GLOMERULONEPHRITIS

BRRH Grand Rounds

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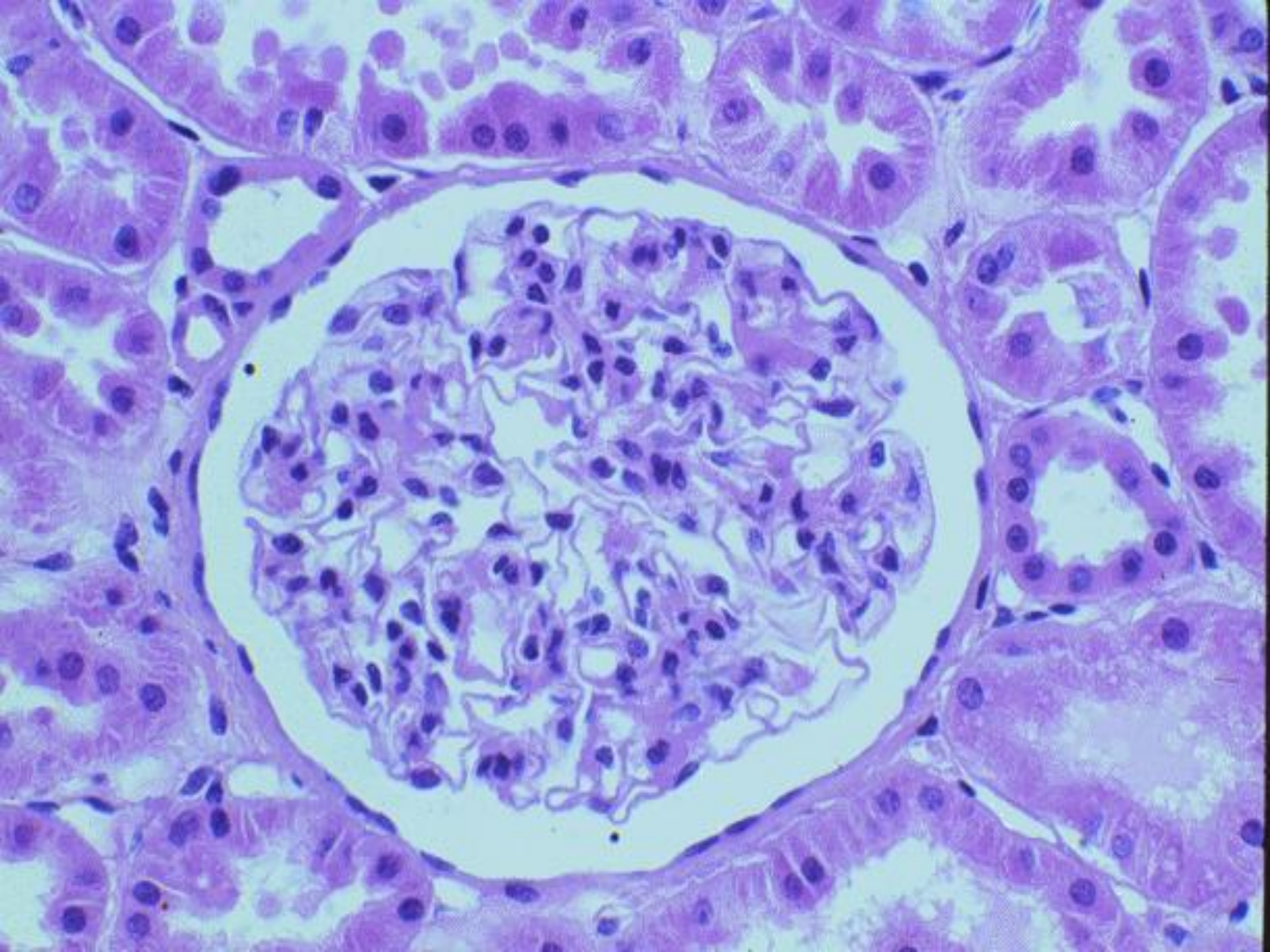
OBJECTIVES

- General review of glomerulonephritis
- Define glomerular disease:
  - Nephrotic
  - Nephritic
- Review broad differential diagnosis of proteinuria
- Approach to workup and diagnosis of glomerular disease
- Understand the clinical aspects of GN
- Treatment options:
  - Specific therapies targeting immunological causes
  - General therapies aimed at slowing progression

