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3.1 Approach to Hematuria

3.1.1 Abstract

The goal of the initial assessment is to decide if the hematuria is due a medically important cause while avoiding unnecessary investigations.

Important differential laboratory and clinical criteria are the presence or absence of glomerular (deformed) red blood cells or casts, concomitant, persistent proteinuria, systemic features, hypercalciuria, urine crystals, pain, and the patient's age.

This section provides several diagnostic approaches based on the clinical presentation and simple laboratory observations.

3.1.2 Definitions

- Presence of red blood cells (RBC) in urine (>10 RBC per mm^3 of freshly voided, unspun urine or >5 RBC per high power field (HPF) of 10 ml of fresh urine, centrifuged at 2,000 rpm and resuspended in 0.5 ml).
- Macroscopic (gross) hematuria refers to urine that is visibly bloody (bright red to brown or tea (cola) colored). The color depends on the amount of blood, the source of bleeding, and urine acidity. One ml of blood per 1 l of urine is sufficient to render urine visibly "bloody."
- Microscopic hematuria (microhematuria) refers to the presence of RBC without urine discoloration, detected by microscopy or chemical (dipstick) analysis. Threshold for a positive readout is a hemoglobin concentration of approximately 0.6 mg/l.

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- A positive dipstick reaction in the absence of RBC in urine by microscopy suggests hemolysis or myoglobinuria.
- Glomerular diseases, if associated with gross hematuria, usually present with dark-brown (tea or cola) colored urine. Acute, non-glomerular hematuria is generally bright red, often with clots and painful voiding.
- Active glomerulonephritis and acute interstitial nephritis present with increased numbers of dysmorphic RBCs or RBC casts compared with hematuria originating from the lower urinary tract.
- Not all red urine is due to hematuria. Blood may be of menstrual origin or be due to hematospermia. Red urine in the absence of RBC or hemoglobin/myoglobin suggests excretion of other agents that color the urine (see Box 3.1 and Sect. 1.3).

3.1.3 Introduction

- Microscopic hematuria is much more frequent than gross hematuria. It may be transient or chronic. It is often discovered incidentally, e.g., at a routine check during the workup for dysuria, abdominal/flank pain, or extrarenal disease.
- The prevalence of significant disease in children with isolated microhematuria found at random screening is low (<1 to 7.2 %).
- While malignancies of the urogenital tract are an important differential diagnosis in adults, they are rare in children (e.g., Wilms tumor).
- Macroscopic hematuria can be the presenting sign of parenchymal kidney disease (e.g., membranoproliferative glomerulonephritis, Alport syndrome, IgA nephropathy, polycystic kidney disease), yet >40 % of children presenting gross hematuria have no identifiable cause.
- Fifteen to 20 % of patients with painless micro- or macrohematuria have hypercalciuria.
- The prognosis of microhematuria depends on the underlying etiology; it is favorable in most instances.
- The differential diagnosis is wide (Box 3.1). Careful history and complete physical examination are a prerequisite for a focused diagnostic approach.
- Extensive and invasive random laboratory investigations in a child with isolated hematuria are unnecessary and discouraged.
- In contrast, the presence of concomitant proteinuria can indicate clinically important kidney disease and may warrant diagnostic workup and treatment that should be coordinated with a pediatric renal specialist.

3.1.4 Baseline Investigations for Hematuria

- Urine microscopy
- Confirm that urine discoloration is due to blood (dipstick analysis and microscopy)
- Rule out extra-urinary sources of the blood
- Differentiate between glomerular and non-glomerular hematuria (Table 3.1; Figs. 3.1 and 3.2)

Box 3.1 Etiology of Hematuria

1. Glomerular causes

- Acute postinfectious glomerulonephritis (APIGN)
- IgA nephropathy (IgAN)
- Membranoproliferative GN (MPGN)
- Focal-segmental glomerulosclerosis (FSGS)
- Thin basement membrane nephropathy (TBMN) and benign familial hematuria
- Alport syndrome (hereditary nephritis)
- Systemic diseases, immunological causes
 - SLE, HUS, Schönlein-Henoch purpura (SHP), anti-glomerular basement membrane (anti-GBM) disease and Goodpasture's disease, infective endocarditis, shunt nephritis

2. Non-glomerular causes

- Nephrolithiasis, hypercalciuria
- Infections
 - Bacterial urinary tract infection (UTI), leptospirosis, tuberculosis
 - Viral (polyomavirus [BKV] hemorrhagic cystitis; HIV nephropathy)
 - Parasitic (malaria, bilharziosis [*S. haematobium*])
- Tumor/malignancy
 - Wilms tumor/nephroblastoma
 - Renal carcinoma (extremely rare in childhood)
- Polycystic kidney disease (PKD) and other cystic renal diseases
- Hematologic causes (sickle cell anemia with renal papillary necrosis, hemophilia, disseminated intravascular coagulation)
- Vascular anomalies
- Medications (NSAIDs, warfarin, heparin, cyclophosphamide, ifosfamide, hydralazine, propyl thiouracil, allopurinol, penicillamine, etc.)
- Physiological (exercise, fever)
- Trauma, bladder catheterization, surgery

3. Rare or debated causes

- Young girls with recurrent hematuria: suspect abuse, foreign body insertion
- Loin pain-hematuria syndrome is a diagnosis of exclusion
- Nutcracker syndrome: hematuria due to trapping of the left renal vein between the superior mesenteric artery and the abdominal aorta

4. Newborns

- Renal venous thrombosis
- Renal artery thrombosis
- Autosomal recessive polycystic kidney disease (ARPKD)
- UTI
- Obstructive uropathy
- Bleeding and clotting disorders

5. Common causes of “dark urine” mimicking hematuria

- Drugs: rifampin, nitrofurantoin, metronidazole; methyl dopa, levodopa
- Pigments: hemoglobin, myoglobin, bilirubin; urate
- Nutrients: beets, blackberries

Table 3.1 Glomerular versus non-glomerular hematuria

Features	Glomerular hematuria	Non-glomerular hematuria
<i>History</i>		
Dysuria	Absent	Present in urethritis, cystitis
Systemic signs	Edema, fever, pharyngitis, rash, arthralgia	Fever with UTI, pain with calculi
Family history	Possible diagnoses: Isolated hematuria in TBMN Hematuria plus deafness, ESRD in Alport syndrome IgAN, SHP, HUS, SLE	Renal stones, hypercalciuria
<i>Physical examination</i>		
Hypertension, edema	Usually present	Less common
Abdominal mass	Absent	Present in Wilms tumor, obstructive uropathy
Rash, petechiae or purpura, arthritis	SLE, SHP	Absent unless part of drug-induced interstitial nephritis
<i>Urinalysis</i>		
Color	Brown, tea, cola	Bright red; clots may be seen
Proteinuria	2+ or more (≥ 1 g/l)	<2+ (<1 g/l)
Dysmorphic RBCs	>20 %	<15 %
RBC casts	Common	Absent
Crystals	Absent	May be present

Abbreviations: TBMN thin basement membrane nephropathy, SHP Schönlein–Henoch purpura, HUS hemolytic uremic syndrome

- Check for protein (dipstick analysis, chemistry)
- Look for WBC (dipstick, microscopy); rule out urinary tract infection
- Imaging (ultrasonography; CT scan)

3.1.5 Management

Hematuria is a clinical (or laboratory) sign, not a diagnosis. The most common cause of glomerular gross hematuria in children is APIGN, frequently due to streptococcal infection of the throat or skin (Fig. 3.1). The most common causes of non-glomerular gross hematuria are UTI and hypercalciuria or stones (Fig. 3.2). Management of the underlying disorders will be discussed in the following chapters.

3.2 Approach to Proteinuria

3.2.1 Abstract

Proteinuria heralds glomerular and occasionally tubular renal injury. The aim of the initial workup is to discern between transient or functional proteinuria and clinically significant, acute and chronic (progressive) proteinuria. This section provides a

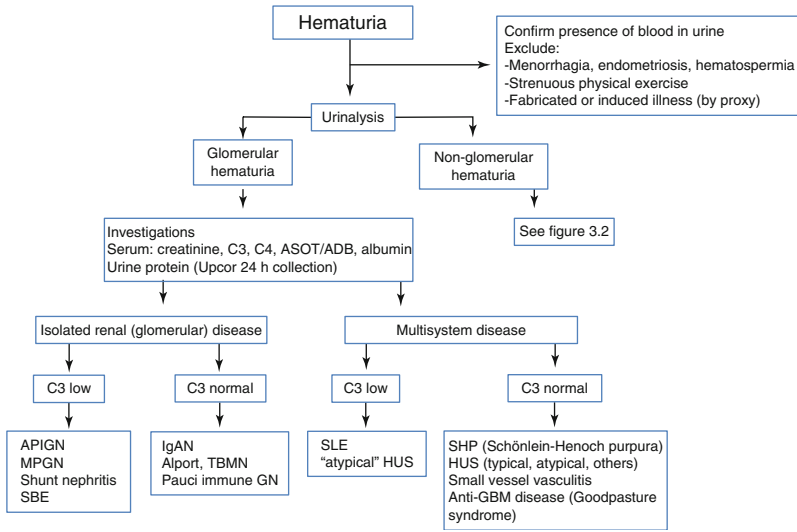


Fig. 3.1 Approach to hematuria. *Abbreviations:* APIGN acute postinfectious GN, ASOT antistreptolysin O titer, GBM glomerular basement membrane, GN glomerulonephritis, HUS hemolytic uremic syndrome, IgAN IgA nephropathy, MPGN membranoproliferative GN, SBE subacute bacterial endocarditis, SLE systemic lupus erythematosus, TBMN thin basement membrane nephropathy, Upc urine spot protein to creatinine ratio

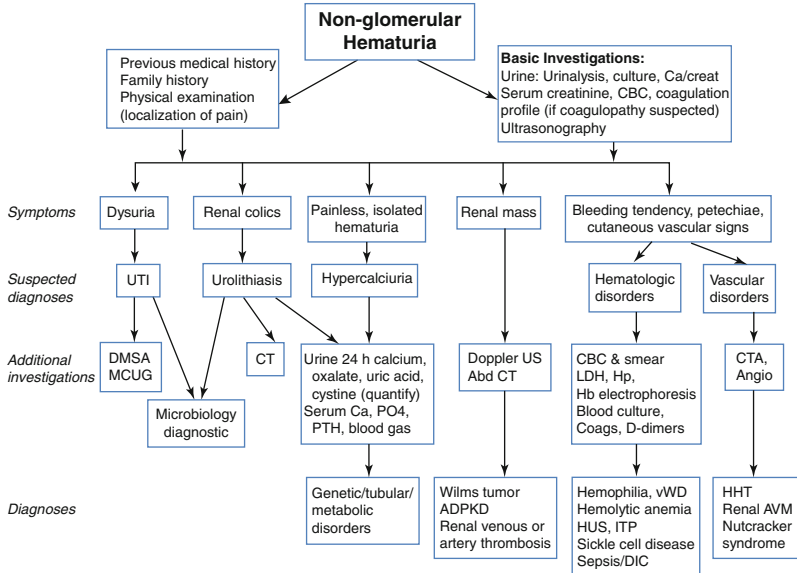


Fig. 3.2 Approach to non-glomerular hematuria. *Abbreviations:* Abd abdominal, ADPKD autosomal dominant polycystic kidney disease, AVM arteriovenous malformation, Ca calcium, CBC complete blood count, creat creatinine, CT computer tomogram, DIC disseminated intravascular coagulation, DMSA dimercaptosuccinic acid renal scan, Hb hemoglobin, HHT autosomal dominant hereditary hemorrhagic telangiectasia, Hp haptoglobin, ITP idiopathic thrombocytopenia, LDH lactate dehydrogenase, MCUG micturition cystourethrogram, US ultrasonography, UTI urinary tract infection, vWD von Willebrand disease

framework for the differentiation of proteinuria and their association with renal parenchymal disease. Specific glomerular diseases are discussed in the remaining sections of this chapter.

3.2.2 Introduction

- Proteinuria is a hallmark of glomerular and/or tubular injury. Both can be associated with hematuria.
- Most acute inflammatory glomerular diseases present with macro- or microhematuria (glomerulonephritis; nephritic–nephrotic syndromes).
- Proteinuria can signal acute disease or be the result of chronic kidney disease secondary to parenchymal fibrosis or scarring with nephron loss and hyperfiltration of the remaining nephrons.
- The aim of evaluating a patient with proteinuria is to differentiate clinically significant, generally persistent (or recurrent) proteinuria from transient or physiological proteinuria.
- Proteinuria can be isolated or present with peripheral edema, hypertension, and (other) extrarenal manifestations.
- For differential etiologies of proteinuria refer to Box 3.2.

3.2.3 Definitions

- Estimation of protein excretion from spot urine samples is best accomplished by the “urine protein to creatinine ratio” (U prot/creat or Upc). It is expressed as g protein/mmol creatinine (normal <0.02) or g protein/g creatinine (normal <0.2). The ratio normalizes urine protein excretion to urine density (concentration of urine creatinine). The units should be added to avoid confusion between conventional and SI unit definitions.
- The use of the ratio circumvents problems of timed urine specimens, such as inaccurate sampling periods, missed samples, or enuresis.
- If practical, obtain first morning urine samples to avoid collection errors and pitfalls due to orthostatic proteinuria.
- The numerator of the Upc (g/g) correlates with the daily protein excretion (per 1.73 m² body surface area; multiply by 8.84 (or by 10 for a quick estimate), if the urine creatinine is expressed in mmol/l).
- Physiologic proteinuria: normal urinary protein excretion <50 mg/m²/day with an upper limit of 100 mg/m²/day or 4 mg/m²/h (adults 150 mg/day) (Table 3.2).
- Physiological proteinuria originates from plasma (60 %), consisting of albumin (30–40 %), IgG (5–10 %), light chains (5 %), and IgA (3 %), and the tubule (predominantly Tamm–Horsfall protein).
- Transient or functional proteinuria: associated with fever, exercise, stress, seizures, or congestive heart failure. It does not reflect renal disease.
- Orthostatic proteinuria can be assumed when proteinuria is limited to periods of upright position (absent in the recumbent position). It rarely exceeds 600 mg/m²/day

Box 3.2 Etiology of Proteinuria

1. Glomerular proteinuria

- Resulting from lesions of the glomerular filtration barrier
- Disorders with prominence of glomerular basement membrane (GBM) changes
 - Hereditary: Alport syndrome, laminin $\beta 2$ mutation
 - Acquired/immunological: Goodpasture's syndrome, membranous nephropathy
- Disorders with prominence of podocyte lesions
 - Hereditary (genetic mutation): congenital nephrotic syndromes (Finnish-type [NPHS1], podocin [NPHS2], etc.)
 - Idiopathic/acquired: minimal change disease, some forms of focal segmental glomerulosclerosis
- Complex inflammatory causes
 - C3 nephropathies (membranoproliferative glomerulonephritis (MPGN), dense deposit disease (DDD)), a HUS, APiGN
- Systemic vasculitides: lupus nephritis (LN), Schönlein–Henoch nephritis (SHN), ANCA-associated vasculitis (AAV)
- Disorders with prominent mesangial involvement: IgAN, SHN, C1q nephropathy (C1qN), LN
- Infection-associated: hepatitis B and C, endocarditis, shunt infection
- Other immunological and secondary forms
- Miscellaneous
 - Hematological disorders: sickle cell disease
 - Reflux nephropathy

2. Tubular proteinuria

- Inflammatory tubular injury: ATN, interstitial nephritis, reflux nephropathy, acute cellular kidney transplant rejection, polyomavirus nephropathy
- Toxic tubular injury: aminoglycosides, chemotherapeutics, antiviral (HIV) medications, heavy metals
- Proximal tubular injury: Fanconi syndrome, proximal tubular acidosis, Dent's disease, nephropathic cystinosis
- Developmental and chronic changes: renal dysplasia, reflux nephropathy, chronic kidney disease

3. Microalbuminuria

- Important parameter of glomerular injury due to diabetes mellitus, possible marker in reflux nephropathy and CKD (associated with glomerular hyperfiltration)

(1 g/day in adults) or Upc 0.1 g/mmol creatinine (1 g/g creatinine). The prevalence of orthostatic proteinuria is highest in adolescents. The prognosis is benign. In the absence of other findings, no additional investigations and follow-up are needed (Fig. 3.3).

Table 3.2 Proteinuria (threshold values)

Proteinuria measurements	Timed sample	Protein to creatinine ratio (U _{pc})	
		Conventional units	Alternative units
Normal urinary protein excretion	<4 mg/m ² /h (<100 mg/m ² /day)	<0.2 g protein/g	<0.02 g/mmol
Proteinuria	>4 mg/m ² /h (>100 mg/m ² /day)	> 0.2 g/g	>0.02 g/mmol
Nephrotic-range proteinuria	>40 mg/m ² /h (>1,000 mg/m ² /day)	>2 g/g	>0.2 g/mmol
Microalbuminuria	30–300 mg/day or 20–200 µg/min (adults) 20–200 mg/m ² /day	30–300 mg/g (0.03–0.3 g/g)	3–30 mg/mmol (0.003–0.03 g/mmol)

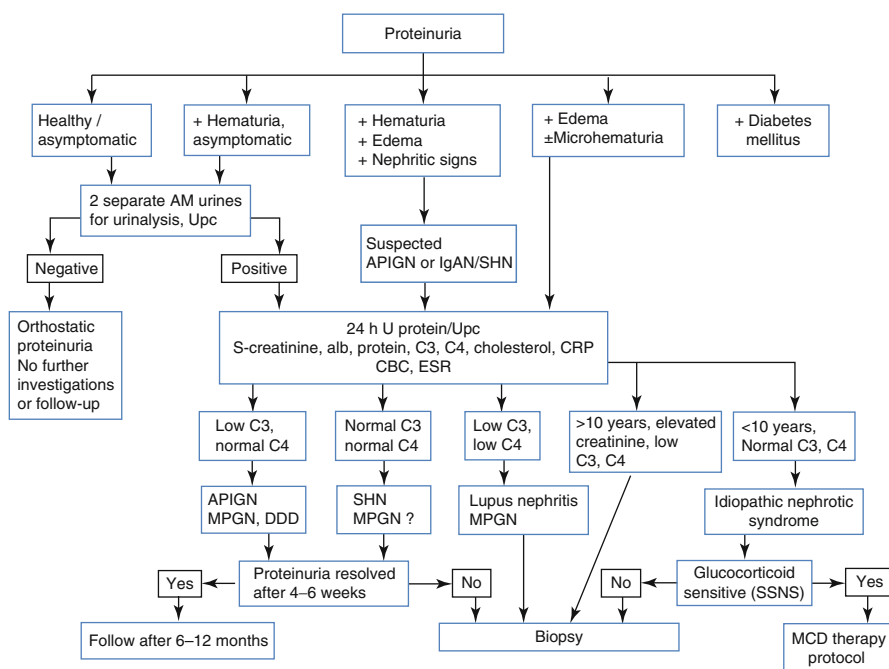


Fig. 3.3 Approach to proteinuria. Abbreviations: APIGN acute postinfectious GN, creat creatinine concentration, CRP C-reactive protein, DDD dense deposit disease or MPGN type II, GN glomerulonephritis, IgAN IgA nephropathy, MPGN membranoproliferative GN, SHN Schönlein-Henoch nephritis, SSNS steroid [glucocorticoid]-sensitive nephrotic syndrome, U_{pc} urine protein to creatinine ratio

- Glomerular proteinuria results from altered permeability selectivity (“permselectivity”) of the glomerular filtration barrier due to various mechanisms often due to genetic or acquired changes of components of the glomerular filtration barrier, such as nephrin in the interpodocyte slit diaphragm or type IV collagen or laminin β2 in the glomerular basement membrane.

- Toxic effects of drugs and environmental agents, such as aminoglycosides, chemotherapeutics, or herbal ingredients may affect tubular cells or glomerular endothelial and epithelial cells (podocytes).
- Glomerular proteinuria can be selective or nonselective. Albumin, IgG, and transferrin are used to characterize the selectivity of glomerular proteinuria.
- In selective proteinuria, the clearance ratio of IgG/albumin is <0.10 (nonselective proteinuria >0.5).
- Microalbuminuria denotes an albumin excretion above the normal range but below a level quantifiable by conventional dipstick analysis (0.06 g/l or 6 mg/dl). It is defined as urine albumin (U alb) excretion of $20\text{--}200\text{ }\mu\text{g/min}$ ($30\text{--}300\text{ mg/day}$) in a timed sample (in adults) or $3\text{--}30\text{ mg/mmol creatinine}$ ($30\text{--}300\text{ mg/g of creatinine}$) in a spot urine sample (see Table 3.2).
- Microalbuminuria is a risk factor for progressive renal insufficiency in patients with diabetes and (possibly) reflux nephropathy or chronic kidney disease.
- *Tubular proteinuria* refers to impaired proximal tubular reabsorption of low molecular weight proteins.
- Markers of tubular proteinuria are β_2 microglobulin, α_1 microglobulin, retinol-binding protein and lysozymes.
- Tubular proteinuria is generally $<1\text{ g/1.73 m}^2\text{/day}$.
- It is seen in acute tubular necrosis, interstitial nephritis, aminoglycoside and other drug toxicity, heavy metal intoxication, Fanconi syndrome and proximal renal tubular acidosis, Dent's disease, and renal hypoplasia/dysplasia.
- It can also be observed as overflow proteinuria when excessive amounts of low molecular weight (LMW) protein overwhelm the (proximal) tubular reabsorption capacity, e.g., Bence Jones proteins.

3.2.4 Proteinuria Methods

- Current methodology uses colorimetric assays (e.g., pyrogallol red for total protein) or immunological assays (e.g., immunoturbidimetry for albumin) and automated equipment. Urine creatinine is measured by the Jaffé method or by precipitation reaction (e.g., picric acid).
- Selective U alb assays are substantially more expensive than measuring total protein, but add little information for most indications.
- U protein dye binding assays can be established where expensive commercial equipment and reagents are lacking.
- U protein can be estimated using sulfosalicylic acid (SSA), even by families after proper instruction; its accuracy is similar to that of (expensive) dipsticks.

3.2.5 Clinical Signs and Symptoms

Proteinuria is often asymptomatic. High protein content lets urine appear frothy, bubbly, and dark yellow. Large (nephrotic-range) proteinuria can result in peripheral edema and other signs and symptoms associated with the underlying glomerular disease.

3.2.6 Basic Investigations

For methods of urine protein determination, see above Sect. 3.2.4 and Chap. 1. The evaluation of children with proteinuria is shown in Fig. 3.3.

3.3 Primary Nephrotic Syndrome

Nephrotic syndrome results from inherited or acquired disturbances of the podocyte and/or glomerular basement membrane (GBM). It is an important reason for nephrology consultations. Primary nephrotic syndrome (nephrotic syndrome without an identifiable systemic or extrarenal disorder) has a cumulative prevalence of about 16/100,000 population <16 years. Reported annual incidence figures range from 1–3 to 8 per 100,000 children.

Sect. 3.3.1 describes diagnostic approaches and management of children presenting with (primary) nephrotic syndrome, followed by brief summaries of the histological diagnoses of minimal change nephrotic syndrome (MCNS) or minimal change disease (MCD) and focal-segmental glomerulosclerosis (FSGS) in Sects. 3.3.2 and 3.3.3. Examples of inherited and genetically defined nephrotic syndromes, including congenital and syndromic forms, are highlighted in Sect. 3.3.4. Current standard (first-line) treatment regimens for idiopathic nephrotic syndrome are based on pioneering cooperative studies in North America and Europe between 1970 and 1990. An important source for diagnostic and treatment recommendations in this and the following sections is the 2012 Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis.

3.3.1 Idiopathic Nephrotic Syndrome (INS)

3.3.1.1 Introduction

- INS is more prevalent in boys than in girls, with onset between 2 and 8 years of age.
- Up to 80 % of children with INS respond to daily glucocorticoid therapy.
- Differentiation between glucocorticoid (steroid)-sensitive (responsive) syndrome (SSNS) and glucocorticoid (steroid)-resistant nephrotic syndrome (SRNS) has important therapeutic and prognostic implications.
- The long-term prognosis (renal function) of children with primary glucocorticoid-sensitive nephrotic syndrome is good.
- The underlying histopathological lesion is minimal changes (MCNS) in the large majority, but some have FSGS or different glomerular diseases, such as membranous nephropathy (MN; Sect. 3.5.3), membranoproliferative glomerulonephritis (MPGN; Sect. 3.5.1).
- In contrast, a large proportion of patients with glucocorticoid-resistant nephrotic syndrome has FSGS and is at risk of developing chronic kidney disease (CKD).

- Etiology and histopathologic lesions of nephrotic syndromes change with age of onset (inherited forms and diffuse mesangial sclerosis during the first 3 to 12 months, MCNS 1–10 years, other forms of primary NS and of secondary forms during adolescence and young adulthood).

3.3.1.2 Definitions

- Nephrotic syndrome (NS) is defined clinically by the combination of large (nephrotic-range) proteinuria, hypoalbuminemia (<25 g/l), and generalized, pitting edema. The accompanying hypercholesterolemia is likely secondary.
- The degree of edema may not be proportional to the proteinuria or hypoalbuminemia. 24-h urine collection is not necessary to establish the diagnosis.
- Nephrotic-range proteinuria may be present in other glomerular diseases or cystinosis, usually not associated with edema or (significant) hypoalbuminemia.
- “Primary” nephrotic syndrome is used synonymously with “idiopathic” nephrotic syndrome (INS). The designation requires exclusion of primary infectious, systemic or malignant diseases (Box 3.3).

Box 3.3 Nephrotic Syndrome: Definitions

Nephrotic syndrome	Clinical syndrome defined by (1) large proteinuria of 3 to 4+ by dipstick or Upc >2 g/g creatinine (>0.2 g/mmol) or >4 mg/m ² /h in a timed urine specimen, (2) hypoalbuminemia <25 g/l, and (3) generalized edema
Primary nephrotic syndrome	Requires exclusion of systemic diseases and other forms of glomerulonephritis (see below)
Secondary nephrotic syndrome	Nephrotic syndrome secondary to systemic disease (e.g., SLE, lymphoma) or infection
Idiopathic nephrotic syndrome (INS)	Primary nephrotic syndrome, where etiology and disease mechanism are not well defined or known
Urinary remission	Urine albumin nil or trace (or proteinuria <4 mg/m ² /h) for three consecutive days
Relapse	Urine albumin 3+ or 4+ (or proteinuria >40 mg/m ² /h) for three consecutive days, having been in remission previously
Frequent relapses (FRNS)	Two or more relapses during 6 months, or more than three relapses during any 12-month period
Glucocorticoid (steroid) dependence (SDNS)	Two consecutive relapses during alternate-day prednisone therapy or within 14 days of its discontinuation
Glucocorticoid resistance (SRNS)	Persistent proteinuria (>2 g/g creatinine) despite high-dose prednisone therapy with 60 mg/m ² (2 mg/kg) daily for 4 weeks, in the absence of infection or nonadherence to medication
Secondary glucocorticoid resistance	Refers to patient who was previously responsive to glucocorticoid therapy

- The term “idiopathic” implies that etiology and disease mechanism are not known in a large percentage of children with primary nephrotic syndrome.

