

Glomerular Diseases:

Primary glomerulonephritis / glomerulopathy

→ Kidney is primarily involved

- Acute proliferative glomerulonephritis (post-infectious)
- Rapidly progressive (crescentic) glomerulonephritis
- Minimal-change disease
- Membranous glomerulonephritis
- Dense deposit disease
- Focal segmental glomerulosclerosis
- IgA nephropathy
- Chronic glomerulonephritis

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Secondary glomerular diseases

→ Glomeruli are involved secondary to a systemic disease

- Systemic immunological disease (eg: SLE)
- Metabolic diseases (eg: Diabetes mellitus)
- Vasculitis: Microscopic polyarteritis/polyangitis, Wegener granulomatosis, Henoch-Schönlein purpura
- Amyloidosis
- Goodpasture Syndrome
- Bacterial endocarditis

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Hereditary disorders:

- Alport Syndrome
- Thin basement membrane disease
- Fabry disease

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Glomerulonephritis may show one/more of 3 basic histological changes:

- (1) increased cellularity
- (2) basement membrane thickening
- (3) hyalinization or sclerosis.

Hib

Increased cellularity (Hypercellularity): ↑ in number of cells in glomerular tufts ⇒ Proliferative glomerulonephritis

→ Reasons for hypercellularity:

- Cellular proliferation of mesangial/endothelial/epithelial cells
- Leukocytic infiltration
- Formation of crescents: formed due to proliferation of parietal epithelial cells & infiltration by leukocytes as a response to fibrin that leaks into urinary space through ruptured basement membrane

Basement Membrane Thickening: may be due to:

- deposition of amorphous electron-dense immune complexes on the endothelial or epithelial side of GBM or within GBM itself
- thickening of basement membrane eg: in diabetic glomerulosclerosis

Hyalinosis & Sclerosis:

Hyalinosis: accumulation of homogeneous eosinophilic material in glomeruli & consists of plasma proteins that have leaked from circulation into glomeruli

Sclerosis: accumulation of extracellular collagenous matrix either in mesangium or in capillary loops or both

Diffuse/generalized: involving all glomeruli in the kidney

Global: involving whole individual glomeruli

Focal: involving only some portion of the glomeruli

Segmental: affecting a part of each glomerulus

Capillary loop/mesangial: affecting predominantly capillary/mesangial regions.

Pathogenesis of Glomerular Injuries:

① Antibody-mediated injury:

* In situ complex deposition:

- Fixed intrinsic tissue antigens eg: anti-GBM nephritis
- Planted antigens:
 - Exogenous: eg: infectious agents, drugs
 - Endogenous: eg: DNA, nuclear proteins

* Circulating immune complex deposition:

- Endogenous antigens: eg. DNA, tumor antigens
- Exogenous antigens: eg. infectious products

② Cell-mediated immune injury

③ Activation of alternative complement pathway

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In Situ Antibodies: antibodies react directly with intrinsic (fixed) tissue antigens or antigens planted in the glomerulus

In Situ Antibodies against Fixed Antigen: Anti-GBM antibody-mediated glomerulonephritis

→ diffuse linear pattern of immunofluorescence

Good Pasture Syndrome: conformational changes in α_3 chain of type IV collagen of GBM

→ the fixed altered GBM antigen produces anti-GBM antibodies against Goodpasture Ag

→ these Ab's may also cross-react with basement membrane of lung alveoli causing lesions in lungs & kidneys

Masugi / Nephrotoxic Nephritis: an experimental model of nephritis produced in rats

In Situ Antibodies against Planted Antigen:

→ planted antigens include viral, bacterial & parasitic products & drugs

→ granular fluoresce on immunofluorescence microscopy

Heymann nephritis: experimental model

Circulating Immune Complex Glomerulonephritis:

→ caused due to trapping of circulating antigen-antibody complexes (Type III Hypersensitivity) within glomeruli

Endogenous Antigens: autoimmune diseases (eg: SLE)

Exogenous Antigens:

- Microbial (bacterial/viral)
- Tumor antigens
- Spirochetal (*Treponema pallidum*)
- Unknown antigens
- Parasitic (*Plasmodium falciparum*)

Electron microscopy: shows electron-dense deposits in the following sites:

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- mesangium
- subendothelial deposits between the endothelium & GBM
- basement membrane
- subepithelial deposits between outer surface of GBM & podocytes

Immunofluorescence Microscopy: granular deposits

Factors that Determine localisation of Immune complexes in the glomerulus:

Charge
size

- highly cationic molecules can cross GBM & appear subepithelially
- highly anionic molecules cannot cross GBM & are trapped subendothelially
- neutral molecules accumulate in mesangium
- large complexes are removed from circulation by mononuclear phagocyte system & do not enter GBM
∴ do not produce glomerulonephritis
- medium size immune complexes are most pathogenic

In situ Antibody mediated glomerulonephritis

Circulating immune complex mediated glomerulonephritis

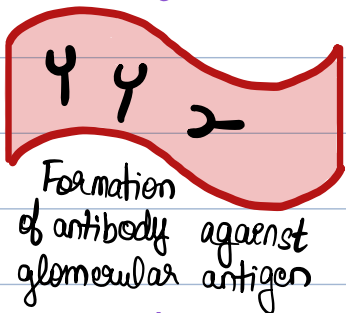
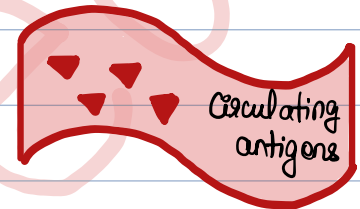
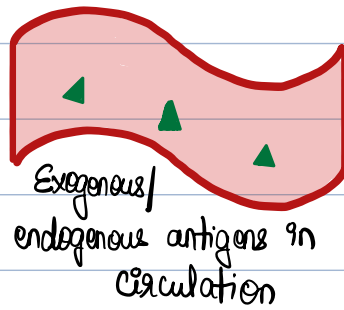
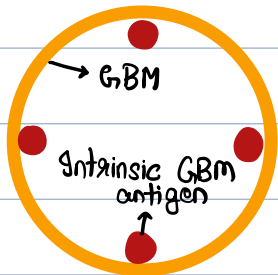
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Fixed glomerular