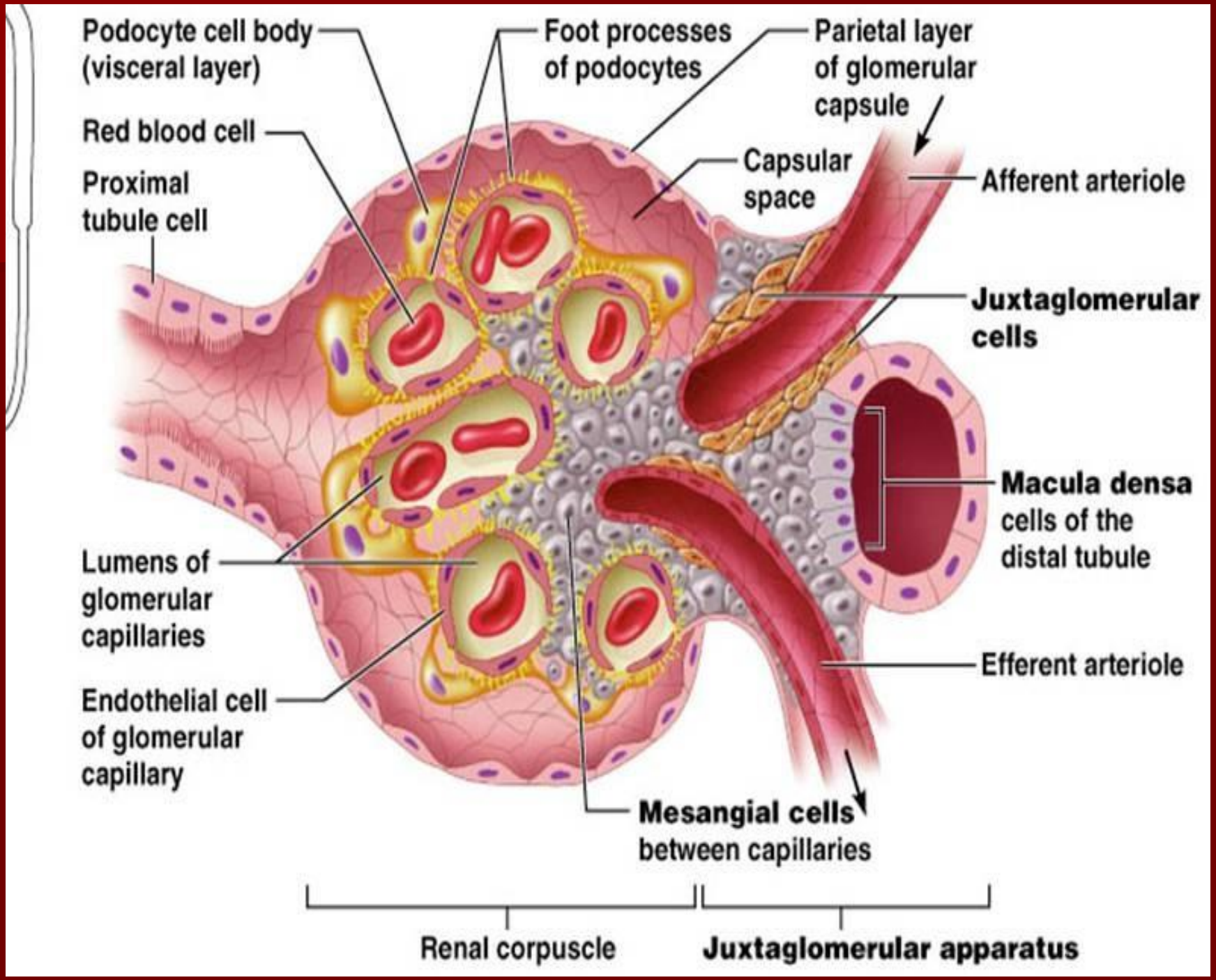


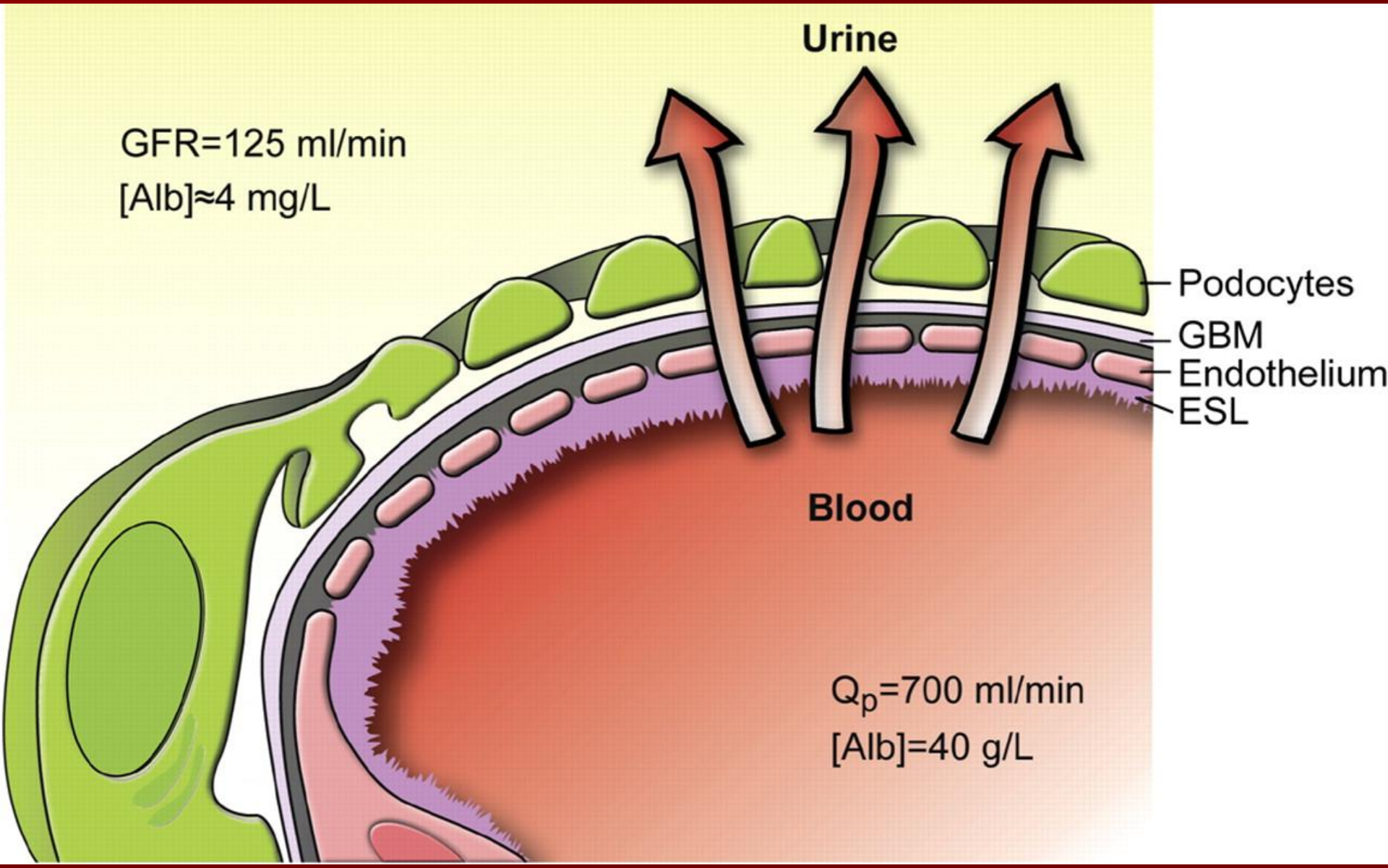
J.D.

- 41 yo female with nephrolithiasis s/p cystoscopy and ureteral stent.
- Baseline creatinine 1.
- HPI: Nausea, vomiting, fever, anorexia, gross hematuria
- Creatinine: 3.8
- Hemoglobin 7.5
- UA: 2+ protein, 3+ blood, SG 1.006, WBC 13/hpf, RBC >180/hpf

Glomerulonephritis

- Glomerular disease is an important cause of renal impairment.
- Early diagnosis is essential to provide effective intervention and improve patient outcomes
- Variable presentation
- Pathology may be localised to the kidney or part of systemic disease


Podocyte cell body (visceral layer)
Foot processes of podocytes
Parietal layer of glomerular capsule
Red blood cell
Capsular space
Afferent arteriole
Proximal tubule cell
Juxtaglomerular cells
Macula densa cells of the distal tubule
Lumens of glomerular capillaries
Efferent arteriole
Endothelial cell of glomerular capillary
Mesangial cells between capillaries
Renal corpuscle
Juxtaglomerular apparatus


Urine
GFR=125 ml/min
[Alb]≈4 mg/L
Podocytes
GBM
Endothelium
ESL
Blood
Q_p=700 ml/min
[Alb]=40 g/L

Glomerular Injury

- Proteinuria: caused by altered permeability of capillary walls
- Hematuria: rupture of capillary walls
- Azotemia: impaired filtration of nitrogenous waste
- Oliguria or Anuria: reduced urine production
- Edema: salt and water retention
- Hypertension: fluid retention and disturbed renal homeostasis

Diagnostic Approach

- Physical exam: BP, edema
- Urinalysis: rbc, rbc casts, wbc, wbc casts
- Urine protein/creatinine
- 24 hour urine for protein
- Serologic testing
- Renal Ultrasound
- Kidney biopsy

Glomerular Syndromes

NEPHRITIC

- Hematuria
- Azotemia
- Variable Proteinuria
- Oliguria
- Edema
- Hypertension

NEPHROTIC

- >3.5g proteinuria
- Hypoalbuminemia
- Edema
- Hyperlipidemia
- Lipiduria

Glomerular Syndromes

NEPHRITIC

- Abrupt onset
- Limited or systemic
- Active immunological response
- Serological testing helpful

NEPHROTIC

- Little inflammation
- Hematuria uncommon
- Hypercoaguable
- Bacterial infections
- Fivefold increase in cardiovascular death
- Serological testing less informative
- Commonest cause: DM