3.3.1.3 Pathology of Idiopathic Nephrotic Syndrome (INS)

- The common histopathological variety seen in children with idiopathic nephrotic syndrome is “minimal change disease” (MCD) or minimal change (or minimal lesion) nephrotic syndrome (MCNS; both terms are used interchangeably). Less commonly seen are focal segmental glomerulosclerosis (FSGS), membranoproliferative (or mesangiocapillary) glomerulonephritis (MPGN or MCGN), or (rarely) membranous nephropathy (MN) as causes of nephrotic syndrome.
- MCNS is characterized by the lack of histological changes by bright-field and immunofluorescence microscopy. Electron microscopy reveals generalized effacement of podocyte foot processes.
- The term FSGS refers to sclerotic lesions that initially affect some glomeruli while sparing others (“focal”). Glomeruli are partially affected (“segmental” sclerosis), but the lesions may progress to global sclerosis with progressive nephron loss. Immunofluorescence is negative. In contrast to MCNS, foot process effacement is not generalized. Up to 25 % of patients with FSGS may not present with nephrotic syndrome.
- The biopsies of some patients with nephrotic syndrome demonstrate mesangial proliferation and/or mesangial deposition of IgM or (dominant) C1q, or collapsing glomeruli with abnormal podocyte morphology. Some pathologists consider them variants of MCNS and FSGS, while others regard them as separate diseases, i.e., mesangial proliferative glomerulonephritis, IgM nephropathy, C1q nephropathy, and collapsing glomerulopathy.

3.3.1.4 Clinical Features

Typical Presentation

- Patients with nephrotic syndrome typically present with periorbital swelling (puffiness), more noticeable in the morning, which progresses to generalized edema or anasarca over days or weeks. Abdominal wall edema and ascites with a “smiling” umbilicus or pleural effusions and scrotal or vulval edema may be seen.
- Microscopic hematuria is found in up to 30 %, but gross hematuria is unusual in INS and suggests an alternative primary diagnosis.
- Nephrotic patients are at risk of intravascular volume depletion despite a fluid gain of up to 20 % of body weight. The presence of edema makes assessment of the intravascular volume status difficult.
- Patients occasionally present with hypertension due to intravascular volume depletion and activation of the renin–angiotensin system.

Atypical Features of Nephrotic Syndrome Suggesting Alternative Diagnoses

- Age <3–12 months and >12 years
- Sustained serum creatinine elevation
- Hypertension
- Gross hematuria

- Low serum C3 or C4
- Evidence of specific infection (HBV, HCV, HIV)

3.3.1.5 Investigations at First Presentation of Nephrotic Syndrome

- Urinalysis and microscopy. Microhematuria is noted in up to 30 % of patients with INS and does not predict poorer outcome. Mild “sterile” pyuria can be present.
- Urine protein to creatinine ratio (Up_c) or 24-h (timed) urine protein estimation.
- Serum albumin, total protein, cholesterol, and creatinine.
- Infectious disease workup including PPD (Mantoux) skin test and chest X-ray in Tb endemic areas, and HIV, HBV, or HCV serology or PCR for patient at risk.
- Kidney biopsy is reserved for infants and older children, those with “atypical” presentation and those unresponsive to 4 weeks of daily high-dose glucocorticoid therapy (Box 3.4).

3.3.1.6 Treatment of Idiopathic Nephrotic Syndrome

First Episode

- Prednisone (or prednisolone, used interchangeably): 60 mg/m² once daily or in 2–3 divided doses (~2 mg/kg/day, max. 60 mg/day) for 4–6 weeks followed by 40 mg/m² (~1.5 mg/kg, max. 40 mg) on alternate days as a single morning dose for the next 4–6 weeks with or without taper. Some authors recommend prolonged glucocorticoid therapy for 6 months after the initial, intense therapy (Fig. 3.4).
- A focus of infection must always be searched and treated. Control of underlying infection can achieve remission in some cases.

Relapse Treatment

- About 70 % of patients with INS will have one or more relapses. Treatment is directed to suppress proteinuria and restore normal serum protein concentrations and to reduce the frequency of future relapses, both with minimal short- and long-term adverse effects.

Box 3.4 Indications for Renal Biopsy in Patients with Nephrotic Syndrome

- Age <12 months or >12 years at presentation
- Glucocorticoid resistance (defined in Box 3.3)
- Proteinuria associated with malformations or “syndromes” (e.g., nail patella syndrome, Lowe syndrome)
- Persistently low plasma C3 and/or C4 (see Fig. 3.3)
- Sustained hypertension not related to glucocorticoid or calcineurin inhibitor therapy
- Serum creatinine elevation (renal failure) for >1 week, not attributable to intravascular volume depletion
- Secondary nephrotic syndrome with features of systemic disease (e.g., SLE, SHP, HIV infection, hepatitis B or C)

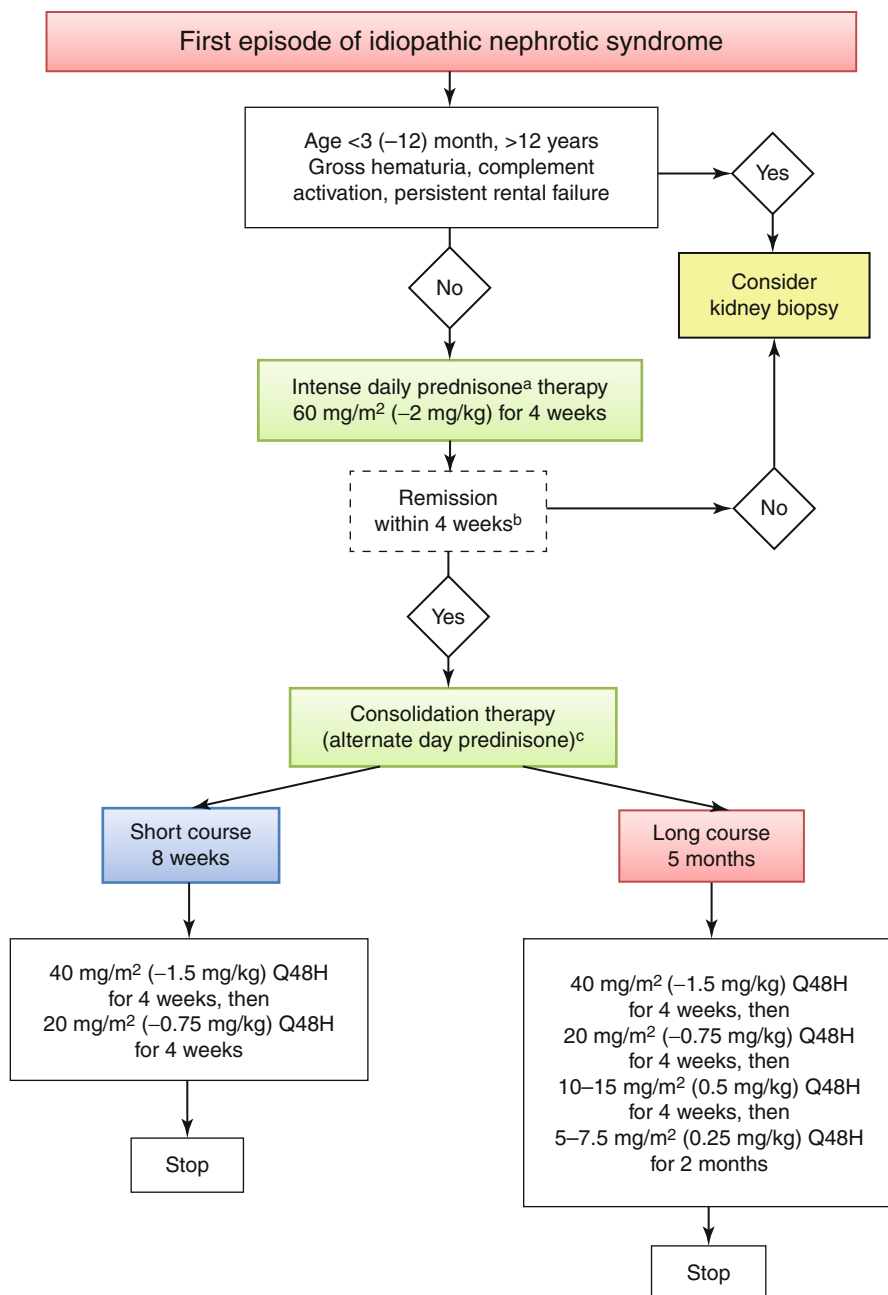


Fig. 3.4 Algorithm for the treatment of a first episode of nephrotic syndrome. ^aPrednisone or prednisolone used interchangeably; max. 60 mg/day, ^bRemission defined as three consecutive days of “negative” or “trace” urine protein (by dipstick). ^cThe 2012 KDIGO Clinical Practice Guideline recommends glucocorticoid therapy for the first episode of glucocorticoid-sensitive INS over a total period of 3–6 months

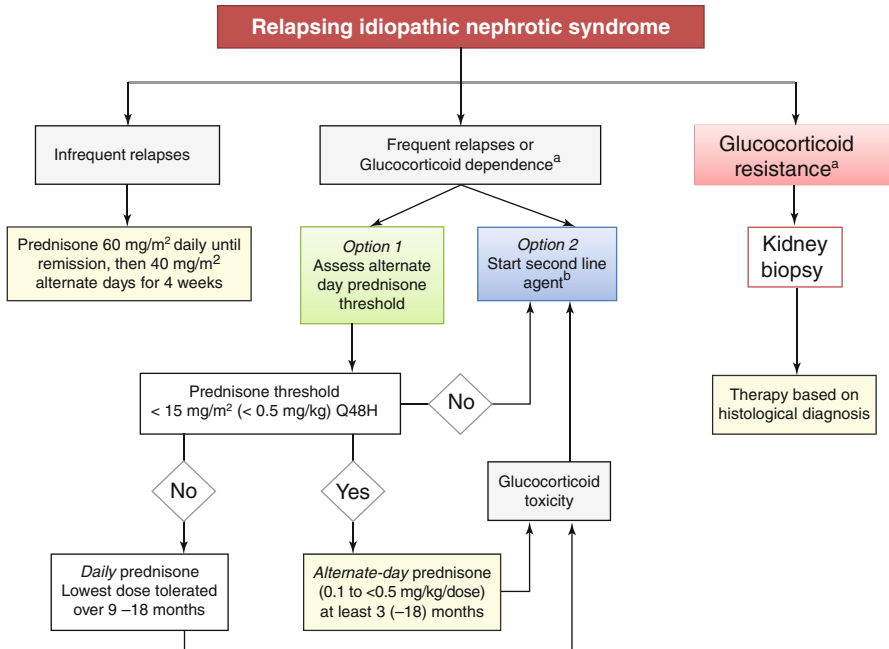


Fig. 3.5 Treatment choices in patients with relapsing idiopathic nephrotic syndrome^a. ^aAs defined in Box 3.3. ^bSee Fig. 3.6 and Table 3.4

- Prednisone remains the only medication to effect remission quickly in patients with glucocorticoid-sensitive, relapsing INS. Prednisone 60 mg/m² per day (see above) usually achieves urinary remission within 7–10 days. Once urine is protein-free for three consecutive days, daily prednisone is switched to a single morning dose of 40 mg/m² (~1.5 mg/kg) on alternate days for 4 weeks and then stopped (Fig. 3.5).

Frequent Relapses and Glucocorticoid (Steroid) Dependence

- Upon achieving remission with daily high-dose prednisone, patient is switched to alternate-day prednisone as above. However, there is no clear consensus about the best long-term approach.
- Option 1: identification of a “threshold” dose of prednisone. Alternate-day prednisone is tapered to 0.5 mg/kg every 48 h. If stable, taper is continued until a dose is reached that still prevents relapses. When a relapse occurs, aim at a maintenance dose just above the last dose where the patient relapsed and continue this dose for 6 months.
- Option 2: introduction of second-line agent, usually in conjunction with prednisone tapering, intended to minimize long-term glucocorticoid adverse effects (Fig. 3.5).

Glucocorticoid Adverse Effects

- Prednisone and prednisolone have similar potency (1:1 conversion) and toxicity profiles.
- “Threshold” for glucocorticoid toxicities varies among individuals.
- Controversy about safety of long-term glucocorticoid at low dose.
- Monitor patients receiving long-term prednisone (see Table 3.3).

Table 3.3 Major adverse effects of glucocorticoids

Organ system	Adverse effect	Remarks
Skin, soft tissue	Skin thinning, striae, purpura, acne, alopecia, hypertrichosis	Dose and duration dependent, within first 2 months of treatment. May occur with 7.5 mg/1.73 m ² /day
	Cushingoid, weight gain (increased appetite)	
Eye	Posterior subcapsular cataract	Noted in 10–38 % of children treated chronically Generally bilateral, develops slowly, may stabilize with lowering of prednisone dose Dose and duration dependent (no minimal safe dose) Annual ophthalmological exam
Cardiovascular	Fluid retention, blood pressure rise	Mineralocorticoid effect
	Ischemia, heart failure	Accelerated atherosclerosis (elevated lipoprotein levels)
Bone	Osteoporosis, avascular necrosis of bone (AVN), vertebral fractures	May occur with “normal” bone mineral density (accumulation of microfractures) Supply vitamin D, calcium supplements
Muscle	Myopathy	Proximal motor weakness upper and lower extremities
Growth	Impaired growth	
GI tract	Gastric ulcer, GI bleeding	Elevated in combination with NSAIDs. Patients may benefit from addition of ranitidine or proton pump inhibitor (e.g., lansoprazole)
CNS	Mood swings, insomnia, pseudotumor cerebri	Mood changes (euphoria, depression) occur within days of treatment
Endocrine	Hyperglycemia, diabetes	Dose dependent; may need insulin injections; reversible with glucocorticoid discontinuation
	Growth retardation	More with daily than alternate-day dosing Some loss of height can be permanent Monitor height Q 3 months
Immune system	Suppresses proinflammatory cytokines and phagocyte function	Avoid live virus vaccines if prednisone dose >20 mg/1.73 m ² /day for ≥14 days Risk of severe varicella, tuberculosis exacerbation

- *Methylprednisolone* is derived from hydrocortisone. The biological $T_{1/2}$ is 12–36 h, relative potency $1.25\times$ versus prednisolone, suitable for IV use.
- *Dexamethasone* is a fluoridated glucocorticoid with a biological half-life of 36–72 h, anti-inflammatory potency ratio 6.7 versus prednisolone, and minor mineralocorticoid effects (less sodium retention).
- *Deflazacort* is an oxazoline derivative and prodrug of prednisolone that has been claimed to cause less adverse effects during long-term use than prednisone/prednisolone. Based on the potency ratio of deflazacort versus prednisolone of 1.28, the initial dose is 1.5 mg/kg/day followed by down titration according to clinical need. It is not widely prescribed due to cost and limited availability and experience.

Second-Line Agents and Strategies (Fig. 3.6)

- Second-line agents are introduced to avoid long-term glucocorticoid related adverse effects or as alternative for glucocorticoid resistance. A summary of second-line drugs is given in Table 3.4.

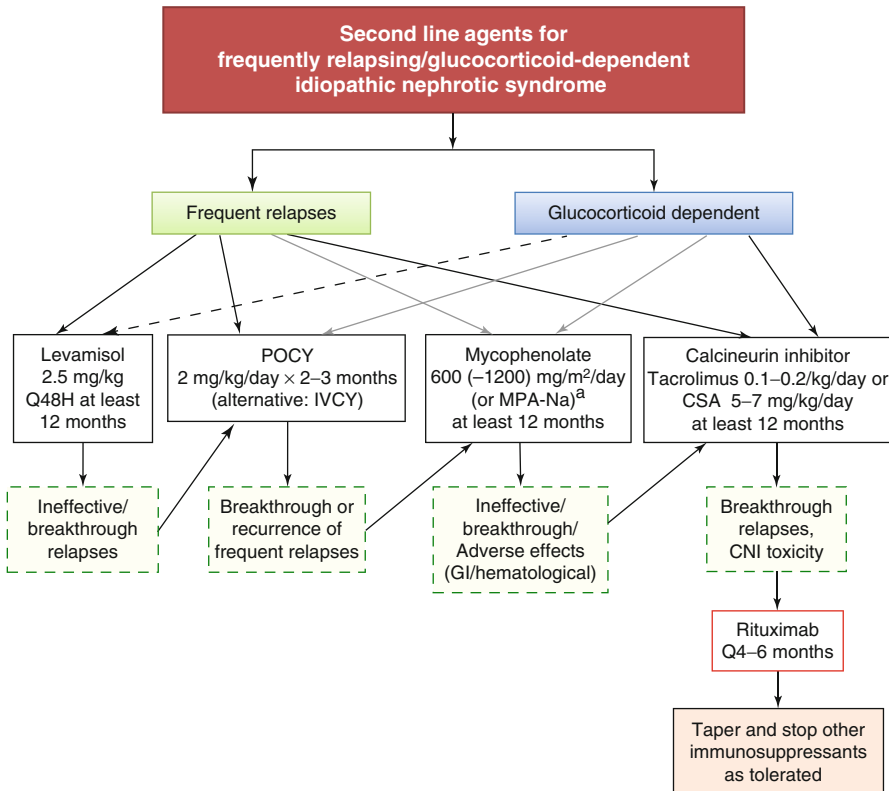


Fig. 3.6 Algorithm for second-line agents for frequently relapsing/glucocorticoid-dependent idiopathic nephrotic syndrome. *Switch from the prodrug MMF to MPA-sodium may alleviate MMF-induced diarrhea and oral ulcers. CNI calcineurin inhibitor, CSA cyclosporin A, IVCY intravenous cyclophosphamide, MPA-Na mycophenolate-sodium, POCY oral cyclophosphamide

Table 3.4 Second-line drugs for idiopathic nephrotic syndrome (MCNS, FSGS)

Drug	Dose [trough level]	Important adverse effects	Remarks
Levamisole	2–2.5 mg/kg on alternate days	Neutropenia, flu-like symptoms, skin rash, gastrointestinal symptoms	Limited availability, not recommended for glucocorticoid-resistant nephrotic syndrome Monitor CBC and differential Q 6–8 weeks
Cyclophosphamide ^a	2–3 mg/kg/day for 8–12 weeks (POCY)	Neutropenia, anemia, gonadal toxicity (more in males than in females) Less frequent: thrombocytopenia, transient alopecia. Hemorrhagic cystitis (with higher doses and insufficient fluid) Hemorrhagic cystitis (rare with this dose and good hydration)	Start POCY after induction of remission. Cumulative dose over lifetime ≤ 168 mg/kg to reduce risk of gonadal toxicity (equals 12 weeks of 2 mg/kg) Monitor CBC Q2wks and stop or reduce dose when absolute neutrophils $< 1.5 \times 10^9/l$
Cyclosporine A (CSA)	500 mg/m ² IV pulses every 4 weeks (6 doses) (IVCY)	Nephrotoxicity, hypertension, hepatotoxicity, hyperkalemia, hypomagnesemia, gingival hyperplasia, hirsutism, tremor	Ensure pre- and post-hydration (IV or PO 2,500 ml/m ² /24 h) Possibly better tolerated than POCY Indicated where oral therapy is not reliable
Tacrolimus	5–7 mg/kg/day \div q12h [100–150 ng/ml] 0.1–0.25 mg/kg/day \div q12h [5–8 ng/ml]	Nephrotoxicity, hypertension, hepatotoxicity, hyperkalemia, hypomagnesemia, gingival hyperplasia, hirsutism, tremor Nephrotoxicity, hypertension, hepatotoxicity, impaired glucose tolerance, hyperkalemia, hypomagnesemia, tremor	Once stabilized, reduce to lowest effective dose Monitor creatinine, electrolytes
Mycophenolate mofetil (MMF)	600–1,200 mg/m ² /day \div BID	Gastrointestinal (colitis, oral aphthous ulcers), anemia, neutropenia	Once stabilized, reduce to lowest effective dose. Monitor creatinine, electrolytes
Rituximab (RTX)	375 mg/m ² per infusion	Allergic-type (cytokine release) reaction with first infusion. Suppression of de novo antibody responses. Suspected risk of JC virus progressive multifocal leukoencephalopathy	Dose decrease or discontinuation if ANC $< 1.3 \times 10^9/l$. Teratogenicity (pregnancy risk) 1–2 doses 1 week apart. If possible, induce remission before initiating RTX. Relapse may occur with recovery of peripheral B cells

^aA alternative alkylating agent (chlorambucil, 0.1–0.2 mg/kg/day PO \times 8 weeks) has similar efficacy, but a lower safety margin than cyclophosphamide (malignancy risk, azoospermia)

- Treatment with second-line drugs depends on availability and affordability, adverse effect profile, physician comfort and family preference.
- Literature and common practice suggest efficacy of (oral) alkylating agents in patients with frequently relapsing or glucocorticoid-dependent nephrotic syndrome (oral cyclophosphamide [POCY], chlorambucil). The reported duration of remission after POCY varies. Early relapses after an alkylating agent are more common in SDNS and FSGS than in FRNS. Although affordable and widely available, there are concerns of drug safety, specifically gonadotoxicity, bone marrow suppression, and severe infection.
- The efficacy of *calcineurin inhibitors* (CNI) is firmly established. Tacrolimus lacks the adverse cosmetic effects of cyclosporin A (CSA), but the latter is more affordable. Both are similarly effective. Many centers perform a renal biopsy after 24 months of CNI treatment.
- *Mycophenolic acid*: diarrhea and colitis due to mycophenolate mofetil (MMF) may be alleviated by switching to mycophenolate sodium (MPA-Na). Note that 1,000 mg MMF is equivalent to 720 mg MPA-Na.
- Experience with *rituximab* (RTX), a monoclonal antibody targeting CD20⁺ B lymphocytes, is still evolving. Costs and uncertainties about long-term infection risks need be considered. RTX appears to have a long-lasting effect in patients with frequently relapsing and glucocorticoid-dependent nephrotic syndrome. Patients who relapse immediately after the recovery of B cells may receive additional (preemptive) RTX infusions after 5–6 months. Patients may discontinue or substantially reduce current second-line agents. Adverse effects include infusion-related allergic-type reactions and delayed onset neutropenia and lung injury. JC virus progressive multifocal leukoencephalopathy has been associated with rituximab treatment in a few patients.

Management of Glucocorticoid (Steroid)-Resistant Idiopathic Nephrotic Syndrome (SRNS)

- Chances of remission diminish drastically after 3 weeks of high-dose daily prednisone treatment. Preparations should be made for a kidney biopsy and genetic testing to avoid excess glucocorticoid toxicity.
- Kidney biopsy is mandatory in patients who do not achieve remission after 4 weeks of prednisone treatment with or without a short course (3 pulses) of 10 mg methylprednisolone (Fig. 3.5).
- The majority of patients with SRNS will have FSGS, diffuse mesangial proliferation, or MCNS by biopsy. The differential diagnoses include membranoproliferative (mesangiocapillary) glomerulonephritis (MPGN) and membranous nephropathy (MN).
- Children (or adolescents) with pathogenic mutations of genes encoding structural podocyte proteins do not benefit from immunosuppressive therapies but require supportive treatment and frequent monitoring. Examples are podocin (*NPHS2*) (in children), α -actinin 4 (*ACTN4*), and transient receptor potential cation channel type 6 (*TRPC6*) mutation (in adolescents and young adults).

- *Methylprednisolone or dexamethasone pulses* with cyclophosphamide have been used in patients where induction of remission has been difficult to achieve (so-called Mendoza protocol). The 2012 KDIGO guideline advises against the use of cytotoxic agents for SRNS.
- In an attempt to minimize overall toxicity, the following modified protocol is proposed for patients with SRNS (Fig. 3.7):
 - Glucocorticoid pulse therapy with IV methylprednisolone (3 pulses of 10 mg/kg Q 48 h) or PO/IV dexamethasone (three doses of 1.5–3 mg/kg or 50–100 mg/m² Q 3 days).
 - Alternate-day PO prednisone.
 - Calcineurin inhibitor (tacrolimus or CSA), to be started in the upper dose range with target (trough) plasma concentrations (C₀) of 5–10 or 150–250 ng/ml, respectively.
 - If patient enters remission, taper prednisone. Adjust CNI dosage according to therapeutic effect.
 - In case of CNI toxicity, consider reducing CNI dose or switch to alternative CNI. Addition of MMF may spare glucocorticoid or CNI.
 - Rituximab does not appear to be effective in the majority of patients resistant to glucocorticoids and other second-line agents.

Adjunctive Therapies

- Patients with glucocorticoid-dependent and glucocorticoid-resistant nephrotic syndrome may develop hypertension as a treatment complication or with progressive chronic kidney disease. Treatment consists of sodium restriction, diuretics, and blockade of the renin–angiotensin system with ACE inhibitor (ACEi) and/or angiotensin receptor blocker (ARB).
- ACEi, such as enalapril, and ARB, such as losartan, decrease proteinuria and are a useful adjunct for patients with SRNS. The antiproteinuric effect is dose dependent. ACEi and ARB can lead to a reversible rise of serum creatinine and potassium and to anemia.
- Lipid-lowering drugs such as the HMG-CoA reductase inhibitors (statins, e.g., atorvastatin) are used in glucocorticoid-resistant patients.
- Consider thrombosis prophylaxis.
- Vitamin D, specifically for patients receiving long-term glucocorticoid therapy or prophylaxis.

Management of Edema, Fluid Balance, and Hypertension

- *Sodium salt restriction.* “No added salt” and avoidance of foods rich in sodium (papads, pickles, baked products, dried and salted fish or meat) to control edema formation and blood pressure.
- *Fluid management.* Do not miss hypovolemia (may be difficult to diagnose in edematous patient). It can lead to acute kidney injury and thrombosis. In children with vomiting, diarrhea, fever, or sepsis, 10–20 ml/kg of 5 % albumin or other colloids are effective.

