Pathology1

Clinical Manifestations of Renal Diseases

❖ **Azotemia**:

- Elevated ↑ **blood urea nitrogen** (BUN) and **creatinine** due to decreased glomerular filtration rate (GFR).

❖ **Uremia**:

- Progression of azotemia with systemic biochemical abnormalities and clinical symptoms.

Characteristics of Uremia

- Failure of renal excretory function.
- Metabolic and endocrine alterations.
- Secondary gastrointestinal (uremic gastroenteritis), neuromuscular (peripheral neuropathy), and cardiovascular (uremic fibrinous pericarditis) manifestations.

Major Renal Syndromes

❖ **Nephritic Syndrome**

- Acute onset, gross hematuria دم بالبول, mild to moderate proteinuria (<3.5 g/day), azotemia, edema, hypertension.
- Usually caused by glomerular inflammation.
- Urinalysis shows RBCs, RBC casts, proteinuria, oliguria قلّة البول .

❖ **Nephrotic Syndrome**

- Heavy proteinuria (>3.5 g/day), ↓ hypoalbuminemia نقصه بالدم, severe edema, ↑ hyperlipidemia, lipiduria. ارتفاع الدهون بالدم والبول
- Protein loss causes hypoalbuminemia → **decreased** plasma osmotic pressure → edema. عندما تفقد الكليه قدرتها على منع تسرب البروتينات خاصه الألبومين
- Hyperlipidemia results from increased lipogenesis and decreased lipid clearance. لما يفقد الجسم البروتين بالبول بحاول الكبد يصنع بروتين ودهون
- Lipiduria due to abnormal glomerular basement membrane (GBM) permeability. -> oval fat bodies

❖ Additional Renal Syndromes

- **Asymptomatic hematuria** (proteinuria): Mild glomerular abnormalities, often detected incidentally.
- **Rapidly Progressive Glomerulonephritis** (RPGN): Rapid loss of renal function over days/weeks; microscopic hematuria, RBC casts, mild-moderate proteinuria; can lead to renal failure **if** untreated.
- **Acute Renal Failure**: Oliguria/anuria قله البول, recent azotemia onset; caused by glomerular, interstitial, vascular injury, or acute tubular necrosis.
- **Chronic Renal Failure**: Prolonged uremic symptoms; end stage of chronic renal diseases.
- **Urinary Tract Infection** (UTI): Bacteriuria بكتيريا بالبول and pyuria وجود صديد خلايا دم بيضاء"بالبول"; includes pyelonephritis and cystitis
- **Nephrolithiasis**: Kidney stones causing renal colic, hematuria, possible recurrence.

❖ Glomerular Diseases :

- Glomerulus is a capillary network surrounded by podocytes and parietal epithelium forming Bowman's capsule.
- Glomerular diseases are a common cause of **chronic kidney disease.**

Normal Glomerulus Structure:

- Comprised of fenestrated endothelial cells, GBMيمنع مرور البروتينات, podocytes خلايا تغلف الكبيبه من الخارج with foot processesاقدام خيطية, and mesangial cells.
- Bowman's space collects plasma ultrafiltrate.
- Podocyte foot processes are connected by slit diaphragms (mainly **nephrin**), crucial for selective filtration.
- Normal filtration excludes large molecules (proteins, blood cells) but allows water and small solutes.

Pathological Tests for Renal Diseases (Renal Biopsy)

- **Light Microscopy** (LM)

- **Immunofluorescence Microscopy** (IF): Detects immune complexes (IgG, IgM, IgA, complement components). Patterns (**granular**, **linear**) help differentiate types of glomerulonephritis.

- **Electron Microscopy** (EM): Visualizes ultrastructure including GBM thickness, podocyte foot processes, and immune complex deposits (electron dense) in mesangial, subendothelial, or subepithelial locations.

Glomerular Filtration Membrane Composition:

- Made of **type IV collagen** ٤, laminin, proteoglycans, fibronectin, glycoproteins.

- Podocytes' foot processes interdigitate and are separated by slit diaphragms.

- Nephrin and podocin maintain selective permeability. لا يسمح بمرور البروتينات

  - **Immunofluorescence Patterns:**

- **Granular** pattern: Immune complexes deposited in a patchy manner (e.g., immune complex glomerulonephritis).

- **Linear** pattern: Uniform antibody deposition along GBM (e.g., anti-GBM disease).

  - **Electron Microscopy Findings:**

- Immune complexes رواسب appear as electron-dense deposits.

- Deposits may be in:

- **Mesangium** النسيج الداعم للشعيرات الدموية بالكبيبة

- **Subendothelial space** (between endothelium and GBM)التهاب شديد

- **Subepithelial space** (between GBM and podocytes)

Pathogenesis of Glomerular Diseases

❖ **Immune Mechanisms**

- Antibody-associated injury detected by IF.

- Antibodies may come from:

1. Circulating immune complexes deposited in glomerulus.
2. Antibodies reacting in situ with glomerular antigens.

3. Antibodies against glomerular cell components.

❖ Non-immune Mechanisms

- Podocyte injury (toxins, cytokines, mutations) leads to foot process effacement and proteinuria.يفقد الغشاء القدره على منع خروج البروتينات

- Nephron loss وحدة التصفية الأساسية causes segmental/global glomerulosclerosis, reducing nephron mass and causing progressive renal impairment.