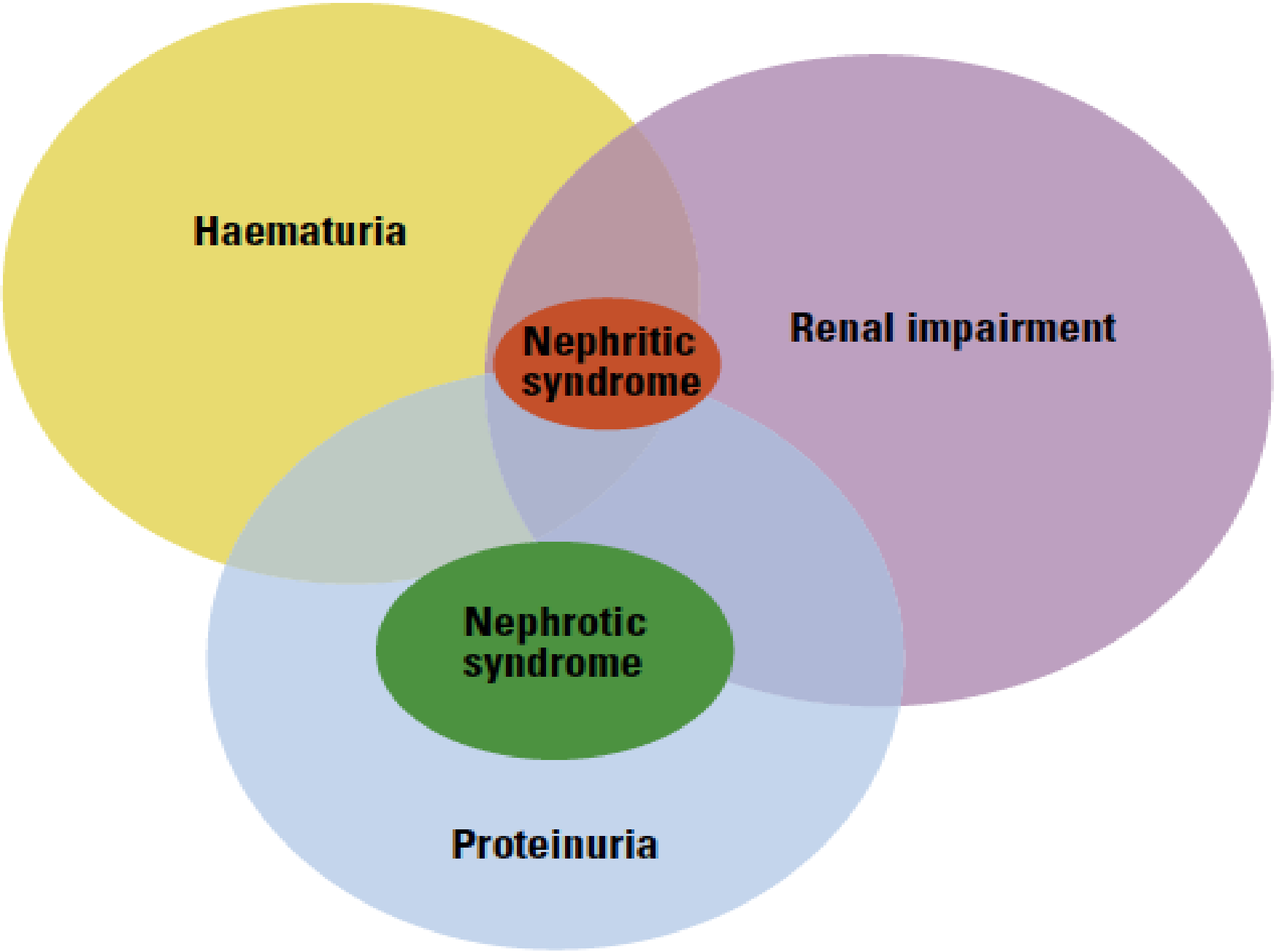

Haematuria
Renal impairment
Nephritic syndrome
Nephrotic syndrome
Proteinuria

Table 1. Common presentations of glomerulonephritis

Presentation	Cause	Specific test
Nephritic syndrome	IgA nephropathy	
	Poststreptococcal GN	ASOT, anti-DNAase B, C3
	SLE	ANA, anti-ds DNA, C3, C4
	Anti-GBM disease	Anti-GBM antibody
	ANCA vasculitis	ANCA
	Mesangiocapillary GN	C3, HBsAg
Nephrotic syndrome	Minimal change disease	
	Membranous GN	HbsAg, chest X-ray, mammogram*
	FSGS	
	SLE	ANA, anti-ds DNA, C3, C4
	Diabetes	Fasting glucose
	Amyloid	Urine Bence-Jones protein, serum and urine protein electrophoresis
GN and infection		
• URTI	Flare of IgA nephropathy	
• Streptococcus	Poststreptococcal GN	
• Hepatitis B	Membranous GN	
• Hepatitis C	Mesangiocapillary GN	
• Endocarditis	Mesangiocapillary GN	
GN and drugs		
• NSAID	Minimal change disease	
• Gold, penicillamine	Membranous GN	
• OCP, quinine	HUS	FBE (schistocytes), LDH, haptoglobin
GN and purpuric skin rash	IgA/HSP	Skin biopsy with immunoflouresence
	SLE	
	ANCA vasculitis	
GN and cancer	Membranous GN	

* Simple assessment for common cancers may include rectal examination, breast examination, mammogram and chest X-ray

GN = glomerulonephritis, SLE = systemic lupus erythematosus, GBM = glomerular basement membrane, ANCA = antineutrophil cytoplasmic antibody, ASOT = antistreptolysin O titre, ANA = antinuclear antibody, ads = double stranded, FSGS = focal segmental glomerulosclerosis, NSAID = nonsteroidal anti-inflammatory drug, OCP = oral contraceptive pill, HUS = haemolytic uraemic syndrome, HSP = Henoch Schonlein Purpura, FBE = full blood examination, LDH = lactate dehydrogenase

TABLE 16-1 Clinical Manifestations of Glomerular Diseases and Representative Diseases that Cause Them*

Asymptomatic Proteinuria
Focal segmental glomerulosclerosis
Mesangioproliferative GN
Nephrotic Syndrome
Minimal change glomerulopathy
Membranous glomerulopathy
Idiopathic (primary)
Secondary (e.g., lupus)
Focal segmental glomerulosclerosis
Mesangioproliferative GN
Type I membranoproliferative GN
Type II membranoproliferative GN
Fibrillary GN
Diabetic glomerulosclerosis
Amyloidosis
Light chain deposition disease
Asymptomatic Microscopic Hematuria
Thin basement membrane nephropathy
IgA nephropathy
Mesangioproliferative GN
Alport's syndrome
Recurrent Gross Hematuria
Thin basement membrane nephropathy
IgA nephropathy
Alport's syndrome
Acute Nephritis
Acute postinfectious GN
Poststreptococcal GN
Poststaphylococcal GN
Focal or Diffuse Proliferative GN
IgA nephropathy
Lupus nephritis
Type I Membranoproliferative GN
Type II Membranoproliferative GN
Fibrillary GN
Rapidly Progressive Nephritis
Crescentic GN
Anti-GBM GN
Immune complex GN
ANCA GN
Pulmonary-Renal Vasculitic Syndrome
Goodpasture's (anti-GBM) syndrome
Immune complex vasculitis
Lupus
ANCA Vasculitis
Microscopic polyangiitis
Wegener's granulomatosis
Churg-Strauss syndrome
Chronic Kidney Disease
Chronic sclerosing GN

TABLE 16-2 Tendencies of Glomerular Diseases to Manifest Nephrotic and Nephritic Features*

DISEASE	NEPHROTIC FEATURES	NEPHRITIC FEATURES
Minimal change glomerulopathy	++++	—
Membranous glomerulopathy	++++	+
Diabetic glomerulosclerosis	++++	+
Amyloidosis	++++	+
Focal segmental glomerulosclerosis	+++	++
Fibrillary glomerulonephritis	+++	++
Mesangioproliferative glomerulopathy†	++	++
Membranoproliferative glomerulonephritis‡	++	+++
Proliferative glomerulonephritis†	++	+++
Acute postinfectious glomerulonephritis§	+	++++
Crescentic glomerulonephritis#	+	++++

other

amyloidosis

diabetic glomerulosclerosis

membranoproliferative glomerulonephritis

proliferative glomerulonephritis

minimal change glomerulopathy

focal segmental glomerulosclerosis

membranous glomerulopathy

Definition of Proteinuria

- Reflects pathological process most commonly at level of GBM.
- Urinary Protein excretion of greater than 150mg per day.

- Normal Protein Excretion Dynamics:
  - 20 % is low molecular (Ig's) 20,000 Daltons
  - 40% higher molecular (albumin) 65,000 Daltons
  - 40 % Tamm-Horsfall mucoprotein by distal tubule.

Proteinuria

- Powerful predictor of progressive renal disease
- Even low level (1+ dipstick) is associated with twofold increased risk of ESRD. (Iseki et al, Kidney Int 1996)
- The more severe, the more likely to have progressive decline of kidney function
- Hallmark of diabetic and hypertensive nephropathy (accounts for the majority of patients with proteinuria)
- Significant (>1g/day) in absence of identifiable cause warrants further investigation

TABLE 5

Common Causes of Proteinuria

Transient proteinuria	Secondary glomerular causes	Tubular causes
Congestive heart failure	Alport's syndrome	Aminoaciduria
Dehydration	Amyloidosis	Drugs (e.g., NSAIDs, antibiotics)
Emotional stress	Collagen vascular diseases (e.g., systemic lupus erythematosus)	Fanconi syndrome
Exercise	Diabetes mellitus	Heavy metal ingestion
Fever	Drugs (e.g., NSAIDs, penicillamine [Cuprimine], gold, ACE inhibitors)	Hypertensive nephrosclerosis
Orthostatic (postural) proteinuria	Fabry's disease	Interstitial nephritis
Seizures	Infections (e.g., HIV, syphilis, hepatitis, post-streptococcal infection)	Overflow causes
Persistent proteinuria	Malignancies (e.g., lymphoma, solid tumors)	Hemoglobinuria
Primary glomerular causes	Sarcoidosis	Multiple myeloma
Focal segmental glomerulonephritis	Sickle cell disease	Myoglobinuria
IgA nephropathy (i.e., Berger's disease)		
IgM nephropathy		
Membranoproliferative glomerulonephritis		
Membranous nephropathy		
Minimal change disease		

NSAIDs = nonsteroidal anti-inflammatory drugs; ACE = angiotensin-converting enzyme; HIV = human immunodeficiency virus.

Adapted with permission from Ahmed Z, Lee J. Asymptomatic urinary abnormalities. Hematuria and proteinuria. Med Clin North Am 1997;81:650.

Hematuria

- >3 rbc/hpf
- Asymptomatic microscopic hematuria occurs in 5-10% of general population
- Most not of glomerular origin
- Less than 10% in patients who do not have proteinuria

