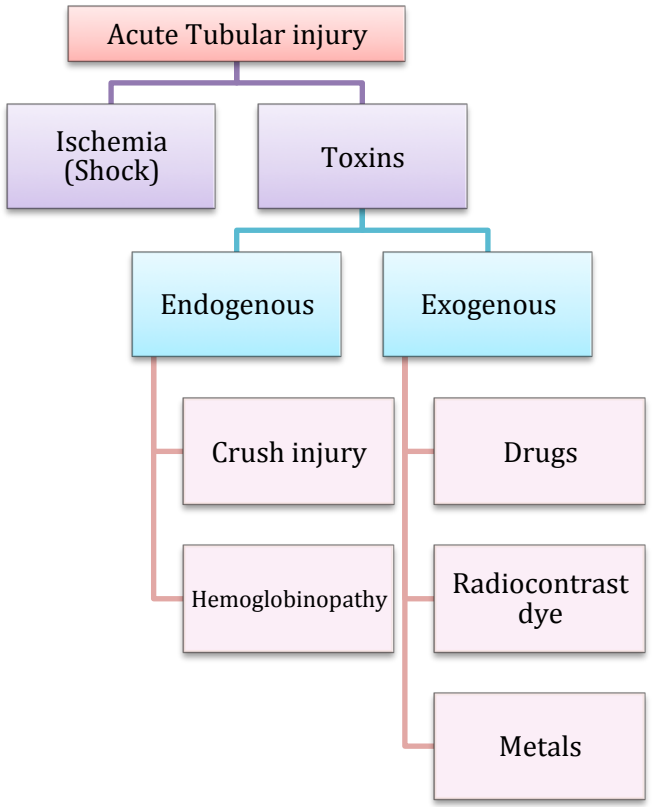
AKI: defined as a sudden decline in renal function. (Within hours to days)

Types	Affects whom mostly?	Definition	Due to
Prerenal	Outpatients	Any condition that decreases renal blood flow would cause a decrease in **(GFR) → azotemia**	Shock, Vascular pathology, Third spacing, Volume depletion , Drug induced
Intrarenal	Inpatients	Happens from the kidney itself	One or more of the four elements, which are: tubules, glomeruli, blood vessels and interstitium.
Postrenal	Both at same %	Results when urine flow is obstructed.	Examples include kidney stones, BPH (Benign Prostatic Hyperplasia), tumors, etc.

Congenital + cystic renal disease	Info
Cystic renal dysplasia	• **Commonest** cystic renal disease in children. • Caused by disorganized renal development. • Can be unilateral or bilateral. • Often associated with poorly formed ureter. • Rarely part of a syndrome.
Autosomal dominant polycystic kidney disease	• Progressive distention of kidney by enlarging cysts. • About 10% require dialysis/ transplantation. • Usually present in adults. • Caused by mutation in two genes PKD1 (85% of cases: chromosome 16) and PKD2 (155 cases, chromosome 4) (also PKD3 in rare cases). • Maybe associated with cysts in liver, pancreas, spleen and cerebral/ coronary artery and aneurysms.
Autosomal recessive polycystic kidney disease	• Rare • **Gene on chromosome 6.** • Liver is always affected. • Large kidneys at birth
Medullary sponge kidney	• Dilated collecting ducts give "spongy" appearance. • 1 case per 5000 populations. • May present with renal infections in adult life. • No obvious genetic link.

Pharmacology:

- **AKI due to shock or trauma** → Mannitol (Osmotic Diuretics)
  MOA: Maintain Urine Flow- Preserve Kidney Function
- **Acute drug poisoning** → Mannitol (Osmotic Diuretics)
  MOA: To Eliminate Drugs That Are Reabsorbed From The Renal Tubules E.G. Salicylates, Barbiturates.
- **Hypertension with renal failure** → Loop Diuretics
  MOA: Inhibit Na+/ K+/2Cl- Co-Transporter In The Luminal Membrane Of The Thick Ascending Loop Of Henle. + Inhibit Ca++ And Mg ++Re-Absorption.
- **Renal failure** → Loop Diuretics
  Increasing The Dose With As GFR Goes Down.
  Or we can use Thiazide Diuretic
- **Edema with Impaired Renal Function** → Loop Diuretics
- **NSAIDs might lead to AKI.**