Renal Syndromes

Syndrome	Key Features	Urine Findings	Main Cause
Nephritic Syndrome	Hematuria, mild proteinuria, azotemia, edema	RBCs, RBC casts	Glomerular inflammation
Nephrotic Syndrome	Heavy proteinuria, hypoalbuminemia, edema	Proteinuria, lipiduria	GBM damage, podocyte injury
Rapidly Progressive GN (RPGN)	Rapid renal failure, hematuria	Dysmorphic RBCs, RBC casts	Severe glomerular injury
Acute Renal Failure	Oliguria/anuria, azotemia	Variable	Glomerular/interstitial injury
Chronic Renal Failure	Prolonged uremia	Variable	End stage renal disease

Pathology2

- Kidneys filter blood, removing waste and toxins, and return clean blood to circulation continuously.

- **Glomerulus**: The main filtration unit, a network of capillaries, filters blood through a specialized membrane.

Glomerular Filtration Barrier

Filtration membrane consists of:

- Endothelial cells (inner layer)

- Glomerular Basement Membrane (GBM, middle)

- Podocytes (epithelial cells, outer layer)

These structures create a barrier that normally prevents protein leakage.

Nephrotic Syndrome: Definition **&** Features

- Nephrotic Syndrome is a clinical complex due to glomerular disease, characterized by:

1. Massive proteinuria (>3.5g/day in adults) – **hallmark feature**

2. Hypoalbuminemia (≤3g/dL)
3. Generalized edema
4. Hyperlipidemia & lipiduria
5. Little or **no** azotemia, hematuria, or hypertension

Mechanisms

- Proteinuria: Damage to the filtration membrane allows proteins (mainly albumin) to leak into urine.
- Hypoalbuminemia: Loss of albumin in urine lowers blood albumin.
- Edema: Low albumin decreases plasma oncotic pressure, causing fluid to leak into tissues.
- Hyperlipidemia & Lipiduria:
- Liver increases lipoprotein synthesis due to low albumin.
- Albumin normally transports lipids; its loss leads to free lipids in blood and urine.
- Azotemia: (high urea/creatinine زياده نواتج النيتروجين) is usually absent; kidney function is often preserved initially.

Clinical Presentation

- Main symptom: Generalized edema (face, eyes, lips, abdomen) – usually what brings patients to clinic.
- Other findings: Proteinuria on urinalysis, normal kidney function tests (creatinine/urea), normal blood pressure.

Diagnosis

- Suspect nephrotic syndrome when there's edema, proteinuria, and normal kidney function.
- Lab tests: Urinalysis (proteinuria), kidney function tests (usually normal), lipid profile (hyperlipidemia).

➢ **Causes of Nephrotic Syndrome**

1. **Primary Glomerular Diseases** (originate in kidney)

- Minimal Change Disease (MCD)
- Focal Segmental Glomerulosclerosis (FSGS)
- Membranous Nephropathy
- Membranoproliferative Glomerulonephritis (Type 1)

Prevalence by Age

- Children: **~65% MCD**
- Adults: Most common is **FSGS** (~**35%**)

2. **Secondary/Systemic Diseases** (affect kidney as part of systemic illness)

- Diabetes Mellitus
- Amyloidosis
- Systemic Lupus Erythematosus
- **Drugs**: gold, penicillamine, heroin
- **Infections**: malaria, syphilis, hepatitis B, HIV
- **Malignancies**: carcinoma, melanoma
- Others: bee-sting allergy

➢ **Primary Diseases in Detail**

❖ **1.Minimal Change Disease** (MCD, Lipoid Nephrosis)

- Most common in **children** (1-7 years)
- Pathogenesis: Unclear; possibly T-cell derived factor damages podocytes (foot process effacement).

Morphology:

- Light Microscopy (LM): Glomeruli appear normal.
- Immunofluorescence (IF): Negative.
- Electron Microscopy (EM): Diffuse effacement of podocyte foot processes, **no** immune deposits.

Clinical Course:

- Nephrotic syndrome in otherwise healthy child.
- **No** hypertension, preserved renal function, selective proteinuria (mainly albumin).
- **Good prognosis:** 90% respond to corticosteroids; <5% develop chronic renal failure after 25 years.
- In adults, response is slower, relapses more common.

❖ **2.Focal Segmental Glomerulosclerosis** (FSGS)

- Most common in **adults**
- Pathology: Sclerosis (fibrosis) affecting some (focal) glomeruli and only part (segmental) of each affected glomerulus.

Can be:

- **Primary** (idiopathic)
- **Secondary** (AIDS, heroin abuse, nephron loss, genetic mutations)

Morphology:

- LM: Sclerosis in some glomeruli/segments.
- IF: Negative.
- EM: Effacement of podocyte foot processes.

Clinical Course:

- Usually presents with nephrotic syndrome.
- Hematuria and hypertension may be present.
- Proteinuria is **non**selective.
- **Poor response** to **steroids**.
- **50%** progress to **renal failure** in 10 years.
- **Adults** have worse prognosis than children.

-Collapsing glomerulopathy:

• a morphologic type of **FSGS**.

Feature	MCD	FSGS
Hematuria	-	+
Hypertension	-	+
Proteinuria	Selective	Nonselective
Steroid Response	Good	Poor
Prognosis	Excellent	Poor

• **poor** prognosis.

• collapse of glomerular tuft and podocyte hyperplasia.

• It may be :**1** Idiopathic, **2** associated with HIV infection هذه اهم معلومة, **3** drug-induced toxicities.

❖ 3. Membranous nephropathy:

• Immune complex (antigen+antibody) deposition in glomerulus which make a imbalance in the architecture of GBM.

Types :

1-**Primary** (85% of cases): antibodies against podocyte antigen **phospholipase A2 receptor** (PLA2R) antigen.

2-**Secondary** to another condition or disease.