TABLE 4

Common Causes of Hematuria

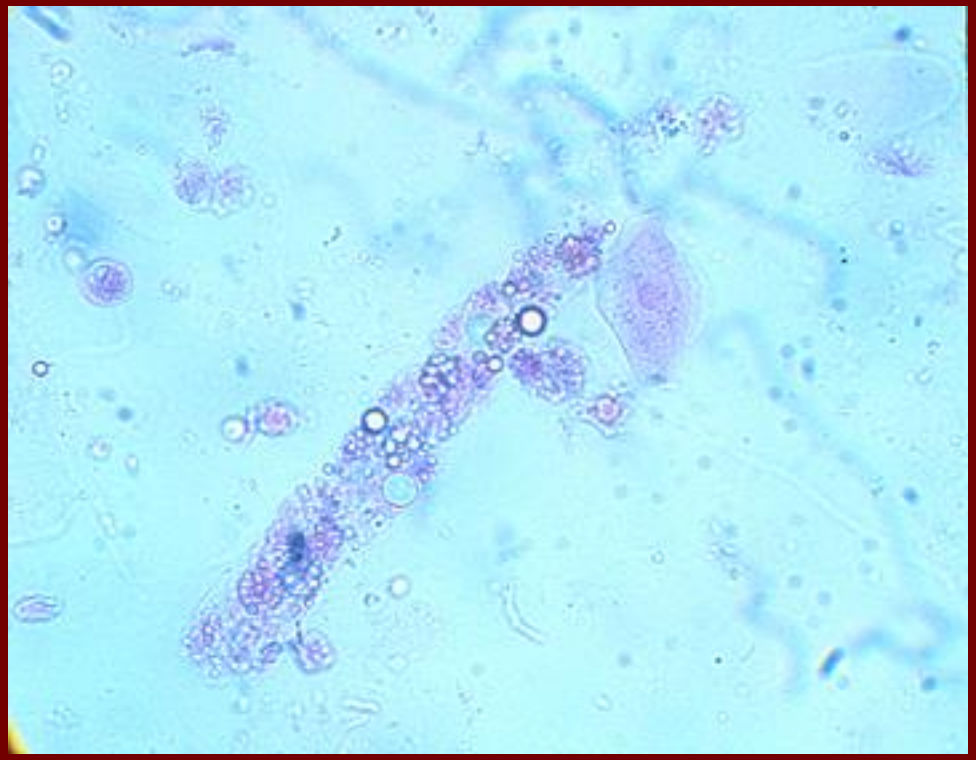
Glomerular causes	Renal causes	Urologic causes
Familial causes	Arteriovenous malformation	Benign prostatic hyperplasia
Fabry's disease	Hypercalciuria	Cancer (kidney, ureteral, bladder, prostate, and urethral)
Hereditary nephritis (Alport's syndrome)	Hyperuricosuria	Cystitis/pyelonephritis
Nail-patella syndrome	Loin pain-hematuria syndrome	Nephrolithiasis
Thin basement-membrane disease	Malignant hypertension	Prostatitis
Primary glomerulonephritis	Medullary sponge kidney	*Schistosoma haematobium* infection
Focal segmental glomerulonephritis	**Metabolic causes**	Tuberculosis
Goodpasture's disease	Papillary necrosis	**Other causes**
Henoch-Schönlein purpura	Polycystic kidney disease	Drugs (e.g., NSAIDs, heparin, warfarin [Coumadin], cyclophosphamide [Cytoxan])
IgA nephropathy (Berger's disease)	Renal artery embolism	Trauma (e.g., contact sports, running, Foley catheter)
Mesangioproliferative glomerulonephritis	Renal vein thrombosis	
Postinfectious glomerulonephritis	Sickle cell disease or trait	
Rapidly progressive glomerulonephritis	**Tubulointerstitial causes**	
Secondary glomerulonephritis	Vascular cause	
Hemolytic-uremic syndrome		
Systemic lupus nephritis		
Thrombotic thrombocytopenic purpura		
Vasculitis		

NSAIDs = nonsteroidal anti-inflammatory drugs.

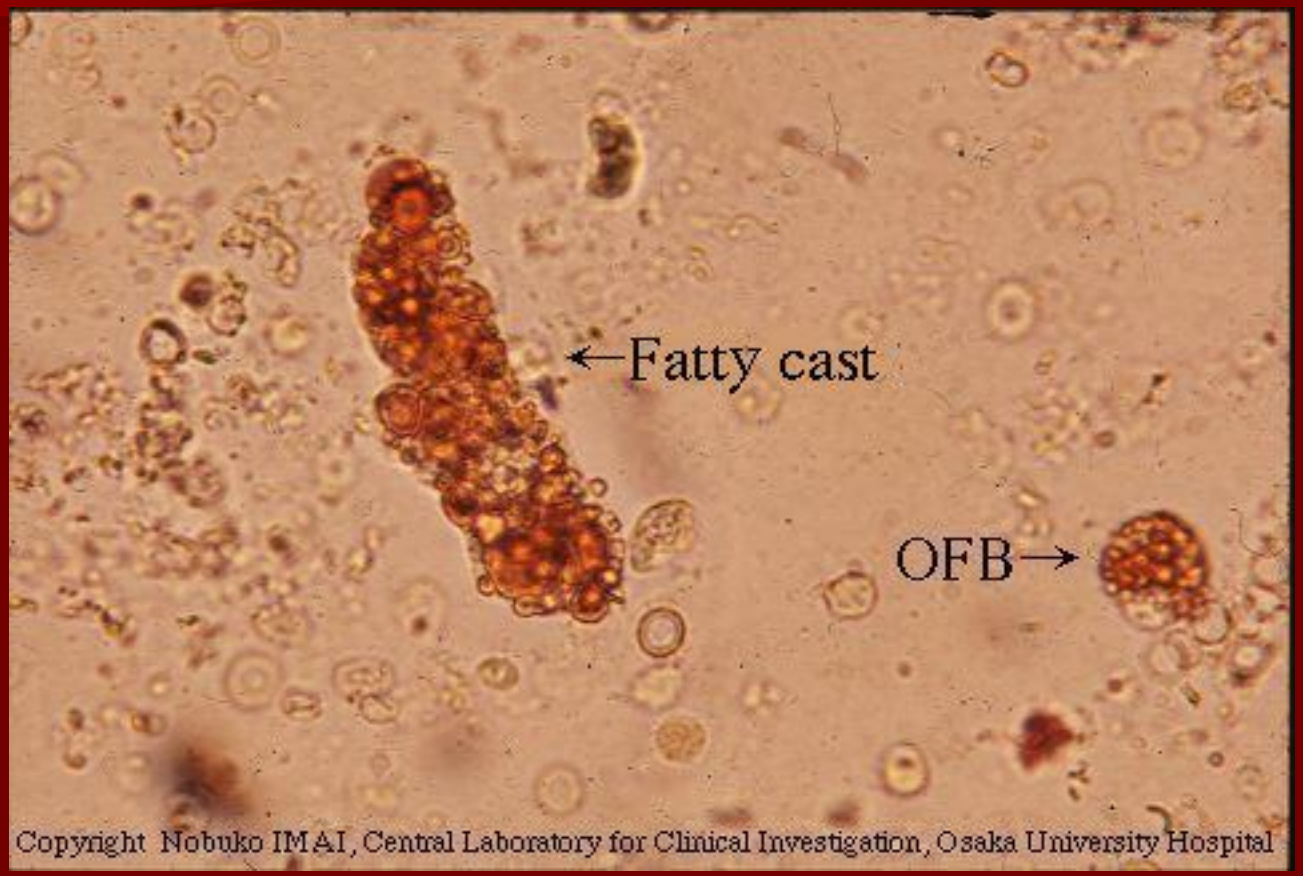
Adapted with permission from Ahmed Z, Lee J. Asymptomatic urinary abnormalities. Hematuria and proteinuria. Med Clin North Am 1997;81:644.