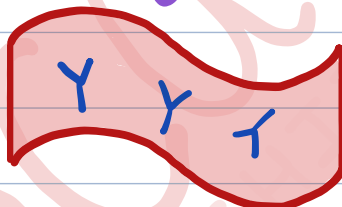
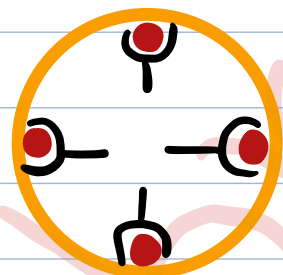
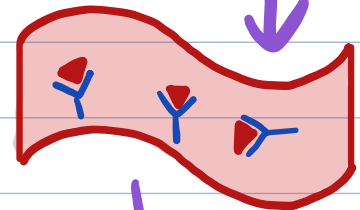
Planted Antigen

Exposure to antigen (exogenous/endogenous)

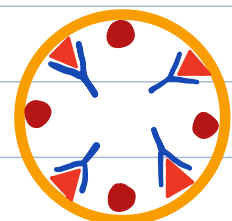
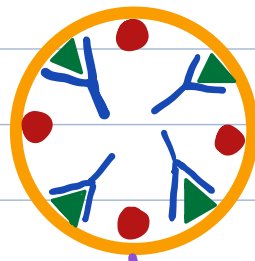
Antigen



Formation of
antigen-antibody
complex in circulation



Formation of antibodies
against planted antigen



Deposition of immune
complexes in GBM

GLOMERULONEPHRITIS

Nephritic Syndrome:

→ characterized by hematuria, dysmorphic red cells, red cell casts in urine, azotemia & oliguria, mild to moderate hypertension

→ proteinuria & edema are common (not as severe as in nephrotic syndrome)

→ one of the causes of nephritic syndrome: acute proliferative glomerulonephritis

Acute Proliferative Glomerulonephritis: increased number of cells within glomerulus due to proliferation of cells of glomeruli &/or infiltration of polymorphs & macrophages

→ mediated by immune-complexes

→ inciting antigen may be exogenous or endogenous:

- exogenous: eg: post-infectious glomerulonephritis
- endogenous: eg: SLE

Poststreptococcal Glomerulonephritis: develops after streptococcal infection

Age: children (6-10 years) & young adults

Etiopathogenesis: → follows streptococcal infection rather than direct primary infection of kidney

→ primary streptococcal infection involves pharynx (pharyngitis) or skin (impetigo / pyoderma)

→ only group A β -hemolytic streptococci are nephritogenic (mainly types 12, 4 & 1)

→ latent period: 1-4 weeks (between streptococcal infection & beginning of glomerulonephritis)

→ immune-complex mediated disease

→ Antibodies against streptococcal antigen: • Anti-streptolysin O • Anti-DNase B

• Anti-streptokinase • Anti-hyaluronidase • Anti-nicotinyl adenine dinucleotidase

→ Hypocomplementaemia is seen due to activation & utilization of complements by immune complexes

→ Electron microscopy shows glomeruli with electron-dense deposits

→ Immune fluorescence shows granular fluorescence

→ Streptococcal antigens in glomeruli: • Nephritis associated streptococcal plasmin receptor (NAPLR)

• Streptococcal pyogenic exotoxin B (SpeB) • Zymogen precursor (z SpeB) • Streptococcal GAPDH

Mechanism of Damage: immune complexes are formed in circulation & deposit within glomeruli

→ immune complexes initiate inflammation by activating complement & humoral & cell-mediators of inflammation

→ inflammatory mediators activate neutrophils & monocytes & stimulate proliferation of endothelial & mesangial cells

Gross: → enlarged kidneys → pale capsular surface & cortex

Microscopy:

Glomeruli: enlarged hypercellular, seen in all glomeruli ∴ diffuse

→ hypercellularity is due to:

- infiltration by leukocytes (neutrophils & monocytes)
- proliferation & swelling of endothelial & mesangial cells
- rarely: proliferation of parietal cells lining Bowman's capsule leading to formation of crescents

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→ obliteration of glomerular capillary lumen (due to hypercellularity)

Tubules: may contain red cell casts in the lumen

↳ tubular epithelial cells may show degenerative changes

Interstitial: may show edema & inflammatory cell infiltrate

Immunofluorescence: granular fluorescence (deposits of IgM, IgG & C3)

Electron microscopy: electron-dense deposits that appear as humps or lumpy deposits (IgG & C3)

Clinical Course: • development of malaise, fever, nausea, oliguria, hematuria (smoky or cola-coloured urine) 1-2 weeks after recovery from sore throat

• periorbital edema, mild to moderate hypertension.

Blood Findings: • raised antistreptococcal antibody titres • hypocomplementaemia

- ↑ blood urea
- ↑ serum creatinine

Urinary findings: • oliguria • mild proteinuria ($< 1\text{g/day}$) • haematuria (smoky or cola-coloured urine)

- red cell casts / dysmorphic red cells

Prognosis: good in children, less benign in adults

Rapidly Progressive (Crescentic) Glomerulonephritis: (RPGN)

- rapid & progressive loss of renal function associated with severe oliguria & signs of nephrotic syndrome
- if not treated, death occurs due to renal failure within weeks to months.
- presence of crescents in most of the glomeruli

Classification:

Type I: aggressive

- caused by anti-GBM antibody
- eg: Goodpasture syndrome

Type II: due to immune complex deposition

- immunofluorescence shows granular fluorescence
- eg: postinfectious glomerulonephritis, lupus nephritis, IgA nephropathy