❖ Causes of Secondary MN

Secondary MN is linked to main categories:

1. **Infections**

- Hepatitis B/C, syphilis, malaria, schistosomiasis, and HIV.
- Syphilis-associated MN often involves novel antigens like neuron-derived neurotrophic factor (NDNF).

2. **Malignancies**

- Solid tumors (e.g., lung, colon) and hematologic cancers.

3. **Autoimmune Diseases**

- Systemic lupus erythematosus (lupus nephritis Class V), rheumatoid arthritis, and Sjögren's syndrome.

4. **Drugs**

- NSAIDs, penicillamine, captopril, gold salts, and mercury (e.g., from cosmetics or occupational exposure).
- Drug-induced MN often resolves after discontinuation.

5. **Inorganic Salts**

- Chronic mercury or gold exposure.

Morphological Features

- Light Microscopy (LM)

- Diffuse thickening of the GBM.
- Silver stain reveals characteristic "spikes" (projections of basement membrane material between deposits).

- Immunofluorescence (IF)

- Granular deposits of IgG and complement (C3) along capillary walls.
- In mercury-induced MN, IgG1 predominates.

- Electron Microscopy (EM)

Subepithelial immune deposits with a "spike and dome" pattern:

- Domes: Immune complexes.
- Spikes: GBM material between deposits.

Pathogenesis:

- **Antigens** (e.g., viral proteins, drugs) bind to the subepithelial GBM, triggering in situ immune complex formation.
- **Complement activation** (C5b-C9) damages podocytes, disrupting the filtration barrier and causing proteinuria.

Clinical Course

- Nephrotic syndrome: Severe proteinuria (>3.5 g/day), hypoalbuminemia, edema.

Prognosis:

- **~40%** progress to renal failure over 2–20 years.
- ~30% achieve partial/complete remission, especially if the underlying cause (e.g., infection, drug) is treated.
- **Poor** response to corticosteroids alone; therapy targets the primary condition.

Management:

1. Address Underlying Cause:

Antivirals for hepatitis B/C, antibiotics for syphilis, or discontinuation of offending drugs.

2. Immunosuppression: Reserved for refractory cases (e.g., **rituximab** for lupus-associated MN).

3. Supportive Care: ACE inhibitors/ ARBs to reduce proteinuria, statins for hyperlipidemia, and anticoagulants for thrombotic risk.

Pathology3

- **Nephritic Syndrome**

- Nephritic syndrome is defined by glomerular inflammation leading to hematuria (presence of RBCs in urine), non-nephrotic range proteinuria (less than 3.5g/day), RBC casts (indicating glomerular origin), oliguria (decreased urine output), hypertension (due to fluid retention and increased renin), and azotemia (impaired renal clearance of toxins).

Pathogenesis of Nephritic Syndrome:

- The syndrome results from inflammation within the glomerular capillaries.
- Leukocyte infiltration leads to the release of chemicals that stimulate proliferation of glomerular cells.
- Injury to capillary walls causes RBCs to leak into urine (hematuria, RBC casts).
- Decreased glomerular filtration rate (GFR) leads to **oliguria**, fluid retention (edema), and azotemia.

- Hypertension results from both fluid retention and increased renin release.

➢ **Glomerular Diseases** Presenting with Nephritic Syndrome:

❖ **Membranoproliferative Glomerulonephritis** (MPGN)

- Characterized by abnormal proliferation of glomerular cells and inflammation.
- Presents mostly as nephritic syndrome, sometimes with combined nephrotic features.

Types:

- **Type I** (**80%** of cases): Immune complex-mediated, often associated with hepatitis B/C, SLE, infected A-V shunts.
- **Type II** (Dense Deposit Disease): Due to excessive complement activation by **autoantibody** (C3 nephritic factor) against C3 convertase, leading to hypocomplementemia.

Morphology:

- Light microscopy: Large glomeruli, lobular appearance, proliferation of mesangial/endothelial cells, leukocyte infiltration, thickened GBM with "tram-track" (double contour) appearance.
- Immunofluorescence: ***Type I*** shows subendothelial deposits of IgG and complement (C1q, C4); ***Type II*** shows C3 deposits in GBM.
- Electron microscopy: ***Type II*** shows dense, ribbon-like deposits in GBM.

Clinical Course: **Poor** prognosis, **no** remission, **40%** progress to end-stage renal failure, worse prognosis for type II, recurrence after transplant possible.

❖ **2. Acute Postinfectious** (Poststreptococcal) **Glomerulonephritis** (PSGN)

- Caused by immune-mediated reaction after a pharyngeal or skin infection, most commonly by group A β-hemolytic streptococci.
- Immune complexes form against streptococcal antigens and deposit in GBM, triggering inflammation.

Morphology:

- Light microscopy: Proliferation of endothelial/mesangial cells and neutrophilic infiltrate.
- Immunofluorescence: IgG and complement deposits in capillary walls.
- Electron microscopy: Subepithelial "humps" of immune complexes.

-**Clinical Features**: Acute onset, **mainly in children**, fever, nausea, nephritic syndrome, gross hematuria, mild proteinuria, low serum complement (C3), elevated anti-streptolysin O titers.

-**Prognosis**: Recovery in most children; self-limited course.

❖ **3. IgA Nephropathy** (**Berger Disease**)

- Most common cause of recurrent microscopic or gross hematuria, especially in children and young adults.
- Hematuria appears 1–2 days after upper respiratory tract infection, lasts several days, recurs every few months.
- Pathogenesis: Abnormal IgA production/clearance, leading to mesangial IgA deposition (with C3), causing glomerular injury.

