

## **\*\*IMPORTANT\*\***

This guide was designed by CAP tutors. It is not meant to replace information you receive in class or textbooks. While it has been reviewed for typos and errors, you must always remember that your professor and the material given by them supersede any information found in this study guide. This guide is a starting point, and is not meant to be an all inclusive document. You must also remember to include mechanisms, pathology, histology, clinical implications, and drugs in your own study materials.

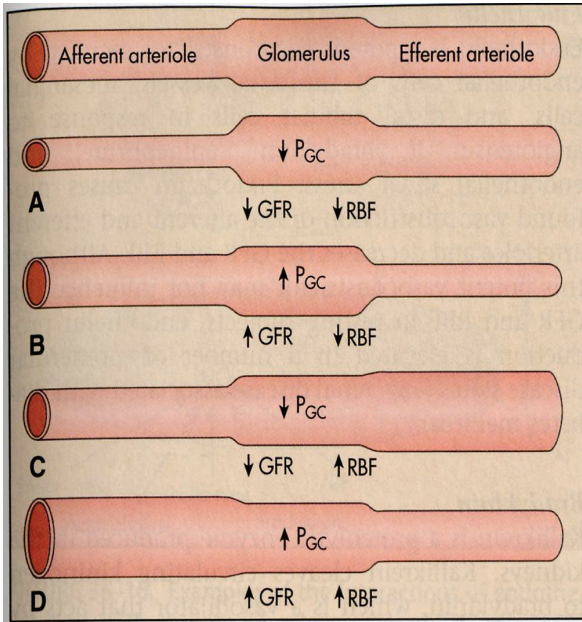
## **Renal II Study Guide**

### **Normal Anatomy & Physiology**

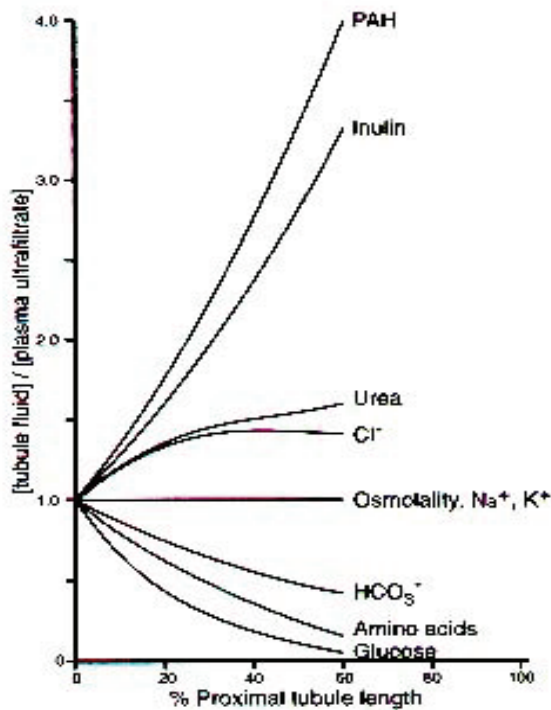
- Kidneys convert > 1700 L of blood per day into ~ 1 L of urine
- Functions = excrete waste products of metabolism, regulate body's concentration of water and salt, maintain appropriate acid balance of plasma, endocrine hormones (erythropoietin, renin, prostaglandins)
- 4 compartments
  - *blood vessels* – 25% of CO (90% to cortex)
    - renal artery → interlobar aa → arcuate aa → interlobular aa → afferent arterioles → glomeruli → efferent arterioles → peritubular vascular network & vasa recta
    - occlusion of any branch → infarction (no dual blood supply)
    - medulla does NOT have its own arterial blood supply – depends on blood emanating from glomerular efferent arterioles
  - *glomeruli* – fenestrated endothelium invested by 2 layers of epithelium
    - visceral epithelium = *podocytes* w/ foot processes, filtration slits, and diaphragm; separated from endothelial cells by basement membrane
      - slit diaphragm = size barrier
        - *nephrin* = transmembrane protein, dimerizes across slit diaphragm
        - *podocin* = CD2-assoc. protein w/in cytoplasm, connects to nephrin and actin
    - parietal epithelium = lines urinary space
    - *glomerular basement membrane (GBM)* – contains thick electron-dense central layer (*lamina densa*) and thin electron-lucent peripheral layers (*lamina rara interna, lamina rara externa*)
      - consists of mostly type IV collagen, laminin, polyanionic proteoglycans (heparan sulfate- negative charge barrier), fibronectin, entactin
      - noncollagenous domain (NC1) at C-terminus of type IV collagen – targets of Ab in anti-GBM nephritis
      - highly permeable to water, small solutes
      - impermeable to large proteins
    - *mesangial cells* = support cells, mesenchymal origin; contractile, phagocytic, capable of laying down matrix and collagen and secreting biologically active mediators
  - *tubules* –
    - *proximal tubules* reabsorb 2/3 of filtered sodium & water; particularly vulnerable to ischemic damage
    - *juxtaglomerular apparatus* = JG cells(modified smooth muscle cells of afferent arteriole- secrete renin) , macula densa( Na sensor in the distal convoluted tubule); small endocrine organ (renin)