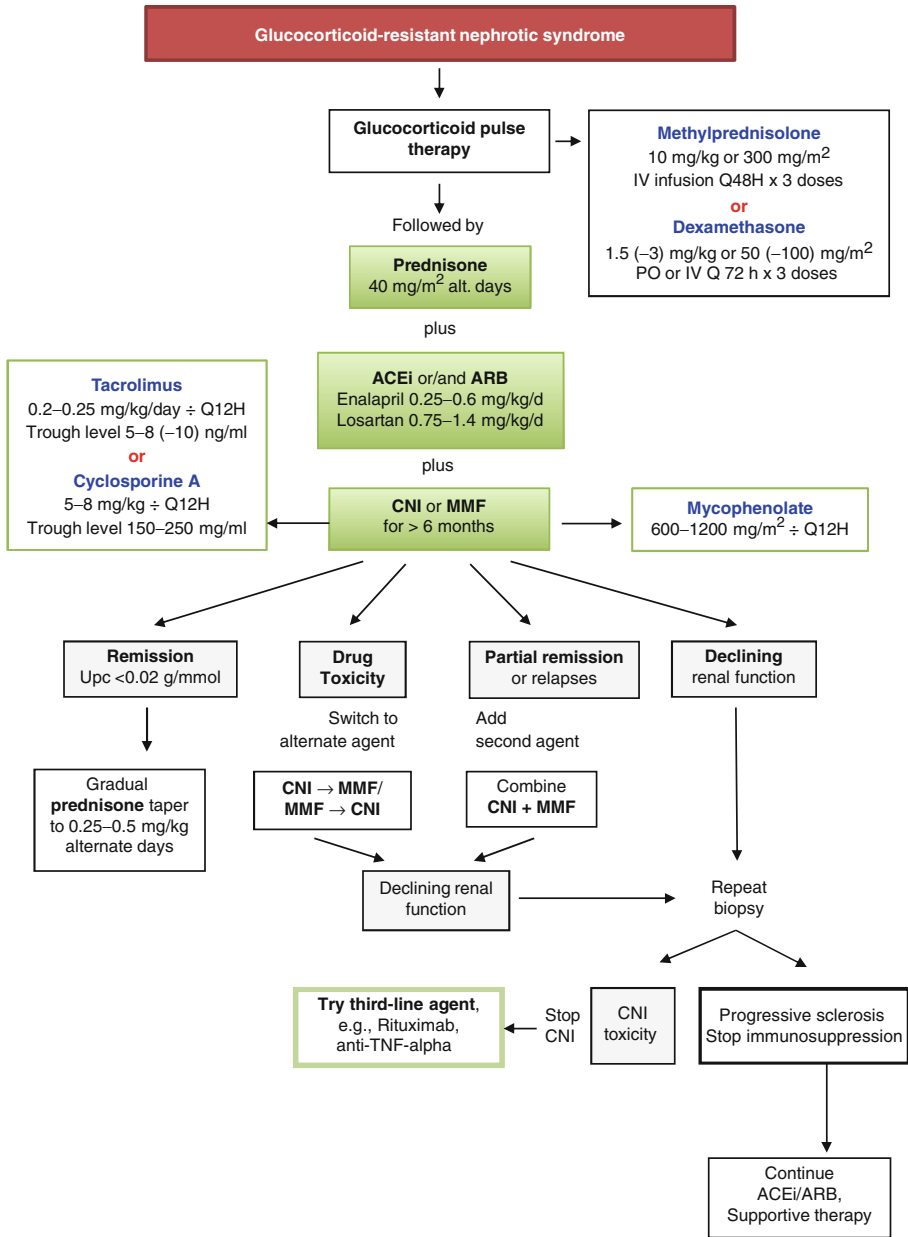


Fig. 3.7 Algorithm for treatment of glucocorticoid-resistant nephrotic syndrome

- **Albumin infusion.** Temporarily increases intravascular oncotic pressure and improves renal perfusion. 0.5–1 g/kg of salt-poor 20 or 25 % albumin over 4 h in patients who are volume depleted and have severe edema. Albumin is often combined with IV furosemide 0.5–1 mg/kg once or twice during and at the end of the albumin infusion. Note that albumin is rapidly lost in the urine, and additional doses may be needed.
- **Diuretics.** If albumin is unavailable, diuretics alone can be given when edema, pleural effusion, or severe ascites cause respiratory distress and scrotal swelling/skin breaks. *Exercise caution* and ensure that child is not intravascularly depleted. Regimens include intermittent IV furosemide at doses up to 1–2 mg/kg every 8–12 h with careful monitoring of vital signs in hospital or as a continuous infusion of 0.05 mg/kg/h (titrate to effect). Monitor renal function and electrolytes.
- **Outpatients** may receive oral furosemide, with or without a *thiazide* (hydrochlorothiazide 1–2 mg/kg/day).
- **Metolazone** (0.2–0.4 mg/kg/d ÷ QD or BID) is a thiazide-like diuretic with action at both the proximal and distal tubules.

Complications in Children with Primary Nephrotic Syndrome

Infections

- In the pre-antibiotic and pre-steroid era, many children with nephrotic syndrome died of infection and/or malnutrition. Bacterial infections, commonly due to encapsulated gram-positive and or gram-negative bacteria, specifically *S. pneumoniae*, *H. influenzae*, *E. coli*, and *K. pneumoniae*, have been attributed to the urinary loss of IgG and complement components. They present as spontaneous bacterial peritonitis, septicemia, cellulitis, diarrhea, upper and lower respiratory, or urinary tract infection.
- If a serious bacterial infection is suspected, cultures must be taken and broad-spectrum antibiotics initiated until bacterial culture results become available (see Table 3.5).

Table 3.5 Infections in children with nephrotic syndrome and antibiotic therapies

Presentation	Organism	Choice of antibiotics
Peritonitis	<i>S. pneumoniae</i> , group A hemolytic streptococci (<i>S. pyogenes</i>), <i>E. coli</i>	Cefotaxime or ceftriaxone for 7–10 days ^a Ampicillin + aminoglycoside for 7–10 days
Pneumonia	<i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>S. aureus</i>	PO amoxicillin, amoxicillin/clavulanate (co-amoxiclav) IV ampicillin and aminoglycoside, or cefotaxime/ceftriaxone for 7–10 days
Cellulitis	Staphylococci, <i>S. pyogenes</i> , <i>H. influenzae</i>	PO cloxacillin, cephalexin, or amoxicillin/clavulanate (co-amoxiclav) Severe/complicated cellulitis IV/IM ceftriaxone for 7–10 days ^a
Fungal infections	<i>Candida</i> , <i>Aspergillus</i> spp.	Skin, mucosa: PO fluconazole for 10 days Systemic: IV fluconazole or amphotericin for 14–21 days

^aInitial therapy may be parenteral for 5 days; once patient is nontoxic and accepting orally, the medication may be administered orally

- Antibiotic prophylaxis for all children with nephrotic syndrome is not recommended but may be indicated in individual patients and under specific circumstances.
- Common viral infections, mostly of the upper respiratory tract, may trigger relapses. Exposed children should be monitored for proteinuria.
- Glucocorticoids and other immunosuppressants increase the susceptibility to life-threatening varicella-zoster virus (VZV) infection. Nonimmune children should receive immunoglobulin (VZIG) within 96 hours of exposure and/or acyclovir (intravenously, if poor absorption or compliance is suspected).
- Immunosuppressed patients may develop fungal infections, such as oral thrush and *Candida* esophagitis, tinea versicolor, and tinea corporis.
- Note that immunosuppressive therapy can mask clinical signs of infection.

Hypercoagulopathy

- Nephrotic syndrome increases the risk of thrombosis and thrombosis-related complications, such as deep venous thrombosis, renal venous thrombosis, pulmonary emboli, and cerebral infarction.

Acute Kidney Injury

- May be due to intravascular volume depletion (prerenal failure) or renal hypoperfusion, use of nephrotoxic drugs, renal venous thrombosis, or sepsis.

Electrolyte Disturbances

- Spurious hyponatremia may be seen due to hyperlipidemia or where the laboratory measures electrolytes by flame photometry. True hyponatremia may develop due to diuretics.

3.3.1.7 Prognosis

- Seventy percent of patients with glucocorticoid-responsive nephrotic syndrome relapse at least once. Around 50 % of the latter will have frequent relapses or become glucocorticoid dependent.
- Outcome is often poor in glucocorticoid-resistant patients (SRNS). They are at risk of chronic or end-stage kidney disease and recurrence of nephrotic syndrome after renal transplantation (see Sect. 3.3.3).

3.3.1.8 Long-Term Management of Children with Nephrotic Syndrome

Nutrition

- No change of diet other than sodium salt restriction is needed in children with initial presentation or relapse of nephrotic syndrome and normal kidney function.
- Prednisone stimulates appetite and weight gain. Encourage physical activity and avoidance of calorie-rich snacks and soft drinks.
- Patients with persistent proteinuria receive normal protein intake in a balanced diet.

Immunization of the Child with Nephrotic Syndrome

- Live vaccines are contraindicated in children receiving immunosuppressive or cytotoxic medication (e.g., varicella, measles, mumps, rubella, rotavirus, oral polio).
- Live vaccines should be deferred until
 - Prednisone dose is <1 mg/kg/day (<20 mg/day) or <2 mg/kg/dose on alternate days (<40 mg/dose)
 - More than 3 months after the last cyclophosphamide or chlorambucil dose
 - More than 4 weeks after the last calcineurin inhibitor or mycophenolate dose
- Immunosuppression is not a contraindication for inactive (killed) vaccines, but the vaccine response is likely to be reduced.
- *Hepatitis B* vaccine should be given to all unvaccinated or non-immune children
 - Higher glucocorticoid doses at the time of immunization appear to diminish the short-term, but not the long-term vaccine response
- Immunization, particularly against encapsulated bacteria including *H. influenzae*, *S. pneumoniae* and *N. meningitidis* should be initiated, if they have not been obtained previously.
- *Pneumococcal* vaccine: Unimmunized children up to 2 years of age should receive 2–4 doses of the 13-valent (or at least the 7-valent) conjugate pneumococcal vaccine. For previously unimmunized children between 2 and 5 years old, give two doses of the available conjugate vaccine 4–8 weeks apart, followed 8 weeks later by administration of one dose of the 23-valent polysaccharide vaccine. Children older than 5 years receive a single dose of the 23-valent polysaccharide vaccine. Revaccination every 5 years should be considered for children who continue to have active nephrotic syndrome.
- Not all pneumococcal serotypes are included in the vaccines, and antibody levels may fall during a relapse; hence, previously vaccinated children may develop pneumococcal peritonitis and sepsis, as well as infections by other pathogens, despite having been vaccinated.
- *Seasonal Influenza vaccines* are given to patient and family to reduce preventable relapses and morbidity.
- *Varicella* vaccine is given as 2 doses, 1–3 months apart.
- Defer *oral polio vaccine* (OPV) to patients and to siblings unless patient is in stable remission off immunosuppressants or can be isolated from vaccinated family members.

Adrenal Suppression and Dosing of Glucocorticoids During Stress

- Patients who have received high-dose glucocorticoids daily for more than 2 weeks in the past 1 year or those with a morning cortisol level <10 nmol/l require supplementation of cortisol during surgery, including dentistry, anesthesia, or serious infections or burns (Box 3.5).
- A physiological hydrocortisone dose is 10 mg/m²/day corresponding to 2.5 mg/m²/day of prednisolone and 0.25 mg/m²/day of dexamethasone.

Box 3.5 Recommendations for Patients with Adrenal Insufficiency

Name of patient _____

Record # _____ Date of birth _____

Weight _____ kg Height _____ cm Surface area _____ m²

IN CASE OF STRESS (temperature >38.5 C, infection, diarrhea, surgery)

- Double each dose of prednisone/prednisolone or hydrocortisone for the duration of the episode or give 2.5 mg/m² BID (AM, afternoon)
- Triple each dose for a more important stress (e.g. temperature >39 C) or give 3.75 mg/m² BID (AM, afternoon)

IN CASE OF VOMITING: give dose parenterally in HOSPITAL

- Hydrocortisone 50 mg/m²/dose (maximum 50 mg/dose)
- = _____ mg hydrocortisone IV or IM with volume expansion (saline bolus) Q 4–6 h until vomiting has stopped

IN CASE OF ADRENAL CRISIS (fatigue, weakness, hypotension, tachycardia, abdominal pain, nausea, vomiting):

- Patient has to go to HOSPITAL immediately.
- Administer hydrocortisone IV or IM with volume expansion (saline bolus). Repeat Q 4–6 h until patient has recovered and is able to take PO medication

For questions, contact _____

At the _____ (hospital/office) Tel _____

Date Name of physician Signature License #

3.3.1.9 Support and Information for Patients and Families

- Provide written information about nephrotic syndrome (e.g., website)
- Examples:
 - Teach Albustix testing of (morning) urine and early detection of relapses.
 - Provide diary (calendar) with medication dosing schedules, appointments, and space to enter urine dipstick results and record clinical events.
 - Patients may create their own manual or electronic spreadsheets.

- Provide form sheet for “Recommendations for patients with adrenal insufficiency” to be carried in wallet (Box 3.5).
- Avoid self-medication. Encourage patient/family to speak to designated contacts (MD, nurse).

3.3.2 Minimal Change Nephrotic Syndrome (MCNS)

- The majority of children with INS have MCNS (MCD).
- MCNS incidence peaks between 2 and 6 years of age.
- Tell-tale signs are periorbital and dependent edema. Ascites, pleural effusion, and scrotal or labial edema may also occur. Patients are usually not hypertensive. Upto 30 % have microhematuria.
- Probability of MCNS (and glucocorticoid responsiveness) is greater than 90 % for a young child with typical features of nephrotic syndrome. Hence, kidney biopsy is reserved to children with unsatisfactory glucocorticoid response and/or “atypical” presentation.
- On light microscopy, the glomeruli are normal with normal capillary walls and normal cellularity. A mild mesangial hypercellularity may be noted. Immunofluorescence microscopy is negative, although some cases show deposits of IgM, IgG, and C3. The significance of IgM deposits (and whether they represent a separate entity) is not known. Ultrastructural changes are always present in MCNS, involving podocytes and mesangial cells. Podocyte foot process fusion is constant and generalized.
- MCNS, diffuse mesangial proliferation, and focal segmental glomerulosclerosis (FSGS) are considered separate diseases because of differences in response to glucocorticoids and subsequent clinical course. However, some think of MCNS and FSGS as a spectrum of the same disease. Transition of MCNS to FSGS has been reported.
- More than 90 % patients with MCNS will respond to glucocorticoid therapy. Proteinuria will resolve within 10 days of initiation of glucocorticoid therapy in the majority of children. In late responders, it may take up to 4 weeks.
- Relapses are common and are often triggered by viral respiratory tract infections. Seventy percent of glucocorticoid-responsive nephrotic syndrome will have at least one relapse. Half of these will have frequent relapses or become glucocorticoid-dependent. Relapses of proteinuria continue till onset of puberty or even into adulthood.
- Glucocorticoid sensitivity is the most important prognostic indicator. Renal function remains normal in children with (frequent) relapses who do not exhibit secondary glucocorticoid resistance.

3.3.3 Focal Segmental Glomerulosclerosis (FSGS)

- FSGS is a histological description without etiological specificity.
- It is characterized by proteinuria with or without full-blown nephrotic syndrome; patient may demonstrate “atypical” features, such as hypertension and hematuria, poor response to glucorticoids and progression to CKD. Progression

to end-stage renal disease. Depending on the populations studied, up to 70 % of patients with FSGS fail to respond to glucocorticoid therapy.

- Risk factors for progression to CKD include black ethnicity, poor response to glucocorticoids and other immunosuppressive agents, persistence of proteinuria, elevated serum creatinine at presentation, and importance of interstitial fibrosis by kidney biopsy.
- FSGS may be primary or secondary. Causes of secondary FSGS include hyperfiltration injury (decreased nephron mass), reflux nephropathy, morbid obesity, sickle cell nephropathy, HIV or parvovirus infection, and heroin abuse.
- There is a concern that the incidence of FSGS is increasing worldwide.
- Genetic forms of FSGS have been described. They are generally glucocorticoid resistant (see Sect. 3.3.4). FSGS lesions due to known mutations do not recur in the transplanted kidney unlike other forms of primary FSGS.
- Renal biopsy shows segmental scarring involving some but not all of the sampled glomeruli. Affected glomeruli are initially localized in deep cortex and may be missed. The glomerular scars are composed of collapsed glomerular capillaries, adhesions between the tuft and Bowman's capsule, and hyaline deposits. Podocyte dysregulation is accompanied by podocyte detachment from the glomerular basement membrane. Uninvolved areas of the glomerulus appear normal.
- A pathological classification of FSGS has been proposed – the “Columbia” classification – with five histological variants: “FSGS not otherwise specified,” perihilar variant, cellular variant, tip variant, and collapsing variant. Glomerular tip variants have been associated with better outcomes and the collapsing variant with the worst outcome.
- Collapsing glomerulopathy is a distinct form of FSGS. These lesions are also seen in HIV associated nephropathy, recurrent nephrotic syndrome after renal transplantation, and parvovirus B19 or CMV infection. The prognosis is poor.
- The management of FSGS can be challenging. Specific treatment options include high-dose methylprednisolone, intravenous cyclophosphamide, calcineurin inhibitors, mycophenolate mofetil, rituximab, anti-TNF-alpha antibody, plasmapheresis, and ACE inhibitors/ARB to reduce proteinuria (see Fig. 3.7).
- Recurrence risk of FSGS after renal transplantation is highest in patients with disease onset between 6 and 12 years of age and progression to ESRD within 18 to 36 months in the absence of an identifiable genetic mutation (see also Chap. 11).

3.3.4 Inherited Forms of Nephrotic Syndrome

3.3.4.1 Introduction

- Defects in various genes have been associated with the development of nephrotic syndromes that are generally glucocorticoid-resistant (Table 3.6)
- Affected individuals may present postnatally (“congenital nephrotic syndrome”) or during childhood or adolescence (“late-onset FSGS”)
- The percentage of children with primary nephrotic syndrome and FSGS due to currently identifiable genetic mutations beyond the first year of life is <10 %

Table 3.6 Genetic forms of nephrotic syndrome

Gene locus	Inheritance	Encoded protein	Protein localization	Clinical manifestation
<i>NPHS1</i>	AR	Nephrin	Podocyte and slit diaphragm	Congenital (Finnish-type) nephrotic syndrome
<i>NPHS2</i>	AR	Podocin	Podocyte and slit diaphragm	Childhood-onset FSGS
<i>PLCE1 / NPHS3</i>	AR	Phospholipase C ϵ -1	Podocyte	Non-syndromic DMS (28 % all DMS), FSGS
<i>WT1 / NPHS4</i>	AD	Wilms' tumor 1 protein	Podocyte (transcription factor)	Denys–Drash (DMS), Frasier (FSGS)
<i>LAMB2 / NPHS5</i>	AR	Laminin β 2	GBM	Pierson syndrome (DMS), isolated FSGS
<i>ACTN4 / FSGS1</i>	AD	α -actinin 4	Podocyte	Adult-onset FSGS (incomplete penetrance, slow progression to ESRD)
<i>TRPC6 / FSGS2</i>	AD	Transient receptor potential cation channel 6	Podocyte	Adult-onset FSGS
<i>CD2AP / FSGS3</i>	AR or AD	CD2-associated protein	Podocyte and slit diaphragm	Early and adult-onset FSGS
<i>INF2 / FSGS5</i>	AD	Actin polymerization regulatory protein inverted formin 2	Podocyte	Familial FSGS (variable penetrance, onset from child- to adulthood)
<i>LMX1B</i>	AD	LIM homeobox transcription factor 1-beta	Podocyte	Nail patella syndrome: dystrophic nails, absent or hypoplastic patella, iliac horns, FSGS, moth-eaten appearance of mesangium and GBM
<i>MYH9</i>	AR	Non-muscle myosin heavy chain IIA	Podocyte	FSGS (May–Hegglin, Sebastian, Fechtner, and Epstein syndromes)
<i>SCARB2</i>	AR	Lysosome membrane protein 2	Lysosome	Syndromic FSGS
<i>SMARCAL1</i>	AR	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A-like protein 1	Podocyte	Schimke immuno-osseous dysplasia

Abbreviations: AD autosomal dominant, AR autosomal recessive, DMS diffuse mesangial sclerosis, FSGS focal segmental glomerulosclerosis, GBM glomerular basement membrane

- Affected genes encode for proteins involved in the development, structure and function of podocytes
- All hereditary proteinuric syndromes show typical flattening (effacement) of podocyte foot processes and loss of a normal slit diaphragm
- They usually do not respond to glucocorticoids or other immunosuppressants and do not recur in the transplanted kidney

3.3.4.2 Congenital Nephrotic Syndrome (CNS)

- Congenital nephrotic syndrome (CNS) is defined as the presence of nephrotic syndrome within the first 3 months of life
- CNS can be inherited or caused by spontaneous mutation, or acquired due to maternal (transplacentally transmitted) antibodies or cytokines, or congenital infections (Box 3.6)

3.3.4.3 Finnish-Type Congenital Nephrotic Syndrome (FCNS)

- Autosomal recessive disorder with highest incidence in Finland
- It is caused by a defect in the *NPHS1* gene, which codes for the protein nephrin, a podocyte transmembrane protein and structural component of the slit diaphragm between podocyte foot processes
- FCNS is resistant to immunosuppressive therapy
- Infants with FCNS are born prematurely; placental weight >25 % of their birth weight; edema is present at birth or shortly afterward
- Massive proteinuria leads to malnutrition and poor somatic growth
- Patients are highly susceptible to bacterial infections including peritonitis, pneumonia and cellulitis
- Very low serum albumin levels and net loss of immunoglobulin G (IgG), vitamin D, thyroglobulin-binding protein (leading to hypothyroidism), antithrombin III and transferrin

Box 3.6 Etiologies of Congenital Nephrotic Syndromes

Primary (genetic)	Identifiable or suspected genetic mutation	Finnish-type (FCNS)
		Denys-Drash syndrome (DDS)
		Frasier syndrome (FS)
		WAGR syndrome
		Galloway-Mowat syndrome
		Secondary Primary FSGS
Secondary (acquired)	Transplacental transmission (very rare)	Fetal nephrotic syndrome due to maternal antibodies or cytokines to (e.g. FSGS, SLE)
		Congenital infection
	Cytomegalovirus (CMV)	
	Hepatitis B virus (HBV)	
	Rubella virus	
		<i>T. gondii</i> (toxoplasmosis)
		<i>T. pallidum</i> (syphilis)

- Thromboembolic complications are common
- Renal function is normal at birth, but declines after the first year of life
- Histological lesions are characterized by irregular dilatation of the proximal convoluted tubules and increased mesangial matrix and hypercellularity, leading to glomerular sclerosis and interstitial fibrosis
- Genetic analysis obviates need for kidney biopsy
- High amniotic fluid alpha-fetoprotein levels aid in prenatal diagnostic
- Management is challenging: Daily infusions of albumin may be needed, diuretics, gamma globulin infusions, tube feeding for adequate nutrition, thyroxin supplementation, and ACE inhibitor and indomethacin therapy to reduce proteinuria
- Many infants require uni- or bilateral nephrectomy to stop massive protein losses and malnutrition
- No disease recurrence in the graft, parents can be organ donors

3.3.4.4 Denys–Drash Syndrome (DDS)

- DDS presents in infancy with proteinuria or nephrotic syndrome and ambiguous genitalia in a chromosomally male (46, XY) child
- DDS is caused by a heterozygous, generally spontaneous, point mutation of the Wilms tumor suppressor gene (*WT1*) resulting in loss or altered structure of the functionally important zinc finger domain (encoded by exons 8 and 9). *WT1* is also a critical regulator of kidney and gonadal development
- The typical histological lesion is diffuse glomerular mesangial sclerosis, identified by kidney biopsy
- The glomerular lesion progresses to end-stage renal failure by 4 years of age
- The Wilms tumor risk is 90 %
- Frequent, proactive echographic monitoring (e.g. every 3 months) and nephrectomy with the first appearance of suspected tumor lesions are recommended. Preemptive (pretransplant) bilateral nephrectomy if hemodialysis or peritoneal and back-up hemodialysis are feasible
- Most centers wait 1 year to kidney transplantation following Wilms tumor removal (and chemotherapy)

3.3.4.5 Frasier Syndrome (FS)

- FS should be suspected in any child with glucocorticoid-resistant nephrotic syndrome and ambiguous genitalia, and in phenotypically females with nephrotic syndrome and amenorrhea (male pseudohermaphroditism: normal-appearing female external genitalia, streak gonads 46, XY karyotype)
- FS is caused by an intronic mutation of *WT1* (intron 9)
- The histopathological lesion is focal segmental glomerulosclerosis
- Proteinuria begins between age 2 and 6 years, progression to ESRD during or after adolescence
- FS is not associated with Wilms tumor, but with an increased risk of gonadoblastoma

3.3.4.6 WAGR Syndrome

- Acronym of Wilms tumor, aniridia, genitourinary malformations, and mental retardation
- WAGR syndrome is caused by a microdeletion in chromosome 11p13 affecting *WT1* and *PAX6* that encode proteins involved in eye development
- Many patients with WAGR syndrome eventually develop ESRD
- Wilms tumor risk is ~50 %

3.3.4.7 Pierson Syndrome (PS)

- PS is characterized by congenital nephrotic syndrome with microcoria and buphthalmos
- It is due to a mutation in *LAMB2* coding for the GBM protein laminin $\beta 2$
- The histopathological lesion is diffuse glomerular mesangial sclerosis
- Patients progress rapidly to ESRD

3.4 Acute Glomerulonephritis

Acute GN, defined by hematuria (characteristically macroscopic), proteinuria, acute renal dysfunction, hypertension and fluid retention, requires an etiological diagnosis. It may follow an acute or sustained focal infection and often involves activation of complement. The course can be self-limited or require immunosuppressive, at times aggressive treatment.

The approach to a child with acute GN is depicted in Fig. 3.8.