Infection		Definition	Morphology	Clinical features	Info
Tubulointerstitial nephritis	Renal papillary necrosis	Ischemic necrosis of the tips of the renal papillae.		Usually associated with long term persistent abuse of phenacetin + diabetes mellitus	
	Acute drug included interstitial nephritis	The abnormalities in acute drug-induced nephritis are in the interstitium. Usually triggered by penicillin derivatives or NSAIDs & diuretics.	Eosinophils are characteristic. → In the interstitium. → With some drugs, interstitial non-necrotizing granulomas with giant cells may be seen.	Resolves on cessation of the inciting drug. The glomeruli are normal except in some cases caused by NSAIDs, in which the hypersensitivity reaction also leads to podocyte foot process effacement and the nephrotic syndrome.	
Pyelonephritis	Acute	One of the most common diseases of the kidney and is defined as inflammation affecting the tubules, interstitium, and renal pelvis.	Urinary white cells, and white cells casts in the urine (this latter finder is pathognomonic of acute pyelonephritis). - Grayish white areas of inflammation & abscess formation.	Flank pain Fever, chills and malaise Dysuria, frequency and urgency Pyuria Leukocytosis,	Usually unilateral. Complications Papillary necrosis. Pyonephrosis Perinephric abscess
	Chronic	A disorder in which interstitial inflammation (at the beginning) and scarring (later) involve in the calyces and pelvis.	*Scarring* & *fibrosis* of the kidney. *Glomerular sclerosis.* If bilateral, the involvement is *asymmetric*	Causes almost always include chronic urinary tract obstruction and repeated bouts (attacks) of acute inflammation. Consequences include renal hypertension and end-stage renal disease.	An important cause of *chronic renal failure* *Two types:* **1)** Reflux nephropathy **2)** Chronic Obstructive pyelonephritis
	Renal TB	Renal tuberculosis secondary to hematogenous spread of tubercle bacilli. ○ Caseating necrosis			
	Staghorn calculus	- Staghorn calculus in pelviureteric junction. - Obstruction which causes stagnation then infection.			
Cystitis		It's the finding of microorganism in the bladder with or without clinical symptoms and with or without renal disease. -	Cystitis with Malakoplakia: Results from defects in phagocytic or degradative function of macrophages, such that phagosomes become overloaded with undigested bacterial products (foamy macrophages)	Frequency – Urgency - Suprapubic pain - Cloudy or foul-smelling urine	Characteristic include pyuria and often hematuria but urinary white cell cast are not found -

Infection	Definition	Clinical features	Info
Urolithiasis	This condition is characterized by the formation of calculi (stones) in the urinary tract. The incidence is increased in men. Mostly unilateral.	- Pain in the lower back part or in the lower abdomen " **flank pain** ", which might move to the groin. Pain may last from hours to minutes. - Nausea, vomiting. - Hematuria. - Burning during urination (dysuria), foul smell in urine, chills, weakness and fevers for urinary tract infection.	
Calcium stones	CALCIUM OXALATE and PHOSPHATE (70%). (Either one or both)	They are associated with hypercalciuria.	They are radiopaque (can be seen by using x-rays).
Struvite stones	Magnesium ammonium phosphate (15-20%) - (Struvite stone). They can form large staghorn (struvite) calculi (casts of renal pelvis and calyces).	These stones are formed in alkaline urine, which is caused most often by ammonia producing or "splitting" (urease-positive) organisms, such as proteus vulgaris or staphylococcus.	They are radiolucent. But if they were mixed with calcium phosphate, they become radiopaque.
URIC ACID & URATE stones	Uric acid stones are associated with hyperuricemia in approximately half of the patients; hyperuricemia can be secondary to gout or to increased cellular turnover, as in the leukemias or myeloproliferative syndromes.		
Cysteine stone	They are almost always associated with cystinuria or genetically determined aminoaciduria.		

Drug	Trimethoprim	Sulfamethoxazole	Nitrofurantoin
Mechanism of action	Inhibit Dihydrofolate reductase	Inhibit Dihydropteroate synthetize	Inhibits bacteria various enzymes and damages DNA. + Prodrug: active when find bacteria start work + Spectrum: E-coli + staph. Saprophyticus.
Pharmacokinetics	- Given orally+ Well absorbed - Widely distributed - Excreted in urine - More lipid soluble than TMP	Given orally +Rapidly absorbed Widely distributed Metabolized by liver Excreted by urine	- Oral complete Absorption - Metabolized (75%) in liver - Excreted rapidly no systemic antibacterial - Urinary pH <5.5(acidic) to enhance activity. - Turns urine to a dark orange-brown
Adverse effects	Allergy ,Nausea, vomiting, Anemia (hemolytic, Megaloblastic)		GI disturbances (must be taken with food) - Headache and nystagmus -Hemolytic anemia (G6PD deficiency)
Contraindications	Pregnancy - Nursing mother - Infants under 6 weeks - Renal or hepatic failure - Blood disorders		Pts with G6PD deficiency – Neonates - Pregnant women (after 38 wks. of pregnancy)
Therapeutic Uses	Acute, Complicated and Recurrent urinary tract infections		Its usefulness is limited to lower UTI's & cannot be used for upper UT or systemic infection.

