Practical Approach in Glomerular Disease

Aida Lydia

Division of Nephrology and Hypertension

Cipto Mangunkusumo Hospital

Jakarta

- Epidemiology and Classification
- Pathogenesis
- Clinical feature
- Laboratory studies
- Kidney biopsy
- Differential Diagnosis of GN

Introduction

- Glomerulonephritis (GN) is serious disorder that can lead to end-stage renal disease (ESRD), other serious morbidity, or death.
- GN is particular topic in nephrology with many clinical variants
- Could be asymptomatic or full blown
- Patients may come with abnormal urinalysis as the only presentation.
- Little is know about the epidemiology of GN, since no large-scale examination of GN incidence and prevalence is available.

Research Article

Kidney Diseases

Kidney Dis
DOI: 10.1159/000500142

Received: February 25, 2019
Accepted after revision: April 4, 2019
Published online: June 11, 2019

A Global Evolutionary Trend of the Frequency of Primary Glomerulonephritis over the Past Four Decades

Keng Thye Woo[a] Choong Meng Chan[a] Cynthia Lim[a] Jason Choo[a]
Yok Mooi Chin[a] Esther Wei Ling Teng[a] Irene Mok[a] Jia Liang Kwek[a]
Alwin H.L. Loh[c] Hui Lin Choong[a] Han Kim Tan[a] Grace S.L. Lee[a] Evan Lee[b]
Kok Seng Wong[a] Puay Hoon Tan[c] Marjorie Foo[a]

[a]Department of Renal Medicine, Singapore General Hospital, Singapore, Singapore; [b]Department of Renal Medicine, National University of Singapore, Singapore, Singapore; [c]Department of Pathology, Singapore General Hospital, Singapore, Singapore

Epidemiology

Table 3. Primary GN: histological presentation over 4 decades

	Histology	1st decade (D1), *n* (%)	2nd decade (D2), *n* (%)	3rd decade (D3), *n* (%)	4th decade (D4), *n* (%)	*p* (χ^2) D1 vs. D2 vs. D3 vs. D4	*p* (χ^2) D3 vs. D4
1	Minimal change	97 (9)	87 (13)	151 (19)	141 (20)	<0.00001	0.68157
2	Focal global sclerosis	72 (6)	83 (12)	31 (4)	7 (1)	<0.00001	0.00031
3	Mesangial proliferative GN	357 (32)	112 (17)	55 (7)	26 (4)	<0.00001	0.00507
4	IgA Nx	473 (42)	300 (45)	316 (40)	191 (27)	<0.00001	<0.00001
5	FSGS	57 (5)	41 (6)	115 (15)	177 (25)	<0.00001	<0.00001
6	Membranous GN	38 (3)	42 (6)	90 (11)	102 (15)	<0.00001	0.0787
7	Crescenteric GN	5 (1)	1 (1)	8 (1)	20 (3)	<0.00001	0.00956
8	Others	28 (2)	0	20 (3)	39 (5)	NA	0.00302
	Total	1,127 (100)	666 (100)	786 (100)	703 (100)		

FSGS, focal and segmental glomerulosclerosis; GN, glomerulonephritis; IgA Nx, IgA nephritis; NA, not applicable.

Woo, Keng-Thye. Kidney Dis. DOI:10.1159/000500142

Epidemiology

Table 2. Primary GN: clinical presentation over 4 decades

Clinical presentation	1st decade (D1), *n* (%)	2nd decade (D2), *n* (%)	3rd decade (D3), *n* (%)	4th decade (D4)	*p* (χ^2) D3 vs. D4	*p* (χ^2) D1 vs. D2 vs. D3 vs. D4
Hematuria and proteinuria	569 (50)	236 (35)	240 (30)	95 (13)	<0.00001	<0.00001
Gross hematuria	98 (9)	26 (4)	12 (2)	9 (1)	0.68718	<0.00001
Nephrotic syndrome	363 (32)	238 (36)	357 (45)	313 (45)	0.72852	<0.00001
Acute nephritis	11 (1)	44 (7)	14 (2)	43 (6)	0.000013	<0.00001
Chronic renal failure	30 (3)	3 (<1)	55 (7)	93 (13)	0.00006	<0.00001
Hypertension	47 (4)	93 (14)	94 (12)	131 (19)	0.00033	<0.00001
Others	9 (1)	26 (4)	14 (2)	19 (3)	0.22785	0.000074
Total	1,127 (100)	666 (100)	786 (100)	703 (100)		

GN, glomerulonephritis.

Woo, Keng-Thye. Kidney Dis. DOI:10.1159/000500142

Classification of Glomerular Disease

Glomerular Disease

Defect in glomerular filtration barrier causing one or more of the following: glomerular proteinuria, glomerular hematuria or decrease in GFR.

Primary Glomerulopathy

Begins in the glomerulus and causing damage only to the glomerulus- Primary FSGS

- Minimal change disease
- Post-streptococcal acute GN
- Idiopathic membranous nephropathy
- Anti-GBM disease
- IgA nephritis
- Primary FSGS

Secondary Glomerulopathy

Glomerular disease due to systemic disease

- Diabetic nephropathy
- Lupus Nephritis
- Amyloidosis
- ANCA-related vasculitis
- Type 1, 2, 3 cryoglobulinemia
- infection-related GN

2nd degree FSGS

Glomerular disease due to severe nephron loss. The remaining nephron will be hyperperfused and having focal segmental sclerosis.

- Nonglomerular CKD causing severe nephron loss
- .

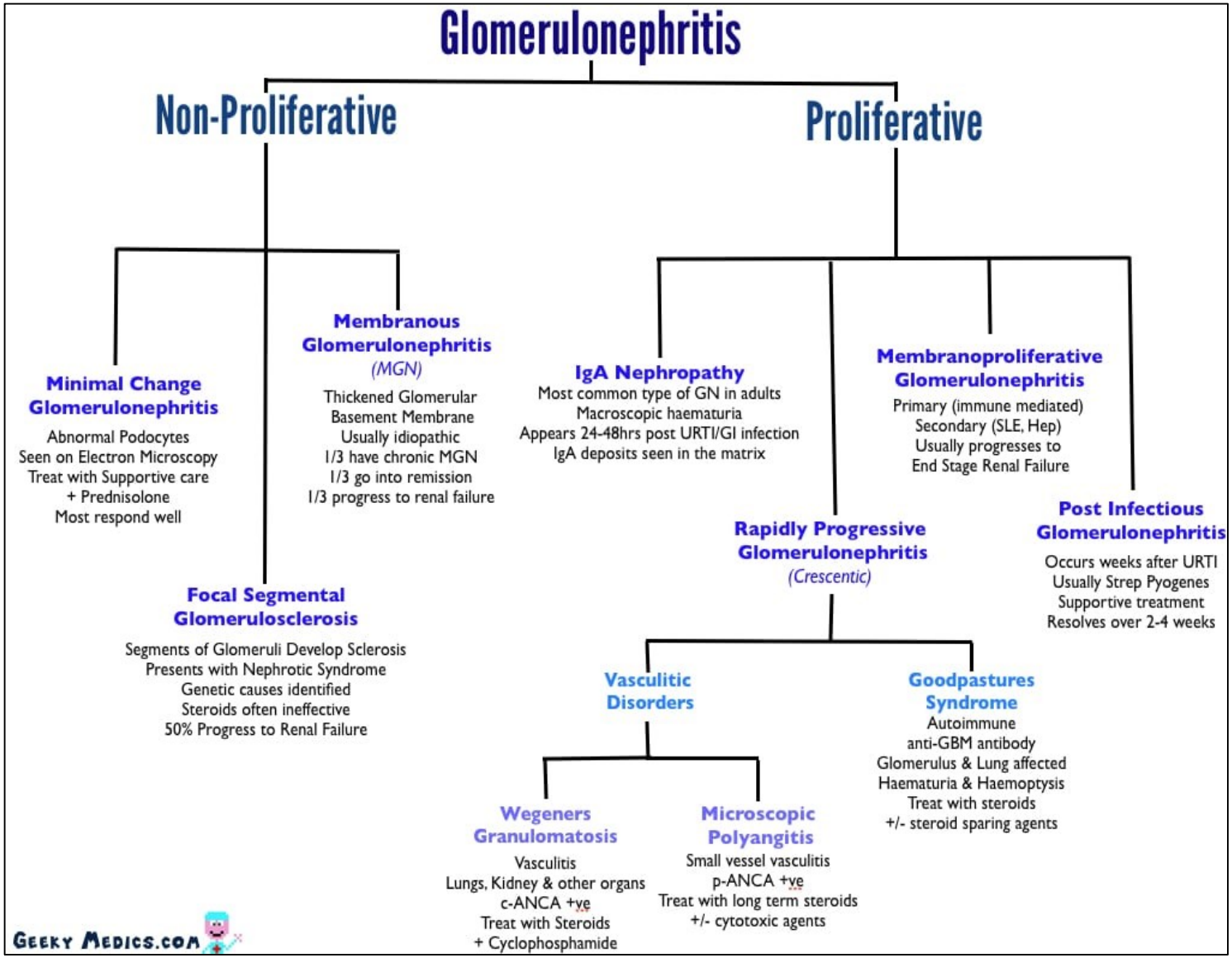
Am J Nephrol 2013

Main causes of FSGS

Primary FSGS
Circulating podocyte-toxic factor(s)
Secondary FSGS
Maladaptive response to hyperfiltration
Reduced nephron mass
Unilateral renal agenesis
Oligomeganephronia
Severe obesity
Low birth weight
Drugs and toxins
Heroin (?)
Interferon (alpha, beta, gamma)
Bisphosphonates (eg, pamidronate)
Anabolic steroids
mTOR inhibitors
Calcineurin inhibitors
Anthracyclines
Lithium
Viruses
HIV
Parvovirus B19
Simian virus 40
Cytomegalovirus
Epstein-Barr virus
Other causes
Healing phase of focal proliferative glomerulonephritis (ANCA-associated vasculitis, IgA nephropathy, lupus nephritis), membranous nephropathy
Sickle cell anemia
Thrombotic microangiopathy
Fabry disease
Glucose-6-phosphatase deficiency (glycogen storage disease I, von Gierke disease)
Hemophagocytic syndrome
Fibrillary glomerulonephritis
Genetic FSGS (renal limited and syndromic)
Mutations in slit diaphragm complex genes: *NPHS1** (nephrin), *NPHS2** (podocin), *CD2AP**¶, *TRPC6*¶, *PTPRO** (*GLEPP1*), *MYO1E**
Mutations in cytoskeleton genes: *ACTN4*¶, *MYO1E**, *INF2*¶, *ARHGAP24*¶, *ARHGDIA**, *MYH9*¶ (Epstein syndrome, Fechtner syndrome), *ITGB4**
Mutations in cell matrix genes: *COL4A3*, *COL4A4*, *COL4A5*Δ, *LAMB2** (Pierson syndrome)
Mutations in genes involved in DNA repair, transcription, or nuclear transport: *WT1*¶ (Denys-Drash syndrome, Frasier syndrome), *NUP93*, *XPO5* (exportin 5), *PAX2*, *LMX1B** (Nail-patella syndrome), *WDR73* (Galloway-Mowat syndrome, nephro-cerebellar syndrome), *LMNA* (partial lipodystrophy), *SMARCAL1**
Mutations in genes involved in cell signaling: *PLCE1**, *TRPC6*¶, *KANK4*
Mutations in lysosome genes: *SCARB2** (action myoclonus)
Mutations in cilia genes: *TTC21B*