Type III (Pauci-immune): idiopathic

- have circulating antineutrophil cytoplasmic antibodies (ANCA)
- eg: Wegener granulomatosis, ANCA-associated

Goodpasture Syndrome: anti-GBM antibodies cross-react with pulmonary alveolar basement membranes causing pulmonary haemorrhage associated with acute renal failure

Pathogenesis:

Genetic predisposition: high prevalence of certain HLA subtypes (eg: HLA-DRB1)

- Goodpasture antibodies result from conformational changes in $\alpha 3$ chain of type IV collagen of GBM

gross: • enlarged & pale kidneys • may show petechial haemorrhages on cortical surfaces (flea bitten kidney)

Microscopy: → presence of crescents in most of the glomeruli

- crescents are formed by proliferation of parietal epithelial cells lining Bowman capsule & infiltration of monocytes & macrophages into urinary spaces
- crescent formation is stimulated by fibrin leaked into Bowman space through ruptured GBM
- crescents indicate severe glomerular injury
- tubular lumen may show casts & red cells
- interstitium shows edema with few inflammatory cells

Immunofluorescence: linear GBM fluorescence

Electron microscopy: ruptures in GBM which make it leaky

Clinical Course: patients present with recurrent haemoptyses or life-threatening pulmonary haemorrhage, hypertension & edema

→ Haematuria, RBC casts, moderate proteinuria

→ Uraemia is the cause of death

12:20

Urolithiasis: (Renal Calculi, Stones) - most common cause of upper urinary tract haematuria

- Nephrolithiasis (renal stones) $\Rightarrow$ stones within collecting system of kidney
- Urolithiasis (urinary calculi/stones) $\Rightarrow$ stones anywhere within collecting system of urinary tract

$\rightarrow$ Age: peak at 20-30 years

$\rightarrow$ Male predominance

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Etiology: familial & hereditary predisposition:

- many inborn errors of metabolism (gout, cystinuria)
- $\rightarrow$ dietary deficiency of vit. A causes desquamation of epithelium
- $\rightarrow$ dehydration increases concentration of urinary solutes & are liable to precipitate
- $\rightarrow$ infection favours formation of calculi $\rightarrow$ urinary stasis
- $\rightarrow$ decreased urinary citrate $\rightarrow$ changes in urinary pH

Pathogenesis: 2 main steps of stone formation - initiation & saturation

① Supersaturation: initiation starts with supersaturation of urine (increased urinary concentration of solutes, decreased urine volume)

② Precipitation of crystals: deficiency of inhibitors of crystal formation (pyrophosphates, citrates, osteopontin, nephrocalcin)

$\rightarrow$ organic mucoprotein forms the nidus for crystal precipitation

General Features: • unilateral (80%) • single/multiple • site: renal calyces, pelvis, bladder

• Shape: smooth contour / irregular jagged mass

Types of Renal Stones:

① Calcium oxalate &/or Calcium phosphate (80%) - causes: (calcium oxalate stones are birefringent)

- idiopathic hypercalcaemia
- hyperoxaluria
- idiopathic
- hypercalcaemia & hypercalcaemia
- hyperuricaemia

② Struvite (Mg , NH_4^+ , PO_4^{3-}) (10%) • urinary tract infection

③ Uric acid (7%) • hyperuricaemia • hyperuricosuria • idiopathic

④ Cystine (2%)

⑤ Unknown (1%)

① Calcium Stones: composed of calcium oxalate &/or calcium phosphate

→ stones are radiopaque

Etiology:

- Hypercalcaemia without hypercalcaemia
- Hyperuricosuria
- Idiopathic
- Hypercalcaemia & hypercalcaemia
- Hyperoxaluria

Morphology:

→ Calcium oxalate stone: • irregular in shape • hard • covered with sharp projections (which may cause haemorrhage of renal pelvis & the blood may cover the stone making it black) • radiodense

→ Calcium phosphate stone: soft & pale

② Struvite / Triple Stones (Mg, NH_4^+, PO_4^{3-}):

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Etiology: develop after urinary tract infections by urea-splitting bacteria (eg: Proteus) which convert urea to ammonia → produces alkaline pH + slowing of urine flow → precipitation of magnesium & ammonium phosphate & calcium phosphate

Morphology: • yellow-white • solitary • hard to soft, friable • largest stones

- sometimes fill the pelvis & calyces to form a cast of these spaces ∴ called staghorn calculus
- easily seen on radiograph

Complications: intractable UTI, pain, bleeding, perinephric abscess

③ Uric Acid & Urate Stones:

Etiology: found in patients with hyperuricemia & diseases involving rapid cell turnover

→ uric acid is insoluble in acidic urine ⇒ predispose to uric acid stones

Morphology: • radiolucent • smooth, hard • yellow-reddish brown • multiple • <2mm diameter

- show lamination on cut-section
- diamond/barrel shaped

④ Cystine stone: • hexagonal • radiopaque • yellow & waxy • small, round, smooth

→ associated with cystinuria

→ stones form at acidic pH of urine

Clinical Features: may be asymptomatic or may obstruct urinary flow or produce ulceration & bleeding

- small stones may pass into ureters producing colic & ureteral obstruction
- larger stones remain silent & may present with haematuria
- stones predispose to superimposed infection & may cause significant renal damage

Complications:

- hematuria
- hydronephrosis
- pyelonephritis, pyonephrosis
- carcinoma (squamous metaplasia → squamous cell carcinoma)

[17:27]

Wilms Tumor (Nephroblastoma): most common primary kidney tumor in children (2-5 years)

→ highly malignant primary embryonal tumor

Pathogenesis & Genetics: mostly sporadic & unilateral

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→ mutation in tumor suppressor gene WT1 on chromosome 11p13.

(WT2 gene imprinting)

→ Associated congenital syndromes: • WAGR syndrome • Denys-Drash syndrome • Beckwith-Wiedemann syndrome

WAGR syndrome (Wilms tumor, Aniridia, Genital anomalies, mental retardation): germline deletions of 11p13

→ WT1 & PAX6 gene are located at chromosome 11p13.

