis; RBC: red blood cell



outline the plan for evaluation in patients with gross hematuria and persistent microscopic hematuria, respectively.

Evaluation for Glomerular Hematuria

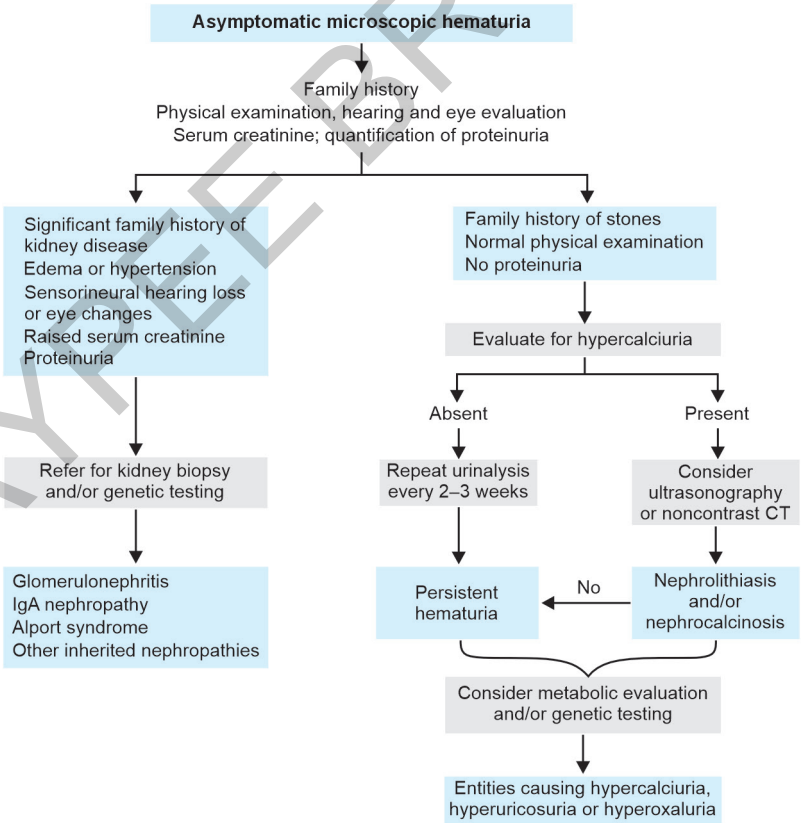
Urine culture is important to detect a urinary infection, although most children with pyelonephritis have other features (fever, flank pain, and pyuria), and occasionally gross hematuria. Since GN is an important cause of renal hematuria, detailed investigations are required. These include estimation of blood levels of creatinine, urea, protein, albumin, and cholesterol, appropriate serologies (antistreptolysin O and streptozyme

BOX 7.1: Causes of hematuria

Common
Glomerulonephritis
Pyelonephritis
Stones
Hemorrhagic cystitis (viral)
Idiopathic hypercalciuria
Urethritis
IgA nephropathy

Less common
Trauma
Exercise
Arteriovenous malformations
Polycystic kidney disease
Renal and bladder tumors
Anatomic malformations: Ureteropelvic junction obstruction
Coagulation disorders, e.g., von Willebrand disease

Flowchart 7.2: Approach to evaluation of persistent microscopic hematuria



for postinfectious GN), complement C3 and C4 (postinfectious GN, lupus, and C3 glomerulopathy), antinuclear antibody (ANA) (lupus), hepatitis B surface antigen and hepatitis C antibody (hepatitis-induced nephritis), and antineutrophil cytoplasmic antibody (granulomatous polyangiitis and microscopic polyangiitis). Urinalyses of family members are done for suspected familial nephritis. Other tests are performed if indicated, based on the history and physical examination, and include renal ultrasound or computed tomography (CT) to look for polycystic kidney disease or renal masses (e.g., Wilms tumor), sickle cell screen, and renal arteriogram to identify arteriovenous malformations. Patients with unexplained hematuria with proteinuria or significant family history should undergo next-generation sequencing to screen relevant genes, including those for hereditary nephropathies **(Annexures 9.3; 9.4, p 845)**.