Morphology:

- Light microscopy: Variable findings.
- Immunofluorescence: Mesangial IgA (with C3) deposition-diagnostic.
- Electron microscopy: Mesangial deposits.

Clinical Course: Variable prognosis; may progress to chronic kidney disease.

Disease	Usual Presentation	Age Group	LM Findings	IF Findings	EM Findings	Prognosis
MPGN Type I	Nephritic/Nephrotic	Adults	Tram track	IgG, C1q, C4	Subendothelial deposits	Poor
MPGN Type II	Nephritic/Nephrotic	Adults	Tram track	C3	Dense deposits	Poor
PSGN	Nephritic	Children	Hypercellularity	IgG, C3	Subepithelial humps	Good
IgA Nephropathy	Nephritic	Children/Young	Variable	IgA, C3	Mesangial deposits	Variable

✓ Nephritic syndrome is characterized by hematuria, mild proteinuria, oliguria, hypertension, and edema.

- Diagnosis relies on clinical features, laboratory findings (urinalysis, complement levels, serology), and renal biopsy with light microscopy, immunofluorescence, and electron microscopy.

- Prognosis varies by <u>disease type</u> and patient **age**, with MPGN having the poorest outcome and PSGN in children the best.

Disease	Usual Presentation	Age	LM	IF	EM	Prognosis
MCD	nephrotic	Children	none	negative	Effaced foot processes	good
FSGS	nephrotic	adults	Segmental sclerosis	negative	Effaced foot processes	Progressive
MNP	nephrotic	adults	Thickened GBM	IgG+ C3+	Sub-epithelial spikes and domes	Progressive
MPGN-type1	Nephritic/ nephrotic	adults	Tram track	Ig s	Subendothelial deposits	poor
MPGN-type2	Nephritic/ nephrotic	adults	Tram track	C3+	Dense deposits	poor
IgA nephropthy	nephritic	Children, young adults	variable	IgA+	Mesangial deposits	variable
PSGN	nephritic	children	hypercellularity	IgG+ C3+	Subepithelial deposits (humps)	good

Pathology4

DISEASES AFFECTING <u>TUBULES</u>, <u>INTERSTITIUM</u>, AND <u>COLLECTING SYSTEM</u>

Urinary Outflow Obstruction

➢ **1-Renal Stones** (**Urolithiasis**/**Nephrolithiasis**)

- Stones can form anywhere in the urinary collecting system
- Most commonly found in the <u>kidney</u> (1% of all autopsies)
- Can be **symptomatic** (painful hematuria, renal colic) or **asymptomatic**
- **<u>Uni</u>**<u>lateral</u> in **80%** of cases
- Composition: 98% inorganic salt + 2% organic matrix (nidus)

Types by composition:

- Calcium oxalate/calcium oxalate **+** phosphate (**80%**, most common)
- Struvite (magnesium ammonium phosphate) (<10%)-alkaline urine❗
- Uric acid (6-7%) – acidic urine❗

- Cystine (2%, least common)

Causes of Renal Stones:

1. **Supersaturation of urine with stone constituents**

- **50%** of calcium stone patients have hypercalciuria without hypercalcemia
- 5-10% have both hypercalcemia and hypercalciuria

2. **Presence of a nidus** (core)

- Urates, desquamated epithelial cells, bacterial colonies

3. **Urine pH**

- Struvite stones form in alkaline urine (UTIs)
- Uric acid stones form in acidic urine (pH <5.5)

4. **Infections** (urea-splitting bacteria like Proteus vulgaris and Staphylococcus)

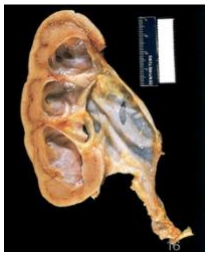
5. **Disorders causing hyperuricemia/high cell turnover**

- Gout, leukemia, tumor cell lysis after chemotherapy

6. **Genetic/metabolic abnormalities**

- Cystine stones related to amino acid transport defects

➢ **2- Hydronephrosis** تمدد بالحوض بسبب انسداد بالمسالك البولية وعدم تصريف البول



- Dilation of renal pelvis and calyces due to obstruction
- Accompanied by kidney parenchyma atrophy
- Can be sudden or insidious تدريجي-> حسب شدة ومكان الانسداد
- Obstruction can occur at any level from urethra to renal pelvis
- If **un**treated, leads to renal parenchymal damage and dysfunction

Causes of Hydronephrosis:

1. **Congenital**

- Urethral atresia لا يوجد فتحة للإحليل، ما يمنع خروج البول
- Valve formations in ureter or urethra صمامات تسبب انسداد كلي أو جزئي
- Aberrant renal artery compressing ureter يضغط عالحالب وبعمل انسداد
- Renal ptosis with torsion/kinking of ureter هبوط عن مكانها يؤدي لالتواء أو انحناء بالحالب

2. **Acquired**

- Foreign bodies (calculiحصيات بولية, necrotic papillae)
- Tumors (prostatic hyperplasia, bladder tumors, cervical/uterine cancer)
- Inflammation (prostatitis, ureteritis, urethritis)
- Neurogenic (spinal cord damage)

➢ **Tubulointerstitial Nephritis** (**TIN**) التهاب الأنابيب الكلوية والنسيج المحيط بها

- Inflammation of tubules and interstitium
- Causes: bacterial infection, **drugs** مضادات حيوية،مدرّات, metabolic disorders ك ارتفاع الكالسيوم أو حمض اليوريك, physical injury (radiation), autoimmune reactions متلازمة شوغرن،الذئبة الحمراء
- Duration: **acute** (days to months) or **chronic** (longer duration)