3.4.1 Acute Post-Infectious (Poststreptococcal) Glomerulonephritis (APIGN/APSGN)

3.4.1.1 Abstract

- APIGN/APSGN is the most common form of acute glomerulonephritis in childhood.
- *Pathogenesis*: Immunologically mediated, inflammatory disorder of the renal parenchyma that is characterized by alternative complement pathway activation and exudative, proliferative glomerulonephritis. Manifestation after a latent period of 1–3 weeks after upper respiratory tract infection/pharyngitis or 3–5 weeks after pyoderma, caused by group A hemolytic streptococci (*S. pyogenes*) and other infectious organisms.
- *Clinical Features*: Triad of (gross) hematuria, arterial hypertension, and generalized edema (acute nephritic syndrome). Spectrum ranges from microhematuria to nephrotic syndrome, severe renal failure, and encephalopathy or seizures due to hypertension (posterior reversible encephalopathy syndrome, PRES).
- *Investigations*: Basal tests include urinalysis and microscopy (red blood cell casts), serum creatinine, electrolytes, and C3. Plasma C3 is almost always

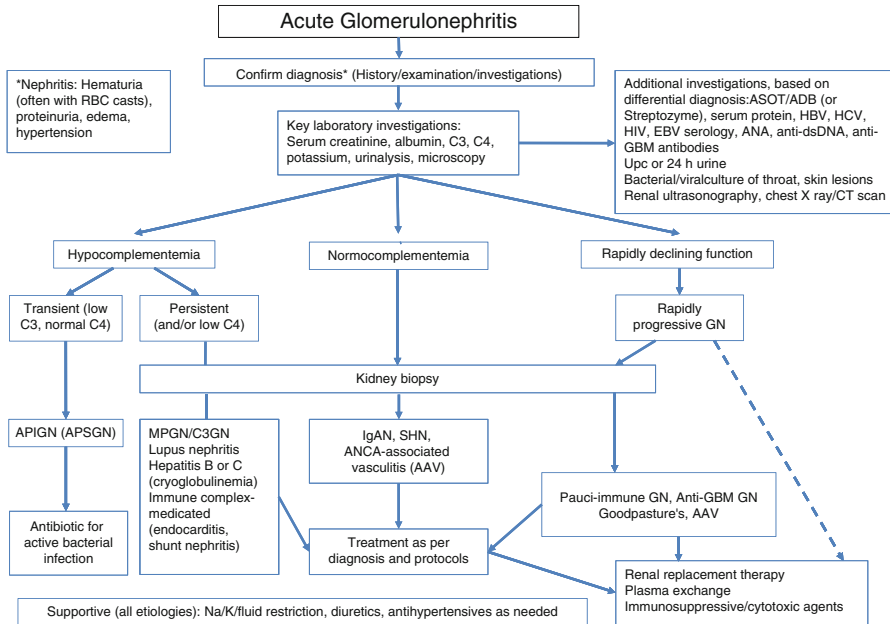


Fig. 3.8 Suggested approach to children with acute nephritis. *Abbreviations:* ASOT anti-streptolysin O titer, ADB anti-DNAse B, GBM glomerular basement membrane, APIGN acute post-infectious glomerulonephritis (GN), APSGN acute post-streptococcal GN, MPGN membranoproliferative GN, LN lupus nephritis, SHN Schönlein–Henoch nephritis

decreased during acute illness. Elevated antistreptolysin (ASOT) or anti-DNAse B (ADB) antibody titers (or streptozyme test) indicate preceding streptococcal infection.

- *Histological Findings:* Kidney biopsy shows endocapillary proliferation by light microscopy, granular deposits of C3 and IgG in capillary loops by immunofluorescence, and typical, large subepithelial “humps” by electron microscopy. Renal biopsy is indicated if C3 remains low after 6–8 weeks and with persisting proteinuria or declining kidney function.
- *Treatment:* Symptomatic therapy, including control of blood pressure and edema. Dialysis, although rarely indicated, is needed for severe AKI with oligoanuria, uncontrolled hyperkalemia, or fluid overload unresponsive to loop diuretics.
- *Antibiotics:* Antibiotic treatment does not change course of (or prevent) disease but may limit spread of nephritogenic strains of β -hemolytic *streptococci*.
- *Prognosis:* Excellent outcome in >95 % of cases. Progression to end-stage renal disease or recurrence of APSGN is extremely rare.

Vignette

A 5-year-old boy presents with acute onset of bloody urine which frightens the family. Parents also report that their child lost energy and appetite over the last 2 days, that he complains of headache and one-time vomiting without diarrhea, and that he looks swollen. He was previously healthy, except that some mosquito bites on his leg became infected about 3 weeks ago.

You quickly determine that the child has moderate facial and limb edema. There is no rash but cellulitis on his left shin. He is afebrile. Blood pressure is 135/95 mmHg, and he appears irritable. You ask for urine and blood samples. While awaiting the results, the child has a seizure.

3.4.1.2 Introduction

Postinfectious glomerulonephritis is one of the earliest described renal diseases. While group A β -hemolytic streptococci (GAS) are responsible for the vast majority of APIGN, other organisms can lead to a similar presentation. APIGN (APSGN) is one of the commonest causes of community-acquired, acute kidney injury in children. The prognosis is excellent in most cases. The exact disease mechanism is still debated.

3.4.1.3 Definition

APSGN is the prototype of an acute nephritic syndrome. It is an immune-mediated, glomerular inflammatory disorder leading to acute kidney injury (AKI), often with gross hematuria, hypertension, and generalized edema. About 85 % of cases follow an infection by beta-hemolytic streptococci. Hence, the terms APIGN and “post-streptococcal GN” (APSGN) are often used synonymously. The hallmark of all forms of APIGN is the transient activation of the alternative complement pathway with subepithelial glomerular deposition of C3 (and IgG/IgM) and depletion of plasma C3.

3.4.1.4 Epidemiology

- APIGN affects school children with a peak from 4–10 years of age.
- The disease burden is highest in resource-poor countries and disadvantaged populations.
- More than 80 % of cases are linked to infections by Lancefield group A (GAS) and occasionally C or G beta-hemolytic streptococci.
- Incidence 9.5–28.5 new cases per 100,000 person-years.
- Glomerulonephritis risk approaches 5 % of pharyngitis and 25 % of pyoderma cases in epidemics of nephritogenic *S. pyogenes* infections.
- The serotype most frequently associated with pyoderma-associated APSGN is M49; others are M2, M42, M56, M57, and M60. Common pharyngitis APSGN-associated M types are 1, 4, (12) and 25. Newer studies use molecular-based

typing of the *emm* gene encoding the hypervariable M protein and multilocus sequence typing.

- APIGN due to streptococcal pharyngitis peaks during winter and early spring; APIGN due to pyoderma peaks in late summer and early fall. The latter is more common in tropical and subtropical regions.
- APIGN occurs at any age but peaks in children ages 6–10 (2–12) years.
- Male to female ratio 2:1.1.
- APIGN is associated with conditions that favor spread of the causative organism.
- Siblings are at risk of developing subclinical nephritis.

3.4.1.5 Etiology and Pathogenesis

- Exact mechanism of glomerular injury is debated.
- Pattern of hypocomplementemia in APIGN reflects activation of the alternative complement pathway (AP): plasma C3, C5, and properdin levels are transiently decreased in the presence of preserved concentrations of C4.
- Current hypotheses:
 - Antibodies bind to streptococcal antigen(s) planted in the glomerular basement membrane leading to alternative complement pathway activation.
 - Two streptococcal proteins, glyceraldehyde phosphate dehydrogenase (also known as nephritis-associated plasmin receptor) and cationic proteinase exotoxin B (SPEB) with its zymogen precursor, have been identified in the GBM of APSGN patients and proposed as pathogenic antigens.
 - M-like and non-M proteins including fibronectin-binding (Fba) and streptococcal collagen-like proteins (Scl) bind complement factor H (CFH) and/or CFH-related protein 1 (CFHR-1), regulators of the C3 and C5 convertases of complement activation pathways. While some of these proteins have been associated with bacterial immune evasion, their role for the pathogenesis of APIGN remains speculative.

3.4.1.6 Clinical Features

- AKI with classical triad of gross hematuria, hypertension, and edema (classical nephritic syndrome).
- The clinical spectrum ranges from asymptomatic microhematuria to severe disease. Complications due to hypertension, renal failure, and cardiac insufficiency (Table 3.7).
- Hypertension (60 %) can be associated with headache, vomiting and altered mental status, hypertensive encephalopathy with risk of seizure, and hypertensive congestive cardiac failure.
- Abnormal urinalysis, transitory hypocomplementemia, and increased ASOT indicate subclinical nephritis (e.g., in siblings).

3.4.1.7 Laboratory Investigations

- Useful investigations are detailed in (Table 3.8)

Table 3.7 Clinical manifestations of APIGN

Condition	Remarks
Hypertension	Headache, vomiting, seizures, somnolence/altered mental status Risk of posterior reversible encephalopathy syndrome (PRES) with visual changes and focal neurological signs
Edema	Facial/periorbital, dependent, or generalized edema (more frequently in young children) Ascites, pleural effusion Cardiac insufficiency (orthopnea, dyspnea, cough, pulmonary crackles/edema, and gallop rhythm)
Hematuria	Dark-brown urine (cola- or tea-colored) in one-third of patients; remainder microscopic hematuria
Proteinuria	Mild to moderate, rarely nephrotic range (>1 g/m ² /day)
Oliguria	Transient oliguria in 50 %, complete anuria rare
Acute kidney injury	Nausea, vomiting fatigue, weakness, pallor
Others	Back pain and abdominal discomfort, fever, weight gain (edema)

Table 3.8 Investigations in APIGN

Investigation	Comments
Urine	Dipstick analysis Hematuria, proteinuria Urine microscopy Red blood cell (RBC) and mixed cellular casts Dysmorphic RBCs Leukocytes (sterile pyuria) Proteinuria <2 g/l in 85 % of cases (U protein/creatinine <2 g/g) Nephrotic presentation may herald poor renal outcome
Complement	Reduced plasma C3 and CH50 in >90 % of cases Normalize within 6–12 weeks after presentation Plasma C4 generally normal
Bacterial/viral identification	Pharyngeal swab Index patient and siblings (opportunity of preventing spread of nephritogenic strain) Culture of beta-hemolytic streptococci Rapid streptococcal antigen test Skin swab Suspected pyoderma Alternative etiologies <i>S. pneumoniae</i> (rare), <i>S. aureus</i> and other non-streptococcal bacteria Viral infections (e.g., EBV, parvovirus B19)

(continued)

Table 3.8 (continued)

Investigation	Comments
Serology	Antistreptolysin O titer (ASOT) Elevated in 70–80 % of APIGN cases 1–5 weeks after infection, decrease to preinfection levels after several months Unreliable for streptococcal pyoderma or infection by other organisms
	Streptozyme test Simple, sensitive hemagglutination assay detecting antibodies against several streptococcal antigens (streptolysin O, DNaseB, hyaluronidase, streptokinase, anti-nicotinamide adenine dinucleotidase (NADase))
	Anti-Dnase B (ADB) Elevated in 80–90 % of cases of pyoderma-associated APSGN
Kidney biopsy	Indications (rare): Alternative diagnosis (e.g., MPGN, IgAN) Normal serum C3/CH50 Persistently low serum C3 or CH50 (>12 weeks after onset) Persistent GN/deteriorating renal function

Table 3.9 Spectrum of histological finding in APIGN

Modality	Findings
Bright-field microscopy	Endocapillary proliferative glomerulonephritis with diffusely increased cellularity, occasionally with abundant polymorphonuclear neutrophils (exudative GN) Enlarged, bloodless glomeruli secondary to capillary occlusion, normal-appearing glomerular basement membrane Infiltration of macrophages and lymphocyte in glomeruli and tubulointerstitial compartment
Immunofluorescence	Discrete deposits of C3, IgG, and IgM in the mesangium and in the glomerular basement membrane (“starry sky”) Heavy, “garland”-like GBM deposits (associated with nephrotic-range proteinuria and poorer outcome)
Electron microscopy	Subepithelial electron-dense deposits (“humps,” a hallmark lesion of APSGN) containing mainly C3 and IgG/IgM (and streptococcal antigens, e.g., SPEB) Note that “humps” may also be found in other nephritides, e.g., lupus nephritis

3.4.1.8 Kidney Biopsy

- Kidney biopsy is indicated (1) when kidney function fails to recover or (2) declines rapidly, and (3) when C3 levels fail to normalize or (4) proteinuria persist beyond 2–3 months
- Expected biopsy results are shown in Table 3.9

3.4.1.9 Treatment of APIGN

Treatment is based on the clinical severity of the illness focusing on control of blood pressure, edema, and consequences of acute renal failure (Table 3.10). Patients with

Table 3.10 Treatment of APIGN

Indications and treatment modalities	Remarks
Hypertension and fluid overload	Restriction of sodium and fluid intake Loop diuretics (furosemide) Antihypertensive drugs If blood pressure is not controlled with diuretics Preferably calcium channel blocker or angiotensin-converting enzyme inhibitor (ACEi)
Pulmonary edema (rare) Hypertensive urgency or emergency (with or without CSN symptoms)	Loop diuretics, O ₂ therapy Oral agents (nifedipine, hydralazine, minoxidil) Intravenous agents (nitroprusside, nicardipine, labetalol – dosing see Chap. 7)
Hyperkalemia	Loop diuretic K restriction, sodium polystyrene sulfonate Inhaled bronchodilator, IV calcium or bicarbonate, or insulin drip If refractory, dialysis
Dialysis or continuous venovenous hemofiltration	Life-threatening hyperkalemia Severe fluid overload unresponsive to diuretics Rapidly progressive GN with persistent oligoanuria
Antibiotics	Obtain throat cultures from patient, family members, and close contacts Treat those infected to minimize spread of nephritogenic strain Oral penicillin V for 10 days (<25 kg = 250 mg twice daily, >25 kg 500 mg twice daily) Erythromycin (40 mg/kg for 10 days) or derivative for patients allergic to penicillin
Glucocorticoids, other immunosuppressants	Rarely indicated

milder disease, i.e., normal BP and mild renal failure, may not be hospitalized but require BP monitoring. Patients with elevated BP, oligoanuria, hyperkalemia, or severe edema should be treated as inpatients.

3.4.1.10 Prognosis and Outcome

- Short- and long-term prognosis of APIGN in children is excellent.
- >95 % of the patients recover renal function within 3–4 weeks.
- Chronic or progressive kidney disease <1 % of children (higher percentage in adults).
- The superimposition of APSGN in patients with diabetes mellitus or metabolic syndrome may increase risk of CKD.
- Recurrence of APSGN extremely rare due to streptococcal type-specific, long-lasting immunity and limited number of nephritogenic GAS strains.

3.4.2 Infection-Induced Immune Complex Glomerulonephritis (ICGN)

3.4.2.1 Abstract

Sustained, focal infections can result in glomerulonephritis. Classical examples are subacute bacterial endocarditis (SBE) and ventriculo-atrial (and rarely ventriculo-peritoneal) shunt nephritis.

Infectious organisms release soluble antigens that are deposited in glomerular structures, either directly or after complexing with specific antibodies.

ICGN has also been described after acute infective carditis and chronic otitis media, tonsillitis and abscesses, and associated with portal fibrosis or portocaval shunts, or congenital and acquired syphilis.

The diagnosis involves bacterial culture, serological or molecular antigen detection, urinalysis, and biochemical testing and evidence of complement activation.

Treatment targets the primary infection and occasionally the inflammatory processes directly.

The risk of recurrence in the absence of persistent or new infections is negligible.

Vignette (1)

A 17-year-old adolescent presents to the emergency room because of gross hematuria following several weeks of intermittent fever, night sweat, decreasing energy, non-defined weight loss, and myalgia. Medical history is significant for a small, muscular ventricular septum defect (VSD). She has been well at the time of her last cardiology checkup 3 months earlier. A week prior to her current illness, she had pierced her navel. On physical examination, she appears acutely ill, dyspneic, and moderately edematous. The temperature is 38.5 °C, pulse 120/min. A pansystolic murmur of Levine III/IV is noted at the fourth left sternal border. She has mild splenomegaly and dark red, painful papules on her finger tips. The umbilical area is indolent. Urine is positive for blood (+++) and protein (1 g/l). Laboratory exam reveals serum creatinine 180 μmol/l (2.0 mg/dl), neutrophilia and anemia (hemoglobin 90 g/l [9 g/dl]), elevated sedimentation rate and C-reactive protein. No antinuclear (ANA), anti-glomerular basement membrane (GBM), and anti-neutrophil cytoplasmic antibodies (ANCA) are detected. Repeat blood cultures grow *Propionibacterium acnes*.

Vignette (2)

A 7-year-old boy presents with malaise, headache, vomiting, fever, and gross hematuria. He has a ventriculoatrial shunt for hydrocephalus that had been changed 3 years prior to the current presentation. Physical examination reveals

lethargy, pallor, skin rash and hepatosplenomegaly. BP is 130/90 mmHg. Laboratory findings include normocytic anemia (hemoglobin 83 g/l [8.3 g/dl]), elevated serum creatinine 185 μ M [2.1 mg/dl], estimated GFR 0.39 ml/s/1.73 m² [23 ml/min/m²], and abnormal urinalysis with large hematuria and proteinuria (>3 g/l by dipstick). Serum C3 and C4 are profoundly decreased. Repeat blood cultures grow coagulase-negative Staphylococcus.

3.4.2.2 Definition

ICGN is caused by immunologically mediated inflammatory processes linked to the deposition of a microbial antigen, immunoglobulin and C3 in glomerular basement membranes and mesangium, induced by focal intra- or extravascular infection. It is commonly associated with classical (CP) or alternative pathway (AP) complement activation and depletion of serum C3, C4 and total hemolytic complement (CH₅₀). Best-known examples are subacute/infective endocarditis (SBE/IE) and “shunt nephritis” due to an infected ventriculoatrial (VA) shunt.

3.4.2.3 Etiology and Pathogenesis

- Subacute or chronic infection by bacterial or other microbial agents that release soluble antigens into the circulation.
- The most common organisms are low-virulence bacterial pathogens, such as *Streptococcus viridians* and coagulase-negative staphylococci (*S. epidermidis*).
- Other organisms associated with ICGN are *S. aureus*, *S. pyogenes*, *S. pneumoniae*, anaerobic streptococci, *Salmonella spp.* (*S. typhi*) and *Brucella spp.* and *Treponema pallidum*.
- Primary infections include abscesses of the brain or other organs, ventriculo- and portosystemic shunt infections, osteomyelitis, pyelonephritis, pneumonia/pleuroempyema, otitis media, and enterocolitis.
- Congenital syphilis causes GN along with rash, rhinitis, and osteochondritis and full-blown nephrotic syndrome with anasarca 2–3 months postnatally.
- Chronically released antigen(s) elicit a humoral immune response and formation of antigen–antibody (immune) complexes (IC). Circulating ICs become trapped in the glomerulus or form in situ after antigen deposition in the glomerular basement membrane and mesangium.
- CP and AP complement activation lead to local inflammation due to chemokine production, such as C3a and C5a, and expression of adhesion molecules.
- Sustained inflammation results in focal necrotizing or diffuse proliferative glomerulonephritis with progressive renal injury.
- Some forms of infective carditis cause localized infarcts and glomerular vasculitis without apparent immune deposits.

3.4.2.4 Clinical Features

- Systemic signs: picture of chronic infection, primary organ impairment, generalized inflammation, and renal injury.
- Intermittent or persistent fever, weight loss, lethargy, arthralgia, lymphadenopathy, and hepatosplenomegaly.

- VA shunt infections may present with lethargy and seizures.
- Renal and urinary findings: gross or microscopic hematuria, large proteinuria, arterial hypertension, and acute kidney injury.
- Classic picture of SBE: peripheral stigmata such as (conjunctival) petechiae, splinter hemorrhages (linear hemorrhagic lines in the nail beds, images see <http://199.231.142.148/dermnet/Splinter-Hemorrhage>), Roth spots (retinal hemorrhages with pale or yellow center image see <http://www.ao.org/theeyeshaveit/optic-fundus/roth-spot.cfm>), Osler's nodes (painful, palpable, erythematous lesions most often involving the pads of the fingers and toes, image), and Janeway lesions (nontender, macular lesions most commonly involving the palms and soles; images, see: http://www.childrenshospital.org/cfapps/mml/index.cfm?CAT=media&MEDIA_ID=1887).

3.4.2.5 Investigations

- Basic Laboratory Investigations
 - Blood culture (preferably repeat cultures)
 - CBC and differential with blood smear (peripheral leukocytosis/neutrophilia)
 - Serum creatinine
 - C-reactive protein or sedimentation rate (elevated), C3, C4 and CH50 (decreased)
 - Urinalysis with quantitative assessment of proteinuria and microscopy
 - Cerebrospinal fluid (CSF) in case of suspected cranial pathology or shunt infection
- Extended Laboratory Investigations:
 - Serological (specific antibody or antigen detection) and nucleic acid-based tests (e.g., bacterial DNA and RNA).
- Kidney Biopsy:
 - In cases of persistent renal disease or worsening renal function, see Table 3.11.
- Imaging Studies:
 - Cardiac echography (to detect vegetations on valves and/or tips of VA shunt), CT scan (VP shunt integrity), enhanced head CT or MRI for brain abscess, targeted ultrasound, gallium scan (osteomyelitis, occult abscess)

Table 3.11 Histological findings of shunt nephritis in kidney biopsy

Bright-field microscopy	Endocapillary proliferation, double-countered capillary walls, lobular accentuation in MPGN-type lesions Focal necrotizing or diffuse mesangial or membranoproliferative GN. Crescent formation in up to 50 % of proliferative GN following SBE Congenital and acquired syphilis can present as proliferative or membranous GN Interstitial nephritis or cortical necrosis in 10 % of renal biopsies or autopsies
Immunofluorescence/immunohistochemistry	Granular IgM, IgG, (IgA), and C3
Electron microscopy	Subendothelial, mesangial, and subepithelial electron-dense (immune) deposits

3.4.2.6 Treatment

- Subacute Bacterial Endocarditis/Infectious Carditis:
Intravenous (IV) antibiotics directed by bacterial culture and sensitivity
Empiric therapy with vancomycin due to ubiquitous penicillin (methicillin)-resistant staphylococci and streptococci
Total duration of antibiotics (IV and PO) 4–6 weeks
- Shunt Nephritis
IV antibiotics until surgical removal of infected VA or VP shunt.
Antibiotics alone are rarely able to eliminate the biofilm on implanted devices.
- Other Infections
Effective treatment of brain abscesses, pleural empyema, and other focal or systemic infections will resolve associated GN.
- Crescentic or progressive GN
Anecdotal use of glucocorticoids or cytotoxic agents.

3.4.2.7 Prognosis and Outcome

- Renal outcome of GN associated with SBE, shunt nephritis, or other focal or chronic infections is favorable with early diagnosis and treatment.
- Delayed removal of infected VA shunt may result in chronic renal injury and progression to ESRD.
- Urinary findings persist during weeks to months following the eradication of the bacterial organism in cases of SBE.
- Complement levels normalize after eradication of the infection and healing of the renal lesions.

3.4.3 Rapidly Progressive Glomerulonephritis (RPGN)

RPGN must be considered a medical emergency that requires a rapid (etiological) diagnosis and aggressive treatment in an attempt to divert irreversible loss of kidney function.

3.4.3.1 Definition

RPGN is a clinical entity characterized by acute GN with progressive loss of renal function over days to weeks. The histopathological hallmark is the presence of crescents; hence, it is also called crescentic glomerulonephritis. The diagnosis of crescentic GN rests on the detection of crescents in >50 % of glomeruli.

3.4.3.2 Etiology and Pathogenesis

- RPGN can be classified in 3 groups based on the pathophysiology and histopathological presentation: anti-GBM disease, immune-complex GN and pauci-immune GN (see Box 3.7).
- The spectrum of diseases underlying RPN and crescentic GN include
 - SHP (Sect. 3.6.2) and IgAN (Sect. 3.5.2)
 - Anti-GBM GN and Goodpasture's disease (very rare in children)
 - ANCA associated vasculitis (AAV) and pauci-immune vasculitis (Sect. 3.6.3)

Vignette

A 12-year-old boy is brought with worsening generalized edema, oliguria, and gross hematuria since 4 days. There is no history of sore throat, skin rash, joint pain or fever in the recent past. Blood pressure is 150/100 mmHg. Urine analysis shows protein +++, plenty of RBCs, RBC casts and occasional WBC. His serum creatinine is 185 $\mu\text{mol/l}$ (2.1 mg/dl). Family history is non-contributory. Two days later, his creatinine has risen to 334 $\mu\text{mol/l}$ (3.4 mg/dl).

Box 3.7 Classification of RPGN

Anti-glomerular basement membrane disease

Anti-GBM GN, Goodpasture's syndrome, post kidney transplantation in Alport syndrome

Pauci-immune RPGN

- ANCA-associated vasculitis and renal limited vasculitis (see Box 3.10 and Sect. 3.6.3)
- Idiopathic crescentic GN
- Medications: penicillamine, hydralazine, propylthiouracil

Immune complex RPGN

- IgA nephropathy, SHN, membranoproliferative GN, membranous nephropathy
- Infection associated GN: acute poststreptococcal/postinfectious GN, subacute bacterial and infective endocarditis, shunt nephritis, visceral abscesses, human immunodeficiency virus, hepatitis B and C, syphilis
- Systemic disease: SLE, Schönlein–Henoch purpura, cryoglobulinemia, mixed connective tissue disorder, juvenile chronic arthritis

3.4.3.3 Pathogenesis of Crescent Formation

- Crescent formation starts with a break in the glomerular capillary basement membrane leading to influx of macrophages, T cells into the Bowman's space.
- The influx of cells causes release of inflammatory mediators such as interleukin-1 and tumor necrosis factor-alpha.
- Proinflammatory cytokines contribute to epithelial cell proliferation and crescent formation.
- Fibroblast growth factor and transforming growth factor-beta (TGF-beta) induce deposition of collagen resulting in fibro-cellular and fibrous crescents.

3.4.3.4 Clinical Features

- Renal:
 - Most patients (80–90 %) present with signs of acute GN, including gross hematuria, oliguria, hypertension, and edema and, occasionally, with hypertensive emergency with encephalopathy or congestive heart failure.

- Extrarenal:
 - Upper (nasal discharge, polyps, sinusitis) and lower respiratory tract involvement (pneumonitis, pulmonary nodules, asthma, pulmonary hemorrhage) with or without vasculitic rash: ANCA-associated vasculitis (AAV), pauci-immune vasculitis (see Sect. 3.6.3)
 - Hemoptysis, pulmonary hemorrhage: Goodpasture’s disease, AAV
 - Arthralgia, skin rash/purpura, anemia: systemic lupus erythematosus, SHP
 - History of sore throat, pyoderma: acute poststreptococcal nephritis

3.4.3.5 Investigations

- Urine analysis: moderate to large proteinuria (2+ to 4+), RBC, WBC, RBC or granular casts
- Serial, frequent monitoring of serum creatinine, electrolytes
- Serology:
 - Antistreptolysin O: poststreptococcal RPGN
 - Complement: C3 consumption in APIGN/APIGN, SLE and MPGN/C3 GN
 - ANA, anti-dsDNA: positive in SLE
 - Antineutrophil cytoplasmic antibodies (ANCA): perinuclear (pANCA/MPO) and cytoplasmic (cANCA/PR3): pauci-immune vasculitis (see Sect. 3.6.3, Box 3.10)
 - Circulating anti-glomerular basement membrane (GBM) antibody: anti-GBM nephritis, Goodpasture’s syndrome (with pulmonary involvement)
 - Hepatitis serology
- X-ray, CT chest: ANCA-associated vasculitis (AAV), Goodpasture’s disease
- Renal biopsy

3.4.3.6 Renal Histopathology

- Crescents are the pathognomonic feature of RPGN (see Table 3.12 and Sect. 3.4.3.3).