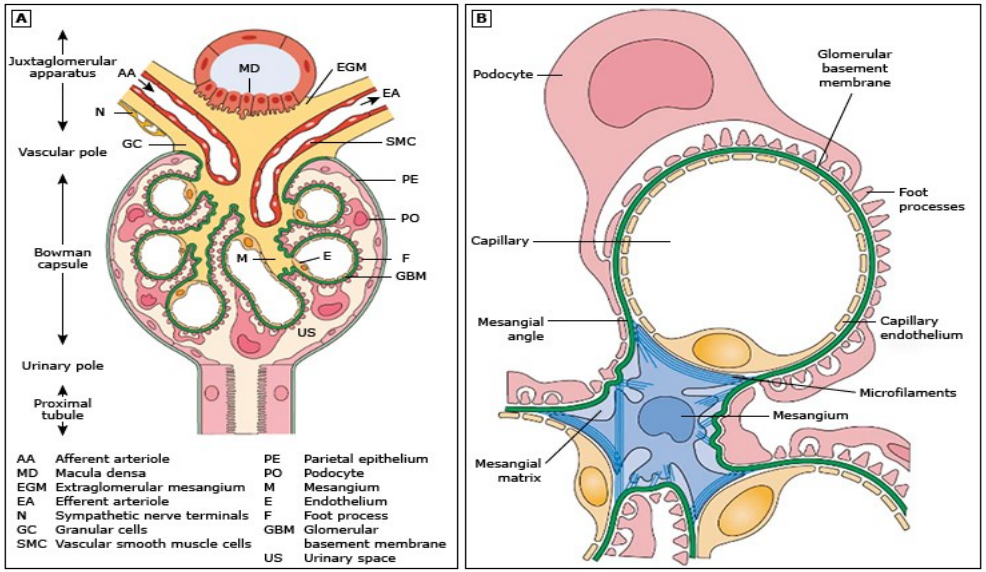
FSGS: focal segmental glomerulosclerosis; mTOR: mammalian (mechanistic) target of rapamycin; ANCA: antineutrophil cytoplasmic autoantibodies; IgA: immunoglobulin A.
* Pattern of inheritance in the most common genetic forms: Recessive.
¶ Pattern of inheritance in the most common genetic forms: Autosomal dominant.
Δ Pattern of inheritance in the most common genetic forms: Monogenic (X-linked/autosomal) and digenic inheritance described.

Adapted from: De Vriese AS, Sethi S, Nath KA, et al. Differentiating primary, genetic, and secondary FSGS in adults: A clinicopathologic approach. J Am Soc Nephrol 2018; 29:759.


Glomerulonephritis
Non-Proliferative
Proliferative
Minimal Change Glomerulonephritis
Abnormal Podocytes
Seen on Electron Microscopy
Treat with Supportive care
+ Prednisolone
Most respond well
Membranous Glomerulonephritis
(MGN)
Thickened Glomerular Basement Membrane
Usually idiopathic
1/3 have chronic MGN
1/3 go into remission
1/3 progress to renal failure
Focal Segmental Glomerulosclerosis
Segments of Glomeruli Develop Sclerosis
Presents with Nephrotic Syndrome
Genetic causes identified
Steroids often ineffective
50% Progress to Renal Failure
IgA Nephropathy
Most common type of GN in adults
Macroscopic haematuria
Appears 24-48hrs post URTI/GI infection
IgA deposits seen in the matrix
Membranoproliferative Glomerulonephritis
Primary (immune mediated)
Secondary (SLE, Hep)
Usually progresses to
End Stage Renal Failure
Post Infectious Glomerulonephritis
Occurs weeks after URTI
Usually Strep Pyogenes
Supportive treatment
Resolves over 2-4 weeks
Rapidly Progressive Glomerulonephritis
(Crescentic)
Vasculitic Disorders
Goodpastures Syndrome
Autoimmune
anti-GBM antibody
Glomerulus & Lung affected
Haematuria & Haemoptysis
Treat with steroids
+/- steroid sparing agents
Wegeners Granulomatosis
Vasculitis
Lungs, Kidney & other organs
c-ANCA +ve
Treat with Steroids
+ Cyclophosphamide
Microscopic Polyangitis
Small vessel vasculitis
p-ANCA +ve
Treat with long term steroids
+/- cytotoxic agents
GEEKY MEDICS.COM

Importance of the site of glomerular injury

- The major determinant of whether the patient presents with GN and an **active urine sediment (nephritic syndrome**) or with proteinuria **(nephrotic syndrome)** and **hematuria,** the **site** of glomerular injury—particularly, which **glomerular cells are targeted.**
- There are three major types of resident glomerular cells: **epithelial cells (visceral and parietal)**, **endothelial cells**, and **mesangial cells.**

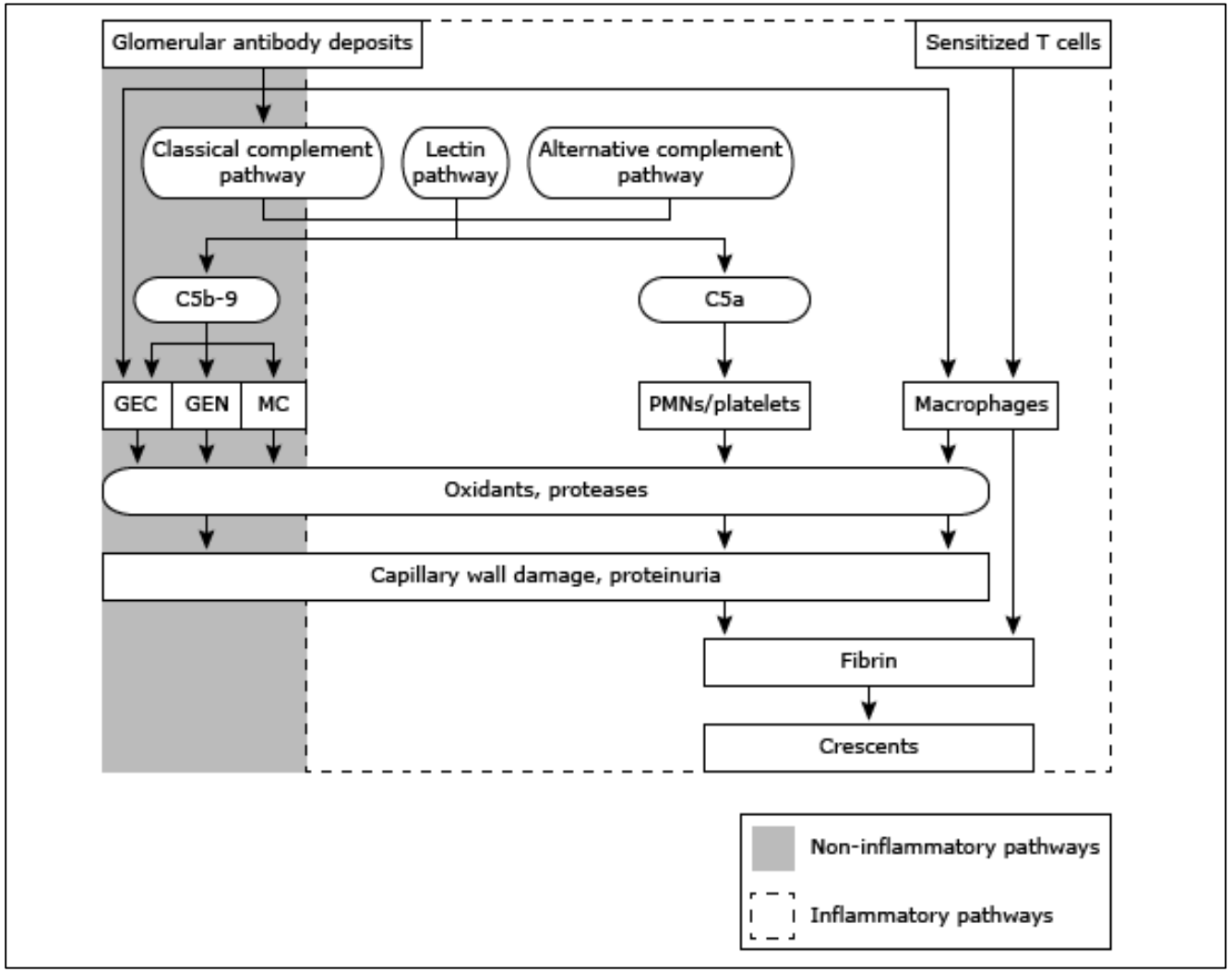


Pathogenesis

- Most forms of GN are thought to be **immune-mediated.**
- The immunopathogenesis of GN is often complex and may be the result of of **genetics** and unfavorable **environmental** conditions. Genetic factors clearly predispose certain individuals to develop immune responses that can lead to GN.
- Glomerular injury is usually mediated by the actions of multiple elements of both the **innate and the adaptive immune systems,** resulting in diverse **clinical and pathologic manifestations.**

Am J Nephrol 2013

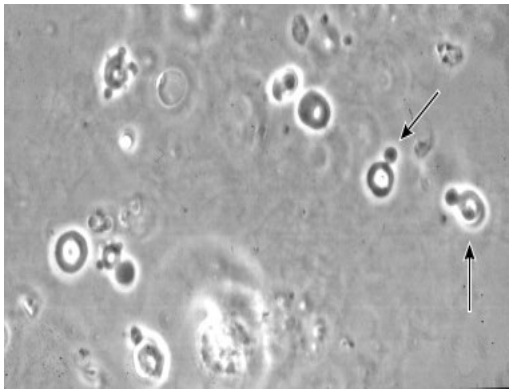
Mechanism of Glomerular Injury

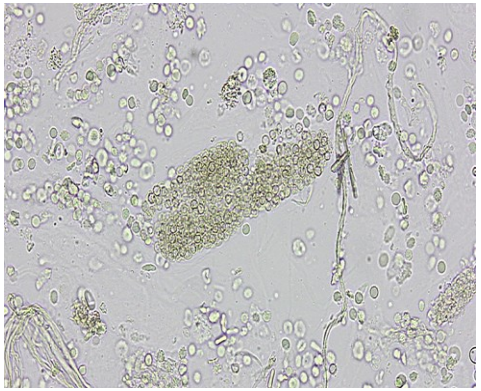


Uptodate 2019

Mechanism of Immune Injury: Inflammatory and Non-Inflammatory

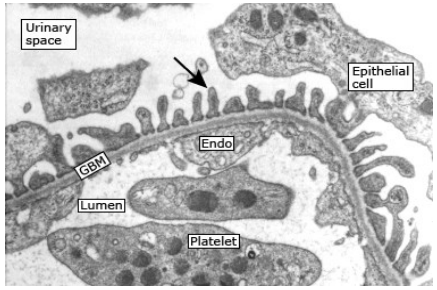
- **Inflammatory injury GN** is characterized by **glomerular infiltration** by hematopoietic cells such as **neutrophils and macrophages** and/or **proliferation of resident glomerular cells.**





Am J Nephrol 2013

Mechanism of Immune Injury

- **Noninflammatory GN** resulting from immune injury usually target the **glomerular podocyte.**
- 

- associated with major functional changes in the glomerulus that result in an **increase in glomerular permeability to albumin** and other proteins
- The major clinical features of noninflammatory glomerular lesions are proteinuria and the **nephrotic syndrome**, with **little or no hematuria** and no red blood cell casts.
- Common causes of immune-mediated nephrotic syndrome without inflammatory changes are **minimal change disease (MCD**) and **membranous nephropathy (MN).**

Clinical Manifestations:

- Hematuria and/or proteinuria:
  Urinalysis, RBC dysmorphic, RBC cast
- Renal insufficiency
- Hypertension
- Edema
- Hypercoagulability
- Systemic findings?