Pharmacology:

- **Ca Calculi (Calcium nephrolithiasis due to hypercalciuria)** → thiazide diuretic
  MOA: **↑Urinary NaCl Excretion, ↑Urinary K Excretion (Hypokalemia), ↑Urinary Magnesium Excretion, ↓Urinary Calcium Excretion & ↑Calcium Re-absorption (Hypercalcemia). (Enhance parathyroid hormone activity, which is responsible for Ca reabsorption).**
- **Nephrolithiasis** → **hydrochlorothiazide (Thiazide diuretics)**
  MOA: **Na and Cl cotransporter in DCT, increases Urinary Na, K, Mg BUT↓ urinary Ca (hypercalcemia)**
- **Cystinuria** → Acetazolamide
  (Carbonic Anhydrase Inhibitor)
  MOA: Urinary Alkalization To Enhance Renal Excretion Of Acidic Substances (Cysteine)

Pharmacology of UTIs

Drug	Tetracyclines e.g. Doxycycline	Aminoglycosides e.g. GENTAMICIN	Cephalosporins			Fluoroquinolones -Ciprofloxacin - Moxifloxacin -Gatifloxacin
			1st	2nd	3rd	
Spectrum	-	- (Gram -) aerobic organisms. - Bactericidal	Gram +	Mainly gram -	More effective on Gram -	Ciprofloxacin gram –ve pseudomonas species Moxifloxacin and Gatifloxacin gram-ve and gram +ve
Mechanism of action	Inhibit protein synthesis by binding reversibly to 30 s subunit	Inhibits protein synthesis by binding to 30S irreversibly	Inhibit bacterial cell wall synthesis (bactericidal)			Inhibits DNA gyrase enzyme
Pharmacokinetics	▪ Given orally - long acting ▪ Absorption is 90-100% in the upper s. intestine Food & di & tri-valent cations impair absorption ▪ Protein binding 40-80 % ▪ Distributed well, including CSF ▪ Cross placenta and excreted in milk ▪ Largely metabolized in the liver	▪ (IV) or (IM). Poorly absorbed orally ▪ Cross placenta -active in alkaline medium ▪ Excreted unchanged in urine	▪ Short T1/2 ▪ Elimination through tubular secretion and/or glomerular filtration ▪ 1,2 Oral (Cefixime) ▪ 3 I.V mostly			▪ Orally or parentally. ▪ Concentrates in many tissues (kidney, prostate, lung, bones and joints), ▪ Excreted mainly trough the kidney ▪ Has long half-life.
Adverse effects	▪ GIT upsets (give with food) ▪ Thrombophlebitis i.v. ▪ Hepatic toxicity (prolonged therapy with high dose) ▪ Brown discoloration of teeth (children) ▪ Deformity or growth inhibition of bones (children) ▪ Phototoxicity ▪ Vertigo ▪ - Superinfections.	- Ototoxicity - Nephrotoxicity - Neuromuscular blocking effect	▪ Hypersensitivity reaction (avoid or use with caution in patient with penicillin allergy) ▪ Thrombophlebitis ▪ Diarrhea ▪ Superinfections			▪ Nausea, vomiting and diarrhea. ▪ CNS effects (confusion, insomnia, headache and anxiety) ▪ Damage of growing cartilage ▪ Phototoxicity
Contraindications	- Pregnancy - Breast feeding - Children (below 10 yrs.)	-				- Patients under 18 years. - Pregnancy - Breast-feeding Women
Therapeutic Uses	▪ Treatment of UTI's due to Mycoplasma (Neisseria gonorrhoeae usually co-infection with Mycoplasma) & Chlamydia ▪ 100 mg p.o. bid for 7 days. ▪ Prostatitis	Severe infections caused by (gram -) organisms (Pseudomonas or Enterobacter).	3rd generation: severe / complicated UTIs acute prostatitis			-Patients under 18 years. -Pregnancy -Breast-feeding Women

Nephrotic Syndrome: Includes a group of conditions characterized by increased basement membrane permeability, permitting the urinary loss of plasma proteins, particularly low-weight proteins such as albumin.