Evaluation of Nonglomerular Hematuria

This includes urine culture for bacteria and viruses if cystitis is suspected, early morning urine for spot calcium-to-creatinine ratio to screen for hypercalciuria (followed by 24-hr calcium excretion), X-ray abdomen, and ultrasonography. Where indicated, a noncontrast helical CT scan is done to look for renal stones and platelet function tests for von Willebrand disease. Invasive tests including cystourethroscopy or retrograde pyelography (for AV malformations, hemangiomas, or polyps) are seldom required. Next-generation sequencing is useful in patients with metabolic abnormalities, including hypercalciuria and hyperuricosuria **(Annexures 9.3; 9.7, p 845)**.

Management

Management is directed toward the identified underlying disease. If the evaluation does not yield a diagnosis, which often occurs with isolated microscopic hematuria, the patient is counseled and monitored for change in clinical features and for appearance of hypertension or proteinuria.

PERSISTENT MICROSCOPIC HEMATURIA

Immunoglobulin A nephropathy, Alport syndrome, and occasionally other diseases may initially manifest with microscopic hematuria. The incidence of these disorders is not clear, as renal biopsy is not performed until other abnormalities (proteinuria and hypertension) appear.

Immunoglobulin A Nephropathy

Immunoglobulin A nephropathy is the most common form of primary GN worldwide, although there are differences in its prevalence in different regions. Its prevalence varies from 5 to 140 per million children per year and represents 5–30% of kidney biopsies performed across the globe.

The condition is common in Japan, Korea, Taiwan and Australia, and less frequent in Europe and USA. The condition is not uncommon in children in India.

IgA nephropathy is characterized by the presence of predominant or codominant IgA deposits in the glomeruli. Other conditions that could result in similar immunofluorescence findings include IgA vasculitis, systemic lupus erythematosus, chronic liver disease, psoriasis, dermatitis herpetiformis, celiac disease, and non-Hodgkin lymphoma.

Pathogenesis

The pathogenesis of IgA nephropathy is now better understood. Multiple pathophysiological "hits", in a genetically predisposed individual, may result in the disease **(Flowchart 7.3)**. Galactose deficient IgA (GD-IgA) is produced in the mucosa after stimulation by various antigens, including microbes. Individuals prone to IgA nephropathy maintain high-systemic levels of GD-IgA, against which IgG- or IgA-directed autoantibodies can be stimulated. This leads to circulating immune complexes containing the autoantibody and the GD-IgA. Through specific and nonspecific interactions, these complexes accumulate in the mesangium, and generate molecular and cellular immune responses. Over time, this process can lead to the characteristic findings of hematuria and proteinuria, and also drives glomerular and tubulointerstitial sclerosis. Some patients show activation of the alternate complement pathway with C3 and properdin deposition. Plasma levels of IgA are increased in a proportion of patients, but do not correlate with severity of histologic lesions.