Table 3.12 Renal biopsy findings in RPGN

	Anti-GBM GN	Immune complex RPGN	Pauci-immune RPGN
Light microscopy	Focal glomerular capillary vasculitis to diffuse, exudative (crescentic) and necrotizing GN (CNGN)	Diffuse exudative glomerular proliferation (APIGN/LN) Duplication/splitting of glomerular basement membrane (MPGN/C3 GN) Mesangial proliferation (IgAN/SHN)	Segmental fibrinoid necrosis, karyorrhexis and crescents
Immunofluorescence (IF)	Linear deposits of IgG along the capillary walls	C3/IgG (APIGN) C3 deposits (MPGN/CE GN) Full-house IF (SLE) IgA deposits (IgAN/SHN)	No or scanty immune deposits

Abbreviations: RPGN rapidly progressive glomerulonephritis (GN), APIGN acute post-infections GN, LN lupus nephritis, MPGN membranoproliferative GN, SHN Schönlein–Henoch nephritis

- They may be circumferential or segmental, with compression of the glomerular tuft.
- Crescents may be cellular, fibro-cellular or fibrous, based on the duration of the disease.

3.4.3.7 Treatment

- RPGN must be diagnosed promptly and treatment initiated urgently to preserve renal function.
- An etiological diagnosis, usually by means of kidney biopsy and serology, is important as specific treatments evolve.
- For the treatment of specific underlying diseases presenting as RPGN, refer to Sect. 3.6.
- Aggressive immunosuppressive therapy is inappropriate in patients with mainly chronic versus active lesions by kidney biopsy.
- Extrarenal manifestations should prompt adequate immunosuppressive therapy regardless of the degree of kidney disease.

Induction phase:

- Three to five doses of IV methylprednisolone (10–20 mg/kg/day) followed by 1.5–2 mg/kg/day of oral prednis(ol)one for 4–6 weeks with gradual tapering to 0.5 mg/kg/day by 3 months
- Cyclophosphamide IV (500–750 mg/m²/dose every 4 weeks for 3–6 doses) or PO (2 mg/kg for 8 weeks).

Maintenance phase:

- Prednisone 0.5–1 mg/kg alternate days, with slow tapering
- Azathioprine 2 mg/kg/day or mycophenolate mofetil at 800–1,200 mg/m²/day for 12–24 months

Antibody mediated or refractory disease:

- Plasmapheresis: e.g., in patients with anti-GBM disease or pauci-immune vasculitis presenting with RPGN and/or diffuse pulmonary hemorrhage
- The therapeutic role for B-cell depleting (rituximab), anti-cytokine and anti-complement antibodies is evolving

3.4.3.8 Prognosis

- The prognosis depends on the underlying etiology, severity of disease, and time to initiation of treatment.
- With adequate treatment, >50 % of patients show partial or complete recovery of renal function

3.5 Chronic Glomerulonephritis and Immune Nephropathies

This section combines an etiologically diverse group of (chronic) nephropathies that display varying degrees of glomerular inflammation.

3.5.1 Membranoproliferative Glomerulonephritis

Membranoproliferative glomerulonephritis (GN), also known as mesangiocapillary GN, is a chronic disease characterized by thickening and splitting of the glomerular basement membrane (GBM) with mesangial proliferation and mesangial interposition into the GBM. Median age at onset is 10 years, but ranges from 5 years to young adulthood.

Based on light and electron microscopic features, such as location of the immune deposits and GBM appearance, MPGN is classified as MPGN type I, MPGN type II and MPGN type III. Subsequently, type II MPGN has been recognized as a distinct disorder and termed dense deposit disease (DDD; Box 3.8).

An evolving, immunofluorescence (IF) microscopy-based nomenclature refers to the demonstration of isolated or dominant C3 deposits (C3 GN) versus the mixed presence of IgG and complement. The new diagnostic term C3 GN encompasses DDD and MPGN type III, as well as a proportion of MPGN type I cases. Excluded are secondary forms of MPGN that are more frequently seen in adult patients.

3.5.1.1 Etiology and Pathogenesis

- Persistent consumption of complement and low circulating concentrations of C3 in plasma are found in 80–95 % of (primary) type I and type III MPGN and essentially all DDD patients
- Complement activation via the classical pathway (CP) is present in > 40 % of type I MPGN, often associated with hepatitis C virus (HCV) infection and cryoglobulinemia. Conversely, in one large series > 80 % of patients with HCV infection and cryoglobulinemia had MPGN type I lesions
- C4 is not depleted in plasma nor deposited in the kidney in patients with DDD or type III MPGN (see Table 3.13)
- Activation of the terminal complement components C5-C9 is common in type III, but rare in type I MPGN or DDD

Box 3.8 Traditional Classification of Membranoproliferative Glomerulonephritis (MPGN)

MPGN type I

- Primary/idiopathic
- Secondary
 - Infections: hepatitis B, hepatitis C, HIV, schistosomiasis, malaria
 - Auto-immune: cryoglobulinemia, SLE, Sjogren's syndrome
 - Malignancy: B cell lymphoma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia

MPGN type II (dense deposit disease, DDD)

- Primary/idiopathic
- Partial lipodystrophy

MPGN type III

Table 3.13 MPGN renal histology

Modality	MPGN type 1	MPGN type 2 (DDD)	MPGN type 3
Light microscopy	Endocapillary and mesangial proliferation (proliferative GN) Lobular accentuation of glomerulus, mesangial matrix expansion Silver stain: double contour of GBM, “tram track” appearance, mesangial interposition	Enlarged glomeruli due to increased cellularity (proliferation) Silver stain: thickened GBM	Complex laminal lesions caused by iterative subepithelial and subendothelial deposits
Immunofluorescence	IgG and/or C3 (and often C4) present in the periphery of glomerular lobules (“fringe” pattern)	Abundance of C3 deposits in GBM and mesangium, rarely IgG/A/M or C4	C3 deposits in capillary loops and mesangium. C4 is rarely present, IgG only in small amounts in 50 %
Electron microscopy	Intact GBM with subendothelial and mesangial deposits, mesangial proliferation, and matrix expansion/interposition	Intramembranous dense deposits (DD) in GBM; DD also in Bowman’s capsule and tubular basement membrane	Thickened GBM with patchy dense deposits

- MPGN has been linked to the detection of autoantibodies to complement components
- The autoantibodies C3 nephritic factor (C3Nef or NF), stabilize physiological C3 and C5 convertases, presumably by interfering with the control of classical (NfC), alternative (NfA) or terminal (C5 convertase) pathway regulation (NfT)
- This may lead to the deposition of C3 fragments in the glomerulus and generation of complement-derived proinflammatory chymokines
- Genetic mutations or functional inactivation of critical AP regulators have been found to underly the occurrence of all types of MPGN/C3 GN (see Sect. 3.7.6 for a schematic diagram of the complement cascade and its regulators)
- The term C3 GN hence separates “primary” or “idiopathic” MPGN of all types from secondary forms of type I MPGN (see Box 3.8)

3.5.1.2 Clinical Presentation

- MPGN types cannot be differentiated clinically due to widely overlapping features.
- They may present as asymptomatic microhematuria and proteinuria, nephrotic syndrome or acute GN (nephritic syndrome) with gross hematuria and hypertension
- Acute nephritic syndrome with gross hematuria, hypertension, mild hypoalbuminemia and initially normal renal function can be found in all forms of MPGN (20–30 %)

- Nephrotic syndrome is present in 1/3 of type I and type III MPN and 50 % of DDD. It has been associated with a poor prognosis
- In contrast, clinically mild or asymptomatic presentation has been reported in about 60 % of type III, 20 % of type I and rarely in type II/DDD

3.5.1.3 Laboratory Evaluation

- Urinalysis, microscopy, 24-hour collection for protein and creatinine or spot urine protein/creatinine
- Renal function and related biochemical markers
- Kidney biopsy (see Table 3.13)
- Search for infectious or malignant causes (see Box 3.8)
- Serology: ANA, other antibodies and markers of primary autoimmune disorders (see Box 3.8)
- Serum complement studies: C3, C4, CH50 and, where available, C3Nef (C3 nephritic factors), CFH (factor H), SC5b-9 (soluble terminal complement complex or MAC)
- Alternative complement pathway regulator gene mutation screen

3.5.1.4 Therapy

- Treatment options are limited
- Mainstay is initially daily, then alternate-day prolonged oral prednisone over several years
- Mycophenolate or calcineurin inhibitor can be tried as second-line agents
- The 2012 KDIGO guideline suggests PO cyclophosphamide or MMF plus low-dose alternate-day or daily prednisone for up to 6 months in patients with idiopathic MPGN with nephrotic presentation and renal function decline
- Indications for the use of rituximab (MPGN type I) and of eculizumab are evolving
- Angiotensin-converting enzyme inhibitors (ACEi) and/or receptor blockers (ARB) should be used to control hypertension and reduce proteinuria
- Statins are recommended to control hyperlipidemia
- Consider thrombosis prophylaxis for recalcitrant nephrotic syndrome with profound hypoalbuminemia

3.5.1.5 MPGN Type 1

- MPGN can present as asymptomatic hematuria or proteinuria (40–50 %), acute nephritic syndrome (25 %), nephrotic syndrome (25–30 %), rapidly progressive glomerulonephritis, or CKD.
- MPGN may manifest in the context of an acute (upper respiratory tract) infection (“syninfectious GN”) may also present as syninfectious glomerulonephritis.
- Secondary type I MPGN is associated with hepatitis C, SLE, or neoplasia.
- Serum C3 is reduced in 70–80 % of patients with type I MPGN, and 40 % will have low C4 levels
- Renal histopathology: see Table 3.13

Prognosis

- More than 50 % of patients progress to end-stage renal disease in 10 years; risk factors are nephrotic range proteinuria and hypertension.
- Recurrence risk following renal transplantation is 20–30 %.

3.5.1.6 Type II MPGN (Dense Deposit Disease)

- Type II MPGN/DDD accounts for <20 % of pediatric MPGN.
- DDD has been linked to the presence of an autoantibody, C3NeF (C3 nephritic factor), that binds to and stabilizes the alternative C3 convertase C3bBb, thus preventing degradation of this complex and resulting in continuous consumption of C3. The complement abnormality precedes development of GN.
- C3 nephritic factor may also be associated with partial lipodystrophy, an occasional precursor to type II MPGN.
- The presence of C3 nephritic factor suggests a role for complement dysregulation in the pathogenesis of MPGN type II. The presence of C3NeF or mutated complement factor H (CFH) or other alternative pathway regulators may lead to excess C3 activation and glomerular deposition of C3 metabolites, the “dense deposits”.

Clinical Features

- Age of onset is the second decade of life. Males and females are equally affected.
- Patients may present with mild proteinuria and microscopic hematuria. 50 % of patients are nephrotic, and about 1/3 have hypertension. AKI and rapid progression to ESRD are unusual.
- Dense deposits of C3 are known as “Drusen”; found as yellow and white dots between Bruch’s membrane and the retinal epithelial cell layer, the deposits lead age related macular degeneration.
- DDD can be associated acquired partial lipodystrophy due to complement-mediated destruction of adipocytes.

Prognosis

- Progression to ESRD is seen within 1 year of onset with proteinuria and hypertension.
- Recurrence risk after renal transplantation is high (about 50–100 %).

3.5.1.7 MPGN Type III

- Rare variant of MPGN associated with unregulated alternative complement pathway activation
- Typically less (often focal) mesangial proliferation compared with type I MPGN, but clinical and histological differentiation from the latter is not reliable.
- Presentation with nephrotic proteinuria and/or crescents have portends an increased risk of CKD progression.
- Subendothelial, intramembranous, and subepithelial deposits and a frayed and disrupted GBM.
- In comparison to other types of MPGN, patients with type III MPGN are more likely to have asymptomatic proteinuria with hematuria.

3.5.2 IgA Nephropathy

3.5.2.1 Abstract

IgA nephropathy (IgAN) represents worldwide the most common primary glomerulopathy.

Secondary IgAN is rare.

IgAN is typically diagnosed during teenage years and young adulthood. Natural disease progression leads to end-stage renal disease within 20 years of diagnosis in 30–35 % of patients (range 20–50 %).

The rate of disease progression is modifiable.

Pathogenesis has been related to the mesangial deposition of hypoglycosylated IgA1 resulting in glomerular and related tubulointerstitial inflammation and fibrosis.

Familial occurrence has been reported and genetic factors postulated, but no causal gene mutation has been identified.

Kidney biopsy is important to estimate the degree of acute and chronic tissue injury.

Treatment focuses on antiproteinuric and antihypertensive medications through the blockade of the renin–angiotensin–aldosterone system (ACE inhibitors, ARB) and glucocorticoids. The role of (other) immunosuppressants, cytotoxic agents, polyunsaturated fatty acids (fish oil), coagulation or platelet modifying agents, and tonsillectomy remain controversial.

IgAN may recur after kidney transplantation.

Vignette

An 11-year-old boy presents to the emergency room with gross hematuria 2 days after the beginning of a sore throat with a 1-day fever. He has mild flank pain. Parents report that their child experienced 2 similar episodes over the preceding year. Family history is significant for an uncle who started chronic dialysis at the age of 35 years. Physical examination reveals a healthy appearing, normally grown boy with no edema, rash, purpura or petechiae, and no pallor. He is presently afebrile. The manual blood pressure is 105/75 mmHg. Urinalysis reveals >100 RBC/ μ l, occasional WBC, and no cellular casts; protein is 1 g/l per dipstick analysis. Repeat urinalysis 2 weeks later shows <5 RBC/ μ l and no protein.

3.5.2.2 Introduction

IgA nephropathy, first described by Berger and Hinglais in 1968, is worldwide the most common primary glomerulopathy. It represents between 20 and 40 % of glomerular diseases in Asia and Europe. Biopsy practices and genetic factors may contribute to the reported geographic variation. Most children with progressive IgAN do not reach ESRD until adulthood.

3.5.2.3 Definition

Primary IgAN is a primary immune-complex glomerulopathy characterized immunohistologically by the presence of dominant glomerular (mesangial) IgA deposits, often associated with C3 and IgG deposits and inconsistently with morphological evidence of local inflammation.

3.5.2.4 Etiology and Pathogenesis

- Exacerbation of symptoms (macroscopic hematuria with or without proteinuria and, occasionally, flank pain), is triggered by non-specific mucosal viral or bacterial infections.
- Mesangial IgA deposits are composed of polymeric IgA1. The frequent detection of C3 (and, if searched for, properdin and the terminal membrane attack complex C5b-9), but not C1q and C4, suggest alternative complement pathway activation in IgAN.
- Abnormal galactosylation and sialylation at the hinge region of IgA1 molecules changes their mesangial cell binding. However, it remains unclear, whether hypoglycosylated IgA1 is sufficient to induce IgAN. Diagnostic testing for abnormally glycosylated IgA is not routinely available.
- Genetic factors have been implicated in disease susceptibility and progression. Familial clustering is known. Aberrant IgA1 galactosylation appears to be inherited in some families. A causal genetic mutation remains to be identified.

3.5.2.5 Clinical Features

- Recurrent macroscopic hematuria with or without proteinuria is the hallmark of childhood IgA nephropathy and is the most common presenting symptom.
- For other disease manifestations, see Table 3.14.

3.5.2.6 Laboratory Investigations

- Investigations focus on differential causes of hematuria and (occasional) loin pain (see Figs. 3.1 and 3.2 in Sect. 3.1 and Table 3.15).
- Decreasing kidney function and nephrotic-range proteinuria are of prognostic importance.
- Serial follow-up is recommended to identify progression to CKD.
- IgAN is largely a diagnosis of exclusion. A positive diagnosis requires a kidney biopsy.
- Extended laboratory evaluation if secondary IgAN is suspected or to be ruled out.

3.5.2.7 Pathological Diagnosis

- Diagnosis of IgA nephropathy requires a kidney biopsy (see Table 3.16).
- Biopsies can be graded according to the amount of mesangial cell proliferation on the basis of WHO criteria as (1) minimal glomerular lesions, (2) focal mesangial proliferation, (3) diffuse mesangial proliferation.
- The International IgA Nephropathy Network has identified four histopathological lesions of independent prognostic importance, abbreviated as “MEST”: mesangial (M) and endocapillary hypercellularity (E), segmental glomerulosclerosis (S) and tubular atrophy and interstitial fibrosis (T) (Table 3.16)

Table 3.14 Clinical features of IgA nephropathy

Features	Comments
Age of presentation and gender preference	Diagnosis during second and third decade of life. Male predominance (2:1–6:1) Uncommon in persons of African descent Familial predisposition (up to 20 %)
Microscopic hematuria	Associated with (mild) proteinuria in 20–60 %
Macroscopic hematuria	Up to 60 % of patients have at least one, usually more episodes of macrohematuria Manifests 1–2 days after mucosal (upper respiratory tract) infection Generally painless, occasionally with loin pain Duration (24–48 h), occasionally up to a week
Acute nephritic syndrome	In 23 %, associated with (severe) acute glomerular injury with or without AKI, usually reversible
AKI with macroscopic hematuria	Uncommon, may represent first manifestation of IgAN Kidney function to baseline after normalization of urine color Incomplete recovery of renal function in 25 % Duration of macroscopic hematuria >10 days is a risk factor of persistent kidney impairment
Nephrotic syndrome	Uncommon presentation (<10 %), with unfavorable prognosis Differentiate from minimal change NS with incidental IgA staining
Flank or abdominal pain	Occasionally with macroscopic hematuria
Rapid progressive GN	Characterized by extensive crescents and rapidly progressive course 40 % of patients with IgA RPGN are ≤16 years old
Hypertension	Infrequent in pediatric IgAN, unless patient has CKD
End-stage renal disease (CKD 5)	25 % of patients 10 years after diagnosis, 40–50 % after 20 years

Table 3.15 Diseases associated with diffuse mesangial deposits of IgA (“secondary IgAN”)

Primary diagnosis	Comments
Schönlein–Henoch purpura nephritis	Renal histological findings indiscernable from IgAN
Systemic lupus erythematosus (lupus nephritis)	
Chronic liver disease/cirrhosis	
Celiac disease	
Inflammatory bowel disease	Crohn’s disease, ulcerative colitis
Infections	Disseminated tuberculosis, leprosy, mycoplasma infection and toxoplasmosis
Dermatitis herpetiformis	
Ankylosing spondylitis	
Cystic fibrosis	
Bronchiolitis obliterans	
Mixed cryoglobulinemia	
Monoclonal IgA gammopathy	
Neoplasms	Hodgkin and T cell lymphoma, mycosis fungoides, solid cancers of lungs and colon

Table 3.16 Spectrum of histological finding in IgA nephropathy

Modality	Morphological findings ^a
Light microscopy	<p>Characteristic finding is mesangial enlargement due to hypercellularity and increased matrix</p> <p><i>Glomerular findings</i></p> <p><i>Mesangial</i> proliferation (>4 cells/peripheral mesangial area) with varying degrees (defined as diffuse >50 % glomeruli, focal (<50 % of glomeruli), global (involving more than half of the glomerular tuft), or segmental (involving less than half of the glomerular tuft)</p> <p><i>Endocapillary</i> hypercellularity (hypercellularity due to increased number of cells within glomerular capillary lumina)</p> <p>Cellular and fibrocellular crescents (<i>extracapillary lesions</i>). Crescents (see Sect. 3.4.3.3) if present, usually affect <50 % of glomeruli. Crescentic IgAN requires that >50 % glomeruli are affected)</p> <p><i>Tubulo-interstitial changes</i> (interstitial fibrosis and tubular atrophy; acute tubular injury)</p> <p><i>Vascular</i> (arterial) lesion</p> <p><i>Other changes</i> include segmental and global <i>glomerulosclerosis</i> and interstitial lymphocytic infiltration</p>
Immunofluorescence	<p><i>Mesangial IgA deposits</i> (predominant)</p> <p>May extend to mesangio-capillary junctions and into capillary wall</p> <p>Can be associated with C3 (about 2/3 of biopsies), IgG (1/3), IgM (10 %) or IgG/IgM (10 %)</p>
Electron microscopy	<p><i>Electron-dense deposits</i> in mesangium (granular masses beneath lamina densa in perimesangium and expanded mesangium [matrix])</p> <p>Deposits in glomerular capillary wall (mainly subendothelial and subepithelial, adjacent to mesangium)</p> <p>Lysis of glomerular basement membrane (GBM)</p> <p>Diffuse foot process effacement limited to patients with (large) proteinuria</p>

^aThe International IgA Nephropathy Network has identified four histopathological lesions of independent prognostic importance: *mesangial* (M) and *endocapillary hypercellularity* (E), *segmental glomerulosclerosis* (S) and *tubular atrophy and interstitial fibrosis* (T), which have been validated for children and adults (Oxford MEST score). Endocapillary hypercellularity appears to be responsive to immunosuppressive therapy

3.5.2.8 Therapeutic Management

- There is presently no curative treatment for IgAN.
- Pathological risk factors identified in the Oxford Classification have not been validated to guide treatment choices.
- *Graded treatment recommendations* include antiproteinuric and antihypertensive therapies, glucocorticoids, and immunosuppressive/cytotoxic agents.
- Antiproteinuric and antihypertensive therapy
 - Normalize BP to <90th (ideally 50th percentile) percentile for age and height (<120/80 mmHg) using ACE inhibitors or ARBs as first-line agents.
 - Start ACE-I or ARB, if proteinuria is >0.5 g/1.73 m²/day.
 - Titrate ACE-I or ARB as tolerated to keep proteinuria <1 g/1.73 m²/day.

- Glucocorticoid therapy
 - Add glucocorticoids if proteinuria of ≥ 1 g/1.73 m²/day persists despite 3–6 months of optimized RAS targeting therapy (ACEi or ARB).
 - A suggested regimen consists of methylprednisolone pulses on 3 subsequent days at months 1, 3, and 5, and oral prednisone (or equivalent) at a dose of 0.5 mg/kg on alternate days for 6 months.
 - An alternative regimen starts with oral prednisone at 0.8–1 mg/kg/day for 2 months, followed by a reduction every month by 0.2 mg/kg/day over the next 4 months.
 - There are no published recommendations on how to proceed after 6 months. Options include (1) to continue antiproteinuric and antihypertensive therapy, if proteinuria remains between 0.5 and 1 g/1.73 m²/day, with or without continued alternate-day prednisone (e.g., 0.25 to 0.5 mg/kg QOD) or with fish oil (see below).
- Immunosuppressive and cytotoxic agents
 - There is insufficient evidence that immunosuppressive agents other than glucocorticoids are beneficial in the majority of patients.
 - According to the 2012 KDIGO practice guideline, combining prednisone and azathioprine (or cyclophosphamide), with or without antiplatelet agents, does not add benefit, but may increase occurrence of adverse effects. Japanese experience suggests improved outcome with the combination treatment (prednisolone, azathioprine, warfarin, and dipyridamole) in cases of *severe* IgA nephropathy.
 - Clinical trials employing MMF in (adult) patients with IgAN are heterogeneous and inconclusive. MMF was reported to be beneficial in a Chinese trial, but ineffective in placebo-controlled studies involving Caucasian patients. The KDIGO Guideline does not suggest the use of MMF in IgAN.
- Fish-oil supplements/Omega-3 (polyunsaturated) fatty acids
 - Beneficial cardiovascular effects in part by lowering BP and triglyceride levels
 - Typically supplied as 460 mg EPA and 380 mg DHA (1 g, for children <50 kg) and 920/760 mg (2 g, for children >50 kg)
 - Randomized controlled trials with omega-3 fatty acid supplements for IgAN showed no clinically significant improvement of kidney survival
 - The KDIGO guideline suggests trying fish oil in patients with persistent proteinuria ≥ 1 g/day (per 1.73 m²) despite 3–6 months of optimized renin/angiotensin blockade. Despite higher-quality evidence for treatment with glucocorticoids as step-up therapy than with fish oil, the latter may be used in patients with glucocorticoid toxicity.
- Antiplatelet/anticoagulation agents
 - KDIGO advises against use these agents for IgAN.
- Tonsillectomy
 - Tonsillectomy has no proven benefit in IgAN.
- Atypical forms of IgAN
 - *MCNS with mesangial IgA deposits*

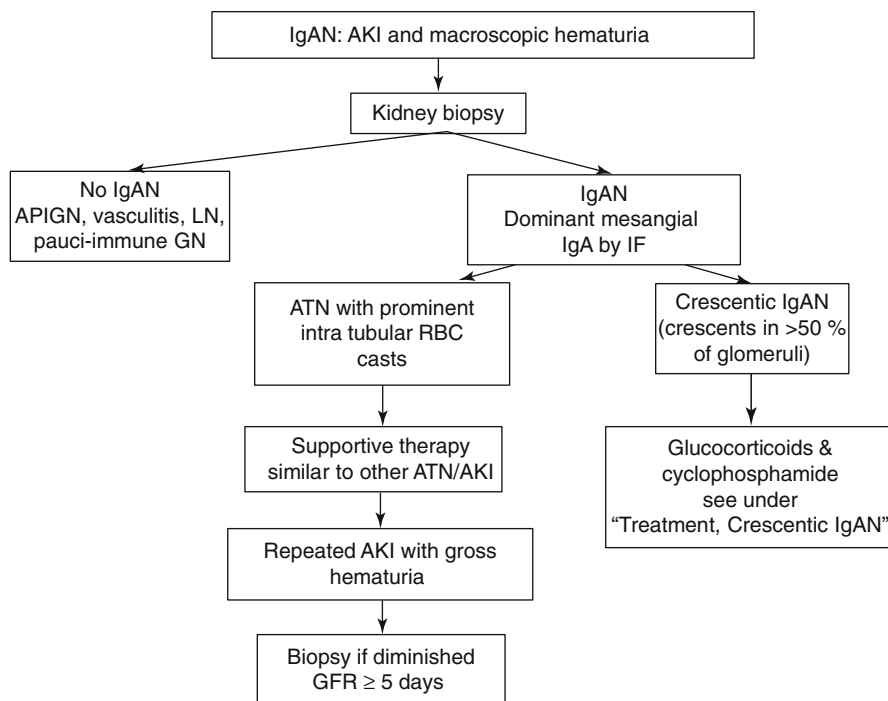


Fig. 3.9 Management of IgA with AKI and macroscopic hematuria. *AKI* acute kidney injury, *ATN* acute tubular necrosis, *APIGN* acute postinfectious GN, *GN* glomerulonephritis, *IF* immunofluorescence/immunohistology, *LN* lupus nephritis

Patients with nephrotic syndrome and coincidental histological findings of minimal lesions and IgAN should be treated like MCNS (see Sects. 3.3.1.6 and 3.3.2).