Underlying disease	Definition	LM	EM	IF	Info
Minimal change disease	**Diffuse Epithelial Cell Disease,** Benign disorder	Normal	Diffuse **effacement of epithelial foot processes.**	-	Most often in young children. Chiefly albumin (selective proteinuria).
Focal segmental glomerulosclerosis	Characterized by sclerosis within capillary tufts of the deep juxtamedullary glomeruli with focal or segmental distribution.	-	Diffuse foot process effacement	-	Occurs in somewhat older patients Increased matrix Obliteration of capillary lumina Higher incidence of hematuria and hypertension Non-selective proteinuria
Membranous glomerulonephritis	An immune complex disease of an unknown etiology	Global subepithelial deposits seen by the glomerular basement membrane spike reaction on silver stain.	Greatly thickened capillary walls, which are visible by light microscopy too.	Immunoglobulin G (IgG) or C3	Teenagers and young adults **Azotemia** **Little response to steroids.**
Diabetic nephropathy	(Kimmelstiel-Wilson nodules).	-	Striking increase in thickness of the glomerular basement membrane.	-	Characterized by arteriolar hyalinization, mesangial matrix expansion and glomerular basement thickening.
Amyloidosis	Most often, there are associations with chronic inflammatory diseases	Subendothelial and mesangial amyloid deposits are characteristic.	-		Can be identified by reactivity of amyloid with special stains (e,g, Congo Red) and by birefringence under polarized light.
SLE class 5	-	Diffuse thickening of the peripheral capillary walls associated with an increase in mesangial matrix.	-	-	Silver methenamine (jones) stains reveal a spike and dome pattern to be present along the peripheral capillary loops where the wall of the capillaries cut tangentially; there is a moth-eaten appearance of the capillary wall.
Nephritic Syndrome: Characterized by inflammatory rupture of the glomerular capillaries, with resultant bleeding into the urinary space; proteinuria and edema may be present but usually are mild.					
Poststreptococcal glomerulonephritis	It is immune complex disease with the antigen being of streptococcal origin	**Increased cellularity**	Electron- dense "humps	"Lumpy bumpy" immunofluorescence for IgG or C3	Most often follows or accompanies infection (tonsillitis, streptococcal impetigo, infected insect bites) with **nephritogenic strains of group A B-hemolytic streptococci.**

Rapidly progressive (crescentic) glomerulonephritis (RPGN): It progresses rapidly to renal failure within weeks or months, laboratory findings typical of the nephritic syndrome, and often-severe oliguria.

Underlying disease		Definition	LM	EM	IF	Info
Good pasture syndrome (Anti-GBM)		A hereditary nephritis associated with nerve deaflines and ocular disorders	Segmental necrosis, fibrinoid necrosis and PMNs in the area, with a cellular crescent	Irregular glomerular basement membrane thickening with foci of splitting of the lamina densa.	Linear glomerular basement membrane staining with lgG	The cause **is mutation in the gene for the 5-chain type IV collagen**
Immune Complex-Mediated Crescentic Glomerulonephritis		-	**Segmental necrosis** and GBM breaks with resultant crescent formation.	Discrete deposits.	Characteristic granular ("lumpy bumpy") pattern of staining of the GBM and/or mesangium for immunoglobulin and/or complement	This disorder usually does not respond to plasmapheresis.
Pauci-Immune Crescentic Glomerulonephritis		Without immune complex deposition	**Segmental necrosis** and GBM breaks with resulting crescent formation	No deposits are detectable	Studies for Immunoglobulin and complement are negative	Associated with antineutrophilic cytoplasmic antibodies (ANCAs) typically are found in the serum,
Membranoproliferative glomerulonephritis	Type I	Caused by circulating immune complexes.	**By LM they are similar:** **1.** The glomeruli are large, with an accentuated **lobular appearance** 2. **Proliferation of mesangial and endothelial cells** **3.** Infiltrating leukocytes **4. GBM is thickened** 5. Glomerular capillary wall often shows a double contour			Characterized by diffuse endocapillary proliferation, which results in a lobular, uniform appearance of glomeruli.
	DDD	The glomerulus shows a membranoproliferative pattern, with endocapillary proliferation and GBM splitting				There is dense transformation of nearly the entire thickness of the glomerular basement membrane, with associated endocapillary proliferation.