→ Nephrogenic rests: small foci of persistent primitive blastemal cells, which are precursor lesions of Wilms tumors

• seen in renal parenchyma adjacent to bilateral Wilms tumors.

Gross: • large, single, round • well-circumscribed mass • usually unilateral (90%)

• cut-section: - soft, bulging, homogeneous - tan to gray
- foci of haemorrhage, cyst formation, necrosis

Microscopy: 3 components that resemble normal fetal tissue are seen:

① Blastemal component: small, round/oval blue cells with scanty cytoplasm, arranged in sheets, nests & trabeculae

② Immature stromal (mesenchymal) component: undifferentiated fibroblast-like spindle cells

→ may show smooth muscle, skeletal muscle or fibroblast differentiation

③ Immature epithelial component: epithelial cells show differentiation in the form of small abortive (embryonic) tubules or immature glomeruli

→ tumor shows triphasic (all 3 cell types) combination (may be biphasic/monophasic)

→ Anaplasia associated with TP53 mutations & do not respond to chemotherapy

Clinical Features: most children present with abdominal mass

→ hematuria, pain abdomen, intestinal obstruction, pulmonary metastases

Spread:

- Local spread: to perirenal soft tissues
- Lymphatics: spread to regional lymph nodes
- Hematogenous: to lungs, liver & peritoneum

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Prognosis: children younger than 2 years have a better prognosis

→ invasion of renal capsule is associated with poor prognosis

→ anaplasia indicates poorer prognosis

Cystic Diseases of Kidney: heterogeneous group of hereditary/acquired disorders characterized by presence of unilateral or bilateral renal cysts.

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Classification:

① Polycystic Kidney disease:

- Autosomal dominant (adult) polycystic disease
- Autosomal recessive (childhood) polycystic disease

② Medullary cystic disease:

- Medullary sponge kidney
- Nephronophthisis

③ Multicystic renal dysplasia

④ Acquired (dialysis-associated) cystic disease

⑤ Localised (simple) renal cysts

⑥ Renal cyst in hereditary malformation syndromes (eg: tuberous sclerosis)

⑦ Glomerulocystic disease

⑧ Extrarenal renal cysts (pyelocalyceal cysts, hilar lymphatic cysts)

Autosomal Dominant (Adult) Polycystic Kidney Disease:

- ADPKD $\Rightarrow$ hereditary disorder characterized by multiple cysts in both kidneys
- these cysts expand & cause destruction of kidney parenchyma $\Rightarrow$ renal failure.

Genetics: Mutations in:

- PKD1 gene on chromosome 16p13.3 code for polycystin-1 (85% cases)
- PKD2 gene on chromosome 4q21 code for polycystin-2. (15% cases)

Pathogenesis: exact pathogenesis is unknown

- polycystins are extracellular molecules present in primary cilia of tubular epithelial cells, involved in cell-cell or cell-matrix adhesion
- cilia act as mechanosensors of fluid flow in lumen of tubules
- renal cystic disease is a type of ciliopathy
- $\therefore$ mutations of PKD gene $\rightarrow$ altered polycystins $\rightarrow$ defects in mechanosensing $\rightarrow$ disrupted calcium signalling $\rightarrow$ dysregulation of cell polarity, abnormal cell proliferation & cell-matrix adhesion

- abnormal proliferation of tubular epithelium → tubule becomes covered by an undifferentiated epithelium → repeated cycles of cell proliferation → dilatation/expansion of the tubule wall into a cyst
- thickening of basement membrane in affected tubules
- initially, cyst fluid is derived from glomerular filtrate
- later, the cystic segment gets disconnected from the original tubule & fluid is secreted by epithelial cells lining cysts into cyst cavity.
- abnormal proliferation of tubular epithelial cells & expanding volume of intraluminal fluid ⇒ progression of cyst size

Gross: • bilateral • markedly enlarged, weight is increased & each may reach upto 4 kg

- external surface: bosselated with numerous cysts of varying size (upto 3-4 diameter) with no intervening parenchyma

Microscopy: • numerous cysts with functioning nephrons between

- cysts can arise in all segments of nephron ∴ show variable lining epithelia
- lining: cuboidal & columnar epithelium
- clear serous fluid or more commonly - turbid, red to brown, haemorrhagic fluid
- intervening renal parenchyma: may be normal or may show foci of interstitial fibrosis & pyelonephritis

Clinical Features: majority patients are asymptomatic until 4th decade

- presentation: flank pain (heaviness/dragging sensation), bilateral abdominal masses, renal colic (due to passage of blood clots in urine), hypertension, renal failure

Extra renal Associated Congenital Anomalies: • polycystic liver disease • intracranial berry aneurysms in circle of Willis • mitral valve prolapse

Autosomal Recessive (Childhood) Polycystic Kidney Disease: ARPKD

- ↳ categorized into: perinatal, neonatal, infantile, juvenile

Etiology: mutations of polycystic kidney hepatic disease (PKHD1) gene which encodes for fibrocystin (polyductin)

- highly expressed in epithelial cells of collecting ducts & thick ascending loops of Henle

Gross: both kidneys are markedly enlarged, have smooth external appearance $\therefore$ retain their reniform configuration

→ cut-section: medulla & cortex are replaced by numerous small cysts

- cysts tend to be linear & radiate from medulla to outer cortex $\therefore$ gives sponge-like appearance to kidney

Microscopy: • cylindrical cyst • all cysts are lined by cuboidal epithelium, reflecting their origin from collecting ducts

Features: → cysts in liver also → patients who survive infancy may develop congenital hepatic fibrosis

→ bland periportal fibrosis & proliferation of well-differentiated biliary ductules.