- *interstitium* – amts. of proteoglycans in interstitial tissue of medulla increase w/ age and in presence of ischemia

**Important Diagrams and Equations:**



	Prerenal RF	Intrinsic RF
Fractional excretion of $Na^+$	< 1 Hyaline casts	>1 Proteinuria
Urine $Na^+$ conc.	<10 mg/dL	>20 mg/dL
Urine Cr: Plasma Cr	>40	>20
BUN: Cr	>20	< 10-15



Renal Clearance	$C_x = U_x V / P$	$C_x = \text{clearance}$ $U_x = [\text{urine}]$ $V = \text{urine flow rate}$ $P = [\text{plasma}]$
-----------------	-------------------	---

Inulin clearance ~ GRF: freely filtered and neither reabsorbed nor secreted

PAH clearance ~ Plasma Renal Flow: PAH is both filtered and actively secreted in the proximal tubule. All PAH entering the kidney is excreted.

### Clinical Manifestations of Renal Diseases

- **Azotemia** = elevated blood urea nitrogen (BUN) and creatinine levels; usually related to decreased GFR. 3 types are prerenal (hypoperfusion), renal, and postrenal (obstruction).
- **Uremia** = azotemia plus other metabolic and endocrine alterations resulting from renal damage-- for example: azotemia + hypernatremia, metabolic acidosis with hyperkalemia, hyperuricemia, anemia, pericarditis
- **Acute nephritic syndrome = glomerular syndrome, acute onset of grossly visible hematuria, mild to moderate proteinuria, HTN**
  - **Classic presentation of acute Poststreptococcal glomerulonephritis**
- **Nephrotic Syndrome = heavy proteinuria, hypoalbuminemia, severe edema, hyperlipidemia, lipiduria- frothy urine**
- **Acute renal failure** = oliguria or anuria w/ recent onset of azotemia
  - Rapid, frequently reversible deterioration of renal function
- **Chronic renal failure:** prolonged symptoms and signs of uremia
  - End result of all chronic renal parenchymal diseases
  - THE MAJOR CAUSE OF DEATH from renal disease
  - **Disease Progression:** Diminished renal reserve (GFR 50%, serum BUN & creatinine normal, asymptomatic) → renal insufficiency (GFR 20-50%, azotemia, anemia, HTN, polyuria, nocturia) → renal failure (GFR < 20-25%, edema, metabolic acidosis, hypocalcemia, overt uremia w/ neurologic, GI, and/or CV complications) → end-stage renal disease (GFR < 5%)
  - **Systemic Manifestations:** dehydration, edema, hyperkalemia( can cause cardiac arrhythmias), metabolic acidosis(d/t decreased acid secretion and HCO<sub>3</sub> generation), hyperphosphatemia, hypocalcemia, secondary hyperparathyroidism, renal osteodystrophy (bone changes resembling osteomalacia or rickets), anemia (failure of erythropoietin production), GI bleeding, myopathies, peripheral neuropathy, encephalopathy, sallow skin color, pruritus (itching), dermatitis

### Congenital Anomalies

- **Renal agenesis** – total bilateral agenesis incompatible w/ life; Ureteric bud does not form. Oligohydramnios. Facial deformities. Pulmonary hypoplasia. Death.
  - Unilateral agenesis compatible w/ life if no other abnormalities exist → opposite kidney enlarged (compensatory hypertrophy)
- **Hypoplasia** – bilateral → extremely rare; no scars, reduced # of renal lobes and pyramids
- **Ectopic kidneys** – us. just above pelvic brim or w/in pelvis – normal kidneys but abnormal location predisposes to bacterial infections
- **Horseshoe kidneys** – fusion of upper or lower poles of kidneys, continuous structure across midline anterior to great vessels; **Ascent arrested at level of the inferior mesenteric artery**. Associated with Turners & Wilms tumor.