Systemic findings

- Constitutional – fevers, chills, weight loss, night sweats, fatigue
- Eye – retinitis or uveitis
- Ear, nose, and throat – epistaxis, sinusitis, oral ulcers
- Cardiovascular – murmurs, pain (pericarditis), or heart failure
- Lungs – hemoptysis, infiltrates, or nodules
- Abdomen – enteritis, colitis, or pancreatitis
- Nervous system – seizures or peripheral neuropathy
- Extremities – digital ischemia or infarction
- Skin – purpura or rash
- Musculoskeletal – arthritis, arthralgias, myalgias
- Infections – particularly evidence of *Staphylococcus*, *Streptococcus*, hepatitis virus, or human immunodeficiency virus (HIV), syphilis
-

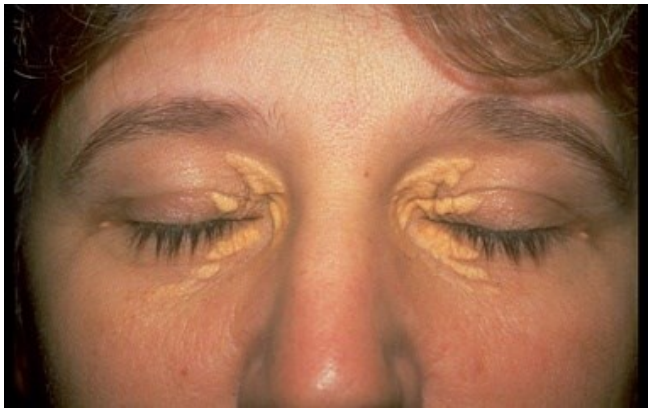
History Taking

- Patients may come with symptoms or asymptomatic
- Oedema, hypertension, history of infection may be present
- Systemic illness: SLE, diabetes, hypertension, amyloidosis, vasculitis
- Family history: Alport syndrome, genetic-related FSGS, familial IgA disease

Clin J Am Soc Nephrol 2017

Physical Examination

- General appearance
- Vital signs
- Pitting edema→ nephrotic syndrome, heart failure, hepatic cirrhosis
- Xanthelasma, Muehrcke lines→ Nephrotic syndrome
- Other manifestations of systemic disease



Xanthelasma

Muehrcke lines

Comprehensive Clinical Nephrology 2015
Am J Nephrol 2013

Laboratory Studies

- Urinalysis
- 24-h urine collection
- Urine albumin-creatinine ratio (UACR)
- Serum albumin
- LDH
- Complete blood count
- C3, C4, ANA, anti ds DNA
- Serum protein
- electrophoresis + free light chain
- HBsAg, Anti-HCV, Anti-HIV
- ANCA
- Routine CKD workup: Electrolytes, blood glucose, intact PTH, blood urea nitrogen, serum creatinine, lipid profile, calcium, phosphate.

Am J Nephrol 2013
Kidney Inter Suppl 2012

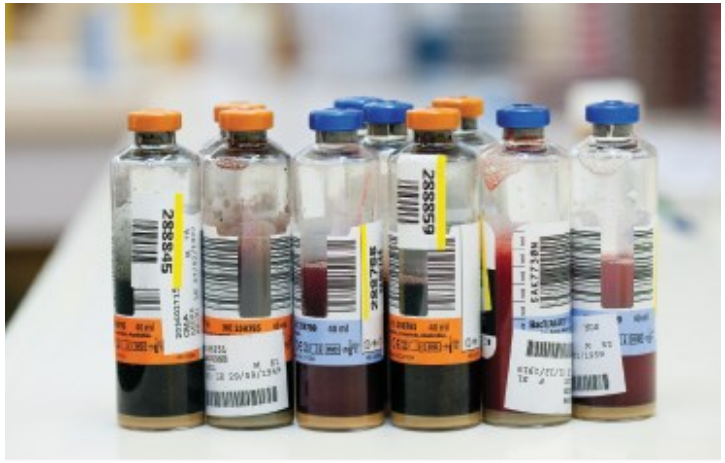
Laboratory Examination

Classification and characterization of proteinuria types

Classification of proteinuria	Clinical setting	Typical level of proteinuria
Transient proteinuria	Fever, heavy exercise, vasopressor infusion, albumin infusion	<1 g/day
Persistent proteinuria – orthostatic proteinuria	Uncommon over age 30 years, may occur in 2 to 5 percent of adolescents	<1 to 2 g/day
Persistent proteinuria – overflow proteinuria	Myeloma (monoclonal light chains), Hemolysis (hemoglobinuria), Rhabdomyolysis (myoglobinuria)	Variable, could be nephrotic range
Persistent proteinuria – glomerular proteinuria	Primary glomerular diseases, secondary glomerular diseases, diabetic nephropathy, hypertensive nephrosclerosis	Variable, often nephrotic range
Persistent proteinuria – tubulointerstitial proteinuria	Heavy metal intoxications, autoimmune or allergic interstitial inflammation, medication-induced interstitial injury	<3 g/day
Post-renal proteinuria	Urinary tract infections, nephrolithiasis, genitourinary tumor	<1 g/day

Additional Studies (Optional)

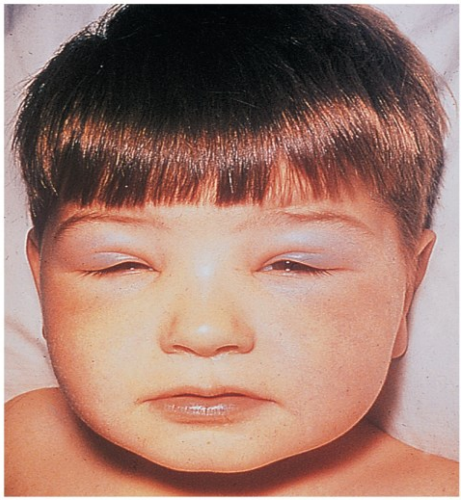
- Blood culture
- Anti-GBM assay
- D-dimer
- Immunoglobulins (IgA, IgG, IgM)
- Chest X-ray
- Kidney biopsy

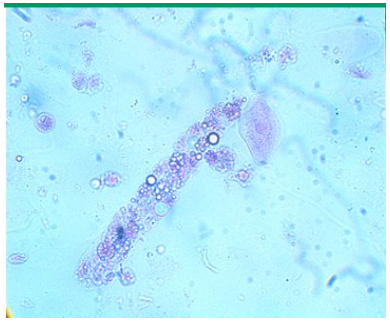


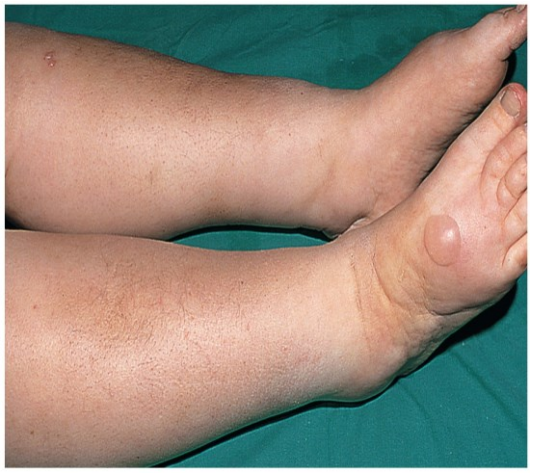
Am J Nephrol 2013
Kidney Inter Suppl 2012

Nephrotic Syndrome

- The most pathognomonic glomerular disease
- Proteinuria, hypoalbuminemia, oedema, hypercholesterolemia, lipiduria
- Could progress to ESRD
- From mild condition to “anasarca oedema”







Am J Nephrol 2013
Comprehensive Clinical Nephrology 2015
Kidney Inter Suppl 2012

Differential Diagnosis of Nephrotic Syndrome

Common Glomerular Diseases Presenting as Nephrotic Syndrome in Adults		
Disease	**Associations**	**Serologic Tests**
Minimal change disease (MCD)	Allergy, atopy, NSAIDs, Hodgkin disease	None
Focal segmental glomerulosclerosis (FSGS)	African Americans HIV infection Heroin, pamidronate	— HIV antibody —
Membranous nephropathy (MN)	Idiopathic drugs: gold, penicillamine, NSAIDs Infections: hepatitis B and C; malaria Lupus nephritis Malignancy: breast, lung, gastrointestinal tract	Anti-PLA_2R antibody Hepatitis B surface antigen, anti–hepatitis C virus antibody Anti-DNA antibody —
Membranoproliferative glomerulonephritis (MPGN) type I	C4 nephritic factor	C3 ↓, C4 ↓
Dense deposit disease (MPGN type II)	C3 nephritic factor	C3 ↓, C4 normal
Cryoglobulinemic MPGN	Hepatitis C	Anti–hepatitis C virus antibody, rheumatoid factor, C3 ↓, C4 ↓, CH50 ↓
Amyloid disease	Myeloma Rheumatoid arthritis, bronchiectasis, Crohn disease (and other chronic inflammatory conditions), familial Mediterranean fever	Plasma free light chains Serum protein electrophoresis, urine immunoelectrophoresis C-reactive protein
Diabetic nephropathy	Other diabetic microangiopathy	None

Comprehensive Clinical Nephrology 2015

Renal pathology in primary nephrotic syndrome

▪ Minimal change disease
▪ Focal segmental glomerulosclerosis
▪ Membranous nephropathy
▪ Membranoproliferative glomerulonephritis: C3 glomerulonephritis, dense deposit disease, and "idiopathic" immune complex-mediated membranoproliferative glomerulonephritis*

RBC: red blood cell.
* Indicates those disorders that could also present as a nephritic-nephrotic syndrome (RBC, RBC casts with nephrotic-range proteinuria).