❖ **Drug-Induced Interstitial Nephritis:**

1. **Acute Drug-Induced Interstitial Nephritis**

- Common drugs: synthetic penicillins (methicillin, ampicillin), antibiotics, diuretics, NSAIDs
- Pathogenesis: immune mechanisms (IgE-mediated Type I & T-cell-mediated Type IV hypersensitivity)
- Morphology: interstitial infiltration of lymphocytes, plasma cells, macrophages, eosinophils, neutrophils; **normal glomeruli**
- Clinical course: appears 2-40 days **after** drug exposure with fever, eosinophilia, rash (25%), discolored urine

- Renal abnormalities: hematuria, minimal/**no** proteinuria, leukocyturia
- Management: withdrawal of offending drug leads to recovery

2. **Chronic Drug-Induced** (Analgesic Nephropathy)❗

- Caused by long-term consumption of analgesics (especially aspirin and acetaminophen)
- Can cause chronic interstitial nephritis with renal papillary necrosis
- Pathogenesis: covalent binding, oxidative damage, inhibition of prostaglandin synthesis
- Outcomes: progressive renal impairment, chronic renal failure, hypertension
- Rare complication: increased risk of transitional cell carcinoma of renal pelvis

➢ **Acute Tubular Necrosis❗/Injury (ATN/ATI)** السبب الأكثر شيوعا للفشل الكلوي الحاد (يعالج)

- Characterized by damaged tubular epithelial cells and acute suppression of renal function
- **Most common cause** of acute renal failure❗
- **Reversible** if treated properly and quickly (due to tubular epithelial cells' capacity to regenerate)
- Clinical manifestations: electrolyte abnormalities ك ارتفاع البوتاسيوم, acidosis, uremia, fluid overload احتباس سوائل, often oliguria قله بول
- **Proximal tubular** epithelial cells particularly sensitive to hypoxemia and toxins❗

Types of ATN/ATI:

1. **Ischemic ATI** (most common)

- Associated with hypovolemia or shock (hypotensive shock, severe trauma, acute pancreatitis, septicemia, mismatched blood transfusion, hemolytic crises, myoglobinuria)

- Leads to vasoconstriction, reduced GFR الارتشاح, tubular injury

2. **Nephrotoxic ATI**

- **Caused by** poisons (heavy metals like mercury), organic solvents (carbon tetrachloride), drugs (gentamicin, antibiotics, radiographic contrast agents مواد التباين الشعاعي بالتصوير)

Morphology and Management:

- Morphology: tubular epithelial necrosis, sloughed cells and debris in tubular lumen causing partial obstruction
- Management: supportive care while tubular regeneration occurs
- Prognosis: **good** chance of recovery in previously healthy patients; less complete recovery in those with preexisting chronic kidney disease

Pathology5

"Cystic Diseases of the Kidney"

- A cyst is a fluid-filled space.
- Kidney cysts can be simple and harmless or part of inherited diseases that may cause renal failure and threaten life.
- The clinical significance of kidney cysts varies widely.

Types of Renal Cysts

1. **Simple Renal Cysts**

- May be single or multiple, typically 1–5 cm in diameter, filled with clear fluid, and confined to the cortex.
- Usually discovered incidentally or due to hemorrhage/pain.
- No clinical significance but important to differentiate from tumors.
- Prognosis is favorable.

2. **Dialysis-Associated Acquired Cysts**

- Occur in patients with chronic renal failure on prolonged dialysis.
- Cysts form in both cortex and medulla.❗

- Complications: hematuria, pain, and a dramatically increased risk of renal carcinoma (up to 100 times higher than the general population).❗

- Pathogenesis involves chronic inflammation and irritation in atrophic or degenerated renal parenchyma, leading to mutations and possible malignant transformation.

3. **Autosomal Dominant** (Adult) **Polycystic Kidney Disease** (**ADPKD**)

- Multiple bilateral cysts(large) eventually destroy renal parenchyma.

- Incidence: 1 in 500–2,000 persons; responsible for 10% of chronic renal failure.

- Caused by mutations in **PKD1** (85–90%, encodes polycystin-1)❗ or **PKD2** (10–15%, encodes polycystin-2).

- Clinical features: **a**symptomatic until the 4th decade, then flank pain, abdominal mass, hematuria, and possible obstruction.

- Complications: **hypertension** (75%), urinary tract **infections** (most common), **vascular aneurysms** (especially in the circle of Willis, risk of subarachnoid hemorrhage), and **chronic renal failure by age 50** (≈25%).

- Pathogenesis: Mutations cause abnormal and progressive tubular cell division, cyst formation, and isolation from the tubule.

4. **Autosomal Recessive** (Childhood) **Polycystic Kidney Disease** (ARPKD)

- Autosomal recessive inheritance, manifests in childhood.

- Incidence: 1 in 20,000 live births.

- Types: perinatal, neonatal, infantile, and juvenile (based on symptom onset).

- Presents early, often with liver cysts and fibrosis.

- Caused by mutations in the **PKHD1** gene (encodes fibrocystin, possibly involved in ciliary function).

- Pathology: Kidneys are enlarged with **small** cysts❗ in both cortex and medulla.

- Comparison: Adult type has large cysts; childhood type has small cysts. Both can lead to renal failure.❗

5. **Medullary Cystic Disease**

Two major types:

- **Medullary Sponge Kidney**: Common, usually benign.
- **Nephronophthisis-Medullary Cystic Disease Complex** (Medullary-Uremic Type): Less common, almost always associated with renal dysfunction, starts in childhood, cysts at cortico-medullary junction.
- Clinical features: Polyuria, **polydipsia** عطش شديد وشرب ماء كثيير, progressive renal failure over 5–10 years, family history of renal failure.
- Key presentation: Child with polydipsia, polyuria, renal impairment, and family history.