- **Wilms Tumor** – **WT-1 chromosome 11**- tumor suppressor gene and mutations cause urogenital malformations – *Most common primary renal tumor of childhood*
  - Pathogenesis and genetics
    - 3 groups of people get Wilm's tumors
      - **WAGR syndrome w/ aniridia (absence of iris), genital anomalies, mental retardation; 33% chance of getting Wilm's tumor**
      - *Denys-Drash syndrome* pt's have gonadal dysgenesis (male pseudohermaphrodite) and renal failure; also have 11p13 and a dominant-negative missense mutation in WT-1.
      - *Beckwith-Wiedemann syndrome* has enlarged body organs, hemihypertrophy (muscular or osseous hypertrophy of one side of the face or body), and medullary cysts. 11p15.5 deletion along with a loss of WT-2
    - *Morphology*
      - Large, solitary, well-circumscribed mass that is tan-gray with occasional focal hemorrhage and necrosis – **classic triad of stromal, blastemic (small round blue cells), and epithelial cell types**
        - Epithelial cells are usually abortive tubules or glomeruli
        - Stromal cells are skeletal muscle
        - Cells are scattered throughout the tumor – heterogeneous
    - *Clinical correlation*
      - **Large abdominal masses** that may be unilateral or bilateral; hematuria, abdominal pain after a traumatic accident
      - Have ↑ risk of second primary tumors – bone and soft tissue sarcomas, lymphoreticular neoplasms, brain tumors, genitourinary tumors
      - Treatment = surgical removal and chemotherapy
        - 90% 2-year survival

### **Cystic Diseases of the Kidney:**

- **Cystic Renal Dysplasia:** Abnormal metanephric differentiation leading to obstruction
  - Sporadic, Multicystic enlarged kidney
  - **islands of undifferentiated mesenchyme with cartilage and immature collecting ducts**
- **Nephronophthisis-medullary cystic dz complex:** childhood, progressive, medullary cysts usually at corticomedullary jxn with tubular atrophy and interstitial fibrosis, progressive renal dz, most common cause of end stage renal disease in children and young adults, assoc with portal vein abnormalities in liver
  - 4 types: Sporadic nonfamilial
    - Familial juvenile = autosomal recessive
    - Retinal-renal dysplasia = autosomal recessive with retinal problems
    - Adult onset = autosomal dominant

S/S = polyuria, polydipsia, hyponatremia, acidosis, can be assoc with retinitis pigmentosa, liver fibrosis, cerebellar abnormalities

Genetics: NPH1, 2, 3 = juvenile forms, auto rec. MCKD1, 2 = adult, auto dom

- **Medullary sponge kidney:** multiple cystic dilations of collecting ducts in the medulla, adults, normal renal fxn
- **Dialysis associated:** cortical and medullary cystic change, inc risk of renal cell carcinoma
- **Simple cysts:** normal, usually single, must rule out cancer, cysts = smooth contours, avascular, fluid filled.

	Inheritance	Pathologic Features	Clinical Features/Complications	Typical Outcome
<i>Adult polycystic kidney disease</i>	<b>Autosomal dominant</b> w/ high penetrance- PKD1, PKD2- polycystin 1 AND 2	Large multicystic kidneys, liver cysts, berry aneurysms- subarachnoid hemorrhage	Hematuria, flank pain, UTI, renal stones, HTN	Chronic renal failure beginning at age 40-60 yrs
<i>Childhood polycystic kidney disease</i>	<b>Autosomal recessive-</b> PKHD1 gene- fibrocystin	Enlarged, cystic kidneys at birth	Congenital hepatic fibrosis	Variable, death in infancy or childhood
<i>Medullary sponge kidney</i>	None	Medullary cysts on excretory urography	Hematuria, UTI, recurrent renal stones	Benign
<i>Familial juvenile Nephronophthisis</i>	Autosomal recessive	Corticomedullary cysts, shrunken kidneys	Salt wasting, polyuria, growth retardation, anemia	Progressive renal failure beginning in childhood
<i>Adult-onset medullary cystic disease</i>	Autosomal dominant	Corticomedullary cysts, shrunken kidneys	Salt wasting, polyuria	Chronic renal failure beginning in adulthood
<i>Simple cysts</i>	None	Single or multiple cysts in normal-sized kidneys	Microscopic hematuria	Benign
<i>Acquired renal cystic disease</i>	None	Cystic degeneration in end-stage kidney disease	Hemorrhage, erythrocytosis, neoplasia	Dependence on dialysis