Asymptomatic hematuria/proteinuria: Microscopic hematuria with red cell casts; proteinuria usually <1 gram/24 hours; normal renal function.

Alport syndrome	Alternating areas of extreme thinning of the glomerular basement membrane (~120 nm) with thick, irregular areas with basket weaving are shown.				
IgA nephropathy	An extreme common entity defined by **deposition of IgA in the magnesium.**	Focal necrotizing and/or inflammatory lesions of the glomeruli or by BM anomalies that result in greater capillary fragility.	Confirms the presence of electron-dense deposits in the mesangium.	Mesangial deposition of IgA, often with C3 and other immune complexes (IgG & IgM).	Characterized by benign recurrent hematuria (gross or microscopic) in children

	Definition	Characteristics	Morphology
Chronic Kidney disease	**It's the result of progressive scarring resulting from any type of kidney disease.**	**(1) Azotemia (elevated urea and creatinine) of renal origin is always an associated feature.** **(2) In advanced stages, renal failure results in uremia; the term uremia denotes the biochemical and clinical syndrome characteristic of symptomatic renal disease.** **A. Uremic syndrome clinical features due to increase urea and creatinine** **1. Skin manifestations → pruritus, uremic "frost", skin** **2. Cardiac manifestations → uremic pericarditis** **3. Neurological manifestations → peripheral neuropathy** **4. Pulmonary complications → pneumonitis and hemorrhage** **5. Hematopoietic manifestations → anemia, bleeding diathesis** **6. Skeletal abnormalities → renal osteodystrophy (secondary hyperparathyroidism)** **7. Other → metabolic imbalances**	**Advanced scarring of the glomeruli.** **There is also marked interstitial fibrosis** **The small and medium-sized arteries frequently are thick-walled, with narrowed lumina, secondary to hypertension.** **Lymphocytic infiltrate** **Might progress to end- stage kidneys**

Pharmacology:

- **Emergency nephrotic syndrome** → Loop Diuretics (orally or IV)

  MOA: - Inhibit Na+/ K+/2Cl-Co-Transporter In The Luminal Membrane Of The Thick Ascending Loop Of Henle.
  - Inhibit Ca++ And Mg ++ Re-Absorption.
- **Nephrotic syndrome** → Potassium-sparing diuretics

  MOA:
  ↑ urinary Na^+ excretion (Amount of Na normally reabsorbed from the collecting tubules & ducts =5% , thus Potassium-sparing diuretics are weak diuretics.)
  ↓ urinary K^+ excretion (hyperkalemia)

  ↓ urinary H^+ excretion (acidosis)

  Contraindicated in:

  1- Hyperkalemia: due to disease or administration of drugs that already cause hyperkalemia. As in:

  Chronic renal failure (hyperkalemia due to electrolyte balance problem), K^+ supplementation, β-blockers or ACE inhibitors (increase serum potassium)

  2- Liver Disease (dose adjustment is needed).