– *Macroscopic hematuria and AKI* (see Fig. 3.9)

IgAN patients presenting with macroscopic hematuria and AKI should undergo kidney biopsy if renal function fails to improve within 5 days. If histological changes are limited to ATN and intratubular RBC casts, provide supportive treatment only.

Macroscopic hematuria longer than 10 days heralds persistent renal impairment and requires supportive care as other forms of ATN/AKI.

– *Crescentic IgAN*

Defined as IgAN with crescents in >50 % of glomeruli.

Long-term prognosis is poor if associated with rapidly progressive deterioration of kidney function.

Treatment with high-dose glucocorticoids and cyclophosphamide is potentially useful and recommended (see Sect. 3.4.3.7).

A published regimen (Tumlin et al. 2003) consists of 15 mg/kg methylprednisolone pulses for 3 days, followed by daily oral prednisone for a total of 6 months,

combined with six monthly IV cyclophosphamide infusions of 0.5 (–0.75) g/m². Oral prednisone dose 1 mg/kg/day for 2 months is tapered every second month to 0.6, 0.3, and 0.15 mg/kg/day, followed by 10 mg/1.73 m² daily.

3.5.2.9 Prognosis

- Proteinuria is the strongest prognostic indicator for ESRD or accelerated decline of kidney function. In adults, proteinuria above a threshold of 1 g/1.73 m²/day (24 mg/m²/h) has a “dose-dependent” effect, independent of other risk factors.
- Reduction of proteinuria below this threshold (or 50 % reduction of baseline proteinuria) improves long-term outcome.
- Proteinuria cutoffs for partial and complete remission in children are 0.5 g/1.73 m²/day (12 mg/m²/h) and <0.16 g/1.73 m²/day (<4 mg/m²/h), respectively.
- Decline of GFR is faster in patients with poorly controlled hypertension.
- The Oxford Classification of IgAN identified (1) mesangial hypercellularity, (2) segmental glomerulosclerosis, (3) endocapillary hypercellularity, and (4) interstitial fibrosis/tubular atrophy (IF/TA) as independent pathological variables predicting kidney outcome in patients with an estimated GFR of >30 ml/min/1.73 m².

3.5.3 Membranous Nephropathy (MN)

3.5.3.1 Introduction

Membranous nephropathy (membranous glomerulopathy) is a common cause of nephrotic syndrome in adults. It occurs as primary (idiopathic, IMN) or secondary disease. Pediatric MN is rare, accounting for <1.5 % of all children with nephrotic syndrome (up to 5 % of children with glucocorticoid-resistant nephrotic syndrome), compared with 25 % of adults with nephrotic syndrome. The disease is defined by the presence of subepithelial deposits which leads to thickening of the glomerular basement membrane.

3.5.3.2 Etiology and Pathogenesis

- Membranous nephropathy in children is usually secondary to a systemic disease (>75 %), particularly due to hepatitis B or SLE. Other causes are HCV infection, malaria, schistosomiasis and syphilis, drugs or, with advanced age, malignancies (see Table 3.17).
- MN is characterized by subepithelial deposits consisting of immunoglobulins and complement components that result in characteristic, progressive changes of the GBM and in podocyte cytoskeletal abnormalities leading to proteinuria.
- Genetic factors are not well defined. Up to 70 % of (adult) patients with IMN have antibodies to the M-type phospholipase A2 receptor (PLA2R).

3.5.3.3 Clinical Features

- MN occurs at any age from newborn to young adults.
- Male preponderance has been reported by some centers.

Table 3.17 Causes of membranous nephropathy in children

<i>Infections</i>
Hepatitis B, congenital syphilis, hepatitis C, tuberculosis, malaria (<i>Plasmodium malariae</i>), filariasis, schistosomiasis, leprosy
<i>Autoimmune disease</i>
SLE, rheumatoid arthritis, mixed connective tissue disease, Grave's disease, Hashimoto's thyroiditis, primary biliary cirrhosis
<i>Drugs</i>
NSAID, penicillamine, captopril, gold, lithium, mercury
<i>Others</i>
Sarcoidosis, sickle cell disease, sclerosing cholangitis

- Typical presentation as nephrotic syndrome, but up to 20 % have only mild to moderate proteinuria.
- Microscopic hematuria is common; gross hematuria is rare.
- Hypertension in <25 %.

3.5.3.4 Laboratory Investigations

- Urine analysis, 24-h urine protein excretion or at spot Upc, renal function, serum albumin, C3, C4, CH50 and C5b-9 (where available), and renal biopsy
- Rule out secondary forms: hepatitis B surface antigen, IgM to hepatitis C and/or nucleic acid-based molecular assays, syphilis serology, peripheral smear for malaria, antinuclear antibody, anti-dsDNA
- Hypocomplementemia (low C3 and C4) has been reported in 15–64 % of HBV-MN, but is absent in idiopathic MN is typically found with hepatitis B

3.5.3.5 Histopathology (Table 3.18)

3.5.3.6 Therapeutic Management

- Therapy in children is extrapolated from studies in adults.
- Difficulties in the treatment of MN result from its variable course and tendency to spontaneous remission, and the unsatisfactory response to existing therapeutics.
- Spontaneous remission may occur in children with non-nephrotic proteinuria. Non-specific therapy with ACE inhibitors or ARBs, reduced sodium intake (“no added salt”), and mild diuretics to control edema (beware of thrombosis risk).
- Immunosuppressive therapy is indicated in the presence of:
 - Decreased GFR at presentation or follow-up
 - Persistent nephrotic syndrome
 - Thrombosis
- High-dose prednisone (0.5–1 mg/kg per day, up to 60 mg daily) can be tried, with or without three daily pulses of IV methylprednisolone (10–20 mg/kg or up to 600 mg/m² per dose). Note: Children with nephrotic MN will already have received prednisone prior to biopsy. Failure to respond to 2–3 months glucocorticoids justifies the addition of a second-line agent.

Table 3.18 Histopathological features in membranous nephropathy

Light microscopy	<p>May be normal in early stages</p> <p>Pathognomonic feature is thickening of the capillary loops due to subepithelial deposits and deposition of new membrane</p> <p>Silver stain shows characteristic spikes indicating basement membrane between deposits</p> <p>Normal cellularity of the glomerulus</p> <p>Presence of inflammatory cells or mesangial proliferation suggests secondary forms of MN</p>
Immunofluorescence	<p>Fine granular deposits of IgG (IgG4) in subepithelial space</p> <p>Less pronounced staining of IgA and IgM is common, except in SLE-MN. C3 of low intensity is found in up to 95 %; C4 and C1q are typically absent</p>
Electron microscopy	<p>Subepithelial immune deposits</p> <p>Thickening of the basement membrane</p> <p>Effacement of foot processes of podocytes</p>

- Oral cyclophosphamide (2 mg/kg daily for 8–12 weeks), or
- Cyclosporine (4–5 mg/kg) or tacrolimus (0.1–0.15 mg/kg per day, divided in 2 doses; initial target trough levels 5–8 ng/ml)
- Rituximab 375 mg/m² weekly × 4 doses has shown efficacy in adult IMN with minimal degree of tubulo-interstitial injury.
- Treatment of secondary membranous nephropathy targets the underlying cause.

3.5.3.7 Prognosis

- Asymptomatic proteinuria portends good clinical outcome
- High spontaneous remission rate in younger children, usually within 12–18 months
- CKD risk in pediatric MN <25 %
- Poor prognostic factors are nephrotic-range proteinuria, renal dysfunction and hypertension at onset and biopsy showing glomerulosclerosis and/or tubulointerstitial fibrosis

3.5.4 C1q Nephropathy

3.5.4.1 Definition

C1q nephropathy (C1qN) is a glomerular disorder characterized immunohistochemically by prominent mesangial C1q containing immune deposits. Earlier authors emphasized the exclusion of SLE as a prerequisite for the diagnosis of C1qN. Some pathologists do not recognize C1qN as a distinct disease entity.

3.5.4.2 Etiology and Pathogenesis

The etiology of C1qN remains unclear. The pathogenesis and the clinical importance of C1q immune deposits are still to be elucidated.

3.5.4.3 Clinical Signs and Symptoms

- Initial presentation ranges from microscopic hematuria with or without proteinuria to gross hematuria and nephritis or a mixed nephritic–nephrotic picture.
- More than 50 % of pediatric patients present with nephrotic syndrome.

3.5.4.4 Investigations

- The diagnosis depends on the demonstration of dominant or codominant immune staining for C1q and the presence of mesangial or paramesangial immune deposits by electron microscopy.
- Histopathological features associated with C1qN include minimal lesions, mesangial proliferation, focal segmental or global sclerosis, and membranous nephropathy.
- Where studied, serum C3 and C4 concentrations were found to be normal or elevated.

3.5.4.5 Approach and Management

- Diagnostic and treatment are guided by the degree of proteinuria and disease complications.
- Children with nephrotic-range proteinuria and hypoalbuminemia are treated as outlined in Sect. 3.3.1.6 for children with idiopathic nephrotic syndrome.
- Treatment goals for patients with C1qN are remission (or reduction) of proteinuria and preservation or restoration of renal function, independent of the persistence or resolution of C1q deposits.

3.5.4.6 Prognosis and Outcome

- Outcome appears favorable in patients presenting with low-grade proteinuria and minimal tubulo-interstitial or glomerular sclerosis.
- More than 50 % of patients presenting with nephrotic syndrome will experience frequent relapses or glucocorticoid dependence, and about 30 % of these may become glucocorticoid resistant.
- Overall, <15 % of patients with C1qN may progress to chronic kidney disease and ESRD.
- Outcome is poor in patients with C1qN collapsing glomerulopathy.

3.6 Systemic Vasculitis Affecting the Kidney

3.6.1 Abstract

This section describes a diverse group of systemic inflammatory blood vessel diseases (vasculitides) with variable degrees of kidney involvement. Individual diseases are detailed according to their importance and frequency in the pediatric age group including Schönlein-Henoch nephritis (SHN), anti-neutrophil cytoplasmic antibody (ANCA) mediated vasculitis (AAV) and pauci-immune glomerulonephritis, lupus nephritis (LN) and rarer vasculitides.

3.6.2 Definitions

Currently used classifications of childhood vasculitides are derived from the 2012 Chapel Hill Consensus Conference and the related European League against Rheumatism/Paediatric Rheumatology European Society (EULAR/PRES) classification from 2010 that are based on the size of the predominantly affected blood vessels, as shown in Box 3.9 (see also Fig. 3.10).

Box 3.9 Classification of Childhood Vasculitis^a

Childhood vasculitis can be classified based on the size of the blood vessel affected:

1. Large vessel vasculitis (LVV)
 - (a) Takayasu arteritis (TAK), (see Sect. 3.6.5.1)
 - (b) Giant cell arteritis (GCA)
2. Medium-sized vessel vasculitis
 - (a) Childhood polyarteritis nodosa (cPAN) (see Sect. 3.6.5.2)
 - (b) Kawasaki disease (KD) (see Sect. 3.6.5.3)
3. Small vessel vasculitis (SVV)
 - (a) Pauci-immune vasculitis/ANCA-associated vasculitis (AAV) (see Sect. 3.6.3)
 - (i) Microscopic polyangiitis (MPA) (see Sect. 3.6.3.4)
 - (ii) Granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis) (see Sect. 3.6.3.5)
 - (iii) Eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg–Strauss syndrome) (see Sect. 3.6.3.6)
 - (iv) Renal limited vasculitis (pauci-immune necrotizing and crescentic GN (NCGN))
 - (b) Immune complex vasculitis
 - (i) Schönlein–Henoch purpura (SHP)/Schönlein–Henoch nephritis (SHN or IgA vasculitis, IgAV) (see Sect. 3.6.2)
 - (ii) Cryoglobulinemic vasculitis (CV)
 - (iii) Anti-glomerular basement membrane (anti-GBM) disease (see Table 3.12)
4. Vasculitis associated with systemic disease
 - (a) Lupus vasculitis (lupus nephritis, LN) (see Sect. 3.6.4)
 - (b) Vasculitis associated with chronic juvenile arthritis, mixed connective tissue disease and overlap syndromes
5. Vasculitis associated with probable etiology
 - (a) Vasculitides associated with infections, malignancy, drugs, hypersensitivity

^aBased on the 2012 Chapel Hill Consensus Conference (CHCC 2012)

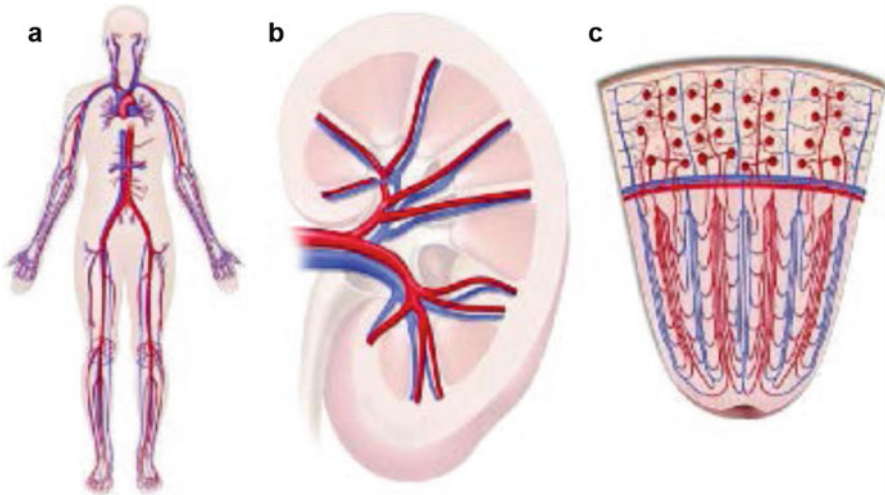


Fig. 3.10 Types of vessels that are defined as large vessels (a), medium vessels (b), and small vessels (c) in the Chapel Hill Consensus Conference nomenclature system. The kidney is used to exemplify medium and small vessels. Large vessels are the aorta and its major branches and the analogous veins. Medium vessels are the main visceral arteries and veins and their initial branches. Small vessels are intraparenchymal arteries, arterioles, capillaries, venules, and veins (With permission from Jennette et al. 2012)

3.6.3 Schönlein–Henoch Purpura Nephritis

3.6.3.1 Abstract

- Schönlein–Henoch purpura (SHP) is the most common vasculitis in children. Manifestations in addition to purpura and/or petechiae (with normal thrombocyte numbers), predominantly of the lower limbs, are abdominal pain (associated with submucosal vasculitis), joint involvement (nondeforming arthritis/arthralgia), and nephritis.
- SHP vasculitis is characterized by granulocytic infiltrates in the walls of small arterioles and venules (leukocytoclastic vasculitis) with immunoglobulin A (IgA) deposits, hence the name IgA vasculitis or IgAV (see Box 3.9).
- About 80 % of children with SHP will develop microscopic and occasionally macroscopic hematuria. One-third of patients with SHP present with abnormal urinalysis (mostly hematuria with or without proteinuria), less than 10 % develop nephritic and/or nephrotic syndrome. Proteinuria is mild and transient in most instances, and both hematuria and proteinuria are expected to resolve within 1–3 months of onset of the purpura.
- In contrast, nephrotic syndrome, severe histopathological changes by kidney biopsy and rapid rise of creatinine (rapidly progressive glomerulonephritis, RPGN) are ominous signs associated with an increased risk of chronic (CKD) or end-stage kidney disease (ESRD).



Fig. 3.11 Typical lower limb purpura in a teenage patient with recurrent Schönlein–Henoch purpura and mild SHP nephritis

- The majority of patients with SHP do not require medical therapy. Patients suffering from severe abdominal pain or arthritis benefit from glucocorticoids or nonsteroidal anti-inflammatory drugs. Glucocorticoids during the acute presentation of SHP (e.g., RPGN) do not prevent the occurrence of GN or affect long-term outcome.
- SHP is an acute, self-limited disease lasting about 4 weeks. Fifteen to 60 % of patients experience one or more purpura recurrences. The long-term prognosis is determined by the severity of the associated glomerulonephritis.

3.6.3.2 Definition

- In accordance with the European League against Rheumatism/Paediatric Rheumatology European Society (EULAR/PRES) criteria, the diagnosis of SHP is based on the appearance of a palpable purpura and/or petechiae predominantly on the lower limbs (Fig. 3.11) and at least one of the following features: diffuse abdominal pain, biopsy (skin, kidney) showing predominant IgA deposition, arthritis or arthralgia, and renal involvement (any hematuria or proteinuria).
- The EULAR/PRES classification provides a sensitivity of 100 %, a specificity of 87 %, and accuracy (area under the receiver operating characteristic curve (AUC)) of 93.5 %.
- SHP nephritis (SHN) is characterized by acute or chronic recurrent nephritis episodes (hematuria, proteinuria) with histological changes of kidney indiscernible from IgA nephropathy (see Sect. 3.5.2, Table 3.16) with mesangial hypercellularity and dominant (mesangial) IgA deposits.

3.6.3.3 Etiology and Pathogenesis

- SHP vasculitis affects small vessels (arterioles and venules) and is mediated by the deposition of IgA-containing immune complexes.

- SHP, similar to IgA nephropathy (IgAN), can be triggered by mucosal infections of the upper respiratory or gastrointestinal tract. No single eliciting antigen has been identified.
- Both SHP/SHN and IgAN have been linked to defective sialylation and galactosylation of IgA1 which may result in circulating (defective) IgA mixed IgA1/IgG immune complex formation.
- Persisting IgA1 containing aggregates can induce a local inflammatory response in glomerular mesangial cells.

3.6.3.4 Clinical Features of SHN

- Manifestations of SHN include isolated microhematuria or gross (macroscopic) hematuria.
- Mild transient proteinuria to nephrotic syndrome.
- Arterial hypertension is rare at presentation and may occur with minimal urinary abnormalities.
- Acute kidney injury (AKI), RPGN (rare).
- Nephrotic syndrome, clinically important hypertension, and progressive kidney failure are rare (<3 %).

3.6.3.5 Laboratory Investigations (see Table 3.19)

3.6.3.6 Renal Histopathology

- Indications for kidney biopsy in SHP/SHN are rising serum creatinine, nephrotic-range or persistent proteinuria (e.g., >20 mg/m²/h or >0.5 g/m²/day).

Table 3.19 Basic investigation and interpretation of laboratory findings in patients with SHP

Material	Test	Expected results and comments
Blood sample	Creatinine	Usually normal. Elevated creatinine may indicate acute or chronic kidney injury. Close follow-up and referral to nephrologist
	Complete blood cell count (CBC) and blood smear	Normal, with or without mild neutrophilia If anemia or pancytopenia, schistocytosis, and/or thrombocytopenia are present, consider SLE, HUS, or related autoimmune disorder
	C3, C4	Normal or elevated (acute phase reactant) If C3 is reduced, consider APIGN If C3 and C4 are reduced, consider SLE
	Albumin (total protein)	Normal. Reduced in SHP with nephrotic syndrome
Urinalysis	Blood, protein	Blood positive in 34 % (range 20–55 %), with or without proteinuria. Follow-up as per algorithm (Fig. 3.12). In 80 %, renal manifestations are present within 4 weeks of SHP onset
	Microscopy	Presence of erythrocyte or mixed cellular casts indicate nephritic syndrome
	Upc	Simple quantitation (and follow-up) of urine protein excretion when urinalysis (Albustix) is positive

- Although severe inflammatory changes and crescents are more frequently found in patients with clinically severe nephritis, no single biopsy classification scheme for the long-term outcome of SHN has been widely accepted or independently validated.
- Tubulointerstitial changes (interstitial mononuclear infiltrate, interstitial edema, tubular injury) and signs of chronicity (interstitial fibrosis and tubular atrophy, fibrous crescents, global sclerosis, and vascular hyalinosis and intimal hyperplasia) – in association with clinical findings (rising creatinine, large proteinuria) – indicate disease progression with poor outcome.

3.6.3.7 Treatment

Patient Monitoring

- Proteinuria usually appears during the first week, but <3 % of patients will develop chronic kidney disease.
- Eighty percent of patients with SHN demonstrate proteinuria within the first 4 weeks and all within 3 months of onset.
- The algorithm (Fig. 3.12) attempts to balance benefit (or risk) with feasibility and costs of monitoring.
- Urine protein monitoring can be done by a nurse or trained parent/family member, provided results are reported back to a physician.
- Patient is discharged from surveillance if free of proteinuria and recurrences by 6 months.
- Follow-up beyond 6 months of patients with persistent SHN/proteinuria.
- Worsening proteinuria or declining renal function should prompt referral to nephrologist for kidney biopsy.

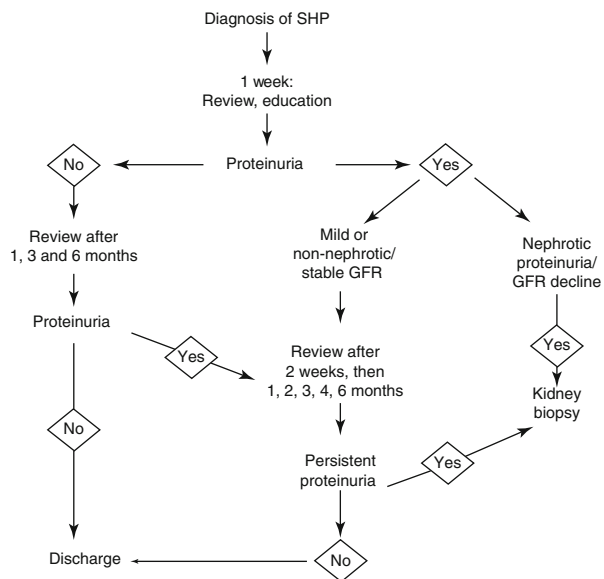


Fig. 3.12 Algorithm for the monitoring for SHP nephritis and indication for kidney biopsy

Medication Therapy of SHP/SHN

- Treatment of SHP is symptomatic and consists of pain medication (usually non-steroidal anti-inflammatory drugs, e.g., naproxen) for arthralgia.
- Severe abdominal pain and arthritis responded to a short course of glucocorticoids.
- In a recently published randomized controlled trial from Finland, prednisone at a dose of 1 mg/kg daily for 2 weeks, followed by a 2-week taper, reduced the severity and duration of abdominal and joint pain.
- Prednisone at this dose was not effective in treating the purpura, preventing nephritis, shortening disease duration or preventing recurrences.
- The 2012 KDIGO Clinical Practice Guideline for Glomerulonephritis suggests that children with SHN and persistent proteinuria $>0.5\text{--}1\text{ g/day}/1.73\text{ m}^2$ ($0.3\text{--}0.6\text{ g/day}/\text{m}^2$) be treated with ACE inhibitor or ARB.
- Treatment of patients with significant renal involvement is controversial.
- Immunosuppressive regimens include glucocorticoids (methylprednisolone pulses [followed by oral prednisone]), cyclophosphamide, plasma exchange, cyclosporine A (CSA)/tacrolimus, or azathioprine.
- CSA or mycophenolate mofetil (MMF) appear to be as effective as glucocorticoid therapy to achieve freedom from proteinuria and maintain long-term renal function.
- A practical regimen for patients with SHN with nephrotic syndrome is prednisone at a dose of $60\text{ mg}/\text{m}^2/\text{day}$ ($2\text{ mg}/\text{kg}/\text{day}$) for 1 month (maximum $60\text{ mg}/\text{m}^2/\text{day}$), followed by $40\text{ mg}/\text{m}^2$ every 2 days (max $40\text{ mg}/\text{dose}$) followed by $0.5\text{ mg}/\text{kg}$ every other day (total duration up to 6 months). ACE inhibitors or ARBs can be added for prolonged proteinuria.
- Cyclophosphamide PO or IV has been used for severe disease.
- Alternatively, CSA (starting dose $5\text{ mg}/\text{kg}/\text{day}$), tacrolimus ($0.1\text{--}0.2\text{ mg}/\text{kg}/\text{day}$ divided in 2 doses; target trough level $4\text{--}6\text{ ng}/\text{ml}$), or MMF ($600\text{--}900\text{ mg}/\text{m}^2/\text{day}$ divided BID) may be initiated for 6 months (to avoid cyclophosphamide-associated adverse effects).

3.6.3.8 Prognosis and Outcome

- The renal outcome of SHP glomerulonephritis is favorable.
- Among patients, who developed CKD following SHN, $>50\%$ presented with a nephrotic–nephritic syndrome, 40% with nephrotic syndrome, and 15% with a nephritic syndrome and/or heavy, non-nephrotic proteinuria. Less than 5% of children with CKD had only hematuria or minimal proteinuria.
- Of patients who developed ESRD during follow-up, all had nephrotic proteinuria at onset and decreased GFR $<70\text{ ml}/\text{min}/1.73\text{ m}^2$ at 3 years. Conversely, less than 20% of children with nephrotic proteinuria and severe histopathological changes and none with crescentic GN ($>50\%$ crescents) is expected to recover normal kidney function if left untreated.
- The relative risk of progression (doubling of serum creatinine) was estimated to be 1.77 for each $1\text{ g}/\text{day}$ of proteinuria. The relative risk rises to 3.8 and 4.7 with impaired GFR (versus normal GFR) and nephrotic-range versus mild proteinuria at onset, respectively.
- Recurrence of non-renal symptoms (purpura) does not correlate with renal outcome.

3.6.4 ANCA-Associated Vasculitis (AAV)

Antineutrophil cytoplasmic antibody (ANCA)-mediated vasculitis, also called pauci-immune vasculitis, is characterized by absence of immune deposits in tissue biopsies by immunofluorescence. It is an important differential diagnosis for rapidly progressive glomerulonephritis (RPGN) in children (see Sect. 3.4.3).

3.6.4.1 Definitions

AAV typically involves small vessels with a predisposition for small arteries, arterioles, capillaries, and postcapillary venules, including small renal vessels (Box 3.9). ANCA (see Box 3.10) are detected in 90 % of patients with small vessel vasculitis. The characteristic glomerular lesions are paucimmune (immunofluorescence-negative) focal and segmental necrotizing and crescentic glomerulonephritis (NCGN). The latter may also occur as renal-limited disease.

3.6.4.2 Clinical Presentation of AAV

- Systemic vasculitides affect a variety of tissues, including upper and lower respiratory tract, central nervous system, eyes, skin and kidney.
- Acute nephritis with microscopic hematuria, dysmorphic RBCs and RBC casts.
- Usually moderate proteinuria $<1 \text{ g/m}^2$ per day.