Disease Type	Age of Onset	Cyst Size/Location	Inheritance	Key Complications
Simple Renal Cysts	Any (often older)	Small, cortical	None	None (benign)
Dialysis-Associated Cysts	Adults on dialysis	Cortex and medulla	Acquired	Renal carcinoma risk, hematuria
ADPKD (Adult)	Adulthood (40s)	Large, cortex & medulla	Autosomal dominant	Hypertension, infections, aneurysms
ARPKD (Childhood)	Childhood	Small, cortex & medulla	Autosomal recessive	Liver fibrosis, early renal failure
Medullary Cystic Disease	Childhood	Cortico-medullary junction	Variable	Progressive renal failure

Pathogenesis &Genetics

- Many cystic diseases are linked to **mutations** affecting ciliary proteins in renal tubular cells, leading to abnormal cell proliferation, cyst formation, and loss of nephron function.

Clinical Importance

- Early recognition and differentiation of cyst types are crucial for prognosis and management.
- Family history and genetic counseling are important, especially for inherited forms.

✓ *Diagnosis* relies on imaging, clinical features, and sometimes genetic testing. *Management* and prognosis vary by type, with some requiring only observation and others needing supportive care or transplantation.

Pathology6

Renal Tumors :

- Benign neoplasms (e.g., small cortical papillary adenomas) are common in adults but usually **un**noticed.
- Most common **malignant** neoplasm: **Renal cell carcinoma** (RCC).
- **Second** most common: **Nephroblastoma** (Wilms tumor, Embryonal tumour), mainly in children.

➢ **Oncocytoma**

- Benign tumor from intercalated cells of collecting ducts (~10% of renal neoplasms).
- Genetics: **Loss of chromosomes 1 & Y.**❗
- Clinical significance: Can mimic malignant tumors; all kidney masses must be evaluated.
- Histology: Abundant mitochondria → tan color(gross appearance), finely granular eosinophilic cytoplasm; central stellate scar ❗on imaging.

➢ **Renal Cell Carcinoma** (RCC)

- Origin: Renal tubular epithelium, mainly in **cortex**.
- Epidemiology: 80-85% of primary malignant kidney neoplasms; 2-3% of all adult cancers; peak in 6th-7th decades; **M:F ratio 2:1.**
- Risk Factors: Smoking, hypertension, obesity, cadmium exposure, acquired polycystic kidney disease, genetic factors.

Classification (Three Main Types)

1. Clear cell carcinoma (most common, 65%)
2. Papillary renal cell carcinoma (10-15%)
3. Chromophobe renal carcinoma (5%)

❖ ***Clear Cell Carcinoma***

- Sporadic and familial forms; associated with **von Hippel-Lindau** (VHL) disease مرض وراثي سائد يزيد خير الأورام والأكياس الكلوية.

- *VHL disease:* Autosomal dominant, predisposes to multiple tumors, bilateral cysts, and clear cell carcinomas.

- *Genetics*: VHL gene mutation (chromosome **3p25**); loss leads to **HIF**(hypoxia induced factor)accumulation → increased **VEGF**(vascular endothelial growth factor) & tumor growth.

- Pathology: Spherical, well-demarcated, yellow/orange/gray-white with cystic/hemorrhagic areas; can invade renal vein, IVC, heart.❗
- Histology: Clear cytoplasm (glycogen/lipid), small round nuclei, sometimes granular cells; grading based on nuclear features.❗
- Aggressive forms: Sarcomatoid differentiation (high grade, aggressive).

❖ ***Papillary* Renal Cell Carcinoma**

- 10-15% of renal cancers; papillary growth pattern, often bilateral/multifocal, early-stage.
- Origin: Proximal tubular epithelial cells.
- Genetics: Mutation of MET proto-oncogene (chromosome **7q**).
- Pathology: Papillary structures with fibrovascular cores, less lipid content, pink or clear cytoplasm, necrosis/hemorrhage/cystic change possible.

❖ ***Chromophobe Renal Carcinoma***

- Least common (5%); arises from intercalated cells of collecting ducts.
- Genetics: **Multiple** losses of entire chromosomes (**hypoploidy**), no specific gene mutation.
- Pathology: Grossly tan-brown, clear flocculent cytoplasm, prominent cell membranes, perinuclear halos; **better prognosis** than other RCC types❗.

➢ **Clinical Features of Renal Cell Carcinoma**

- Most frequent symptom: Hematuria (>50% cases), often intermittent.

- Other symptoms: Flank pain, palpable mass (classic triad), fever, polycythemia (from ↑ erythropoietin), **paraneoplastic syndromes** (hypercalcemia, hypertension, Cushing's(↑ Adrenocorticotropic Hormone-ارتفاع الكورتيزول) ،hormonal effects).

➢ **Urinary Bladder Tumors**

Bladder cancer: ~5% of all cancers.

Types:

1. Urothelial carcinoma (most common, aka transitional cell carcinoma)
2. Squamous cell carcinoma (3-7%)
3. Adenocarcinoma (rare, from metaplasia due to chronic irritation)

Epidemiology: **M**>F, 80% between 50-80 years.

Risk Factors

- Smoking الأهم, occupational carcinogensصناعيات, cyclophosphamide/radiation, family history, Schistosoma haematobium دودة طفيلية تعيش حول المثانة(for SCC), genetic mutations.