Urinalysis findings in Nephrotic Syndrome

- Fatty Cell Casts

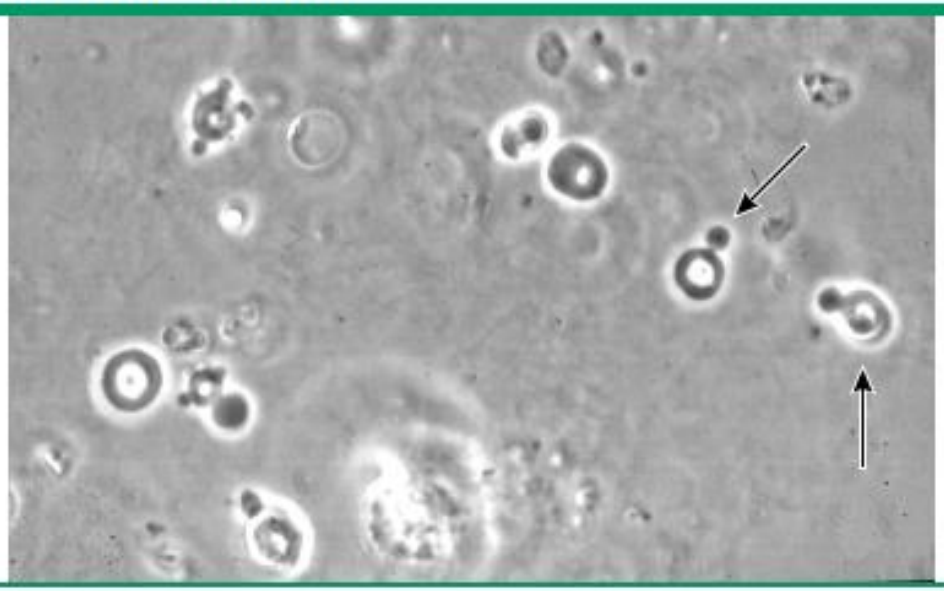


Fatty Casts & Oval Fat Bodies



Urinalysis findings in Nephritic Syndrome

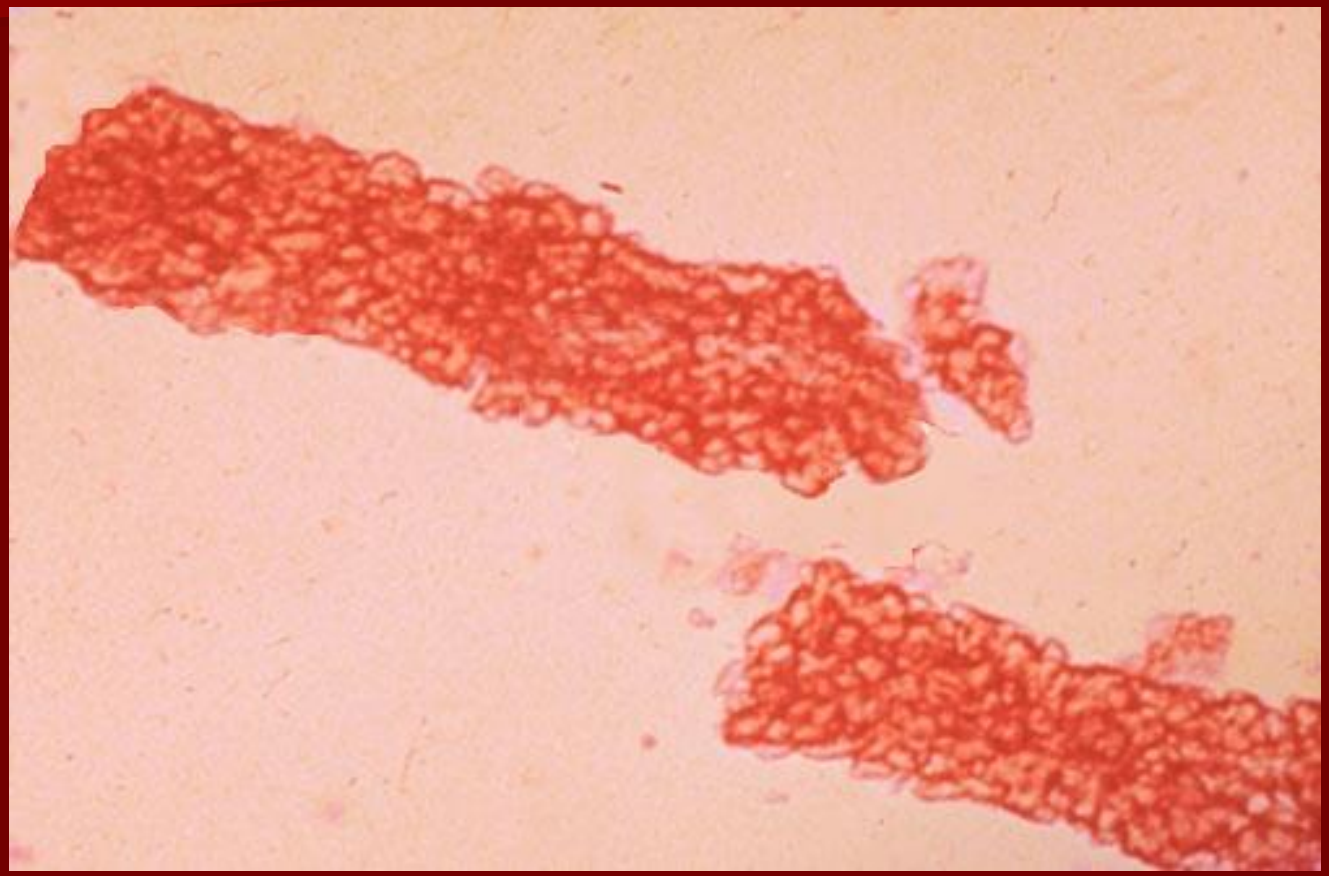
Phase contrast micrograph showing dysmorphic red cells in urine sediment



Phase contrast microscopy showing dysmorphic red cells in a patient with glomerular bleeding. Acanthocytes can be recognized as ring forms with vesicle-shaped protrusions (arrows).

Courtesy of Hans Köhler, MD.

Red cell casts: virtually diagnostic of glomerulonephritis or vasculitis



Glomerulonephritis

Non-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

Proliferative

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

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

Goodpastures Syndrome

Autoimmune
anti-GBM antibody
Glomerulus & Lung affected
Haematuria & Haemoptysis
Treat with steroids
+/- steroid sparing agents

Membranous Nephropathy

- Approximately 15% to 33% of adults with proteinuria and the nephrotic syndrome have membranous nephropathy.
- Membranous nephropathy is usually idiopathic (70-80%) but may occur secondary to conditions such as infections or drugs.
- Idiopathic or secondary antigen deposited in the GBM and are associated with subsequent antibody-antigen interaction.
- This in situ immune complex formation activates the complement cascade that causes glomerular capillary wall permeability and proteinuria in animal studies.
- Membranous nephropathy usually manifests as the nephrotic syndrome, but some patients may have asymptomatic proteinuria w/ microscopic hematuria.

Membranous Nephropathy: Secondary Causes

- Neoplasm:
  - Solid organ (lung, kidney, breast, colon)
- Infection
  - Hepatitis B, C, Malaria, Syphilis, Leprosy
- Drugs
  - Penicillamine, Gold, NSAIDs, mercury, captopril
- Immunologic
  - SLE, MCTD, Thyroiditis, RA, Sjogrens
- After renal transplant
  - Recurrent or de novo
- Sickle Cell Anemia

Membranous Nephropathy

- Clinical Features:
  - 60-70% present with nephrotic syndrome
  - 30-40% present with asymptomatic proteinuria, usually sub-nephrotic
  - 10% have decreased GFR
  - 30-40% microhematuria
  - 10-20% granular casts
  - 10-20% hypertension
- Thromboembolic events
  - Renal vein thrombosis in 10-30%
- Hyperlipidemia

Membranous Nephropathy

- Idiopathic diagnosis made by exclusion, not pathology
- Secondary usually based on history and laboratory findings with some pathologic features
- Testing: ANA, Complements, RF, Hep B & C, Thyroid antibodies, Cryoglobulins, CXR, CT Chest, mammogram, stool for occult blood, colonoscopy, PSA.

Membranous Nephropathy

- 1/3 chronic
- 1/3 spontaneous remission
- 1/3 progress to ESRD

Membranous Nephropathy

Who do you treat?

- 3 studies used to assess risk stratification (Toronto GN Regsitry, Helsinki University, Italian Idiopathic Membranous Nephropathy Study)
  - Low risk: proteinuria< 4 g/d, CrCl normal for 6 mos
    - 8% risk of progression of CKD
  - Moderate risk: proteinuria 4-8 g/d, CrCl nl to slight decrease over 6 months
    - 50% risk of progression of CKD
  - High risk: proteinuria 8 g/d for 3 months, CrCl < nl
    - 75% risk of progression of CKD over 5 years

Membranous Nephropathy

- ACE inhibitors/Angiotensin Receptor Blockers
- Statins
- Anticoagulation
- Steroids alone ineffective
- Cyclophosphamide with steroids
- Cyclosporine or Tacrolimus +/- steroids
- Rituximab (resistant)

Minimal Change Disease

- Accounts for 10% to 20% of all cases of primary nephrotic syndrome in adults. In children, it accounts for almost 90% of cases.
- This condition is usually idiopathic but may develop secondary to use of NSAIDs or lithium.
  - Hodgkins lymphoma and other less-common lymphomas or leukemias; thymoma; and malignancies of the kidney cells, duodenum, and pancreas also may be associated with minimal change disease.
- A diagnosis of minimal change disease can be established in patients with effacement or flattening of the podocytes seen on electron microscope
- Manifests as sudden proteinuria that may be significant,
  - the urine protein-creatinine ratio may exceed 9 mg/mg.
  - Microscopic hematuria and hyperlipidemia also may be present.
  - normal findings on light and immunofluorescence microscopy.