→ older children: portal hypertension with splenomegaly

(25:32)

Features	Nephrotic Syndrome	Nephrotic Syndrome
Proteinuria	1-2 g/day	> 3.5 g/day
Hematuria	Present	Absent
Hypertension	Present	Absent
Hypoalbuminemia	Absent	Present (serum albumin < 3 g/dL)
Hyperlipidemia, lipiduria	Not seen	Present
Edema	Mild	Moderate/severe
Azotemia, Oliguria	Present	Absent
Urine microscopy	RBCs & RBC casts	Fatty casts

Nephrotic Syndrome:

- Definition:**
- Heavy proteinuria ($> 3.5\text{g}/24\text{hrs}$)
 - Hypoalbuminemia (serum albumin $< 3\text{g/dL}$)
 - Edema
 - Hyperlipidemia & lipiduria

Pathophysiology:

- Damage to glomerular capillary walls causes increased permeability to plasma proteins.
- majorly, albumin is lost (rarely $\Rightarrow$ globulin)
- hypoalbuminemia $\Rightarrow$ $\downarrow$ colloid osmotic pressure of blood

• Edema: soft, pitting

- Causes: • $\downarrow$ colloid osmotic pressure of blood (due to hypoalbuminemia)
 - $\downarrow$ plasma volume $\rightarrow \downarrow$ GFR $\rightarrow \uparrow$ aldosterone secretion $\rightarrow \uparrow$ salt & water retention
- mostly in periorbital regions & dependent body sites

- Hyperlipidemia: → Causes: - $\uparrow$ synthesis of lipoproteins in liver
 - abnormal transport of circulating lipid
 - $\downarrow$ catabolism of lipids

- Lipiduria: Hyperlipidemia $\rightarrow$ leakage of lipoproteins across glomerular capillary wall $\rightarrow$ leaked lipoprotein is reabsorbed by tubular epithelial cells $\rightarrow$ shed along with degenerated cells $\rightarrow$ appear in urine either as free fat or as oval fat bodies

Complications:

- Coronary atherosclerosis (due to hyperlipidemia)
- Infections (due to loss of immunoglobulins in urine)
- Thrombotic & thromboembolic complications (due to urinary loss of anticoagulants)

Causes of Nephrotic Syndrome:

Primary Disease

- Membranous glomerulopathy
- Minimal change disease FIM³
- Focal segmental glomerulosclerosis
- Membranoproliferative glomerulonephritis
- IgA nephropathy

Secondary / Systemic Disease

- Diabetes mellitus
- Amyloidosis
- SLE MIDAS
- Malignancy
- Infections

Types of Proteinuria:

Highly Selective Proteinuria

- only LMW / intermediate sized proteins leak
eg: albumin, transferrin
- Minimal change disease

Non-selective Proteinuria

- leakage of range of different proteins
eg: immunoglobulins, albumin, etc.
- Membranous nephropathy

Membranous Glomerulopathy / Nephropathy:

→ uniform diffuse thickening of glomerular capillary wall due to accumulation of electron-dense deposits along subepithelial side of GBM.

Etiology:

- Primary (Idiopathic)
- Secondary — Therapeutic drugs (penicillamine) — Malignant neoplasms — Autoimmune disease — Infections — Exposure to inorganic salts (eg: gold, mercury).

Pathogenesis: (chronic immune-complex mediated disease)

- Idiopathic: (Autoimmune disease)

→ autoimmune antibodies directed against phospholipase A2 receptor antigen (PLA2R) on podocytes
Eg: Heymann nephritis (experimental model)

- Secondary: due to circulating immune complexes

Mechanism of Glomerular Injury:

→ Glomeruli DO NOT show inflammatory cells

→ subepithelial immune complex deposits → generates C5b - C9 (membrane attack complex) —

→ MAC damages podocytes of glomerular epithelial cells & mesangial cells → liberates proteases & oxidants → capillary wall injury → leakage of proteins

Light Microscopy:

- Glomeruli: uniform diffuse thickening of glomerular capillary wall

→ normocellular glomeruli

→ silver stains (black colour) or periodic acid schiff stain (pink colour) show characteristic spikes in glomeruli

- Tubules: epithelial cells of PCT show droplets of reabsorbed protein

Electron Microscopy: in between immune deposits, basement membrane material is laid down ⇒ appears as irregular spikes protruding from GBM ⇒ Spike & Dome pattern

- Stage I: capillary walls show mild thickening due to subepithelial dense deposits
- Stage II: GBM material projects as spikes around the dense deposits & stains with silver
- Stage III: immune deposits get buried under the markedly thickened irregular membrane
- Stage IV: buried immune deposits undergo degradation & lysis leaving cavities within the GBM.

Clinical Features:

- sudden onset nephrotic syndrome
- nonselective proteinuria
- does not respond to corticosteroid therapy

[3:53]

Minimal Change Disease: (MCD)

- glomerular changes are absent/minimal
- glomeruli appear normal under light microscopy
- electron microscopy shows diffuse effacement (loss) of podocytes
- Peak incidence: 2-6 years of age

Pathogenesis:

• Immunological Mechanism: Seen when:

- MCD follows a respiratory infection / routine prophylactic immunization
- MCD responds to immunosuppressive drugs
- MCD is associated with atopic/allergic disorders
- increased incidence in patients with Hodgkin lymphoma

• Nonimmunological Mechanism:

- mutations in structural proteins — nephrin & podocin
- mutations in nephrin gene is found in hereditary type of congenital nephrotic syndrome

Mechanism of Proteinuria:

- defects in charge barriers allow anionic proteins (especially albumin) to pass easily through GBM.

Gross: kidneys are mildly enlarged with smooth capsular surface

- Cut-section: yellow to pale cortex

Light microscopy: (glomeruli appear normal)

- Tubules: epithelial cells lining PCT contain lipid vacuoles & glassy (hyaline) protein droplets

⇒ due to tubular reabsorption of lipoproteins passing through damaged glomeruli

- Interstitium: shows mild edema

Electron Microscopy: GBM appears normal without electron-dense deposits

- diffuse effacement (loss) of podocytes

Clinical Features: presents as nephrotic syndrome

- Highly selective proteinuria → Generalized edema → Hypoalbuminemia → Hyperlipidemia
- Urine: Proteinuria, oval fat bodies, fatty casts.