### Glomerular Diseases

Dz	Clinic s/s	Pathogen	LM	Fluorescence	EM
----	------------	----------	----	--------------	----

Post strep proliferative	2 weeks, acute nephritis, periorbital edema, HTN, hematuria, elevated ASO abs	A beta hemolytic strep- after skin infxn or pharyngitis, immune complex deposition	Enlarged hypercellular glom with inflamm cells, endothel cell swelling- <b>“lumpy-bumpy”</b>	Granular, IgG, IgM, C3 Subepithelial immune complex	Humps of deposits on the epithelial side of the membrane
Goodpasture RPGN	increased with HLA-DRB1, hemoptysis, hematuria, proteinuria poor prognosis	Anti-GBM Abs to NC1 protein of alpha 3 type 4 collagen- Type 2 hypersensitivity	Parietal cell proliferation with crescent formation that compress glom	<b>Linear</b> , IgG and C3, fibrin in crescents	nonspecific
Idiopathic RPGN	hematuria, proteinuria	Immune complex deposition in GBM	As in Goodpasture	Granular, IgG, IgA, IgM	nonspecific
Pauci-immune RPGN	Hematuria, proteinuria,	Component of systemic vasculitis, c-ANCA and p-ANCA	Vasculitis with RPGN findings	None	nonspecific
Membranous	Nephrotic syndrome ( <b>most common cause in adults</b> )	Chronic Immune complex deposits, Drugs (captopril, NSAIDS), lung and colon ca, <b>SLE</b> , renal autoimmunity	Diffuse thickening of GBM and cappilaries, no proliferation	Granular, IgG and C3	Subepithelial deposits resembling <b>“spike and dome”</b>
Minimal change	Nephrotic syndrome ( <b>most common cause in kids</b> ), tx with steroids	Cytokines, follows a URI, mutated nephrin = congenital	Normal	Negative	Diffuse loss of podocyte feet (fusion)
Focal segmental glomerulosclerosis	Nephrotic syndrome, hematuria, common, progressive to chronic	Diffuse visceral epithelial cell damage, progression of minimal change dz, nephrin mutations = auto dom, podicin mutations = auto rec (basic slit diaphragm disfxn), can be due to renal mass loss	Hyalinization and sclerosis of glom	Focal IgM and C3	Loss of foot processes

Membranoproliferative type 1	15-25 yo, nephritic with hematuria	immune complex deposition (ag planting), activation of classic and alt complement	Mesangial and endoth cell prolif, inflamm infiltrate, thick GBM, lobular glom, tram track GBM (duplication)	Granular, IgG, C3, C1q, C4	Subendothelial deposits
Membranoproliferative type 2	15-25 yo, nephritic with hematuria, decreased serum C3, factor B and properdin	immune complex deposition (ag planting), activation of alt complement, ab C3NeF that binds and stabilizes C3 convertase (inc activity of cleaving C3)	Mesangial and endoth cell prolif, inflamm infiltrate, thick GBM, lobular glom, tram track GBM (duplication)	Granular or Linear C3 and properdin, on either side of deposits, absent IgG and C1q and C4	Subendothelial deposits
IgA nephropathy (Berger dz)	Recurrent hematuria, proteinuria, 15-25 yo, <b>follows URI</b> ,	Increased serum polymeric IgA with deposition in mesangium, assoc with celiac and liver dz	Mesangial prolif with increased matrix, focal sclerosis,	Granular, mesangial IgA, C3	Mesangial deposits
Chronic glomerulonephritis	ESRD with uremic pericarditis and secondary hyper PTH, HTN,	All glom dz	Diffuse Hyalinized sclerotic glom, tubular atrophy, arterial sclerosis, calcium deposits,	Granular IgG, C3, can be negative	Nonspecific