Minimal Change Disease

- Most common presentation is edema.
- Less frequent infections.
- Renal vein thrombosis and pulmonary emboli more common in adults.
- Not associated with systemic manifestations such as fever, rash, arthralgias.
- In children, may confirm diagnosis by responsiveness to steroids as opposed to kidney biopsy. In adults, cannot confirm diagnosis without biopsy.
- Daily or alternate-day therapy with prednisone, 60 mg/m^2 for 4 weeks followed by 40 mg/m^2 for 4 weeks, is indicated to initially treat minimal change disease.
- Relapse therapy involves similar doses of steroids but for shorter period.
- Fewer than 10% of patients will remain relapse free after initial episode.
- 1/3 have infrequent relapses, 1/3 have frequent relapses: both usually steroid responsive
- 1/3 experience steroid toxicity or are steroid dependent and require second line therapy: 1. cyclophosphamide, 2. azathioprine or MMF, 3. cyclosporine or tacrolimus

Focal Segmental Glomerulosclerosis

- Commonly occurs in young adults
- May present with abrupt onset of nephrotic syndrome
- Idiopathic or secondary
- 35% of idiopathic nephrotic syndrome in adults
- 20-40% of patients have renal survival after 10 years if no remission of nephrotic syndrome
- 65-95% of patients with partial or complete remission experience renal survival at 10 years
- Clinical features: asymptomatic to nephrotic, edema, hypertension (30-50%), microscopic hematuria (25-75%), decreased GFR (20-30%)

Secondary Causes of Focal Segmental Glomerulosclerosis

- Genetic:
  - Mutations in Podocin
  - Mitochondrial cytopathies
- Viral:
  - HIV, Parvovirus B19
- Drug:
  - Heroin, interferon-alpha, lithium, pamidronate
- Reduced Nephron Mass/Hyperfiltration:
  - Oligomeganephronia, unilateral renal agenesis, renal dysplasia, reflux nephropathy, surgical or traumatic ablation, chronic allograft nephropathy, nephron loss
- Other:
  - Obesity, cyanotic congenital heart disease, sickle cell disease

Focal Segmental Glomerulosclerosis: Morphologic Classification

- FSGS-NOS
- Perihilar Variant
- Cellular Variant
- Tip Variant:
  - similar to Minimal Change, associated with good response to treatment and better renal survival
- Collapsing Variant:
  - Similar HIVAN, more common in African Americans, more ominous clinical course

- C1q Nephropathy
- IgM Nephropathy

Focal Segmental Glomerulosclerosis

- 5-10% spontaneous remission
- Most patients develop ESRD 5-20 years after presentation
- Risk factors for rapid progression to ESRD:
  - Massive proteinuria
  - African American race
  - Collapsing Variant
  - Tubulointerstitial Fibrosis
- May recur in transplanted kidney
- Treatment controversial: 10-30% respond to corticosteroids

Focal Segmental Glomerulosclerosis

- Partial remission: 50% reduction in proteinuria
- Complete remission: <300mg/g

- Previously untreated: Prednisone
- If relapse or risk of corticosteroids high: Calcineurin inhibitors +/- low dose corticosteroid
- If steroid resistant or dependent or failed response to calcineurin inhibitors: alternative therapies include MMF or Rituximab.

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+ Prednisolone
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Lungs, Kidney & other organs
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Treat with Steroids
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Microscopic Polyangitis

Small vessel vasculitis
p-ANCA +ve
Treat with long term steroids
+/- cytotoxic agents

Goodpastures Syndrome

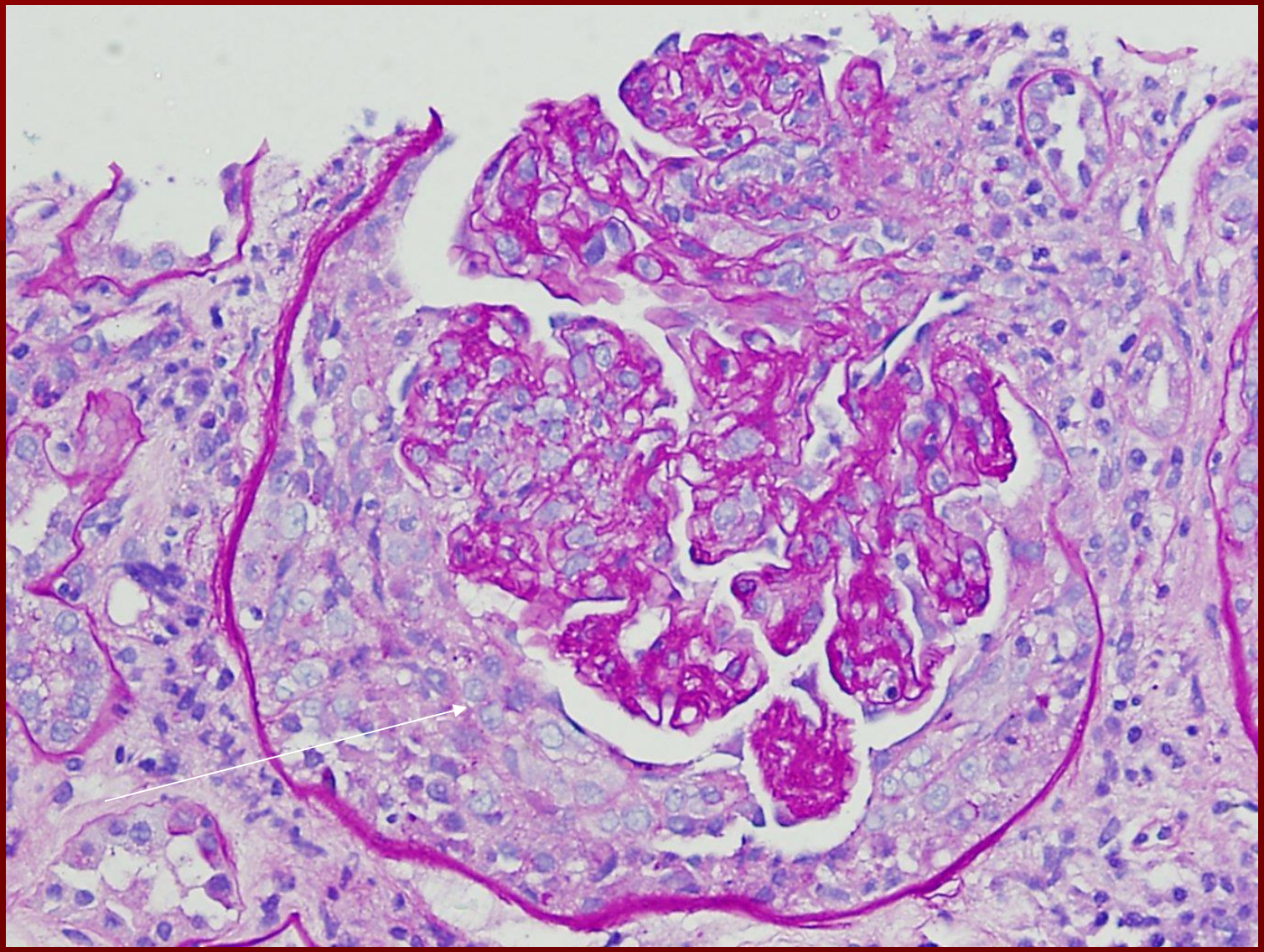
Autoimmune
anti-GBM antibody
Glomerulus & Lung affected
Haematuria & Haemoptysis
Treat with steroids
+/- steroid sparing agents

Acute (proliferative) glomerulonephritis/RPGN

- Acute onset
- Azotemia
- Oliguria
- Edema
- Hypertension
- Proteinuria
- Hematuria
- Active urinary sediment
- $\geq$ 50% loss of kidney function in weeks to months

Crescentic Glomerulonephritis

- Most severe form of GN
- Manifests as RPGN
- Most common biopsy finding in patients with new onset kidney disease with nephritic sediment and SCr > 3.
- Crescents are proliferations of cells within Bowman's capsule that include mononuclear phagocytes and glomerular epithelial cells
- Response to glomerular rupture