Renal pathology in nephrotic syndrome associated with genetic and systemic disorders (secondary nephrotic syndrome)

Podocytopathies: Minimal change or FSGS pattern
Infections: HIV, macrophage activation syndrome, polyomavirus, cytomegalovirus
Drugs: Interferon, pamidronate, NSAIDs, lithium, vaccines, venoms, stings
Malignancies: Thymoma, Hodgkin lymphoma (formerly called Hodgkin disease)
Genetic disorders of podocyte proteins (eg, nephrin, podocin, Alport syndrome, etc.)
Other: Sickle cell, myelodysplastic syndromes, hepatitis C, von Gierke disease, Fabry disease, dysautonomia, obesity
Membranous nephropathy pattern
Autoimmune disease: Lupus
Infections: Hepatitis B, malaria, syphilis
Malignancies: Solid organ tumors, leukemia
Drugs: Gold, mercury, heavy metals, captopril, penicillamine, NSAIDs
Other: Sarcoidosis, Sjögren's syndrome, graft-versus-host disease
Membranoproliferative pattern*
Autoimmune disease: Connective tissue diseases including lupus
Infection: Chronic bacterial infections (eg, endocarditis, VA shunts), hepatitis C
Chronic thrombotic microangiopathy
Malignancy: Monoclonal gammopathy, cryoglobulinemia
Other: POEMS syndrome
Transplant glomerulopathy
Glomerular deposition diseases
Amyloidosis: AL, AA, hereditary amyloidosis, and others
Other monoclonal deposition diseases*: Immunoglobulin deposition disease, immunotactoid glomerulopathy
Hereditary disorders
Alport syndrome*
Fabry disease*
Nail-patella syndrome
Partial lipodystrophy*
APOL1-associated nephropathy
Other
Diabetes mellitus
Idiopathic nodular glomerulosclerosis
Fibrillary glomerulonephritis*
Pregnancy related (includes preeclampsia)

Nephritic Syndrome

- Decrease in GFR, non-nephrotic proteinuria, oedema, hypertension, hematuria
- Classical form: paediatric post streptococcal glomerulonephritis
- Nephritic syndrome can be overlapped with nephrotic syndrome

Nephrotic vs Nephritic Syndrome

Clinical Features	Nephrotic	Nephritic
Onset	Insidious	Abrupt
Edema	++++	++
Blood pressure	Normal	Raised
Jugular vein pressure	Normal/low	Raised
Proteinuria	++++	++
Hematuria	+/-	+++
RBC casts	-	+
Serum albumin	Low	Normal/slightly reduced

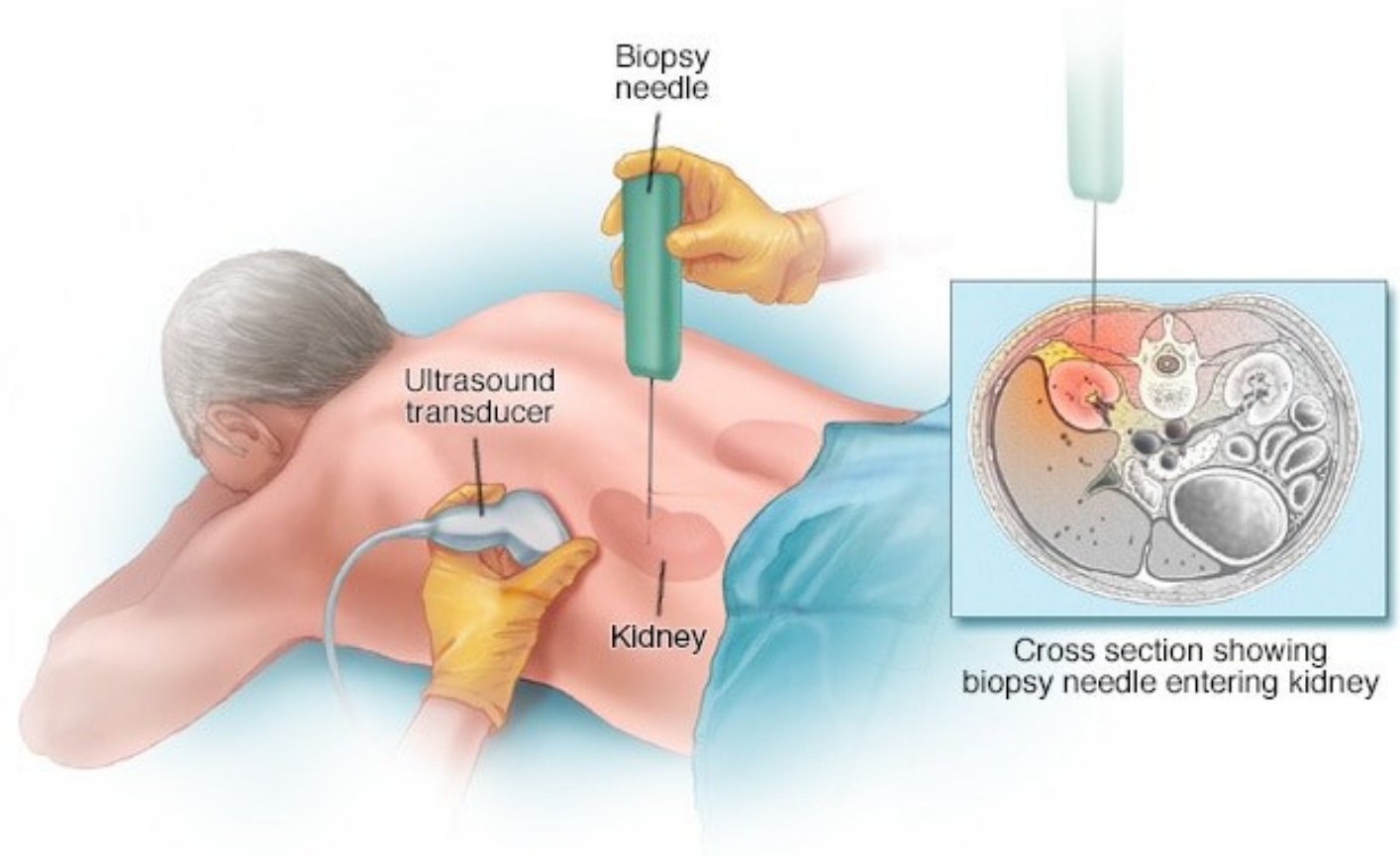
Comprehensive Clinical Nephrology 2015

Differential Diagnosis of Nephritic Syndrome

Common Glomerular Diseases Presenting as Nephritic Syndrome		
Disease	**Associations**	**Serologic Tests**
Poststreptococcal glomerulonephritis	Pharyngitis, impetigo	ASO titer, streptozyme antibody
Other postinfectious disease		
Endocarditis	Cardiac murmur	Blood cultures, C3 ↓
Abscess	—	Blood cultures, C3, C4 normal or increased
Shunt	Treated hydrocephalus	Blood cultures, C3 ↓
IgA nephropathy	Upper respiratory or gastrointestinal infection	Serum IgA ↑
Lupus nephritis	Other multisystem features of lupus	Antinuclear antibody, anti-double-stranded DNA antibody, C3 ↓, C4 ↓

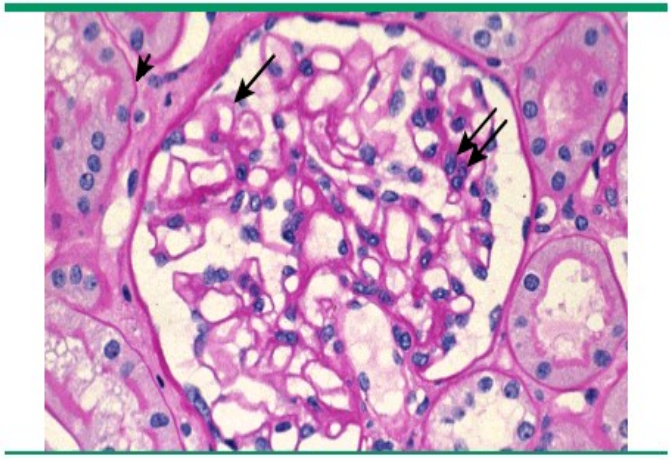
Comprehensive Clinical Nephrology 2015

Is kidney biopsy indicated??
→ Algorythm

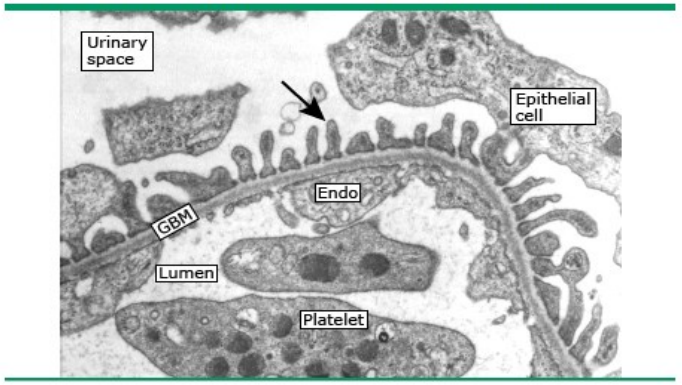


Normal Glomerulus

Normal glomerulus



Electron micrograph of a normal glomerulus

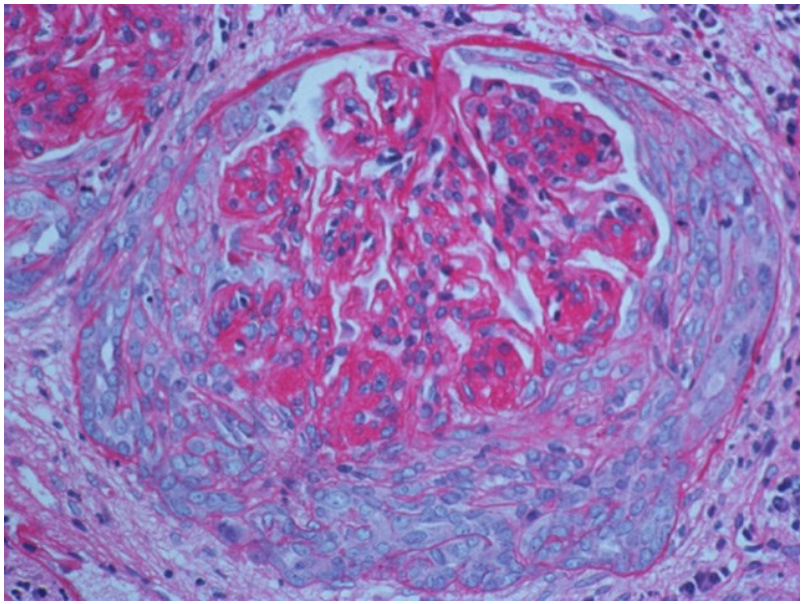


Rapidly Progressive Glomerulonephritis (RPGN)

- Abrupt decrease in renal function (days-weeks)
- Pts may come to ER with uremic syndrome
- Hallmark: crescentic appearance in kidney biopsy
- Biopsy: to differentiate with ATN, hypertensive crises, sepsis

Clin J Am Soc Nephrol 2017

Differential Diagnosis of RPGN



https://medpics.ucsd.edu

Comprehensive Clinical Nephrology 2015

Common Glomerular Diseases Presenting as Rapidly Progressive Glomerulonephritis

Disease	Associations	Serologic Tests
Goodpasture Syndrome		
	Lung hemorrhage	Anti–glomerular basement membrane antibody (occasionally antineutrophil cytoplasmic antibody [ANCA] present)
Vasculitis		
Wegener granulomatosis	Upper and lower respiratory involvement	Cytoplasmic ANCA
Microscopic polyangiitis	Multisystem involvement	Perinuclear ANCA
Pauci-immune crescentic glomerulonephritis	Renal involvement only	Perinuclear ANCA
Immune Complex Disease		
Systemic lupus erythematosus	Other multisystem features of lupus	Antinuclear antibody, anti-double-stranded DNA antibody, C3 ↓, C4 ↓
Poststreptococcal glomerulonephritis	Pharyngitis, impetigo	ASO titer, streptozyme antibody C3 ↓, C4 normal
IgA nephropathy; Henoch-Schönlein purpura	Characteristic rash ± abdominal pain in HSP	Serum IgA ↑ (30%) C3 and C4 normal
Endocarditis		
	Cardiac murmur; other systemic features of bacteremia	Blood cultures ANCA (occasionally) C3 ↓, C4 normal