Clinical Features

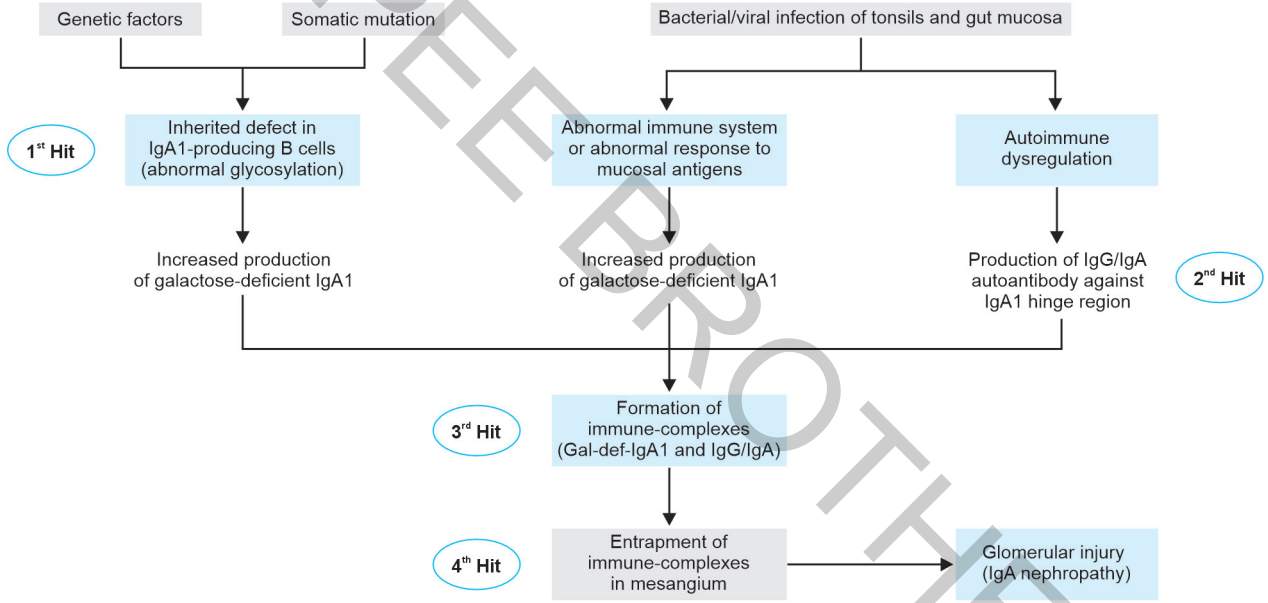
Recurrent gross hematuria is the typical presentation. Flank pain may be associated. Episodes of gross hematuria immediately follow upper respiratory infections (synpharyngitic hematuria), but microscopic hematuria may persist. Microscopic or gross hematuria is more common in children than in adults; children also have higher estimated glomerular filtration rate (eGFR) and lower urine protein excretion. Occasionally, the disorder manifests with acute nephritic features or with heavy proteinuria and nephrotic syndrome, and rarely, with rapidly progressive GN.

Diagnosis

Urinalysis shows presence of RBC and RBC casts with variable degree of proteinuria. The severity of proteinuria should be quantified, since it useful for the management and prognosis of these patients. Serum IgA levels are elevated in 10–15% patients; serum C3 is normal in most cases.

The diagnosis of IgA nephropathy is made on biopsy that shows focal or diffuse proliferation of mesangial cells with increase in mesangial matrix **(Fig. 7.2A)**. Severe cases show segmental fibrinoid necrosis, capsular adhesions,

Flowchart 7.3: Pathogenesis of IgA nephropathy. A four hit hypothesis is proposed. Ig: immunoglobulin; Gal-def: galactose-deficient