[5:23]

Diabetic Nephropathy:

Pathogenesis:

[AGE]

- Nonenzymatic glycosylation of proteins & formation of Advanced Glycation End-Products:

→ Leads to:

- increased synthesis of extracellular matrix (ECM) $\Rightarrow$ $\uparrow$ mesangial matrix
- increased production of reactive oxygen species $\Rightarrow$ apoptosis of podocytes
- direct cross-linking with ECM proteins $\Rightarrow$ thickening of GBM

- Hemodynamic changes: cause glomerular hypertrophy

- Disturbance in polyol pathways: increases glomerular cell susceptibility to oxidative stress.

Morphology:

Glomerular lesions
Renal vascular lesions
Pyelonephritis
Tubular lesions

- Glomerular Lesions:

① Diffuse Thickening of GBM

② Diffuse Mesangial Sclerosis: increase in PAS-positive mesangial matrix & mesangial cells

③ Nodular Glomerulosclerosis: intercapillary glomerulosclerosis / Kimmelstiel - Wilson disease

④ Insudative lesions:

- Fibrin caps: subendothelial accumulations of hyaline material

- Capsula Drops: round nodules adherent to Bowman's capsule

Kimmelstiel - Wilson (KW) lesion:

→ ovoid / spherical, laminated nodules of mesangial matrix within mesangial core & in periphery of glomerulus

→ nodules are PAS positive

→ As disease advances, individual nodules increase in size & compress surrounding capillaries

- Renal Vascular Lesions:

① Hyaline arteriosclerosis (Hyalinosis): involves both afferent & efferent arteriole

② Renal atherosclerosis $\rightarrow$ renal ischemia $\rightarrow$ atrophy of tubules, interstitial fibrosis, contraction of kidney

- Pyelonephritis: tubulointerstitial inflammation of kidney

- ① Acute & chronic pyelonephritis

- ② Necrotizing papillitis / Papillary Necrosis: special pattern of acute pyelonephritis

- Hyaline arteriosclerosis → narrow blood vessels → ↓ blood supply to renal medulla → ischemia
→ necrosis of tips of papillae

- Tubular Lesions: thickening of BM of tubules

- epithelial cells of PCT show extensive deposits of glycogen vacuoles ⇒ Armanni-Ebstein lesions.

- Electron Microscopy: - thickening of lamina densa of GBM

- ↑ in mesangial matrix

- insudative lesions appear as electron-dense masses.

[8:08]

Pyelonephritis: inflammatory disease of kidney affecting tubules, interstitium & renal pelvis.

Causative organisms: gram-negative bacilli which are normal inhabitants of intestinal tract

- E. coli
- Proteus
- Klebsiella
- Enterobacter

→ In immunocompromised patients: Polyomavirus, Cytomegalovirus, Adenovirus.

Source & Route of Infection: Ascending infection
Hematogenous route

• **Ascending Infection**:

→ endogenous infection (source of organism is patient's own fecal flora)

① Colonization of distal urethra & introitus

② Entry from urethra to bladder

③ Urinary tract obstruction & stasis of urine

④ Vesicourethral reflux: propels infected bladder urine into renal pelvis through ureter

⑤ Intrarenal reflux: from renal pelvis into renal parenchyma

• **Hematogenous Route**: due to rich blood supply of kidneys

→ occurs with nonenteric organisms.

UTI are more common in females because of:

- shorter urethra
- absence of prostatic fluid which has antibacterial properties
- hormonal changes

Chronic Pyelonephritis: important cause of end-stage renal disease

Etiopathogenesis:

• **Chronic reflux-associated pyelonephritis**: due to superimposition of a urinary infection on congenital vesicoureteral reflux & intrarenal reflux

• **Chronic obstructive pyelonephritis**: recurrent infections superimposed on obstructive lesions.

Gross: unilateral or bilateral (if bilateral $\Rightarrow$ it is asymmetric)

$\rightarrow$ kidney is reduced in size due to irregular scars $\Rightarrow$ granular contracted kidney

$\rightarrow$ Scars: - coarse, well-defined

- mostly seen in upper & lower poles due to intrarenal reflux

$\rightarrow$ Calyces & renal pelvis: appear thickened & irregular with scarring of mucosal surface

- calyces below scars are dilated, blunted or deformed

- papillae are flattened

Microscopy:

- Interstitium: shows chronic inflammatory infiltrate & fibrosis

- Tubules: show atrophy in some places & hypertrophy/dilation in others

$\rightarrow$ Thyroidization: dilated tubules with flattened epithelium filled with eosinophilic hyaline material resembles colloid containing thyroid follicles

$\rightarrow$ Blood vessels: may show endarteritis obliterans & may show hyaline arteriosclerosis in the presence of hypertension

- Glomeruli: show periglomerular fibrosis

- Calyces: show dense chronic inflammatory infiltrate & fibrosis.

Xanthogranulomatous Pyelonephritis: unusual & rare form of chronic pyelonephritis associated with Proteus infection

$\rightarrow$ kidney shows large, yellow-orange nodules on cut-surface

$\rightarrow$ interstitium shows foamy macrophages, plasma cells & lymphocytes.