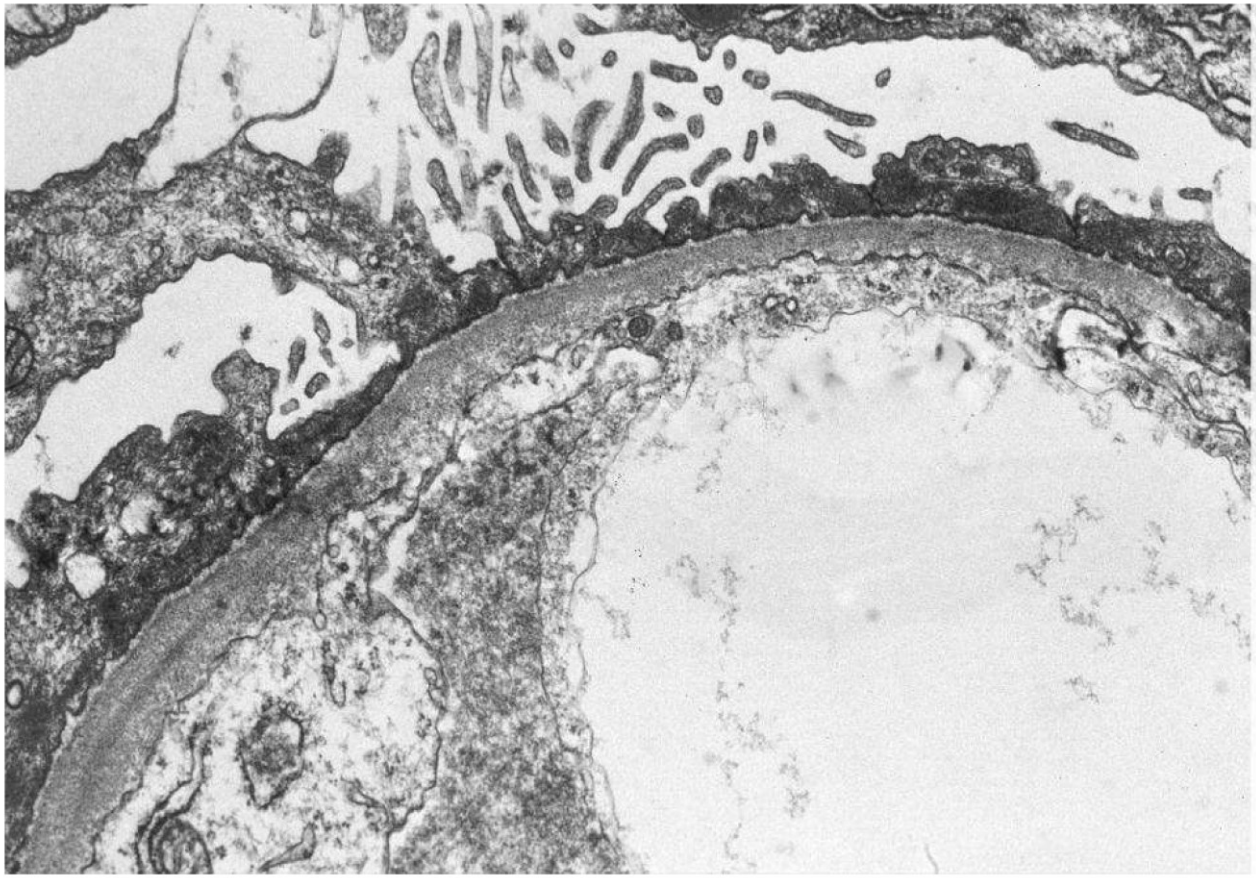
Specific Glomerular Diseases

Minimal Change Disease

- Most common cause of idiopathic nephrotic syndrome in children
- Adults: 10%-15% of idiopathic nephrotic syndrome
- Massive proteinuria
- Oedema
- Good prognosis→complete remission
- Biopsy: Podocyte swelling and foot processes effacement

Clin J Am Soc Nephrol 2017

Minimal Change Disease

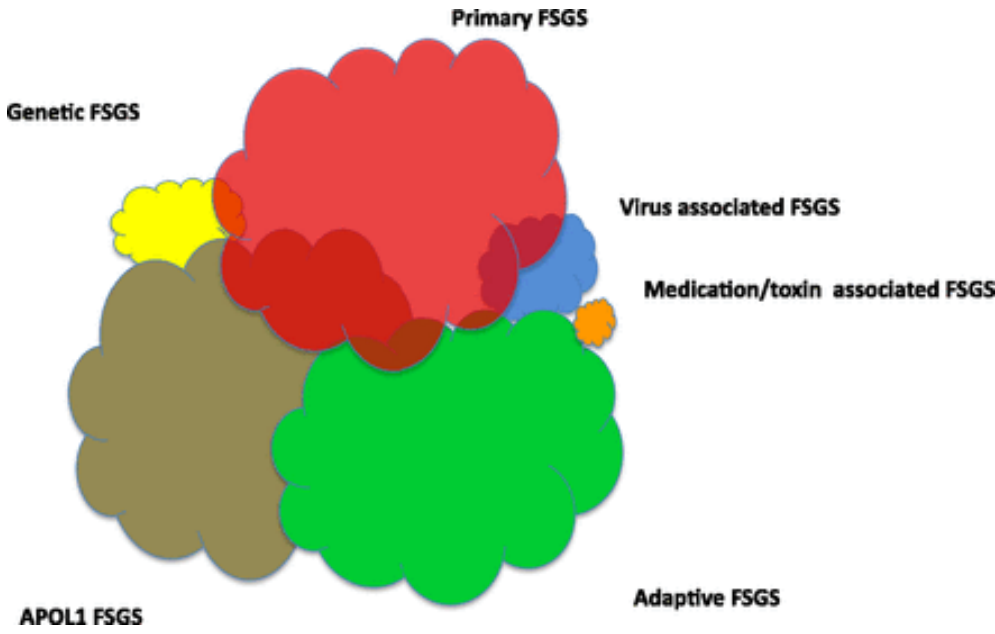


Diffuse effacement of foot processes can be seen on transmission electron microscopy (×800).

Image provided by Agnes Fogo, MD and the American Journal of Kidney Disease's Atlas of Renal Pathology (see www.ajkd.org).

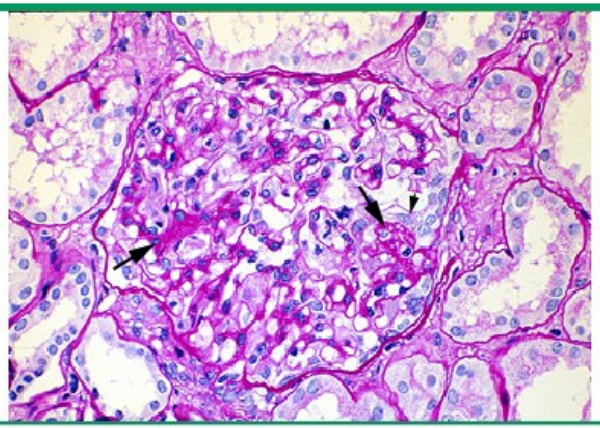
Focal Segmental Glomerulosclerosis (FSGS)

- Most common cause of ESRD in patients with glomerular disease
- Nephrotic or sub-nephrotic proteinuria
- Segmental sclerosis in glomerulus
- Six forms: see picture



Clin J Am Soc Nephrol 2017

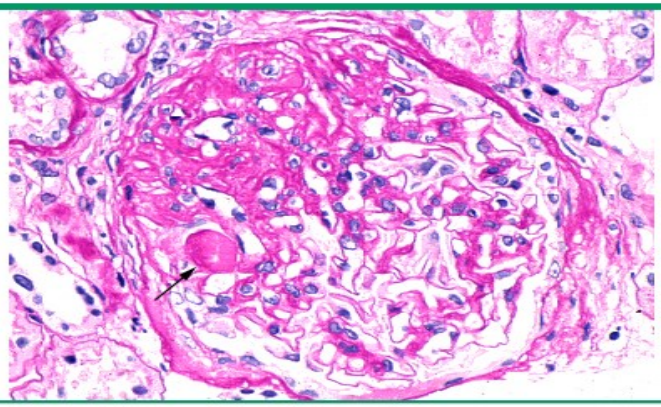
Mild FSGS



Light micrograph shows early changes in focal glomerulosclerosis with segmental capillary collapse (arrows) in areas of epithelial cell injury (small arrowhead).

FSGS: focal segmental glomerulosclerosis.

Moderate FSGS



Light micrograph in focal segmental glomerulosclerosis (FSGS) shows a moderately large segmental area of sclerosis with capillary collapse on the upper left side of the glomerular tuft; the lower right segment is relatively normal. Focal deposition of hyaline material (arrow) is also seen.

Uptodate 2019

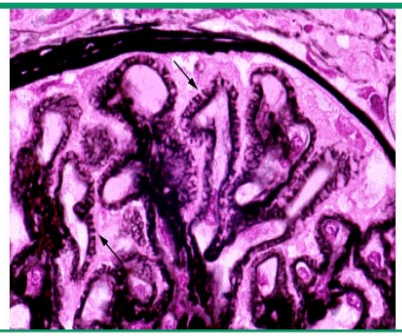
Membranous Nephropathy

- Non-diabetic adult onset nephrotic syndrome
- Primary (80%, only renal involvement) or secondary (20%, multiorgan involvement)
- Thrombosis and infection are common
- Could progress to ESRD
- Biopsy: subepitelial space immune deposition
- Type-M phospholipase A_2 receptor (PLA_2R)→specific in membranous nephropathy

Clin J Am Soc Nephrol 2017

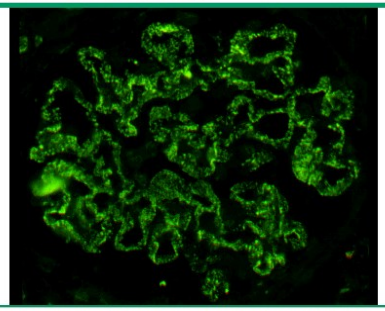
Membranous Nephropathy

Silver stain in membranous nephropathy



Light micrograph silver stain of membranous nephropathy shows a spike appearance (arrows). The spikes represent new basement membrane growing between the subepithelial immune deposits, which are visible on electron microscopy but not with this stain.

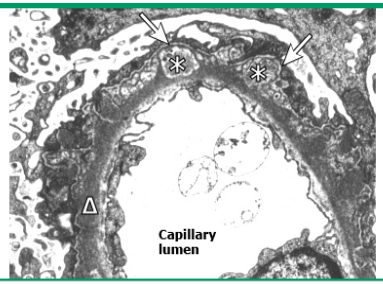
Immunofluorescence microscopy showing membranous nephropathy



Immunofluorescence microscopy in membranous nephropathy showing diffuse, granular IgG deposition along the capillary walls.

IgG: immunoglobulin G.

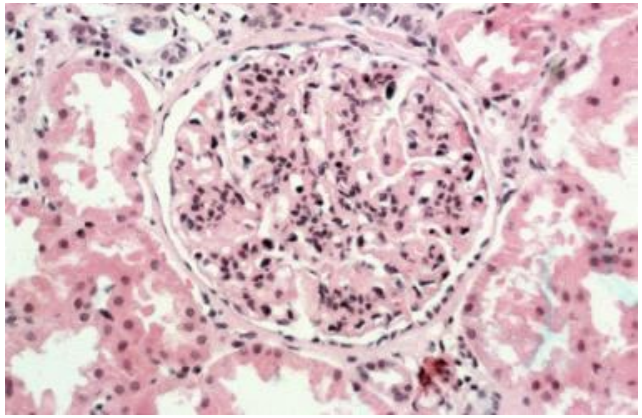
Electron micrograph in stage III membranous nephropathy

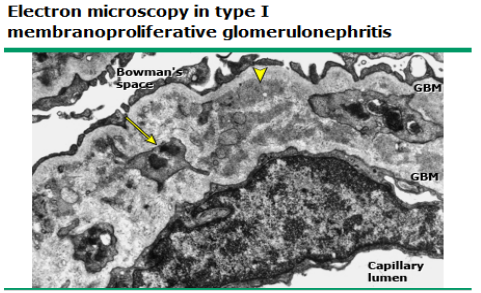


Electron micrograph in stage III membranous nephropathy. The subepithelial immune deposits (asterisk) have a lucent, moth-eaten appearance and have been incorporated into the glomerular basement membrane (Δ) as new basement membrane has grown around the deposits (arrows).