Urothelial Carcinoma: *Two precursor lesions:*

1. **Noninvasive papillary tumor** (most common)
2. **Carcinoma in situ** (**CIS**)

Grading (based on architecture & cytology):

1. Papilloma (benign)
2. Papillary urothelial neoplasm of low malignant potential (PUNLMP)
3. Low-grade papillary urothelial carcinoma
4. High-grade papillary urothelial carcinoma,noninvasive

CIS: Flat, overtly malignant cells, often multifocal, high risk (50-75%) of progression to invasive cancer.

• Invasive urothelial cancer associated with papillary urothelial cancer (usually of high grade) or CIS may superficially invade the lamina propria or extend more deeply into underlying muscle الأخطر.

• The extent of invasion and spread (staging) at the time of initial diagnosis is the most important prognostic factor

• Almost all infiltrating urothelial carcinomas are high grade.

Clinical Features of Bladder Cancer

- Main symptom: Painless hematuria❗.
- Recurrence risk factors: Tumor size, stage, grade, multifocality, mitotic index, dysplasia, CIS in surrounding mucosa.

Tumor Type	Origin/Cell Type	Key Genetics/Features	Prognosis/Notes
Oncocytoma	Intercalated cells (collecting duct)	Loss of chr 1, Y; stellate scar	Benign, mimics malignancy
Clear cell RCC	Renal tubular epithelium	VHL mutation (chr 3p25)	Most common, aggressive
Papillary RCC	Proximal tubular epithelium	MET mutation (chr 7q)	Often bilateral, papillary
Chromophobe RCC	Intercalated cells (collecting duct)	Hypoploidy (chr loss)	Least common, best prognosis
Urothelial carcinoma (bladder)	Urothelium	Various genetic mutations	Most common bladder CA
Squamous cell carcinoma	Bladder (chronic irritation)	Schistosoma (in endemic areas)	Rare
Adenocarcinoma (bladder)	Metaplastic glandular tissue	-	Very rare

Pathology7

Male Genital Tract Pathology

Normal Prostate Structure

- The prostate is made up of two main components: **glandular** and **stromal**.
- **Glands** have two cell layers: a flat basal cell layer and an overlying columnar secretory cell layer.
- The **stroma** contains smooth muscle and fibrous tissue.

❖ *Prostate Zones*

- Divided into: **Central zone** (CZ), **Peripheral zone** (PZ), **Transitional zone** (TZ), and **Periurethral zone.**

Clinical relevance:

- Most carcinomas arise from the **peripheral zone.**
- Nodular hyperplasia (BPH Benign Prostatic Hyperplasia) arises from the **transitional** zone.
- Carcinomas are often detected by rectal examination.
- Hyperplasias more often cause urinary obstruction.

➢ ***Benign Prostatic Hyperplasia*** (**BPH**) تضخم البروستاتا الحميد

- Definition: Common cause of prostatic enlargement due to proliferation of stromal and glandular elements.

- *Epidemiology*: Present in many men by age 40, up to 90% by the eighth decade.

- Pathogenesis: Androgen-dependent growth is central(Dihydrotestosterone),does not occur in males castrated before puberty or with blocked androgen activity دوائيا.

- *Location*: Almost always in the **inner transition zone.**

- *Gross Pathology*: Enlarged prostate with well-circumscribed nodules, may have cystic spaces (dilated glands), urethra compressed to a slit.

Clinical Features:

- Urinary hesitancyصعوبه ببدء التبول, intermittent stream تقطّع مجرى البول, urgency, frequency, nocturiaتبول ليلي.

- Residual urineبقاء البول بالمثانة increases infection risk.

- Can cause complete urinary obstruction, bladder distention, *hydronephrosis*ارتجاع البول للكليتين, and kidney malfunction.

➢ ***Carcinoma of the Prostate***

- *Type*: **Adenocarcinoma** is the most common form, >50 years old.

Predisposing Factors:

1. **Androgens**: Stimulate prostate cell growth.
2. **Heredity**: Higher risk in first-degree relatives الدرجة الأولى, more common/aggressive in African-Americans.
3. **Environment**: Increased risk with westernized diet, higher in Japanese immigrants to the US.
4. **Genetics**: Common gene **re**arrangements (TMPRSS2-ETS "E26 Transformation-Specifi" fusion), PTEN(Phosphatase and Tensin)جين مثبط للورم mutations.

Pathology:

- Moderately differentiated adenocarcinomas.

- Glands are smaller, lined by a single layer of cuboidal/low columnar cells, lack basal cell layer, crowded, **no** branching.

- Grading: **Gleason system** (Grades 1-5 based on glandular differentiation; total score out of 10).
    - Low grade: 6 or less
    - Intermediate: **7**
    - High grade: 8-10

Clinical Features:

- Elevated ⬆️ PSA (Prostate-Specific Antigen) levels.
- Palpable nodules on rectal exam.
- May be found incidentally.
- Bone metastases in "axial skeleton" (osteoblastic lesions) **common**❗.

➢ Testicular Neoplasms

Incidence: 6 per 100,000 males, peak age 15-34.

Types:

1. **Germ cell tumors** (**95%)** – almost all malignant.
2. **Sex cord–stromal tumors** (5%) – usually benign.

Cell Types:

- Germ cells: Line seminiferous tubules.
- Sertoli cells: Support germ cell development.
- Leydig cells: Produce testosterone.

Risk Factors:

1. **More common in whites.**
2. Cryptorchidism الخصية غير النازلة،بغير مكانها: 3-5x increased risk, **10%** of testicular cancer cases.
3. Intersex syndromes: (e.g., androgen **in**sensitivity, gonadal dysgenesis).
4. Inherited factors: Brothers have 8-10x increased risk.