$\rightarrow$ Clinical features: back pain, fever, pyuria, bacteriuria

Causes of Granular Contracted Kidney:

- Chronic glomerulonephritis

- Chronic pyelonephritis

- Nephrosclerosis

[11:28]

Nephrosclerosis: sclerosis of renal arterioles & small arteries

→ Sclerosis of vessels → vessel wall thickening → narrowing of lumen → focal ischemia of renal parenchyma → glomerulosclerosis + chronic tubulointerstitial injury → reduction in renal function

Causes:

- Hypertension
- Diabetes mellitus
- Increasing age

HD

Pathogenesis:

- Medial & intimal thickening: as a response to hemodynamic changes, aging, genetic defects
- Hyaline deposition in arterioles: due to extravasation of plasma proteins through injured endothelium & increased deposition of basement membrane matrix

Gross: bilateral, normal size/reduction in size

- Weight: 110-130g (normal: 150g)
- outer surface: fine, evenly granular
- Cut-section: thinned cortex with scarring

Microscopy:

- Arterioles, Small Arteries: hyaline arteriosclerosis
- Interlobular, Arcuate Arteries: fibrotic thickening of intima with reduplication of elastic lamina & medial hypertrophy ⇒ Fibroelastic hyperplasia
- Tubules: show atrophy
- Interstitial: fibrosis & chronic inflammatory infiltrate
- Glomeruli: sclerosis & thickening of GBM in some glomeruli may be seen

Laboratory Findings: • Mild proteinuria • Hematuria • ↑ serum BUN • ↑ serum creatinine

Causes of flea-bitten kidney:

- Malignant Hypertension
- Subacute bacterial endocarditis
- Rapidly progressive glomerulonephritis
- Henoch - Schonlein purpura

Horseshoe Kidneys: common congenital anomaly of kidney

- fusion of upper poles (10%) or lower poles (90%) with each other
- horseshoe appearance of kidney $\Rightarrow$ continuous across the midline anterior to great vessels.

Hydronephrosis: aseptic dilatation of renal pelvis & calyces due to obstruction of urinary outflow, associated with progressive atrophy of kidney.

Causes: $\begin{cases} \text{structural disorders} \\ \text{Functional disorders} \end{cases}$

- Structural Disorders: — Urinary calculi — Carcinoma of prostate — Bladder tumors
— BPH — Congenit anomalies (urethral strictures, meatal stenosis, etc)
— Inflammation (prostatitis, urethritis)
- Functional Disorders: neurogenic bladder

CUBIC

Pathogenesis: obstruction (Complete/Incomplete) $\rightarrow$ accumulation of urine proximal to obstruction $\rightarrow$ dilatation of affected calyces & pelvis due to back pressure $\rightarrow$ pressure is transmitted through collecting ducts into renal parenchyma $\rightarrow$ Renal atrophy, compression of renal vasculature $\rightarrow$ diminished tubular function $\rightarrow$ reduced GFR, interstitial inflammation & fibrosis

Course: Unilateral or bilateral (depending on level of obstruction)

- Early stage: simple dilation of pelvis & calyces
- Late stage: progressive blunting of apices of pyramids
- Advanced stage: kidney $\Rightarrow$ thin-walled, cystic structure
 $\rightarrow$ renal parenchyma shows destruction due to pressure atrophy & thinning of cortex

Microscopy:

Tubules: dilatation, atrophy

Glomeruli: sclerosis

Interstitium: chronic inflammatory infiltrate & fibrosis

Clinical Features:

- Unilateral complete/partial hydronephrosis ⇒ may be silent due to maintenance of renal function by unaffected kidney
- Bilateral partial obstruction ⇒ polyuria, nocturia
- Bilateral complete obstruction ⇒ oliguria/anuria

[15:03]

Renal Cell Carcinoma (RCC) / Adenocarcinoma of Kidney / Hypernephroma /

Grawitz Tumor: (malignant tumor of kidney)

→ tumors arise from renal tubular epithelium (originally thought to arise from embryonic adrenal rests)

→ Age: 6th - 7th decades of life ; more common in males **O - V - C²HEAT**

Risk factors:

- Cigarette smoking
- Obesity
- Hypertension
- Unopposed estrogen therapy
- Exposure to asbestos
- Chronic renal failure
- Acquired polycystic kidney disease
- Tuberous sclerosis

Types:

- sporadic (96%)
- hereditary/familial (4%)
 - Von Hippel - Lindau (VHL) Syndrome
 - Hereditary leiomyomatosis
 - Hereditary papillary carcinoma
 - Birt - Hogg - Dube Syndrome

Classification:

- clear cell
- papillary
- chromophobe
- collecting duct (Bellini)
- xp11 translocation

① Clear Cell Carcinoma: most common type ; mostly sporadic

→ arises from PCT epithelial cells

→ solitary, unilateral lesion

→ loss-of-function mutation in VHL gene (tumor suppressor gene) on chromosome 3p resulting in:

- stimulation of cell growth
- stimulation of angiogenesis ⇒ due to non-degradation of HIF-1 (hypoxia-inducible factor - 1)

② Papillary Carcinoma: originates from DCT epithelial cells

→ multifocal, bilateral

→ mutations in c-MET (proto-oncogene)

→ Cytogenetic abnormalities:

- Sporadic: trisomies 7, 16, 17
- Familial: trisomy 7

③ Chromophobe Renal Carcinoma: arise from intercalated cells of collecting ducts
→ excellent prognosis

④ Collecting Duct (Bellini Duct) Carcinoma: arises from medullary collecting duct

⑤ Xp11 Translocation Carcinoma: develops in young individuals

→ overexpression of TFE-3 transcription factor

→ tumor cells have clear cytoplasm & papillary architecture

Gross:

- General features: mostly affects upper pole

→ outer surface is bosselated (may distort the renal outline)

- Cut-surface: Tumor ⇒ solid, bright yellow-gray-white

⇒ shows areas of haemorrhage, necrosis, cystic change leading to variegated appearance
(yellow colour is due to prominent lipid in tumor cells)

⇒ circumscribed spherical mass with well-demarcated margins; but may show breach in renal capsule & invasion into perinephric fat

- Venous Invasion: RCC has tendency to invade renal vein

→ it may grow as a continuous cord in inferior vena cava & reach right atrium

Microscopy:

- Clear Cell Carcinoma: solid to trabecular (cord-like); well-differentiated tumor

- * Tumor Cells: clear/granular cytoplasm, nonpapillary (clear cytoplasm is due to glycogen & lipids)
↳ round/polygonal