Membranoproliferative Glomerulonephritis

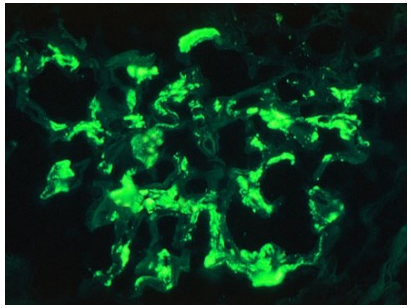
- Refers to type I membranoproliferative glomerulonephritis
- Immune deposition in mesangium and subendothelial space
- In cryoglobulinemic glomerulonephritis caused by hepatitis C virus and lupus nephritis





Clin J Am Soc Nephrol 2017

Ig-A Nephropathy



- Most prevalent glomerulonephritis globally
- Lead to CKD and ESRD
- In developing countries: falsely low prevalence because lack of kidney biopsy data
- Pathogenesis involving genetic and environmental factors → multi hit process
- Aberrant glycocylated IgA
- Patients may come with microscopic hematuria to severe kidney impairment

Clin J Am Soc Nephrol 2017

Kidney biopsy:
Activity and chronicity index

Comparison of the WHO Classification (1995) of Lupus Nephritis with the ISN/RPS Classification (2004)

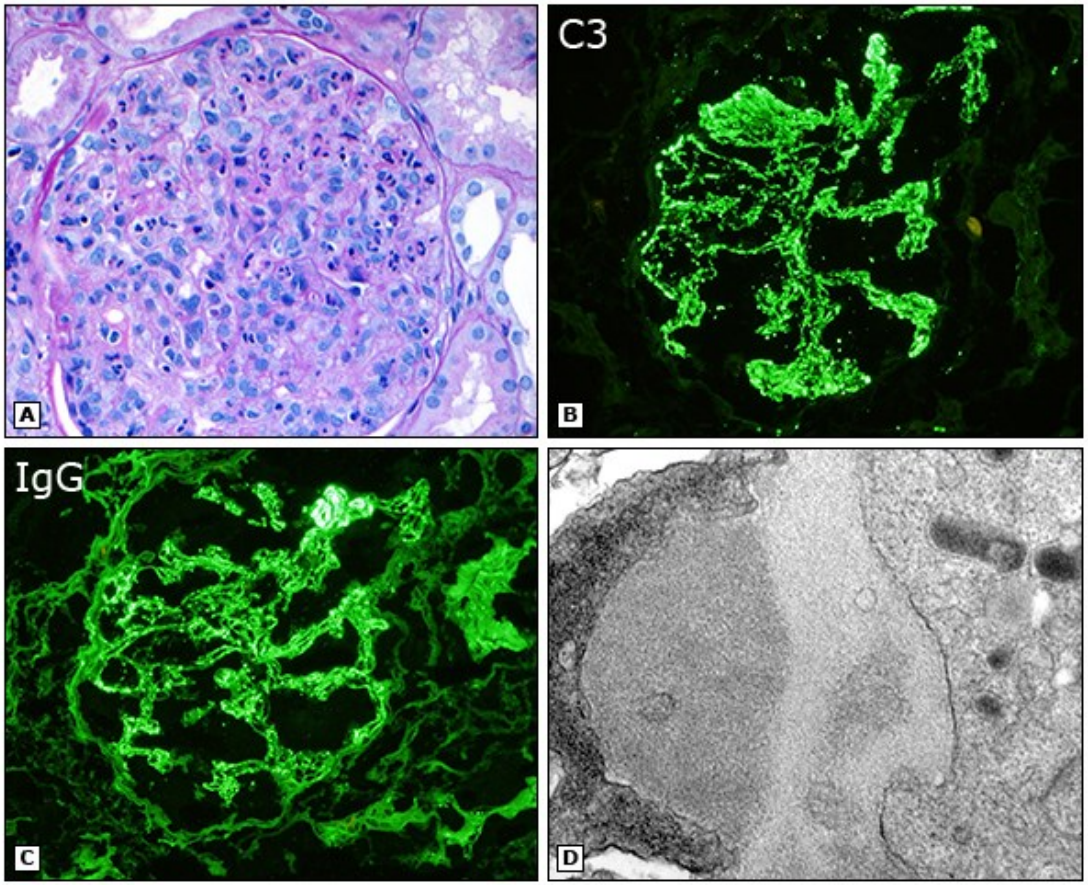
WHO, 1995		ISN/RPS, 2004	
Class	**Definition**	**Class**	**Definition**
I	Normal glomeruli (by LM, IF, EM)	I	Minimal mesangial LN Normal glomeruli by LM, but mesangial immune deposits by IF
II	Purely mesangial disease IIa: Normocellular mesangium by LM but mesangial deposits by IF and/or EM IIb: Mesangial hypercellularity with mesangial deposits by IF and/or EM	II	Mesangial proliferative LN Mesangial hypercellularity with mesangial immune deposits
III	Focal segmental proliferative glomerulonephritis (<50%)	III	Focal LN III (A): Purely active lesions: focal proliferative LN III (A/C): Active and chronic lesions: focal proliferative and sclerosing LN III (C): Chronic inactive lesions with glomerular scars: focal sclerosing LN
IV	Diffuse proliferative glomerulonephritis (≥50%)	IV	Diffuse LN IV-S (A) or IV-G (A): Purely active lesions: diffuse segmental (S) or global (G) proliferative LN IV-S (A/C) or IV-G (A/C): Active and chronic lesions: diffuse segmental or global proliferative and sclerosing LN IV-S (C) or IV-G (C): Inactive with glomerular scars: diffuse segmental or global sclerosing LN
V	Membranous glomerulonephritis Va: Pure membranous Vb: Associated mild mesangial proliferation Vc: Associated focal proliferative disease Vd: Associated diffuse proliferative disease	V	Membranous LN
		VI	Advanced sclerosing LN ≥90% of glomeruli globally sclerosed without residual activity

Post Streptococcal Glomerulonephritis

- After group A streptococcal infection, especially nephritogenic strain
- Onset 7-10 days after infection
- Inflammation with endothelial and mesangial proliferation
- Patients may come with classic nephritic syndrome
- Biopsy: subepithelial space “humps”→immune complex translocation through glomerular basal membrane

Comprehensive Clinical Nephrology 2015

Kidney biopsy findings in poststreptococcal glomerulonephritis



(A) Light microscopy showing a proliferative (exudative) glomerulonephritis. Note numerous neutrophils within glomerular capillaries (Periodic acid Schiff, 40x).
(B) Immunofluorescence microscopy showing bright granular capillary wall staining for C3 (40x).
(C) Immunofluorescence microscopy showing bright granular capillary wall staining for IgG (40x).
(D) Electron microscopy showing a subepithelial electron dense deposit (subepithelial hump, 79900x).

Goodpasture Disease

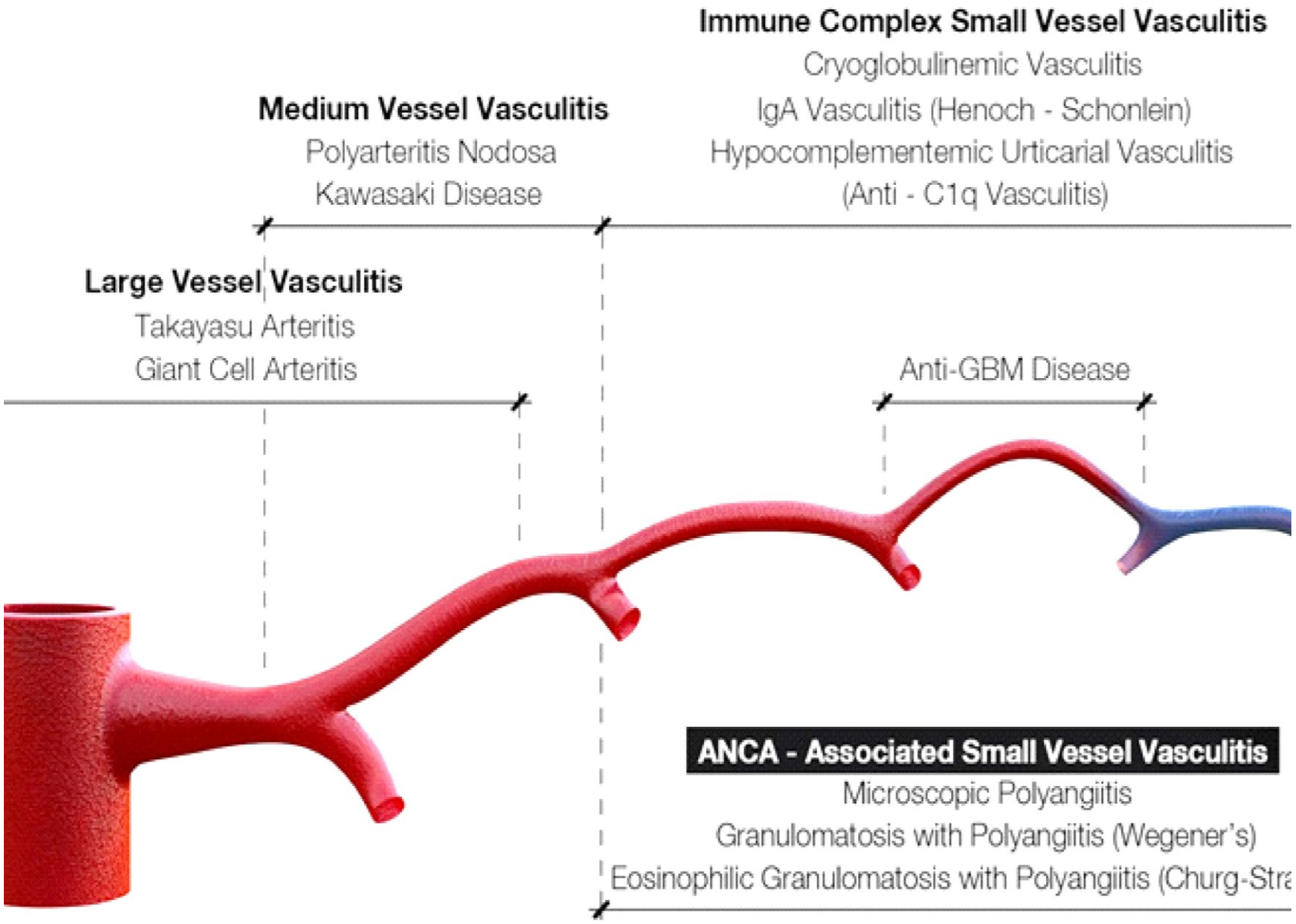
- Also known as anti-glomerular basal membrane disease
- Autoantibody against alpha-3 chain in type-IV collagen in glomerular basal membrane
- Small vessel vasculitis affecting capillaries in lungs and kidneys
- >80% pts come with RPGN
- 50% present with pulmonary haemorrhage