5. Cancer in one testis increases risk in the other.

6. Genetics: Isochromosome **12p i**(12p) in almost **all** germ cell tumors, **KIT** gene mutations in up to 25%.

Classification:

1. Seminomas

2. Non-seminomatous germ cell tumors (**NSGCT**):

Embryonal carcinoma

Yolk sac tumor

Choriocarcinoma

Teratoma

•Tumors may be pure **or** mixed (mixed more common in testis than ovary).

❖ Seminoma

- Frequency: **50%** of testicular tumors.

Features:

- Rare in children.
- Progressive, painless testicular enlargement.
- Histology: Large cells, distinct borders, pale nuclei, abundant cytoplasm, prominent nucleoli, lymphocyte infiltrate.
- Gross: Circumscribed, pale, fleshy, homogeneous mass, usually **no** hemorrhage/necrosis.

❖ Embryonal Carcinoma

Features:

- Sheets of **un**differentiated cells, primitive gland-like structures.
- Large, hyperchromatic nuclei, prominent nucleoli, high mitotic activity.
- ill-defined masses حدودها غير واضحة, hemorrhage, and necrosis❗.

- More aggressive, affects younger adults (20-30 years).

Benign Prostatic Hyperplasia	Common, androgen-dependent, central zone, urinary obstruction, infection risk, hydronephrosis
Prostate Carcinoma	Adenocarcinoma, peripheral zone, risk factors (androgens, heredity, environment, genetics), Gleason grade
Testicular Neoplasms	Germ cell (95%), sex cord-stromal (5%), risk factors (cryptorchidism, genetics, intersex, family history)
Seminoma	50% of tumors, classic features, good prognosis
Embryonal Carcinoma	Aggressive, young adults, sheets of undifferentiated cells, hemorrhage/ necrosis

❖ Yolk sac tumors

- The **most common primary testicular neoplasm in children <3 year.**
- **Good** prognosis in young children.
- In adults, pure form of yolk sac tumors is rare and have a worse prognosis.

Histologically:

- The tumor is composed of low cuboidal to columnar epithelial cells forming Microcysts, Lacelike (reticular) patterns.❗
- A distinctive feature is the presence of structures resembling primitive glomeruli, called **Schiller-Duvall bodies.**❗
- **Alpha- feto-protein** (AFP) usually detected in serum.

❖ Choriocarcinoma

- Highly malignant form of testicular tumor.
- "pure" form is rare, constituting less than 1% of all germ cell tumors.
- Usually mixed with other germ cell tumors.❗
- *Characterized*: Elevated serum level of **HCG**(Human Chorionic Gonadotropin).

Macroscopically:

- The primary tumors may be small even in patients with extensive metastatic disease.
- necrosis and hemorrhage are extremely common.❗

Microscopic examination: (2 cell types)

- **Syncytiotrophoblasts** مصدر الهرمون: large multinucleated cells with abundant eosinophilic vacuolated cytoplasm producing HCG.
- **Cytotrophoblasts**: polygonal cells with distinct borders and clear cytoplasm grow in cords or masses and have a single fairly uniform nucleus

❖ **Teratoma**

• The neoplastic germ cells differentiate along somatic cell lines showing various cellular or organoid components.

• Resonant of the normal derivatives of more than one germ layer.

• May affect all ages.

• In children

- Pure forms of teratoma are common being second in frequency to yolk sac tumors-> الأكثر شيوعا.

• In adults

- Pure teratomas are rare (3% of germ cell tumors).

- frequency of teratoma mixed with other germ cell tumors is high. غالبا ما يكون مختلط مع أنواع أخرى من الأورام

Grossly: Firm masses and cysts with hair, cartilage, bone, and even teeth!

Histologically:

1. **Mature teratomas**:heterogeneous collection of differentiated cells, such as neural tissue, muscle bundles, islands of cartilage, clusters of squamous epithelium, etc.

2. **Immature teratomas:** Contain fetal primitive tissues

• In **pre**pubertal males, mature teratomas usually follow a **benign** course.

• In **post**pubertal males, all teratomas are regarded as potentially **malignant**, being capable of metastasis regardless of whether they are composed of mature or immature elements.

Clinical Features of testicular germ cell neoplasms:

• Present most frequently with a painless testicular mass that is non-translucent.

• Some tumors, especially NSGCT, may have metastasized widely by the time of diagnosis.

• **Biopsy of a testicular neoplasm is contraindicated❗**, because it's associated with a risk of tumor spillage. تسربه وانتشاره إلى الأنسجة المحيطة

• The standard management of a solid testicular mass is **radical orchiectomy**استئصال كامل, based on the presumption of malignancy.

Seminomas and nonseminomatous tumors differ in their behavior and clinical course:

❖ **Seminomas**:

• Often remain confined to the testis for long periods.

• If metastasize, most commonly in iliac and paraaortic lymph nodes.

• Hematogenous metastases occur late in the course of the disease.

❖ **Nonseminomatous germ cell neoplasms:**

• Tend to metastasize earlier, by Lymphatic & hematogenous (liver and lung mainly) routes.

• Metastatic lesions may be identical to the primary testicular tumor or different containing elements of other germ cell tumors.

Serum Assay of tumor markers secreted by germ cell tumors:

• Helpful in diagnosis and follow up (to detect recurrence and response to therapy)

VHCG : ⬆ elevated in patients with **choriocarcinoma**

VAFP : ⬆ elevated in patients with yolk sac tumor.

lactate dehydrogenase (LDH):correlate with the tumor burden (tumor size and load); regardless of histologic type.

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