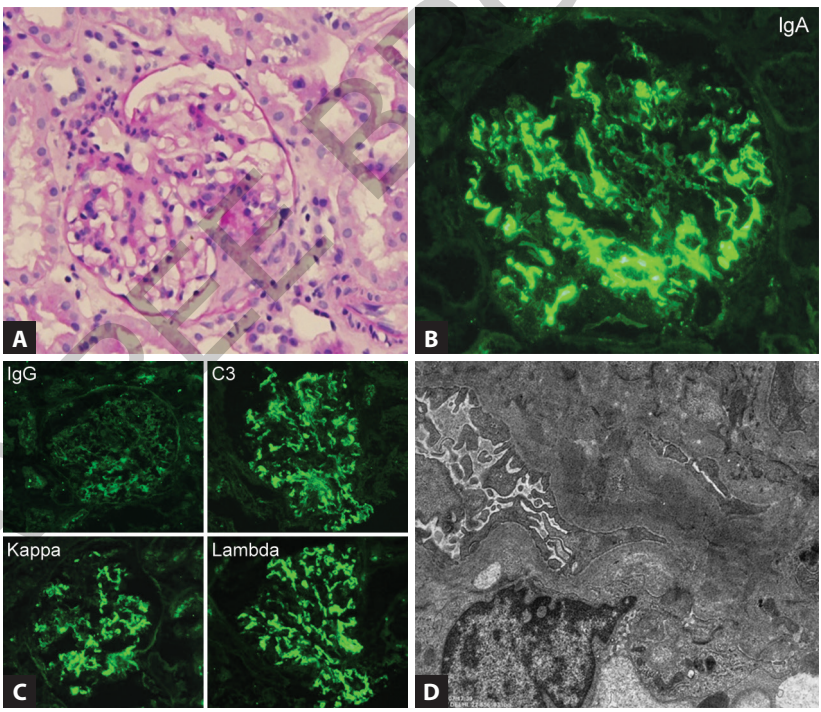


and crescents. Proliferative lesions are observed early in the course and gradually decrease after a few months, when focal segmental sclerosis or hyalinosis may persist. The mesangial deposits are predominantly composed of polymeric IgA1 **(Figs. 7.2B and C)**. Electron microscopy reveals deposits in mesangium, subendothelial, and subepithelial spaces **(Fig. 7.2D)**.

The revised MEST-C Oxford classification incorporates scores for mesangial hypercellularity (M), endocapillary proliferation (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T), and crescents (C) **(Table 7.2 and Figs. 7.3A to E)**. The classification has been validated as a predictor for renal outcome both in adults and children. Staining for KM-55, an antibody directed against galactose-deficient IgA, allows discrimination between mucosal-derived and systemically derived IgA **(Figs. 7.4A to D)**.

Treatment

Treatment of IgA nephropathy is determined based on findings on kidney biopsy, degree of proteinuria, and kidney function **(Table 7.3)**. The primary



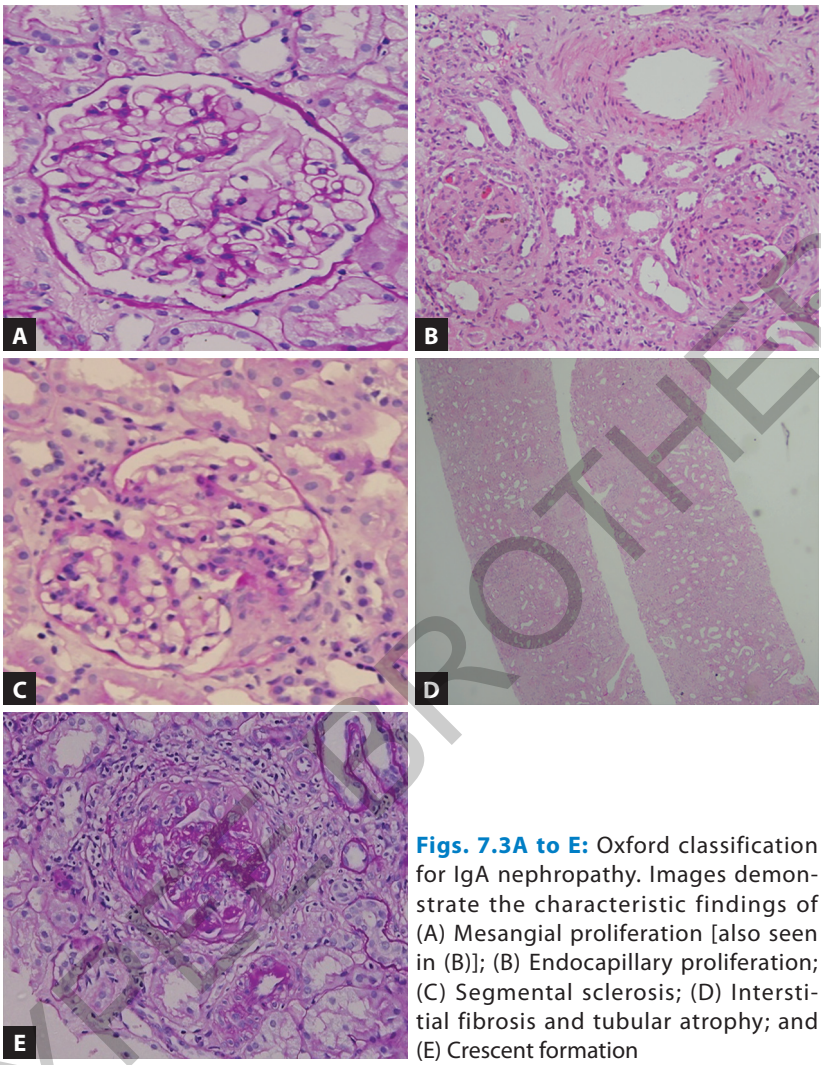
Figs. 7.2A to D: Histology of IgA nephropathy. (A) Light microscopy showing moderate mesangial proliferation and segmental sclerosis (H&E); (B) Immunofluorescence showing positive staining for IgA in mesangial areas; (C) Immunofluorescence showing focal mesangial staining for C3 and kappa and lambda light chains; (D) Electron microscopy shows subendothelial and mesangial deposits