Comprehensive Clinical Nephrology 2015

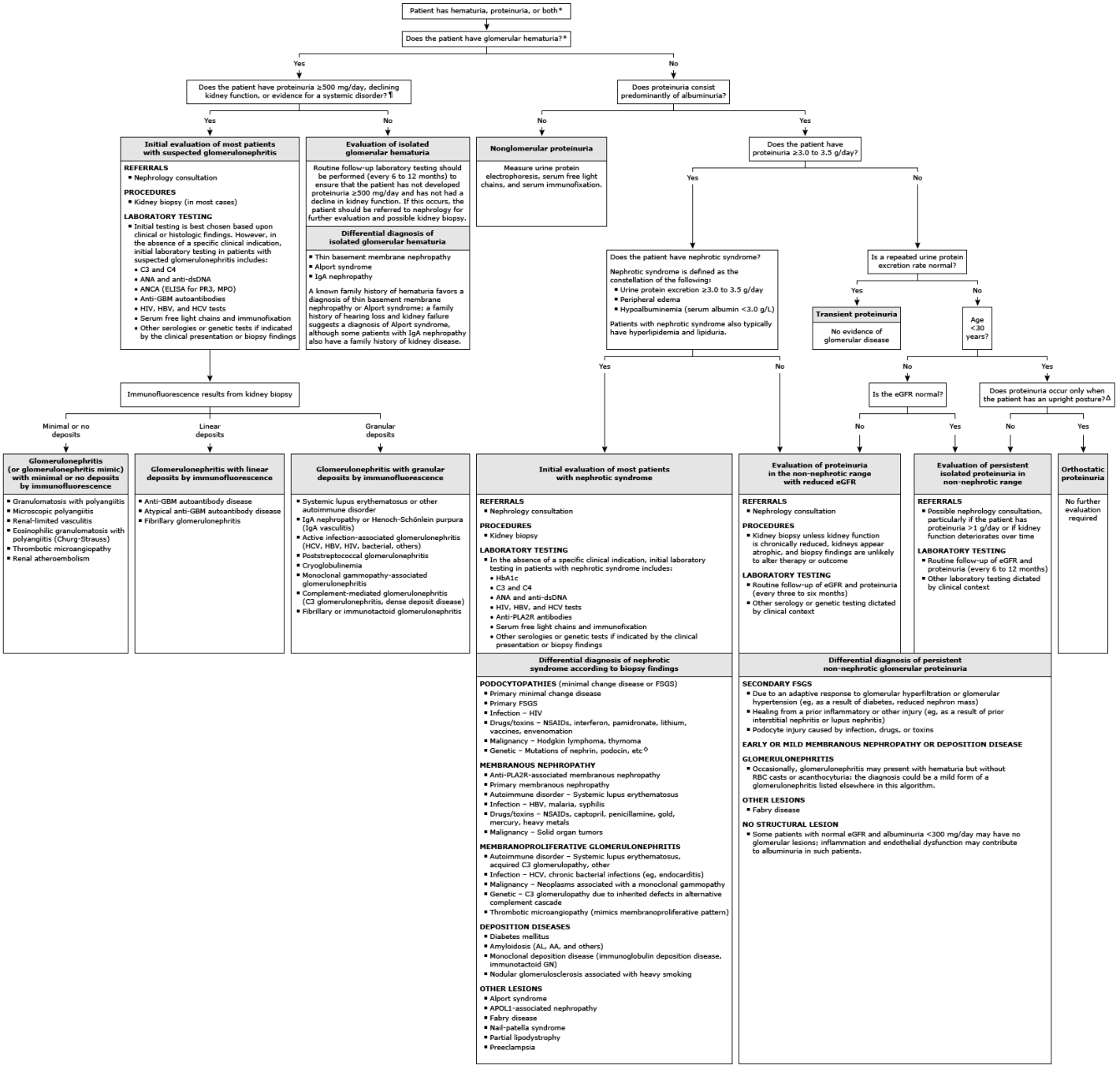
Clin J Am Soc Nephrol 2017

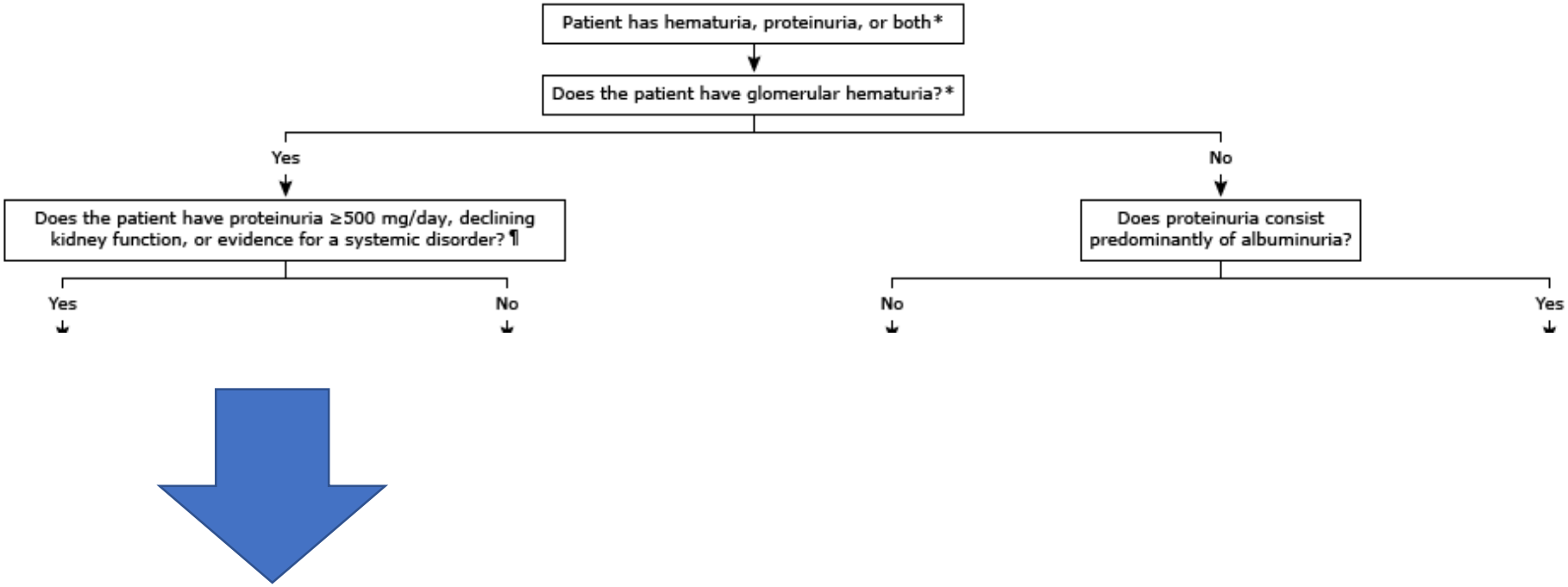
ANCA-related Vasculitis

- Very severe form of glomerular damage
- Common findings: pauci-immune necrotizing glomerulonephritis and crescent type
- Usually in adults >50 years
- 2012 Chapel Hill Consensus:
  - Microscopic polyangiitis→p-ANCA
  - Granulomatosis with polyangiitis (Wegener)→c-ANCA
  - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)→c-ANCA


Immune Complex Small Vessel Vasculitis
Cryoglobulinemic Vasculitis
IgA Vasculitis (Henoch - Schonlein)
Hypocomplementemic Urticarial Vasculitis
(Anti - C1q Vasculitis)
Medium Vessel Vasculitis
Polyarteritis Nodosa
Kawasaki Disease
Large Vessel Vasculitis
Takayasu Arteritis
Giant Cell Arteritis
Anti-GBM Disease
ANCA - Associated Small Vessel Vasculitis
Microscopic Polyangiitis
Granulomatosis with Polyangiitis (Wegener's)
Eosinophilic Granulomatosis with Polyangiitis (Churg-Stra

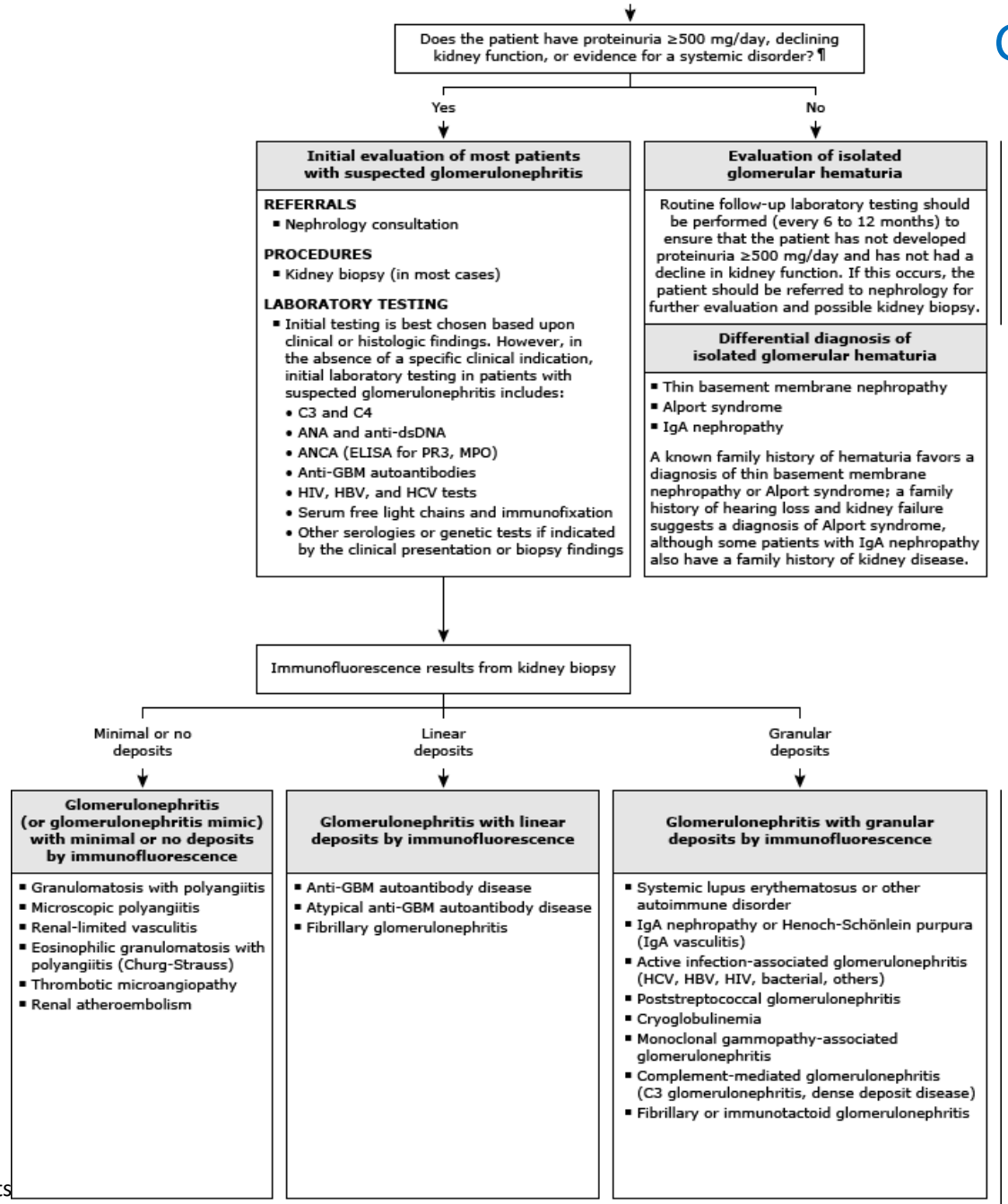
Overview of the evaluation and differential diagnosis of glomerular disease