Box 3.10 Anti-Neutrophil Cytoplasmic Antibodies (ANCA)

- An indirect immunofluorescence assay on ethanol fixed neutrophils is traditionally used to screen for ANCA
- Sera from patients with ANCA-associated vasculitis (AAV) produce distinct pattern of immunofluorescence:
 - Staining around the nucleus is known as perinuclear (pANCA). It is generally associated with antibodies against the enzyme myeloperoxidase (MPO)
 - Diffuse granular staining of the neutrophil cytoplasm is termed as cytoplasmic (cANCA). It corresponds to specificity for the enzyme proteinase 3 (PR3)
- ANCA bind to antigens in the primary granules of neutrophils and peroxidase-positive lysosomes of monocytes
- Another proposed target for ANCA is lysosomal-associated membrane protein 2 (LAMP2)
- ANCA are an important serological marker for pauci-immune vasculitides and glomerulonephritides
- There is evidence that ANCA activate activated neutrophils (and monocytes) and that ANCA-reactive neutrophils activate complement via the alternative pathway
- Testing for ANCA should include an enzyme-linked immunoassay (ELISA) with selective antigen specificity for MPO and PR3

- Rapidly progressive GN with declining kidney function over days to weeks.
- 10 % of patients with AAV and necrotizing crescentic GN (NCGN) suffer severe (diffuse) pulmonary hemorrhage associated with high death rates.
- Minority of patients presents with mild or asymptomatic disease.

3.6.4.3 Microscopic Polyangiitis (MPA)

- MPA is a necrotizing vasculitis with few or no immune deposits and no granulomatous inflammation involving small vessels.
- Extrarenal manifestations:
 - Pulmonary: hemoptysis, pulmonary hemorrhage
 - Upper respiratory: chronic sinusitis, otitis media, nasal passage ulcers
 - Skin: purpuric rashes, leukocytoclastic vasculitis
 - Constitutional: fever, malaise, weight loss, anorexia
- Investigations:
 - Anemia, leukocytosis, thrombocytosis, elevated ESR and C-reactive protein (CRP)
 - C3 and C4 serum complement (normal)
 - ANCA: 65 % of patients are pANCA (anti-MPO) and 10 % cANCA (anti-PR3) positive
 - Chest X-ray, CT chest (pulmonary hemorrhage, pneumonia)
 - Renal biopsy

3.6.4.4 Granulomatosis with Polyangiitis (GPA, Wegener's Granulomatosis)

- Triad of GPA: necrotizing granulomatous inflammation of upper or lower respiratory tract, vasculitis involving small to medium-sized vessels, and necrotizing glomerulonephritis
- Extrarenal manifestations:
 - Upper respiratory tract: sinusitis, epistaxis
 - Lower respiratory tract: pulmonary infiltrates, pulmonary hemorrhage, hemoptysis, pulmonary nodules
 - Constitutional features: fever, weight loss, arthralgia/arthritis, rash
 - Neurological: mononeuritis multiplex, stroke
 - Cardiovascular: pericarditis, myocardial infarction
- Investigations:
 - Anemia, leukocytosis, thrombocytosis, elevated ESR
 - Normal serum levels of C3 and C4
 - ANCA: 80–90 % of patients are cANCA (anti-PR3) positive
 - Chest X-ray, CT chest (granuloma, pneumonia, hemorrhage)
 - Renal biopsy
 - Lung/sinus biopsy (granuloma)

3.6.4.5 Eosinophilic Granulomatosis with Polyangiitis (EGPA; former Churg–Strauss Syndrome)

- EGPA is rare in children.
- Characterized by eosinophil-rich and necrotizing granulomatous inflammation involving the respiratory tract.

- Granulomatous and non-granulomatous extravascular inflammation is common.
- Associated with eosinophilia and asthma.

3.6.4.6 Renal Histopathology of ANCA-Associated Vasculitis

- Renal manifestations are similar in MPA and GPA, and in renal-limited (pauci-immune) NCGN (see also Sect. 3.4, Table 3.12).
- Light microscopy: The hallmark finding is necrotizing injury of the glomerular tuft and crescent formation (necrotizing and crescentic glomerulonephritis). Segmental fibrinoid necrosis, neutrophilic infiltration, karyorrhexis; vasculitis involving interlobular arteries with or without crescents. Late changes are (diffuse) glomerulosclerosis and nephron loss.
- Immunofluorescence: no or minimal deposits with occasional weak positivity for C3. Invariable presence of fibrin deposition.
- Electron microscopy: Display of glomerular endothelial injury (swelling, GBM detachment), gaps in GBM and Bowman's capsule.

3.6.4.7 Treatment of ANCA Vasculitis

- AAV treatment, particularly of MPA and GPA, is similar.
- *Induction therapy*: Glucocorticoids and cyclophosphamide.
- Alternatively, glucocorticoids and rituximab may be used as initial treatment in patients with milder disease (absence of pulmonary hemorrhage and preserved kidney function).
- Methylprednisolone IV (3–6) doses (10 mg/kg per dose or 500 mg/1.73 m²), followed by oral prednisolone (or prednisone) 2 mg/kg per day up to 60 mg per day. Prednisolone is given for 4 weeks and then tapered to alternate-day dosing.
- IV cyclophosphamide (500–750 mg/m²/dose) is given every 4 weeks for 6 months; it is stopped after 3 months, if patient remains dialysis-dependent.
- When oral cyclophosphamide is used, give 1.5–2 mg/kg/day (reduce oral dose for GFR <20 ml/1.73 m²). Adjust daily dose to keep WBC >3/nl.
- Rituximab is dosed 375 mg/m² every week × 4 doses.
- *Maintenance therapy, once remission is achieved*:
 - Oral azathioprine 1–2 mg/kg/day or mycophenolate mofetil (MMF) up to 1 g/1.73 m² twice daily.
 - Methotrexate (0.3 mg/kg per week, not exceeding 25 mg/week) if patient is intolerant to azathioprine and MMF, and if GFR is >60 ml/min/1.73 m².
 - Trimethoprim sulfamethoxazole has been tried in patients with upper respiratory tract disease.
- Maintenance therapy is continued for at least 18 months, if patient remains in remission.
- *Plasmapheresis* is indicated in children with rapidly rising serum creatinine or requiring dialysis, diffuse pulmonary hemorrhage, or poor response to induction therapy.
- All patients with systemic disease should receive immunosuppressive therapy, regardless of kidney function.
- Careful judgement is needed when patients with severe NCGN have already reached ESRD. Immunosuppressants may not be appropriate in the absence of systemic disease.

3.6.4.8 Outcome

- Five-year survival is >80 %.
- About 30 % of patients progress to ESRD.
- Untreated ANCA-associated NCGN has a poor prognosis. Immunosuppressive treatment has dramatically improved short- and long-term survival.
- Histological criteria affecting renal outcome are the percentage of glomeruli with crescents or globally sclerosed glomeruli. The prognosis is favorable in the presence of limited injury (e.g. focal GN, crescents in <50 %) and poor with diffuse (>50 %) global glomerulosclerosis.
- Patients may experience recurrence of AAV or NCGN after kidney transplantation.

3.6.5 Lupus Nephritis (LN)

Systemic lupus erythematosus (SLE) is a multisystemic inflammatory disease associated with autoantibodies to different cell components. The clinical manifestations can be varied depending on the type and extent of organ system involvement. It is a chronic disease characterized by remissions and relapses. The peak incidence in children is around puberty. Ethnicity affects prevalence and severity of SLE and LN. Both are 2–3 times higher in East Asian and Southeast Asian and in native North American children compared with European children. High rates are likewise found among people of African ancestry.

3.6.5.1 Definition

The American Rheumatology Association (ARA, changed in 1988 to “American College of Rheumatology” (ACR)) has put forth the ARA criteria for the diagnosis of SLE. At least 4 of the 11 criteria should be positive to diagnose SLE. Renal manifestations are a part of the diagnostic criteria for SLE. However, some of these manifestations may occur in isolation or may not present early in the disease course (Box 3.11). Lupus nephritis is an important determinant for the survival of patients with SLE. The updated 2012 guideline recommendations of the American College of Rheumatology for the diagnosis and treatment of LN are summarized in Box 3.12.

3.6.5.2 Pathogenesis

Autoantibodies, immune complexes, complement activation, and T lymphocytes are responsible for mediating the damage to various organ systems. Alteration in regulatory T cells increases autoreactive T lymphocytes. Autoantibodies are produced against various components of the cell, especially nuclear components. Dendritic cells play a role in activation of self-reactive T and B cells resulting in the production of autoantibodies.

3.6.5.3 Clinical Features

Extrarenal

- Systemic features: weight loss, loss of appetite, fever
- Skin manifestations: malar rash, discoid rash, photosensitivity, Reynaud’s phenomenon, oral ulcers
- Musculoskeletal: arthralgia, arthritis, tendinitis, myositis

Box 3.11 American Rheumatology Association Criteria for SLE (1982)^a

- Malar rash
- Discoid rash
- Photosensitivity
- Oral ulcers
- Arthritis
- Serositis – pleuritis or pericarditis
- Renal abnormalities – persistent proteinuria >0.5 g/day/1.73m² or $>3+$ or cellular casts in urine
- Neurologic disorder – seizures or psychosis
- Hematologic disorder – hemolytic anemia, leukopenia $4 \times 10^9/l$ ($<4,000/mm^3$) or lymphopenia $1.5 \times 10^9/l$ ($<1,500/mm^3$) or thrombocytopenia $100 \times 10^9/l$ ($<100,000/mm^3$) (on two or more occasions)
- Immunologic disorder – abnormal anti-dsDNA titer, or presence of anti-Sm antigen
- Antinuclear antibody – abnormal titer of antinuclear antibody

^aFour or more criteria, definite SLE; 3 criteria, probable SLE; 2 criteria, possible SLE

Box 3.12 American College of Rheumatology Guideline Recommendations for the Diagnosis and Treatment of Lupus Nephritis*Diagnostic*

- Renal biopsy for all SLE patients with active LN

Therapy

- Induction therapy with MMF or Euro-Lupus cyclophosphamide for active LN class III/IV
- No modification of the induction therapy before 6 months of treatment
- Maintenance therapy with MMF or azathioprine
- Rituximab or calcineurin inhibitor optionally for refractory LN

Adjunctive therapy

- Hydroxychloroquine for all patients with LN
- Blood-pressure control
- Hyperlipidemia treatment with statins
- Angiotensin inhibition for all patients with proteinuria of >0.5 g/1.73 m² per day
- Counseling on suitable contraception and pregnancy risks for all female patients of child-bearing potential

- Hematological: anemia, bleeding manifestation, thrombosis, Coombs test positivity with or without hemolytic anemia, lymphadenopathy, hepatosplenomegaly
- Pulmonary: pneumonitis, pleuritis, pulmonary hemorrhage
- Cardiovascular: myocarditis, pericarditis, (Libman–Sacks) endocarditis
- Neuropsychiatric: headache, chorea, cranial nerve palsy, hemiparesis, seizures

Renal

- Renal manifestations are seen in up to 80 % of patients with SLE, usually within the first 6 months.
- Asymptomatic proteinuria, hematuria, acute nephritis, nephrotic syndrome, rapidly progressive glomerulonephritis, chronic kidney disease, hypertension.
- Hypertension and/or decreased renal function in 40–50 % of patients.

3.6.5.4 Laboratory Investigations

- Urinalysis: proteinuria from mild to nephrotic range, RBC, WBC, RBC casts
- Renal function tests
- Complement: serum C3, C4, CH50 (all typically reduced)
- Serological tests:
 1. Antinuclear antibodies (ANA): highly sensitive (95–98 %), but non-specific
 2. Anti-dsDNA: highly specific for SLE (90–95 %)
 3. Antibodies to ribonucleoprotein, anti-Sm antibody (100 % specific), anti-histone antibodies, and antiphospholipid antibodies may be present
- Skin biopsy, renal biopsy

3.6.5.5 Renal Histopathology

- Histological changes in LN comprise vascular, glomerular and tubulointerstitial lesions. The glomerular lesions are described in terms of mesangial, endothelial and epithelial patterns of injury.
- The WHO morphological classification is widely used to grade the severity of lupus nephritis (Box 3.13). Its latest modification by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) from 2003 is shown in (Boxes 3.14 and 3.15).

3.6.5.6 Treatment

- The treatment is based on the severity of renal and extrarenal disease and renal histopathology (Table 3.20).
- Fig. 3.13 depicts the practical ACR consensus algorithm for adult patients with LN emphasizing the shift from IVCY to MMF.
- Further changes in the medical management of juvenile LN are expected following current trials with biological agents aimed at reducing adverse events associated with exposure to high-dose, long-term glucocorticoids and to cytotoxic agents.

3.6.5.7 Prognosis

- The prognosis of SLE has improved with aggressive therapy.
- Complete or partial remission is usually achieved by 18–24 months.
- Deaths are due to infections, thrombotic, or neurological complications.
- With current treatment regimens, most patients have stable renal functions at 10 years after onset of disease.
- Complications: infections, atherosclerosis, cardiovascular morbidity.

Box 3.13 WHO Morphologic Classification of Lupus Nephritis (Modified in 1982)

Class I Normal glomeruli

- (a) Nil (by all techniques)
- (b) Normal by light microscopy but deposits by electron or immunofluorescence microscopy

Class II Pure mesangial alterations (mesangiopathy)

- (a) Mesangial widening and/or mild hypercellularity (+)
- (b) Moderate hypercellularity (++)

Class III Focal segmental glomerulonephritis (associated with mild or moderate mesangial alterations)

- (a) With “active” necrotizing lesions
- (b) With “active” and sclerosing lesions
- (c) With sclerosing lesions

Class IV Diffuse glomerulonephritis (severe mesangial, endocapillary, or mesangiocapillary proliferation and/or extensive subendothelial deposits)

- (a) Without segmental lesions
- (b) With “active” necrotizing lesions
- (c) With “active” and sclerosing lesions
- (d) With sclerosing lesions

Class V Diffuse membranous glomerulonephritis

- (a) Pure membranous glomerulonephritis
- (b) Associated with lesions of category II (a or b)
- (c) Associated with lesions of category III (a–c)
- (d) Associated with lesions of category IV (a–d)

Class VI Advanced sclerosing glomerulonephritis

Box 3.14 International Society of Nephrology/Renal Pathology Society (ISN/RPS) Classification of Lupus Nephritis (2003)^a

Class I Minimal mesangial lupus nephritis

Class II Mesangial proliferative lupus nephritis

Class III Focal lupus nephritis^aClass IV Diffuse segmental (IV-S) or global (IV-G) lupus nephritis^aClass V Membranous lupus nephritis^bClass VI Advanced sclerosing lupus nephritis^c

^aClass III and IV are further characterized as *A* active, *C* chronic, and *A/C* active and chronic lesions (the activity and chronicity indices are listed in Box 3.15)

^bClass V can occur in combination with class II, III or IV, in which case both will be noted (e.g., “lupus nephritis class II and V”)

^cDesignates biopsy with >90 % global glomerulosclerosis attributed to lupus nephritis without evidence of active glomerular disease

Box 3.15 Active and Chronic Glomerular Lesions as Defined in the ISN/RPS 2003 Classification of Lupus Nephritis

Active lesions^a

Endocapillary hypercellularity with or without leukocyte infiltration and with substantial luminal reduction

Karyorrhexis

Fibrinoid necrosis

Rupture of glomerular basement membrane

Crescents – cellular or fibro-cellular

Subendothelial deposits identifiable by light microscopy (wire loops)

Intraluminal immune aggregates (hyaline thrombi)

Chronic lesions^b

Glomerular sclerosis (segmental, global)

Fibrous adhesions

Fibrous crescents

Interstitial fibrosis

Tubular atrophy

^aActive lesions graded as 0–3 (necrosis and cellular crescents graded 0–6); max. activity score, 24

^bchronic lesions, maximum score 10

Poor Prognostic Factors

- Clinical: younger age, males, African origin, hypertension, renal dysfunction at onset, delay in treatment, response to treatment in the first year
- Class IV lupus nephritis, extensive crescents, necrotizing glomerular lesions

3.6.5.8 Renal Transplantation

- Renal transplant should be deferred until disease activity and the serological markers are quiescent. The duration of quiescence is not well defined but generally accepted as 1–2 years.
- Risk of recurrence of LN in the graft is low.

3.6.6 Other Vasculitides

3.6.6.1 Takayasu Arteritis

- Granulomatous vasculitis involving the aorta and its major branches. Hypertension is the most common manifestation due to either narrowing of the aorta or due to renal artery stenosis.
- Common cause of renovascular hypertension in some Asian countries.
- Weak peripheral unequal pulses, claudications, bruit over the aorta or its branches.
- Angiography shows stenosis or occlusion of affected blood vessels.
- Glucocorticoids may be used during acute phase; reconstructive vascular surgery may be required later.

Table 3.20 Therapeutic regimens for lupus nephritis^a

Disease	Induction	Maintenance
Class II or mild disease	PRED (0.5–1.0 mg/kg/day for 4–6 weeks)	Tapering PRED for 2–3 years after remission AZA (1–2 mg/kg/day) may be considered if no response by 3 months or switch to protocol for moderate disease
Class III or moderate disease	PRED (1.0–1.5 mg/kg/day for 4–6 weeks) AZA 1–2 mg/kg/day, or MMF (900–1,200 mg/m ² /day, or IVCY monthly pulses 0.5–1.0 g/m ² /dose × 6 doses	Tapering PRED for 2–3 years after remission AZA to continue, MMF may be reduced to 750 mg/m ² /day or IVCY quarterly pulses for 18 months
Class IV or severe disease	IV methylprednisolone pulses 20–25 mg/kg/dose (max 1 g) × 3 pulses followed by PRED PO 1.0–1.5 mg/kg/day and IVCY monthly × 6 doses 0.5–1.0 mg/m ² /dose or MMF 1,200 mg/m ² /day × 6 months If treatment-refractory: RTX, PLEX, IVIG	Tapering PRED for up to 5 years after remission IVCY quarterly pulses for 18 months or MMF 750–1,000 mg/m ² /day or AZA 1–2 mg/kg/day
Class V	High-dose PRED (1.0–1.5 mg/kg/day) with ACE inhibition, or May combine with CSA 3–5 mg/kg/day or MMF, or RTX	CSA/ACEi ? Low-dose PRED or repeat RTX (if effective)

^aAll patients with LN should also be treated with hydroxychloroquin and antiproteinuric agents (ACE inhibition) if appropriate

ACEi angiotensin-converting enzyme inhibitor, AZA azathioprine, CSA cyclosporine A (or tacrolimus 0.1–0.2 mg/kg/day), CYP cyclophosphamide, IV intravenous, IVIG intravenous immunoglobulin, MMF mycophenolate mofetil, PLEX plasma exchange, PRED prednisone or prednisolone, RTX rituximab (1 g/m² × 2, two weeks apart)

3.6.6.2 Childhood Polyarteritis Nodosa (cPAN)

- PAN is a necrotizing vasculitis associated with aneurismal nodules along the walls of *medium size* arteries of skin, peripheral nerves, muscles, gastrointestinal tract, and kidneys.
- It does not affect renal arterioles and capillaries and is not associated with ANCA.
- Rare in children.
- Renal manifestations: asymptomatic hematuria, proteinuria, acute nephritis, nephrotic syndrome, hypertension.
- Extrarenal manifestations: fever, malaise, weight loss, myalgia, arthralgia, abdominal pain, visual loss, focal neurological deficits, mononeuritis multiplex, testicular pain and occasionally, cardiac or respiratory manifestations.
- It can be associated with hepatitis B.
- Renal biopsy and renal angiogram may be required for evaluation of renal disease.

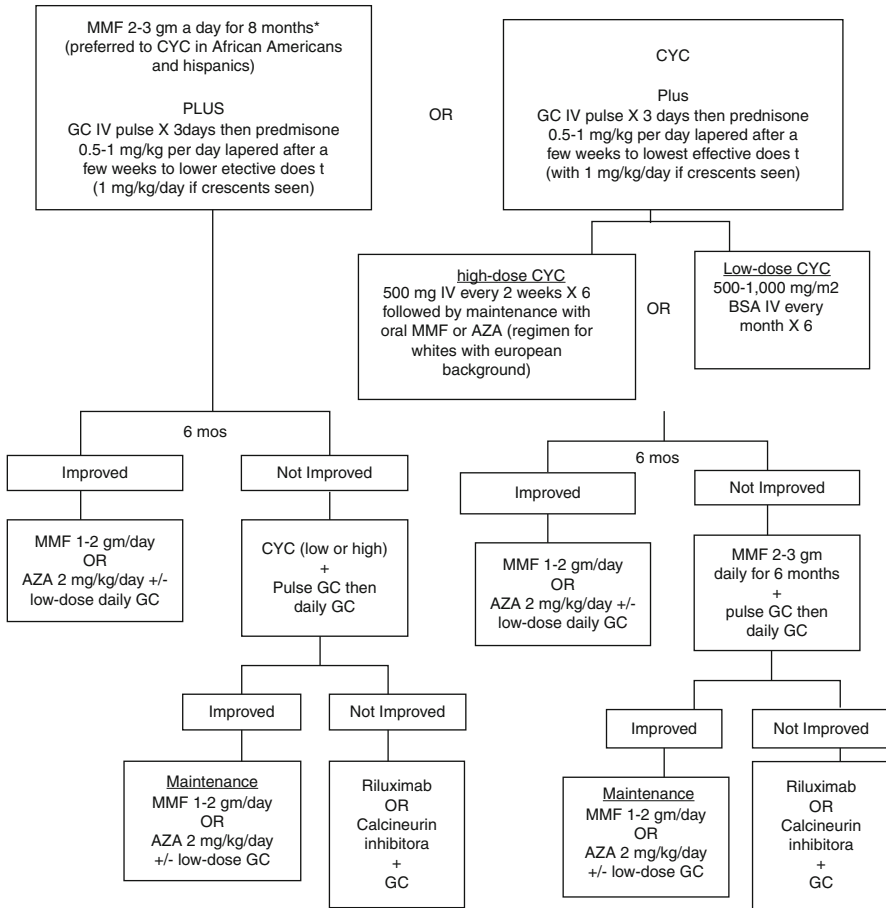


Fig. 3.13 Lupus nephritis class III/IV induction therapy. *The Task Force Panel discussed their preference of MMF over cyclophosphamide (CYC) in patients who desire to preserve fertility; †recommended background therapies for most patients are discussed in section III in the publication. AZA azathioprine, BSA body surface area, GC glucocorticoids, IV intravenous, MMF mycophenolate mofetil (With permission from Hahn et al. 2012)

- Renal medium-sized vessel aneurysms, perfusion defects, collaterals, and delayed emptying of small vessels may be seen on angiography.
- Glucocorticoids and cyclophosphamide are the mainstay of treatment.

3.6.6.3 Kawasaki Disease (KD)

- KD is the commonest pediatric vasculitis (after SHP). Incidence per 100,000 <5 years is 138 in Japan and <18 in Europe and North America.
- Affects infants and young children under 5 years of age.
- Five of 6 diagnostic criteria have to be fulfilled: fever persisting more than 5 days (mandatory), palmar erythema, polymorphous exanthema, bilateral conjunctival injection/congestion, strawberry tongue/red lips and acute, non-purulent cervical lymphadenopathy. Coronary aneurysms may occur.

- Renal involvement may occur with hematuria and proteinuria.
- Treated with aspirin and intravenous immunoglobulin with or without glucocorticoid and (if accessible) infliximab.

3.7 Hemolytic Uremic Syndrome/Thrombotic Microangiopathies

3.7.1 Introduction and Definitions

Hemolytic uremic syndrome (HUS) is defined clinically by the triad of microangiopathic hemolytic anemia, thrombocytopenia and renal involvement/acute kidney injury (AKI). Based on common pathomorphological features, HUS and clinically similar, but etiologically heterogeneous disorders, such as thrombotic thrombocytopenic purpura (TTP), are often referred to as thrombotic microangiopathies (TMA) (see Box 3.16).

TTP is traditionally defined by the added features of neurological involvement and fever. However, the latter two may also be present in HUS and do therefore not distinguish between the two syndromes.

The term “typical” (or “classical”) HUS is reserved for HUS induced by Shiga toxin-producing bacteria (STPB, predominantly Shiga toxin-producing *Escherichia coli* (STEC); STEC HUS). “Atypical” initially referred to all non-STEC HUS, but is now commonly applied to HUS related to the dysregulation of the alternative pathway (AP) of complement (aHUS; Box 3.16, Fig. 3.14).

Despite substantial progress in this field over the past decade, no etiological diagnosis is found in about 40 % of patients with atypical forms of HUS.

3.7.2 Approach to a Patient with HUS

- Children with HUS may present at any age, often, but not exclusively, in the context of an infection.
- In more than 70 %, HUS is preceded by diarrhea, often as colitis with abdominal cramps and frequent discharge of bloody stools (generally indicative of Shiga toxin-induced HUS).
- For prognostic and therapeutic reasons, presumptive classification of the type of HUS or thrombotic microangiopathy and rapid etiological diagnosis are warranted in each case.
- The pathophysiological and genetic workup can be time consuming or remain unsuccessful. In many settings, appropriate laboratories or resources may be lacking.
- The correct etiological diagnosis of aHUS is complex and may involve more than one gene mutation.
- Box 3.17 lists a set of *six key questions* at the time of presentation that help narrow down the possible etiology of the HUS.
- A rationale approach for the diagnosis and initial management of HUS/TMA is provided in Fig. 3.15. The diagram is based on the recommendations of the “European Paediatric Study Group for HUS” from 2009.