Tumors			
Benign			
Tumor	**Info**		
Adenoma	○ This tumor is most often small and asymptomatic. It is derived from renal tubules. ○ It may be a precursor lesion to renal carcinoma.		
Angiomyolipoma	It is often associated with the tuberous sclerosis syndrome.		
Malignant			
Tumor	Definition	Characteristics	Info
Renal cell carcinoma	More common in men, cigarette smoking.	**Gene deletions in chromosome 3;** it can also be associated with **von Hippel-Lindau disease**	The three most common forms are: ▪ Clear cell carcinoma ▪ Papillary renal cell carcinoma ▪ Chromophobe renal carcinoma.
Clear cell carcinoma	Solitary, large and spherical masses, which may arise anywhere in the cortex.	The cut is **yellow to orange to gray-white, with prominent areas of cystic softening or of hemorrhage**.	**The tumor cells may appear almost vacuolated or may be solid.** At the other extreme are granular cells, which have small, round, regular nuclei and granular pink cytoplasm
Papillary renal cell	▪ Exhibit papilla formation with **fibrovascular** cores. ▪ They tend to be **bilateral and multiple.** ▪ They also show **necrosis**, hemorrhage, and cystic degeneration. ▪ The cells may have clear or, more commonly, **pink cytoplasm**		
Chromophobe Renal Carcinomas	▪ The least common, They arise from intercalated cells of collecting ducts. ▪ Tumor cells stain more darkly, so they are less clear than cells in clear cell carcinomas. ▪ Shows extreme **hypodiploidy**, by losing entire chromosomes, including chromosomes 1, 2, 6, 10, 13, 17, and 21. ▪ **Grossly, they tend to be** tan-brown. ▪ The cells usually have clear, flocculent cytoplasm with very prominent, distinct cell membranes, In general, they have a good prognosis		
Wilms tumor	Most common renal malignancy of early childhood Histology shows hypercellular areas comprising undifferentiated Blastema, loose stroma with undifferentiated glomeruloid body.	Associated with deletions of the **short arm of chromosome 11**.	**Can be part of the AGR (or WAGR) complex:** Associated with deletion of the **WT-1** **Associated with Beckwith-Wiedemann syndrome:** Associated with deletion of the **WT-2 gene.**
Transitional cell carcinoma	This cancer is the most common tumor of the urinary collecting system and can occur in renal calyces, pelvis, ureter, or bladder. It's often multifocal in origin.	○ In the renal pelvis its associated with **phenacetin abuse.** ○ This carcinoma is likely to **recur** after removal. ○ Most often, the presenting feature is **hematuria.**	
Bladder carcinoma	By far the common malignant tumor of the bladder in adults is the urthelial-delieverd transitional cell carcinoma (TCC). Not familial.	Two distinct precursor lesions to invasive urothelial carcinoma are recognized: The most common is a noninvasive papillary tumor, other is carcinoma in situ (CIS) Most commonly present with ***painless hematuria***	

Box I. confirmed or suspected risk factors for transitional cell carcinoma:

Smoking	Increases risk up to five times
Analgesics	Mainly associated with renal pelvis transitional cell carcinoma, but also bladder tumors
Occupation	Workers in aniline dye, rubber and chemical industries due to exposure to β-naphthylanine (which in the liver is converted to carcinogen that must be activated in the bladder). These workers need regular bladder checks.
Cyclophosphamide	Can cause bladder cancer in the long term (although used for cancer treatment)
Schistosomiasis	Causes chronic inflammation and metaplasia (squamous) of the bladder mucosa (leading to squamous cell carcinoma)
Chronic infections/inflammation	Some authorities believe that any chronic inflammatory may predispose to cancer

Box II. Grading and staging of bladder transitional cell carcinoma (TNM)

Grade	Definition
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated/undifferentiated
Stage	**Definition**
Tis	In situ carcinoma
Ta	Non-invasive, papillary tumor
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscularis propia
T3	Tumor invades beyond muscularis propia
T4	Tumor invades prostate, uterus, vagina or pelvic wall/abdominal wall
N1	Single lymph node metastases (≤2cm)
N2	Single metastasis (>2cm) or multiple metastases (≤5cm)
N3	Multiple metastases (>5cm)

Allograft		How?	Cells found
Hyperacute rejection		The patient already has the antibodies circulating. After entering the kidney it becomes hemorrhagic, necrotic and polymorphonuclear cells infiltrate after a few hours	→ Necrosis → Hemorrhage → Polymorph nuclear cells
Acute rejection		Happens in days or two weeks. Two types: **T cell mediated:** Grade 1 → tubulointerstitial inflammation Grade 2 → endothelialitis **Antibody mediated**: 1- Cellular injury: ▪ Dilatation of the peritubular capillaries and polymorph or lymphocytes within them. ▪ Acute tubular injury + c4d positive 2- C4d positive in immunofluorescence. 3- Circulating antibodies:	
Chronic		Antibody or t cell mediated	Fibrosis and sclerosis of blood vessels.
Chronic allograft nephropathy		May be from rejection, drug toxicity (cyclosporine) or other things	Fibrosis, arterial sclerosis, and scarring + double contouring in the glomeruli
Drug toxicity		▪ Acute we see the isometric vacuolization in the tubules. ▪ Chronic we see strip fibrosis or nodules in the wall of the blood vessels hyaline nodules.	
Infection	**Polyoma**	▪ In chronic transplant because they are taking a lot of immunosuppressants. ▪ We can see inclusion in the nuclei ground glass appearance and gray. ▪ It is mainly in the tubule.	
	Cytomegalovirus	▪ It makes the cells big and is in the glomeruli and nuclei (everywhere not specific).	

*** A huge thanks to our pharmacology team!**
Good Luck.