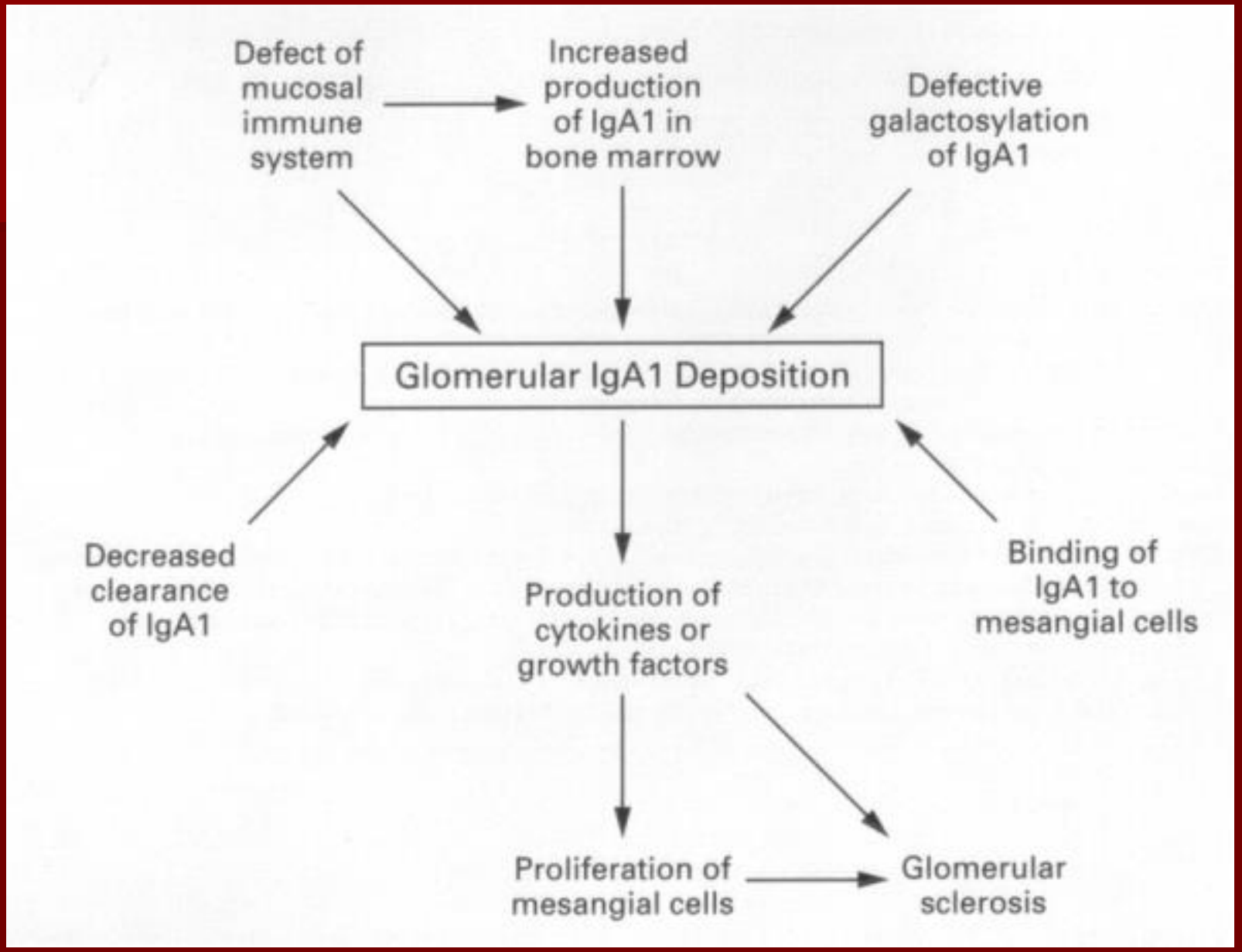
Cellular crescent [arrow], PAS.

Acute glomerulonephritis

- Many are immune mediated inflammatory diseases
- Treatment: corticosteroids, cytotoxic, or other anti-inflammatory or immunosuppressive drugs
- Aggressiveness of the treatment should match the aggressiveness of the disease

IgA Nephropathy

- Most common cause of glomerulonephritis in the world.
- A consequence of defective mucosal immunity in which IgA molecules react to as-yet unidentified antigens.
- IgA nephropathy may only involve the kidney or occur as part of a syndrome that includes skin or liver disease as well as other disorders such as inflammatory bowel disease; celiac disease; ankylosing spondylitis; and infections. IgA nephropathy also may develop in patients with Henoch-Schönlein purpura.
- Present with episode of macroscopic or gross hematuria that is usually associated with a concomitant pharyngitic or gastrointestinal infection.Once deposited in the glomeruli, these immune complexes incite an inflammatory response.
- May have persistent proteinuria.
- Kidney biopsy, IgA is the dominant type of immunoglobulin observed by immunofluorescence microscopy.
- Conservative management with an ACE inhibitor or an ARB is indicated for patients with IgA nephropathy who have good prognostic indicators such as normal kidney function, normal blood pressure, and a urine protein-creatinine ratio less than 1 mg/mg.
- Those with more progressive disease who have elevated serum creatinine levels should receive pulse corticosteroid therapy


Defect of mucosal immune system
Increased production of IgA1 in bone marrow
Defective galactosylation of IgA1
Glomerular IgA1 Deposition
Decreased clearance of IgA1
Production of cytokines or growth factors
Binding of IgA1 to mesangial cells
Proliferation of mesangial cells
Glomerular sclerosis

Primary causes

IgA nephropathy
Schönlein–Henoch purpura

Secondary causes

Diseases of the liver: alcoholic, primary biliary, or cryptogenic cirrhosis; hepatitis B (where endemic); chronic schistosomiasis
Diseases of the intestine: celiac disease; chronic ulcerative colitis; Crohn's disease
Diseases of the skin: dermatitis herpetiformis; psoriasis
Diseases of the bronchus or lung: sarcoidosis, idiopathic pulmonary hemosiderosis; cystic fibrosis; bronchiolitis obliterans
Neoplasia: carcinoma of the lung, larynx, and pancreas; mycosis fungoides
Infection: human immunodeficiency virus; leprosy
Other systemic or immunologic disorders: systemic lupus erythematosus; rheumatoid arthritis; cryoimmunoglobulinemia; psoriatic arthritis; ankylosing spondylitis; Sjögren's syndrome; Behçet's syndrome; Reiter's syndrome; familial immune thrombocytopenia; autoantibody-mediated (monoclonal IgA–mediated) Goodpasture's syndrome
Diseases coincident with IgA nephropathy: antineutrophilic cytoplasmic antibody–associated vasculitis; diabetic nephropathy; membranous nephropathy; Wegener's granulomatosis

IgA Nephropathy

- Synpharyngitic presentation: episode of gross hematuria following URI
- Many are asymptomatic
- 60% of patients diagnosed with IgAN after microscopic hematuria develop gross hematuria on at least 1 occasion
- Small percentage of patients have benign course with either spontaneous remission or persistent microscopic hematuria.
- If no proteinuria or hypertension, good prognosis, conservative treatment.
- Progressive predictors: persistent proteinuria, hypertension, decreased GFR
- Crescentic IgAN has poor prognosis despite immunosuppresive therapy
  - 50% renal survival at 1 year, 20% at 5 years

IgA Nephropathy

- ACE inhibitos/Angiotensin Receptor Blockers
- Statins
- Omega 3 Fatty Acids (mixed results)
- Corticosteroids
- Cyclophosphamide
- Crescentic GN: pulse methylprednisolone followed by Prednisone and Cyclophosphamide
- Alternatives: MMF, CNI

Postinfectious Glomerulonephritis

- Glomerular syndrome follows or accompanies evident bacterial infection
- Acute Nephritic Syndrome or AKI/Oliguria or NS
- Streptococcus and Staphylococcus most common
- Rapid onset of edema, hypertension, heavy proteinuria, hematuria, low UNa, concentrated urine
- Postpharyngitic form: hematuria delayed 10-20 days
- Pathology:
  - acute endocapillary exudative (classical PSGN)
  - endocapillary plus extracapillary (crescentic) GN (SBE)
  - MPGN

Acute Postinfectious Glomerulonephritis

- Spontaneous recovery is the rule
- Rapid onset after pharyngeal or cutaneous infection
- Microscopic hematuria may last a few months
- Usually benign disease
- Children do better

Postinfectious Glomerulonephritis: Rapid or Subacute

- Crescentic
- After septicemia (endocarditis, dental infection)
- Febrile with GN and purpura: consider endocarditis
- Low serum complement in 24%
- Risk factors: alcoholism, drug addiction, malnutrition, low socioeconomic status
- Treatment: antibiotics and possibly surgery
- Corticosteroids, cyclophosphamide and plasmapheresis

Table 21 | Infections associated with glomerulonephritis

Bacterial	**Viral**
Mycobacterium leprae, M. tuberculosis	Hepatitis B and C
Treponema pallidum	Human immunodeficiency virus
Salmonella typhi, S. paratyphi, S. typhimurium	Epstein-Barr virus
Streptococcus pneumoniae, S. virdans, S. pyogenes	Coxsackie B
Staphyloccoccus aureus, S. epidermidis, S. albus	ECHO virus
Leptospira species[a]	Cytomegalovirus
Yersinia enterocolitica[a]	Varicella zoster
Neisseria meningitidis, Neisseria gonorrhoeae[a]	Mumps
Corynebacterium diphtheriae[a]	Rubella
Coxiella burnetii[a]	Influenza
Brucella abortus[a]	
Listeria monocytogenes[a]	
Fungal	**Helminthic**
Histoplasma capsulatum[a]	*Schistosoma mansoni, S. japonicum, S. haematobium*
Candida[a]	*Wuchereria bancrofti*
Coccidiodes immitis[a]	*Brugia malayi*
	Loa loa
Protozoal	*Onchocerca volvulus*
Plasmodium malariae, P. falciparum	*Trichinella spiralis*[a]
Leishmania donovani	
Toxoplasma gondii	
Trypanosoma cruzi, T. bruci	
Toxocara canis[a]	
Strongyloides stercoralis[a]	

ECHO, enteric cytopathic human orphan; GN, glomerulonephritis.
[a]Only case reports documented.