TABLE 7.2: MEST-C criteria in the updated Oxford Classification of IgA nephropathy

Histological variable	*Definition*	*Score*
Mesangial hypercellularity	More than four mesangial cells in any mesangial area	*M0:* <50% of glomeruli showing mesangial hypercellularity *M1:* >50% of glomeruli showing mesangial hypercellularity
Endocapillary hypercellularity	Hypercellularity due to increased number of cells within glomerular capillary lumina	*E0:* No endocapillary hypercellularity *E1:* Any glomeruli showing endocapillary hypercellularity
Segmental glomerulosclerosis	Adhesion or sclerosis (obliteration of capillary lumina by matrix) in part; not the whole glomerular tuft	*S0:* Absent *S1:* Present in any glomeruli
Tubular atrophy, interstitial fibrosis	Estimated percentage of cortex showing tubular atrophy or interstitial fibrosis, whichever is more	*T0:* 0–25% of cortical area *T1:* 26–50% of cortical area *T2:* >50% of cortical area
Cellular, fibrocellular crescents	Percentage of glomeruli with cellular or fibrocellular crescents	*C0:* Absent *C1:* 0–25% of glomeruli *C2:* >25% of glomeruli

M: mesangial hypercellularity; E: endocapillary hypercellularity; S: segmental glomerulosclerosis; T: tubular atrophy/interstitial fibrosis; C: crescents

target of therapy is to achieve reduction of proteinuria (Up/Uc <0.2 mg/mg), normalization of kidney functions and reduction of blood pressure to <90th percentile. Recent KDIGO guidelines emphasize that all patients with IgA nephropathy with significant proteinuria should be managed with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blocker (ARB), salt restriction, and optimal blood pressure control. Patients with crescentic GN should be managed with three to six doses of IV methylprednisolone and IV cyclophosphamide, followed by tapering doses of oral steroids and mycophenolate mofetil or azathioprine for at least 12–18 months. In patients with heavy proteinuria and/or severe histological changes, treatment with oral prednisolone has been proposed. Other medications, including cyclophosphamide, mycophenolate and azathioprine have been used with variable results. Calcineurin inhibitors are considered in patients presenting with nephrotic syndrome and kidney biopsy showing focal segmental glomerulosclerosis (FSGS) with predominant



Figs. 7.3A to E: Oxford classification for IgA nephropathy. Images demonstrate the characteristic findings of (A) Mesangial proliferation [also seen in (B)]; (B) Endocapillary proliferation; (C) Segmental sclerosis; (D) Interstitial fibrosis and tubular atrophy; and (E) Crescent formation

IgA deposits. Patients with advanced disease eGFR <30 mL/min/1.73 m^2 and chronicity on kidney biopsy are best managed with supportive therapy, as immunosuppressive medications are unlikely to be effective.

Enteric-coated slow-release formulation of budesonide has been tested in clinical trials with some success, and the medication was recently approved by the United States Food and Drug Administration (US FDA) for adults with IgA nephropathy and proteinuria. Studies using sparsentan, a dual endothelin and angiotensin receptor antagonist, are also promising. There is limited and unproven evidence on oral therapy with omega-3 fatty acids (6–12 g/day; as fish oil), which is therefore not currently recommended. The role of B-cell inhibition and complement blockers is being examined.