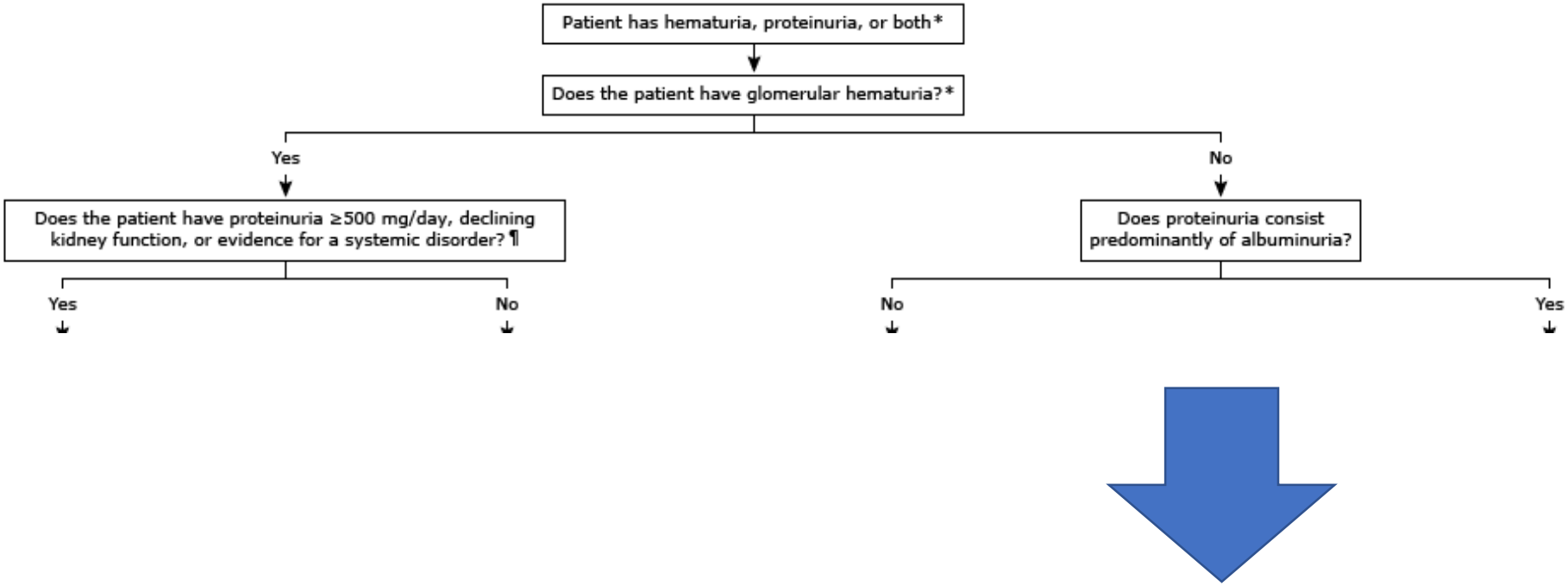


Glomerular diasease: evaluation and differential diagnosis. Uptodate, 2019

Glomerular Proteinuria

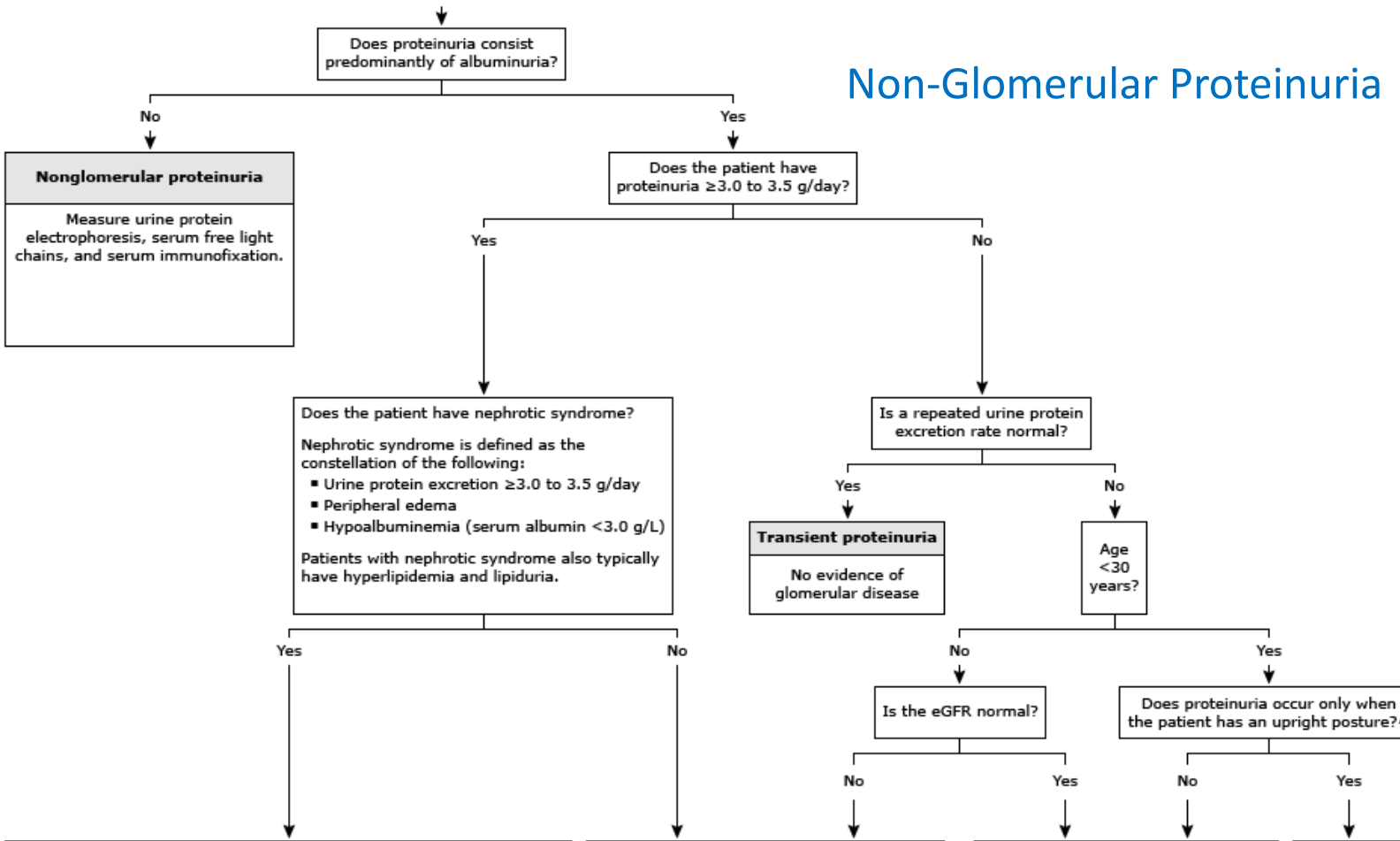


Glomerular diasease: evaluation and differential diagnosis. Uptodate, 2019



Glomerular diasease: evaluation and differential diagnosis. Uptodate, 2019

Non-Glomerular Proteinuria



Glomerular diasease: evaluation and differential diagnosis. Uptodate, 2019

Differential Diagnosis of non-glomerular proteinuria

Initial evaluation of most patients with nephrotic syndrome

REFERRALS
- Nephrology consultation

PROCEDURES
- Kidney biopsy

LABORATORY TESTING
- In the absence of a specific clinical indication, initial laboratory testing in patients with nephrotic syndrome includes:
  - HbA1c
  - C3 and C4
  - ANA and anti-dsDNA
  - HIV, HBV, and HCV tests
  - Anti-PLA2R antibodies
  - Serum free light chains and immunofixation
  - Other serologies or genetic tests if indicated by the clinical presentation or biopsy findings

Evaluation of proteinuria in the non-nephrotic range with reduced eGFR

REFERRALS
- Nephrology consultation

PROCEDURES
- Kidney biopsy unless kidney function is chronically reduced, kidneys appear atrophic, and biopsy findings are unlikely to alter therapy or outcome

LABORATORY TESTING
- Routine follow-up of eGFR and proteinuria (every three to six months)
- Other serology or genetic testing dictated by clinical context

Evaluation of persistent isolated proteinuria in non-nephrotic range

REFERRALS
- Possible nephrology consultation, particularly if the patient has proteinuria >1 g/day or if kidney function deteriorates over time

LABORATORY TESTING
- Routine follow-up of eGFR and proteinuria (every 6 to 12 months)
- Other laboratory testing dictated by clinical context

Differential diagnosis of nephrotic syndrome according to biopsy findings

PODOCYTOPATHIES (minimal change disease or FSGS)
- Primary minimal change disease
- Primary FSGS
- Infection – HIV
- Drugs/toxins – NSAIDs, interferon, pamidronate, lithium, vaccines, envenomation
- Malignancy – Hodgkin lymphoma, thymoma
- Genetic – Mutations of nephrin, podocin, etc◇

MEMBRANOUS NEPHROPATHY
- Anti-PLA2R-associated membranous nephropathy
- Primary membranous nephropathy
- Autoimmune disorder – Systemic lupus erythematosus
- Infection – HBV, malaria, syphilis
- Drugs/toxins – NSAIDs, captopril, penicillamine, gold, mercury, heavy metals
- Malignancy – Solid organ tumors

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS
- Autoimmune disorder – Systemic lupus erythematosus, acquired C3 glomerulopathy, other
- Infection – HCV, chronic bacterial infections (eg, endocarditis)
- Malignancy – Neoplasms associated with a monoclonal gammopathy
- Genetic – C3 glomerulopathy due to inherited defects in alternative complement cascade
- Thrombotic microangiopathy (mimics membranoproliferative pattern)

DEPOSITION DISEASES
- Diabetes mellitus
- Amyloidosis (AL, AA, and others)
- Monoclonal deposition disease (immunoglobulin deposition disease, immunotactoid GN)
- Nodular glomerulosclerosis associated with heavy smoking

OTHER LESIONS
- Alport syndrome
- APOL1-associated nephropathy
- Fabry disease
- Nail-patella syndrome
- Partial lipodystrophy
- Preeclampsia

Differential diagnosis of persistent non-nephrotic glomerular proteinuria

SECONDARY FSGS
- Due to an adaptive response to glomerular hyperfiltration or glomerular hypertension (eg, as a result of diabetes, reduced nephron mass)
- Healing from a prior inflammatory or other injury (eg, as a result of prior interstitial nephritis or lupus nephritis)
- Podocyte injury caused by infection, drugs, or toxins

EARLY OR MILD MEMBRANOUS NEPHROPATHY OR DEPOSITION DISEASE

GLOMERULONEPHRITIS
- Occasionally, glomerulonephritis may present with hematuria but without RBC casts or acanthocyturia; the diagnosis could be a mild form of a glomerulonephritis listed elsewhere in this algorithm.

OTHER LESIONS
- Fabry disease

NO STRUCTURAL LESION
- Some patients with normal eGFR and albuminuria <300 mg/day may have no glomerular lesions; inflammation and endothelial dysfunction may contribute to albuminuria in such patients.

Glomerular diasease: evaluation and differential diagnosis. Uptodate, 2019

THANK YOU