Membranoproliferative Glomerulonephritis (MPGN)

- Hematuria (dysmorphic rbc)
- Variable proteinuria
- Normal or decreased GFR
- Immune complex mediated or complement mediated
- Both types have hypocomplementemia
- Formerly classified as type I, II or III but significant overlap in this classification

Immune Complex Mediated MPGN

- Chronic Infections
  - Hepatitis B and C
  - Chronic bacterial endocarditis, fungal, parasite
- Autoimmune Disease
  - SLE
  - Sjogrens, Rheumatoid Arthritis
- Monoclonal gammopathies

Complement Mediated MPGN

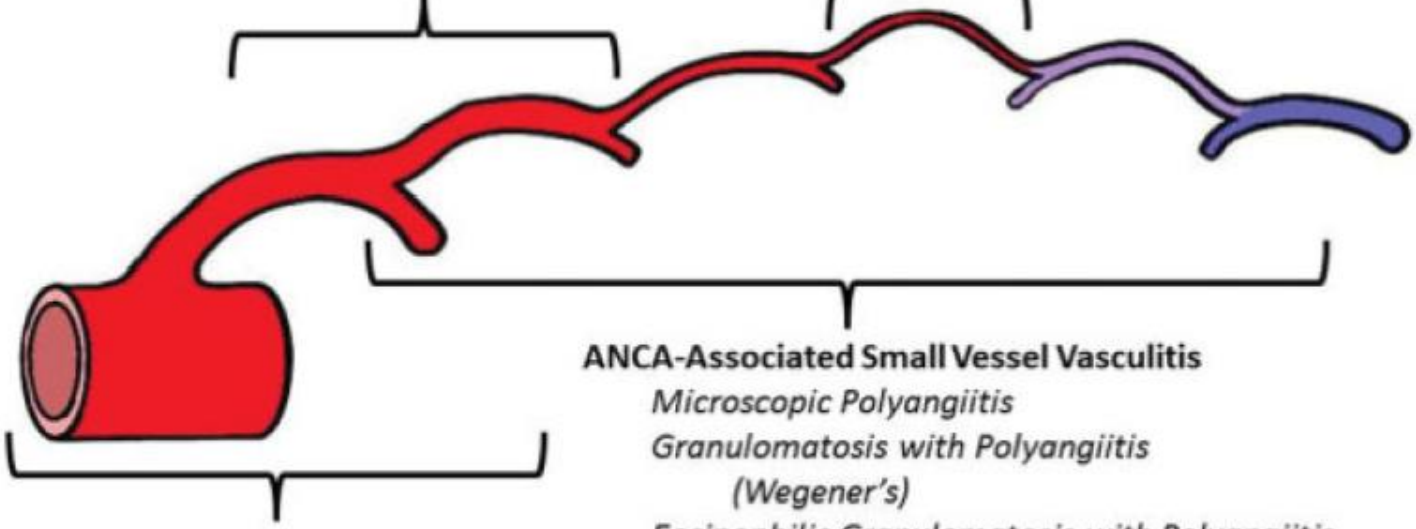
- Less common than immune complex MPGN
- Dense Deposit Disease
- C3 Glomerulonephritis

Membranoproliferative Glomerulonephritis

- Treatment:
  1. Underlying Cause:
     - antiviral (Hep B & C),
     - antimicrobial (endocarditis),
     - chemotherapy
  2. Predictors of Renal Prognosis:
     - Non-nephrotic proteinuria, normal SCr, normal BP = benign prognosis
  3. Rx of GN:
     - Idiopathic Immune Complex Mediated
       - ACE or ARB
       - Steroids +/- cytotoxic, CNI, Rituxan (few randomized trials)
       - Antiplatelets and anticoagulants
     - C3 GN
       - No trials, treat according to cause (Rituximab, Eculizumab)
     - Dense Deposit Disease
       - No trials: Rituximab, Eculizumab, Plasma exchange, Cyclophopshamide, MMF)

Classification of Vasculitis

Chapel Hill Consensus Criteria
Nomenclature update 2012



Immune Complex Small Vessel Vasculitis
Cryoglobulinemic Vasculitis
IgA Vasculitis (Henoch-Schönlein)
Hypocomplementemic Urticarial Vasculitis (Anti-C1q Vasculitis)

Medium Vessel Vasculitis
Polyarteritis Nodosa
Kawasaki Disease

Anti-GBM Disease

ANCA-Associated Small Vessel Vasculitis
Microscopic Polyangiitis
Granulomatosis with Polyangiitis (Wegener's)
Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

Large Vessel Vasculitis
Takayasu Arteritis
Giant Cell Arteritis

ANCA

- Granulomatosis and Polyangiitis (Wegeners)
- Microscopic Polyangiitis
- Renal limited vasculitis
- Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

GPA & MPA

- Common in older adults but occur at any age
- More common in white patients (89% in Glomerular Disease Collaborative Network)
- Pulmonary & Renal Syndrome
- Fatigue, fever, weight loss, arthralgias, rhinosinusitis, cough, dyspnea, pupura, neurologic symptoms
- AKI with active urinary sediment, asymptomatic hematuria
- Rapidly rising creatinine with hematuria, hypertension and edema is medical emergency
- Variable proteinuria, usually subnephrotic
- Skin: leukocytoclastic angiitis, purpura
- Relapses may present differently than initial presentation
- Almost all patients with pauci-immune crescentic glomerulonephritis test positive for ANCA (96%)

GPA & MPA

- All patients warrant treatment due to severity and progression of untreated disease. 90% mortality at 2 years!
- Complete remission does not mean that all parameters return to baseline
- Initial immunosuppressive therapy:
  - Glucocorticoids with either cyclophosphamide or rituximab
  - Mild extrarenal may benefit from methotrexate and glucocorticoids
  - SCr > 5.7, require dialysis, pulmonary hemorrhage or + anti-GBM: plasma exchange with glucocorticoids and cyclophosphamide
- Cyclophosphamide PO vs. IV vs. Rituximab
- Maintenance therapy: (to prevent relapse)
  - Azathioprine, MMF, rituximab, methotrexate
  - Drug induced or MPO + in remission may not require
  - If require dialysis 4 months, only 5% regain function and should avoid excessive immunosuppresion
- PCP prophylaxis

Goodpasture's Syndrome

- Anti-Glomerular Basement Membrane Disease
- Described by Goodpasture in 1919
- Syndrome named in 1957 in report by Stanton and Tange describing patients with pulmonary renal syndrome.
- 1960's: deposition of immunoglobulins along the glomerular basement membrane
- Today: RPGN, pulmonary hemorrhage and anti-GBM
- Bimodal age distribution: 3rd and 6th decades
- Slight preponderance to males
- 1/3 of patients present with isolated GN, rare for isolated pulmonary
- Malaise, fatigue and weight loss
- Pulmonary hemorrhage in 2/3 patients
- CXR: patchy diffuse alveolar shadowing
- Long term pulmonary sequelae are uncommon in treated patients

Goodpasture's Syndrome

- Urine with numerous erythrocytes, red cell casts and mild to moderate proteinuria (rarely nephrotic)
- Hypertension and oliguria are late features
- Pathology: diffuse crescentic glomerulonephritis
- Linear deposition of IgG, sometimes IgA, IgM, C3 along GBM
- Other pulmonary-renal syndromes: ANCA, SLE, HSP, cryoglobulinemia
- 30% of patients may have ANCA as well
- Patients with both rarely recover renal function
- Several patients with Membranous develop Anti-GBM
- May develop in Alports patients after transplant
- HLA-DR2

Goodpasture's Syndrome

- Untreated: rapidly fatal
- Treatment: plasma exchange, cyclophosphamide, corticosteroids
- Dialysis when necessary
- Plasma exchange removes circulating anti-GBM
- Cyclophosphamide prevents further anti-GBM synthesis
- Second line: Cyclosporine, MMF, Rituximab
- 1 year survival now 75-90% but recovery of renal function is 40%
- SCr > 6.8 or oliguria at presentation unlikely to recover renal function
- Kidney transplant after anti-GBM undetectable, although most wait at least 6 months after disappearance of anti-GBM

J.D.

- 41 yo female with nephrolithiasis s/p cystoscopy and ureteral stent.
- Baseline creatinine 1.
- HPI: Nausea, vomiting, fever, anorexia, gross hematuria
- Creatinine: 3.8
- Hemoglobin 7.5
- UA: 2+ protein, 3+ blood, SG 1.006, WBC 13/hpf, RBC >180/hpf

J.D.

- Urine Protein/Creatinine: 2.4
- Hepatitis B: negative
- Hepatitis C: negative
- RF <11
- Cryoglobulins: negative
- DSDNA: 4 (negative)
- C3: 148
- C4: 31
- ASO: 37 (<200)
- ANCA: negative
- **Anti-GBM: 287 (0-19)**

J.D.

- Renal biopsy:
  - **Active crescentic and necrotizing glomerulonephritis**
  - **More than 90% of glomeruli have crescents**
- Treatment:
  - Cyclophosphamide caused neutropenia
  - Methylprednisolone followed by Prednisone
  - Plasma Exchange
  - Hemodialysis

"The bad news is you have a disease unknown to medical science - the good news is I'm going to name it after me."