→ glycogen demonstration: PAS ; Lipid demonstration: oil red O

→ nucleus is small & central

- * Stroma: shows branching vasculature

- Papillary Carcinoma: shows papillary growth pattern

- tumor is composed of cuboidal/low columnar tumor cells

- interstitial foam cells are present in fibrovascular stalk/core of papillary projections

- Psammoma bodies may be seen

- Stroma: scanty, highly vascularized

- Chromophobe Renal Carcinoma: granular cells arranged in solid sheets

- concentration of largest cells around blood vessels

- Tumor cells: prominent cell membrane, pale eosinophilic cytoplasm, perinuclear halo

- Collecting Duct Carcinoma: nests of malignant cells separated by prominent fibrotic stroma

- shows irregular channels lined by highly atypical epithelium with a hobnail pattern

Clinical Features:

- Palpable abdominal mass
- Hematuria

- Costovertebral/flank pain

- RCC can produce ectopic hormones & paraneoplastic syndromes

- Polycythemia (due to erythropoietin)

- Hypercalcemia (due to PTH-rp)

- Hypertension (due to renin)

- Hepatic dysfunction (due to IL-6)

- Feminization / Masculinization

- Cushing's syndrome

Spread:

- Local spread: perinephric fat

- Lymphatic spread: regional lymph nodes

- Hematogenous spread: lungs, bones, liver, adrenal, brain

Transition Cell Carcinoma of Urinary Bladder:

→ composed of urothelial (transitional) cell type

→ multifocal

Precursor lesions: — Non-invasive papillary tumors

— Flat noninvasive urothelial carcinoma / Carcinom in situ (CIS)

Epidemiology: more common in developed countries & urban areas

↳ not familial

→ male preponderance

→ Age: 50-80 years of age

Classification:

① Noninvasive urothelial lesions:

• Papilloma — Urothelial (exophytic) papilloma

— inverted urothelial papilloma

• Papillary urothelial neoplasm of low malignant potential (PUNLMPs)

• Noninvasive papillary urothelial carcinoma — Low grade
— High grade

• Urothelial CIS

② Infiltrating urothelial carcinoma

Pathogenesis:

Risk factors:

• Cigarette smoking

• Industrial exposure to arylamines (used in aniline dye & rubber industries)

• Schistosoma haematobium infection

• Long-term use of analgesics

• Cyclophosphamide

• Radiation exposure

CRIS

Genetic Alterations: — chromosome 9 monosomy / deletion
(involves 2 tumor suppressor genes p16 & p15)
— mutations in p53

Aromatic amines & azo dyes
(metabolized in liver)

↓
Converted to active carcinogenic metabolite in the liver

↓
Detoxified by conjugation with glucuronic acid

↓
Conjugated metabolite is excreted in urine

↓
Deconjugation in urinary tract by enzyme glucuronidase

↓
Release of active carcinogen

↓
Urothelium exposed to carcinogen

↓
Urothelial carcinoma

Gross: tumors mostly arise from lateral or posterior walls at bladder base

↳ single or multicentric

→ purely papillary ⇒ appear as red, elevated excrescences

→ nodular

→ flat.

Microscopy:

- **Exophytic Papilloma:** delicate, finger-like papillary structures
 - central core of loose fibrovascular tissue covered by urothelium of normal thickness
- **Inverted Papillomas:** nodular lesion in bladder mucosa (usually in trigone area)
 - have invagination of inter-anastomosing cords of normal transitional epithelium downwards into lamina propria
- **PUNLMPs:** papillary urothelial tumors with minimal atypia
 - single or multiple
 - **Papillae:** fibrovascular core covered by urothelium
 - ⇒ lining urothelium is thicker & more cellular
 - nuclei are slightly enlarged & more crowded → mitotic figures are rare
 - chromatin is uniformly even → no loss of polarity.
- **Low-grade Noninvasive:** (no invasion beyond basement membrane)
 - branching & delicate papillae
 - papillae are lined by neoplastic transitional epithelium with orderly appearance
 - no loss of polarity → minimal nuclear atypia
- **High-Grade Noninvasive:** (no invasion beyond basement membrane)
 - fused, branching papillae giving a more solid, exophytic appearance
 - loss of polarity → frequent mitotic figures
 - moderate to severe nuclear atypia; irregular prominent nucleoli
 - moderate/marked nuclear pleomorphism → significant nuclear hyperchromasia
 - invasion into lamina propria, muscular layer or entire thickness of bladder wall
 - metastasis by lymphatic & hematogenous routes.
- **Urothelial CIS:** flat urothelial lesion without papillary structure
 - appears as areas of erythema → no invasion of basement membrane
 - mucosa may appear slightly raised with velvety, granular appearance
 - presence of isolated malignant cells (pagetoid spread).

→ Cells: large, abundant eosinophilic cytoplasm

⇒ either have pleomorphic or uniformly large hyperchromatic nuclei, irregular nuclear crowding

⇒ loss of polarity

→ CIS responds to intravesical instillation of BCG

• Infiltrating Urothelial Carcinoma: malignant neoplasm

→ divergent differentiation of lining urothelial cells & invasion beyond basement membrane

→ unifocal or multifocal

→ polypoid, sessile or ulceroinfiltrative

→ Cells: striking nuclear pleomorphism

⇒ numerous mitotic figures, abnormal mitotic figures

⇒ hyperchromatic nuclei

⇒ pale, eosinophilic cytoplasm.

Clinical Course: painless hematuria

→ pyelonephritis or hydronephrosis (if tumor obstructs ureteral orifice)

Component	Reference Value
Volume - 24 hours	600 - 1800 mL
pH	5 - 9
Specific gravity	1.002 - 1.028
24 hour urine Protein	< 150 mg/day
24 hour urine Glucose	50 - 300 mg/day
Random protein	Negative
Random glucose	Negative
24 hour Urobilinogen	1 - 3.5 mg/day
Microalbuminuria (24 hrs)	0 - 30 mg/day.