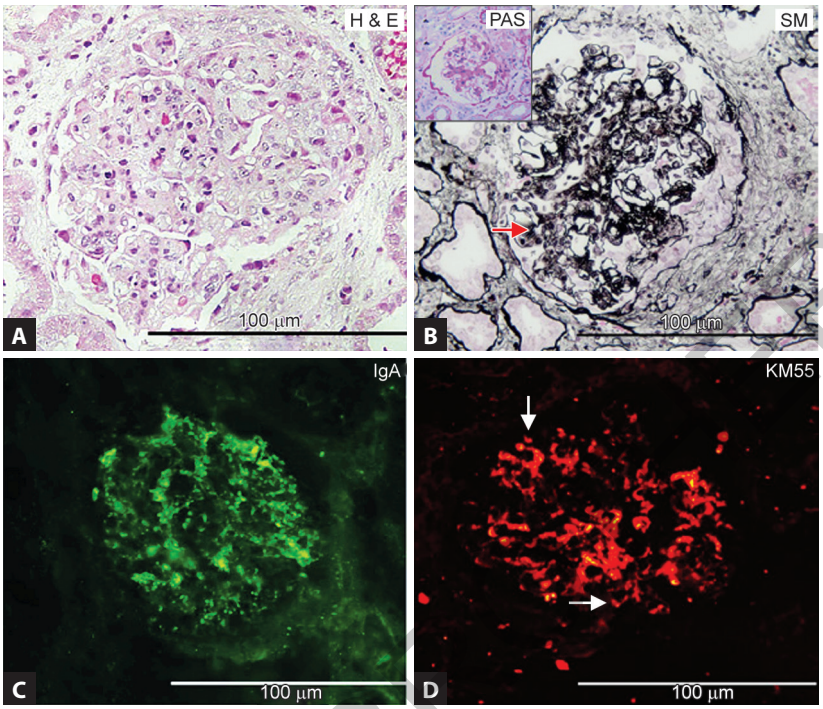


Fig. 7.4A to D: IgA nephropathy secondary to chronic liver disease. (A) Light microscopy indicates endocapillary hypercellularity including neutrophils and a cellular crescent (hematoxylin-eosin, ×40); (B) Segmental reduplication of the glomerular basement membrane (red arrow) (Jones methenamine silver, ×40), while other glomeruli show mesangial hypercellularity (inset, Periodic acid Schiff, ×20); (C) Immunofluorescence for IgA shows 2+ mesangial granular staining (IgA-FITC, ×20); (D) Staining for KM55, an antibody directed against galactose-deficient IgA, shows 3+ mesangial granular staining with capillary-wall extension (white arrows), suggesting mucosal-derived IgA (KM55-phycoerythrin, ×20)

Prognosis and Natural History

The prognosis in children is better than in adults. Approximately 10% children with IgA nephropathy progress to advanced CKD by 10 years from diagnosis, and an additional 20–30% will progress within 20 years. Monitoring of blood pressure, blood creatinine, urinalysis, and protein excretion is recommended. Factors indicating poor outcome include heavy proteinuria, impaired kidney function, and severe kidney histology. A risk prediction tool, developed by the International IgA Network that employs ethnicity, clinical and MEST-C score, has been shown to satisfactorily predict kidney-specific endpoints of 50% decline in kidney function or end-stage kidney disease (ESKD) **(*see* Annexure 7.1)**. A similar tool for children predicts the risk of 30% decline in eGFR or ESKD **(*see* Annexure 7.2, p 203)**.

Pediatric Nephrology

For over three decades, Pediatric Nephrology has been a trusted resource for postgraduate teaching in the specialty. With contributions from more than 30 national and international experts, the 7th edition is thoroughly updated and expanded to ensure that the reader has access to the latest information on diagnoses and therapies. The book should be useful for pediatricians, pediatric nephrologists and urologists, and for trainees in pediatrics and pediatric nephrology.

Highlights of the present edition

- New chapters on C3 glomerulopathy and membranous nephropathy, kidney support therapy, tubulointerstitial diseases and thrombotic microangiopathy
- Extensively revised and updated chapters with emphasis on current understanding of pathogenesis and management
- Algorithms to outline practical approach to common syndromes
- Colored boxes and crisp tables to summarize recent evidence-based guidelines on management from IPNA, KDIGO, KDOQI, ERKNet, ISPN, PRNT, and other organizations
- High quality histopathological images with descriptive legends
- QR codes for online calculators, clinic and ambulatory blood pressure and other resources
- Updated annexures that include practically relevant information
- Web annexures of gene lists for kidney and urological diseases.

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