Box 3.16 Thrombotic Microangiopathies (TMA)

A. Etiologically recognized forms of HUS and TTP

1. Infection induced HUS

1.1 Shiga toxin-producing bacteria (STPB):

Enterohemorrhagic *Escherichia coli* (STEC/EHEC) O157:H7 (worldwide most commonly associated with Shiga toxin-mediated HUS), *Shigella dysenteriae* type 1, *Citrobacter freundii*

1.2 Neuraminidase-producing organisms:

Streptococcus pneumoniae, *Clostridium perfringens*, influenza virus

1.3 Human immunodeficiency virus (HIV)

2. HUS due to disorders of complement regulation (mostly alternative pathway)

2.1 Inherited:

2.1.1 Haploinsufficiency

Soluble (plasma) factors: Factor H (CFH), factor I (CFI), factor H related proteins 1 (CFHR1) and 5 (CFHR5)

Membrane-bound regulators: membrane cofactor (MCP, CD46)

Other proteins interacting with the complement pathway: thrombomodulin (THBD)

2.1.2 Copy number variations:

e.g., CHFR 1/3 deletion, CFH/CHFR1 hybrid

2.1.3 Activating (heterozygous) mutations: CFB, C3

2.2 Acquired:

Anti-factor H (CFH) autoantibody (may be associated with CFHR1/3 deletion)

3. ADAMTS13 (von Willebrand factor-cleaving protease) deficiency (TTP) (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13)

3.1 Inherited:

Upshaw-Schulman syndrome (autosomal recessive)

3.2 Acquired:

ADAMTS13 autoantibody

4. Metabolic deficiencies (not directly complement-related)

4.1 Defective cobalamin metabolism:

Cobalamin processing deficiency of the cblC type (mutations in *MMACHC* [methylmalonic aciduria and homocystinuria, cblC type], autosomal recessive)

4.2 Diacylglycerol kinase-epsilon (DGKE) (autosomal recessive)

5. Drug induced:

Quinine, mitomycin C, ticlopidine, calcineurin inhibitors

B. Speculative/unknown etiology

1. Pregnancy-associated HUS, HELLP syndrome, oral contraceptives

2. Bone marrow/stem cell transplantation (CFHR1/3 deletion?)

3. Superimposed on preexisting disorders/secondary forms:

SLE, antiphospholipid antibody syndrome, malignancy, ionizing radiation

^aGenerally heterozygous mutation leading to reduced expression of functional proteins. Few cases of homozygous deficiencies of CFH and MCP have been described (with severe phenotype)

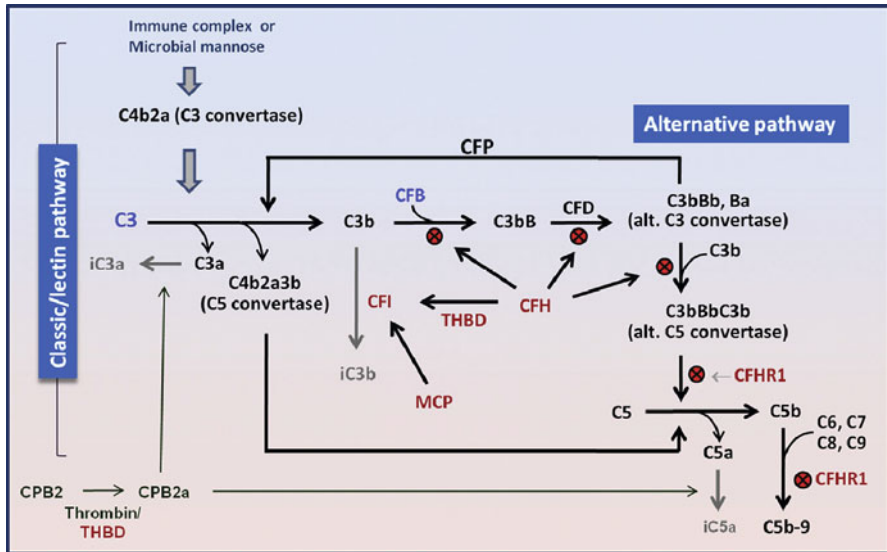


Fig. 3.14 Schematic Diagram of the Major Complement Activation Pathway and their Regulators. Depicted are the soluble regulators CFH (complement factor H) and CFI (complement factor I) who interact with cell bound MCP (membrane cofactor protein) and with THBD (thrombomodulin) to cleave activated C3 (C3b) into inactive iC3 thus preventing uncontrolled (alternative pathway) C3 convertase (C3bBb) and C5 convertase (C3bBbC3b) formation. CFHR-1 (CFH-related protein 1) may regulate C5 convertase and terminal C5b-9 “membrane attack complex” (MAC) assembly. Below-threshold concentrations or inactivating mutations of CFH, CFI, MCP and THBD as well as activating (gain-of-function) mutations of CFB (complement factor B) and C3 have all been associated with a HUS susceptibility due to excessive AP complement activation and MAC formation (With permission from Tsai 2013)

3.7.3 Typical (Enteropathic/STEC) HUS

- Generally preceded by diarrhea or (bloody) colitis.
- HUS risk 8–15 % after *E. coli* O157:H7 colitis, variable with other STEC serotypes/STPB.
- At rare occasions, diarrhea cannot be elicited.
- HUS due to urinary tract infection by STEC has been described.
- Accounts for 70–90 % HUS in preschool children (peak age group 1–5 years).
- STEC transmission with contaminated foods or drinking water, animal contact (Petting Zoo) or person to person.
- Antimotility drugs and certain antibiotics during STEC diarrhea increase the risk of developing HUS.
- Seasonal peak late summer/early fall, but sporadic or epidemic cases are seen year-round.
- Clinical Features

Box 3.17 Six Key Questions

1. Age at presentation?
2. Rapid or insidious onset/chronic HUS?
3. First presentation or recurrence of HUS?
4. Bloody colitis and/or current outbreak/epidemic of STEC infection or shigellosis?
5. Past family history for HUS?
6. Underlying renal or autoimmune disorder?

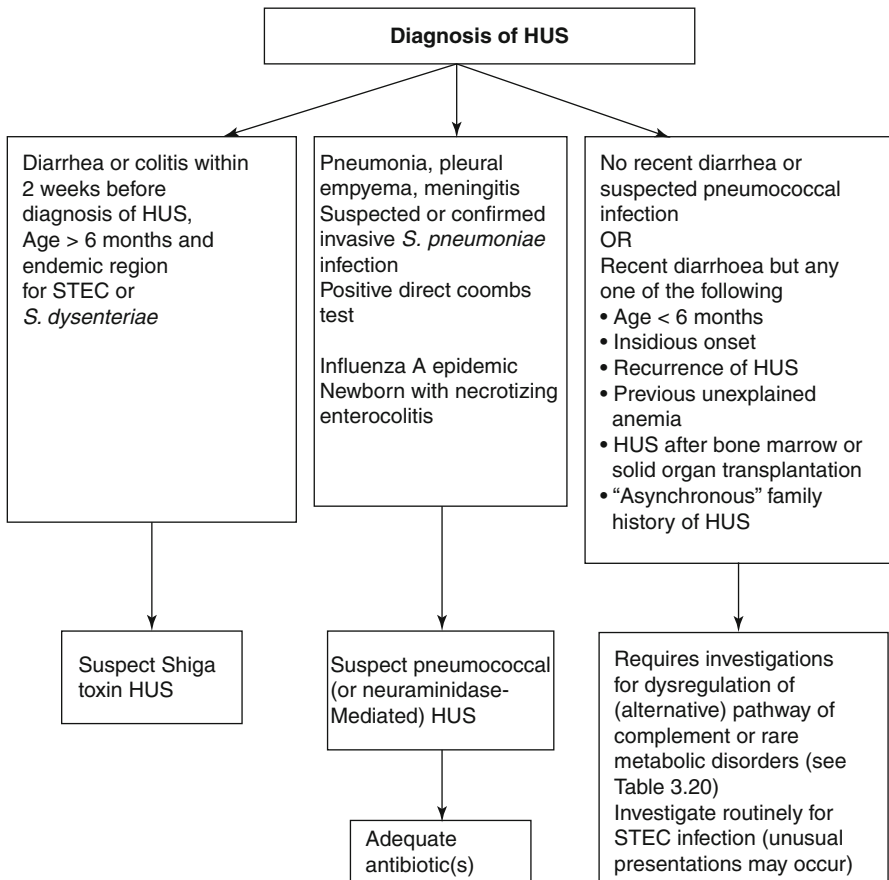


Fig. 3.15 Approach to a patient with HUS

- Triad: acute kidney injury, microangiopathic hemolytic anemia (Coombs negative, schizocytes on peripheral smear), thrombocytopenia; partial or limited HUS refers to the absence of one of the features of the triad.
- Diarrhea is typically frequent and bloody with abdominal cramps.
- Onset of STEC HUS is characterized by sudden clinical deterioration 3–7 (–10) days after begin of diarrhea.
- Moderate extracellular volume depletion. Hypovolemic shock is rare.
- Renal manifestations range from mild hematuria and proteinuria to severe AKI with renal cortical necrosis due to renal (thrombotic) ischemia.
- Other organ systems may be involved, including the gastrointestinal tract (ischemic colitis, perforation, rectal prolapse, intussusception, toxic megacolon, colonic strictures, gallstones), pancreatitis with amylase/lipase elevation or transient, occasionally lasting insulin-dependent diabetes mellitus, CNS (lethargy, irritability, seizures, paresis, coma, cerebral edema, cranial nerve palsy), retinal blindness, and myocardial ischemia or cardiomyopathy.
- Baseline Investigations
 - Complete blood count (anemia, thrombocytopenia) with a peripheral smear (schistocytes), reticulocyte count and LDH (both increased), serum haptoglobin (depleted)
 - Renal function
 - Serum lipase and amylase
 - Coagulation profile
 - Blood group typing and crossmatch
 - Urinalysis and urine culture
 - Stool culture for Shiga toxin producing bacteria and common enteropathogens
 - Fecal Shiga toxin (Vero cell assay, immunological detection); PCR for Shiga toxin and EHEC genes; serotyping of identified coliform organism; serological response to locally relevant O serotypes (Western blot, ELISA)
- Other Investigations (see also Table 3.21)
 - Direct Coombs test
 - Abdominal ultrasonography to rule out underlying structural renal abnormality/pancreatitis/gall stones, appendicitis, gangrenous or perforating colitis
 - CT abdomen if pancreatitis is suspected
 - ECG in case of dyselectrolytemia
 - Echocardiography in case of suspected pericardial perfusion or cardiac failure
 - MRI brain (or CT) in case of focal or complicated seizures, progressive lethargy or (axial) hypotonia
 - Renal biopsy (if doubtful diagnosis or delay in renal recovery): does not reliably differentiate between typical (STEC-mediated) and other forms of HUS/TMA, but useful to assess chronic renal injury/extent of cortical necrosis and renal prognosis
- Treatment
 - Pre-HUS (STEC colitis)
 - Intravenous volume expansion with isotonic saline (start within 4 days of diarrhea onset, if STEC infection suspected or proven)
 - Avoidance of antimotility agents and antibiotics (except *S. dysenteriae*)

Table 3.21 Investigations for HUS and other thrombotic microangiopathies (TMA)

HUS/TMA	Investigations ^a	Comments
STEC/STPB infection (“Typical” of STEC HUS)	Stool or rectal swab culture Free fecal toxin assay PCR for <i>stx</i> gene and STPB virulence markers in stool or bacterial isolates Anti-LPS IgM antibodies against select serotypes, anti-Stx antibodies (in serum)	Consider complement regulator defect in children with severe or unusual course STEC HUS
Infection by <i>S. pneumoniae</i> or other NANase producing pathogen (“Pneumococcal” HUS)	Bacterial culture (blood, CSF, pleural fluid) Respiratory viral antigen/PCR/culture Direct Coombs test Thomson-Friedenreich (TF) antigen detection on RBCs (peanut lectin <i>Arachis hypogaea</i>)	Invasive pneumococcal infection Influenza A virus infection <i>C. perfringens</i> colitis/ necrotizing enterocolitis
Complement regulator deficiency (“Atypical” or complement regulator HUS) Inherited Acquired: anti-CFH auto-antibody	Plasma/serum C3, C4 (CH50, SC5b-9) Factor H (CFH) and factor I (CFI) serum protein level, MCP (CD46) leukocyte surface expression (FACS) Anti-factor H antibody Extended genetic workup for CFH, MCP, CFI, CFB, C3, and THBD mutations and CFHR1/3 deletion	Note that 30 % of a HUS may be triggered by diarrhea Normal plasma concentrations of factors do not exclude diagnosis of a HUS or mutation HUS risk conferred by reduced plasma concentrations or surface expression (MCP), or activating mutations (C3, CFB). Most cases related to heterozygous mutations. More than one complement component can be mutated. CFHR1/3 deletion is associated with anti-CFH antibodies
ADAMTS13 (vWF protease) deficiency (TTP) Inherited: Upshaw-Schulman syndrome Acquired: anti-ADAMTS13 auto-antibody	Plasma ADAMTS13 (protease) activity (<10 % of normal) and protein level If low, test for ADAMTS13 autoantibody (inhibitor) Genetic mutation screen when no inhibitor found	Measure pre-treatment and after recovery
Defective cobalamin metabolism (<i>Cbl-C disorder</i> /cHUS)	Increased plasma and urine methylmalonic (MMA) and homocystein concentrations and hypomethioninemia <i>MMACHC</i> mutation (autosomal recessive) or mutation of other proteins affecting cobalamin metabolism	Manifestation in newborn period, but also anytime later in life

(continued)

Table 3.21 (continued)

HUS/TMA	Investigations ^a	Comments
HIV infection	Serology Viral PCR	
Pregnancy, HELLP syndrome	Pregnancy test, liver enzymes	Investigate (also) for complement dysregulation and ADAMTS13 activity In teenage girl with HUS or TTP always consider pregnancy
Miscellaneous	Antinuclear or anti-DNA antibodies, lupus anticoagulant/ antiphospholipid antibody	Exclude secondary TMA/HUS due to SLE, antiphospholipid syndrome

^aGenetic and some functional assays require access to specialized laboratories

ADAMTS13 a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (von Willebrand factor protease; physiologically cleaves and degrades large vW multimers decreasing their activity), *CFB* complement factor B, *Cbl-C* cobalamin C, *HELLP* hemolysis, elevated liver enzymes, low platelet count, *MCP* membrane cofactor protein, *FACS* fluorescence-activated cell sorter, *MMACHC* methylmalonic aciduria and homocystinuria type C protein, *NANase* neuraminidase, *STEC* Shiga toxin-producing *Escherichia coli*, *STPB* Shiga toxin-producing bacteria, *TTP* thrombotic thrombocytopenic purpura

- Acute kidney injury
 - Fluid and electrolyte management
 - Antihypertensive therapy
 - Initiation of renal replacement therapy (1/3 to 2/3 of patients with STEC HUS require temporary dialysis)
- Management of extrarenal manifestations
- Blood Products
 - Packed red cell transfusion for anemia when Hb <60 g/l (6 g/dl) or when symptomatic (tachypnea, tachycardia, shock). Be mindful of volume overload.
 - Platelet transfusion is rarely indicated unless for active bleeding or invasive surgery.
- Plasma Exchange
 - Practiced in some centers for children with neurological involvement in analogy to treatment of TTP. No evidence base. However, PLEX or anti-complement therapy may be indicated if atypical HUS is suspected.
- Newer therapies on the horizon (experimental)
 - Synsorb Pk – diatomaceous silicon diamide compound linked to an oligosaccharide chain: binds and neutralizes Shiga toxin (negative trial results).
 - Starfish/Daisy – action similar to Synsorb, but several logs higher toxin binding capacity. Not yet trialed in humans.
 - Monoclonal antibodies specific for A subunit of Shiga toxin 2 or to Shiga toxin 1 and 2 combined. Antibodies well tolerated in phase 2 trials, but not yet available for therapeutic use.
 - Vaccination against O157 LPS or Shiga toxin (not yet available).

- Prognosis
 - Acute mortality rate 1–5 %.
 - 5–10 % may develop CKD.
 - After >15 years of follow-up, 20–60 % of patients may have (mild) proteinuria and/or hypertension and/or (mild) renal dysfunction despite full initial recovery.
- Poor Renal Prognostic Factors
 - Very young age
 - Neutrophilia $>20 \times 10^9/l$
 - Severe ischemic injury/hypovolemic shock during the acute phase
 - Anuria >2 weeks
 - Catastrophic CNS disease
 - Gangrenous colitis
 - Severe cortical necrosis on renal biopsy

3.7.4 Pneumococcal (Neuraminidase-Induced) HUS (pnHUS)

- Pneumococcal infections account for one third to one half of all non-enteropathic (non-STEC) HUS.
- Peak age 6–18 months.
- More than 2/3 of pnHUS patients present with pneumonia, often with pleural empyema, and 1/3 with pneumococcal meningitis, bacteremia and other invasive *S. pneumoniae* infections. Prognosis is considered poor.
- Presumed pathological principle is (excess) neuraminidase production.
- Laboratory diagnosis (see Table 3.22).
- Influenza virus A and has also associated with this form of HUS (to be differentiated from aHUS in patients with complement regulator defect).
- Treatment consists of antibiotics, management of pleural empyema or meningitis and transfusion of PRBC as needed.
- Plasma therapy (PLEX), IVIG infusion and blood exchange transfusion (in young infants) have been used.

3.7.5 Atypical (Complement-Induced) HUS (aHUS)

- HUS due to disordered complement regulation can arise at any age.
- Atypical HUS may begin insidiously and follow a fluctuating course. This contrasts with the usually rapid onset of Shiga toxin- and neuraminidase-induced (pneumococcal) HUS.
- Specific regulator defects associated with aHUS and their role in the alternative pathway of complement activation are depicted schematically in Fig. 3.14.
- Serum C3 and C4 concentrations are unreliable to differentiate between atypical and other forms of HUS.

- Familial occurrence of HUS may be synchronous, due to a common source of STEC infection (epidemic HUS or person-to-person transmission), or asynchronous, raising the suspicion of an inherited susceptibility for HUS.
- Mutations of genes encoding complement factors are generally heterozygous mutations leading to reduced protein expression or function (except aHUS-associated mutations of C3 and factor B) (see Box 3.16 and Table 3.21).
- The differential diagnosis of post-kidney transplant HUS includes recurrence of an atypical, inherited form, calcineurin inhibitor-induced HUS or TMA due to antibody-mediated rejection.
- Specific Investigations for select, atypical forms of HUS are detailed in Table 3.21.

3.7.6 Treatment of Atypical HUS

3.7.6.1 Plasma Therapy

- Referral to experienced (pediatric) center is advised due to the complexities of treatment and laboratory workup.
- Current standard of care for first presentation of aHUS is rapid initiation of plasma exchange therapy (PLEX) against (fresh) frozen plasma (Fig. 3.16)
- Rationale for PLEX
 - In case of autoantibodies to factor H (or ADAMTS13), plasma exchange removes the autoantibody and provides additional factor H
 - Mutated C3 or factor B that permits excessive complement activation is removed

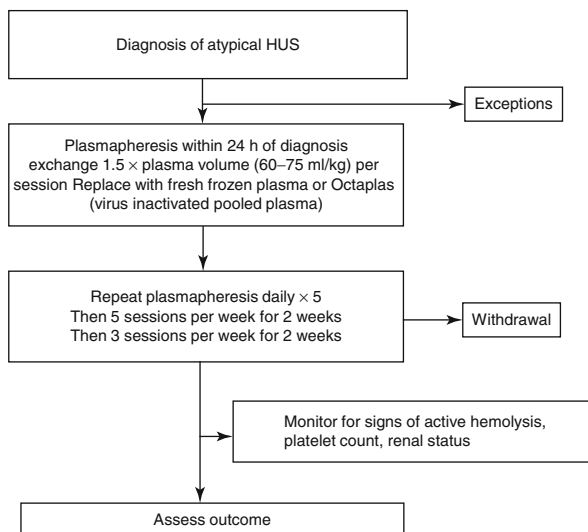


Fig. 3.16 Treatment recommendations for atypical HUS (With permission from Ariceta et al. 2009)

- Where access to PLEX is limited due to lack of expertise or resources, plasma infusions (10–20 ml/kg) may be tried, initially daily, via a peripheral vein.
- Intense plasma infusion therapy may lead to improvement in some patients with CFH or CFI mutation or (genetic) ADAMTS13 deficiency.
- In contrast, patients with (heterozygous) MCP mutation may recover spontaneously within a week. Furthermore, up to 40 % of children with aHUS will not have an identifiable complement regulator defect and/or may not benefit from plasma therapy.

Exceptions from PLEX Initiation Recommendations

- HUS in a sibling of a patient with congenital ADAMTS13 deficiency is likely to have the same diagnosis and might be expected to respond to plasma infusion 10 ml/kg/day every 2–3 weeks.
- Clinical presentation suggestive of early onset cobalamin-C disorder (feeding difficulty, failure to thrive, hypotonia, lethargy, leukopenia, thrombocytopenia, gastrointestinal bleeding, metabolic acidosis, and megaloblastic anemia) which is treated by 5 mg/day of hydroxocobalamin associated with betaine.

Withdrawal from PLEX Therapy

- Alternative diagnosis where the condition is not expected to respond to plasma therapy, for example, cobalamin-C disorder.
- Diagnosis of congenital ADAMTS13 deficiency is made, in which case plasma infusion may help.
- Hematological remission is achieved.

Rationale for Plasma Exchange

1. In case of autoantibodies to factor H, plasma exchange removes the autoantibody and provides additional factor H.
2. Mutated factor B that permits excessive complement activation is removed by plasma exchange.

3.7.6.2 Alternative Treatment Strategies

- Human plasma-derived complement factor H concentrate (not yet available)
- Synthetic (recombinant) complement blockers (not yet available)
- Monoclonal antibodies against activating components of complement such as eculizumab (against C5)
- Glucocorticoids, cyclophosphamide, immunoglobulins, rituximab (mainly for autoantibody induced HUS and TTP, in combination with PLEX or anti-complement agents)

3.7.6.3 Anti-C5 Monoclonal Antibody Therapy

- A complement (C5) blocking monoclonal antibody (mAb), eculizumab, initially developed for treatment of paroxysmal nocturnal hematuria (PNH), has now been approved in several jurisdictions for treatment of aHUS.
- mAb infusions replace or complement PLEX therapy.

- Precautions needed to prevent infections by encapsulated (complement-dependent) bacteria (*Neisseria spp.*, *S. pneumoniae*, *H. influenzae*).
- Treatment should be restricted to experienced centers.

3.7.7 Renal Transplantation in HUS

- STEC (enteropathic) HUS: risk of graft failure is <1 %, living donor possible, provided family history is negative for aHUS.
- Atypical HUS due to complement regulator deficiency or persistent autoantibody: recurrence risk is high (except for isolated MCP mutation).
- In case of anti-Factor H or anti-ADAMTS13 autoantibodies, transplant may be tried after disappearance of antibodies and clinical quiescence for at least one year. Precautions should be made to treat with PLEX in case of TMA in the graft.
- Combined kidney/liver transplantation has been advocated for patients with genetic factor deficiency. Measures include aggressive peritransplant treatment with plasma exchange and/or complement inhibition.

3.8 Other Inherited Glomerular Diseases

3.8.1 Alport Syndrome

3.8.1.1 Introduction

Alport syndrome is an inherited glomerular disease caused by mutations in genes coding for type IV collagen. It is a progressive form of glomerular disease often associated with sensori-neural deafness and ocular abnormalities.

3.8.1.2 Etiopathogenesis

- The alpha (α) 3, 4, and 5 trimers of type IV collagen are found in the glomerular basement membrane, cochlea, and eye.
- The most common form of Alport syndrome is a mutation in COL4A5 genes located on the X chromosome coding for the alpha 5 chain and accounts for about 80 % of patients with Alport syndrome.

Table 3.22 Renal histopathological changes in Alport syndrome

Light microscopy	Mesangial hypercellularity, matrix expansion, presence of lipid-laden foam cells, irregular thickening of capillary walls, glomerulosclerosis in late stages
Immunofluorescence	No immune deposits IF for collagen type IV α 3,4, and 5 is negative in GBM, depending on inheritance
Electron microscopy	Pathognomonic. Diffuse attenuation of the GBM, splitting, splintering, and “basket weave” pattern of lamina densa, intramembranous vesicles or electron-dense granulations

- Males are severely affected, whereas most females have only hematuria; however, some female carriers may develop renal failure.
- Approximately 15 % of patients with Alport syndrome have autosomal recessive inheritance. They have mutation in either the COL4A3 or COL4A4 genes carried on chromosome 2 coding for alpha 3 or alpha 4 chains.
- The remaining patients are heterozygotes for a mutation in the COL4A3 or COL4A4 gene yet may have progressive renal disease.

3.8.1.3 Clinical Features

- The phenotype depends on the genotype and the gender of the patient.
- X linked: persistent microscopic hematuria is seen in almost all patients, both males and females. Gross hematuria is common. Proteinuria and hypertension occur in second decade and progress. End-stage renal disease usually occurs in males by the end of adolescence or early adulthood. Though progression to ESRD is less common and later in females, proteinuria and sensorineural deafness are risk factors for progression.
- Hearing defects: though normal at birth, bilateral symmetric high frequency sensorineural hearing loss occurs in second decade. Hearing loss is less common and later in females.
- Ocular: anterior lenticonus, cataracts, and retinal pigmentation are known associations.
- Rarely: males with X-linked Alport syndrome and female carriers can develop leiomyomas of the esophagus, and female carriers can develop leiomyomas of the genitalia. Platelets with an abnormal number and size have been reported.
- Autosomal recessive: renal manifestations including progression to ESRD are similar to that in X-linked disease. Hearing defects are also known. Males and females are equally affected.
- Family history of hematuria, deafness, and end-stage renal disease should always be asked. Typically mother's male relatives are affected. In about 15 % of cases, there is no family history because the case represents a new COL4A5 mutation or is an autosomal recessive form of Alport syndrome.

3.8.1.4 Laboratory Evaluation

- Urine analysis: proteinuria – usually non-nephrotic range, RBC, RBC casts.
- Serum creatinine, evaluation of renal functions.
- Complement levels – to rule out other diseases.
- Pure tone audiometry and ophthalmological evaluation.
- Renal biopsy: the diagnosis is usually made by a renal biopsy showing thin GBMs with a laminated appearance. This can be confirmed by staining the GBM for the components of type IV collagen. The alpha 5 chain is also present in the epidermal basement membrane. Its absence in a skin biopsy from a male or a mosaic expression in a female by immunostaining with an antibody against the alpha 5 chain is also diagnostic of X-linked Alport syndrome. However, skin basement membrane stains positively in 20 % of affected males. Hence, a positive result does not exclude a diagnosis of Alport syndrome.

- Genetic mutation analysis.
- Family screening.

3.8.1.5 Histopathology

See Table 3.22.

3.8.1.6 Treatment

- ACE inhibitors: currently recommended to preserve renal function in patients with hypertension and/or proteinuria.
- Cyclosporin: calcineurin inhibitors have been tried in few cases aiming to slow progression of renal disease.
- Renal transplantation: First-degree relatives at risk for end-stage renal disease should not be accepted as donors. Alport syndrome does not recur in the graft, but 3–4 % of transplant recipients develop anti-GBM antibodies and a crescentic glomerulonephritis.

3.8.2 Thin Basement Membrane Disease

- Thin basement membrane disease is a histopathological term which includes sporadic and familial cases of hematuria associated with the thinning of basement membrane on electron microscopy.
- The terms thin basement membrane nephropathy and benign familial hematuria are used to describe an autosomal dominant condition with familial microscopic hematuria.
- Heterozygous mutations in the genes COL4A3 or COL4A4 are seen in 40 % cases.
- There is no evidence of proteinuria, hypertension, and progression of renal disease.
- There is no sensorineural hearing loss or ocular defects.
- Renal biopsy: electron microscopy shows diffuse attenuation of the GBM (<200–250 nm) especially at lamina densa.
- No specific treatment is required. Prognosis is excellent. Regular follow-up should be done to detect occurrence of significant proteinuria or hypertension.

Suggested Reading

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