<b>Alport Syndrome (hereditary nephritis)</b>	
<b>Etiology</b>	
Genetic Factors	<ul style="list-style-type: none"> <li>• <i>X-linked</i> form most common – heterogeneous mutations in gene encoding <math>\alpha</math>5-chain of collagen type IV (<i>COL4A5</i>) <ul style="list-style-type: none"> <li>➢ Males express full syndrome</li> <li>➢ Females are carriers &amp; us. only display hematuria</li> </ul> </li> <li>• <i>Autosomal recessive</i> = mutations in <math>\alpha</math>3 or <math>\alpha</math>4 chains <ul style="list-style-type: none"> <li>➢ <i>Glomeruli from pts. w/ Alport syndrome who last <math>\alpha</math>3-chain fail to react w/ anti-GBM antibodies from pts. w/ Goodpasture syndrome</i></li> </ul> </li> </ul>
<b>Pathophysiology</b>	Defective GBM synthesis due to abnormal collagen type IV
<b>Histological Morphology</b>	<ul style="list-style-type: none"> <li>• Glomeruli show diffuse GBM thinning, pronounced splitting and lamination of lamina densa → <b>basket-weave</b> appearance</li> <li>• Interstitial cells accumulate neutral fats and mucopolysaccharides → <b>foamy cells</b></li> <li>• FSGS and global glomerulosclerosis develop as disease progresses → vascular sclerosis, tubular atrophy, interstitial fibrosis</li> <li>• <b>Skin biopsy specimens → absence of <math>\alpha</math>5 collagen staining</b></li> </ul>

<b>Clinical Presentation</b>	<ul style="list-style-type: none"> <li>Gross or microscopic hematuria, erythrocyte casts, proteinuria</li> <li>Nephrotic syndrome is rare</li> <li>Symptoms appear at 5-20 years of age</li> <li>Overt renal failure between ages 20 &amp; 50 for men</li> </ul>
<b>Typical Outcome</b>	Nephritis progressing to chronic renal failure, accompanied by nerve deafness, various eye disorders

### **Thin Basement Membrane Disease (Benign Familial Hematuria)**

<b>Etiology</b>	
Genetic Factors	<ul style="list-style-type: none"> <li><b>Mutations in genes encoding <math>\alpha 3</math> or <math>\alpha 4</math> chains of type IV collagen</b></li> <li>Most patients are heterozygous for defective gene <math>\rightarrow</math> disease resembles autosomal-recessive Alport disease <math>\rightarrow</math> may progress to renal failure</li> </ul>
<b>Histological Morphology</b>	<b>Diffuse thinning of GBM to 150-250 nm</b> (normally 300-400nm)
<b>Clinical Presentation</b>	Asymptomatic hematuria Mild or moderate proteinuria may be present Renal function is normal
<b>Typical Outcome</b>	Excellent prognosis

### **Chronic Glomerulonephritis**

<b>Pathophysiology</b>	END-STAGE glomerular disease fed by many specific types of glomerulonephritis
<b>Morphology</b>	
Gross Appearance	<ul style="list-style-type: none"> <li>Kidneys <b>symmetrically contracted</b> w/ diffusely granular, cortical surfaces</li> <li>Thinned cortex, increased peripelvic fat</li> </ul>
Histological	<ul style="list-style-type: none"> <li>Glomeruli may resemble primary disease in early cases</li> <li><b>Late cases = hyaline obliteration</b> of glomeruli; arterial and arteriolar sclerosis <math>\rightarrow</math> HTN; marked atrophy of assoc. tubules; irregular interstitial fibrosis; interstitial mononuclear leukocytic infiltration</li> <li><b>Dialysis changes = arterial intimal thickening, extensive deposition of calcium oxalate crystals in tubules</b> and interstitium, acquired cystic disease, <math>\uparrow</math> incidence of renal adenomas and adenocarcinomas</li> <li><b>Uremic complications = pericarditis</b>, gastroenteritis, secondary <b>hyperparathyroidism</b>, left ventricular hypertrophy due to HTN, diffuse alveolar damage in lungs (uremic pneumonitis)</li> </ul>
<b>Clinical Presentation</b>	<ul style="list-style-type: none"> <li>Pts. present w/ nonspecific symptoms – loss of appetite, anemia, vomiting, weakness</li> <li>Proteinuria, HTN, azotemia, edema</li> <li>Most pts. have HTN</li> <li>Dominant clinical manifestations are us. cerebral or cardiovascular</li> </ul>

<b>Typical Outcome</b>	Slowly progresses to renal insufficiency or death from uremia during span of years
<b>Other</b>	<b>one of the MOST COMMON CAUSES of chronic renal failure</b>

**Glomerular Lesions Associated w/ Systemic Diseases** (*Secondary glomerulonephritis*)

<b>Systemic Lupus Erythematosus</b>	
<b>Pathophysiology</b>	<b>Subendothelial</b> deposits
<b>Clinical Presentation</b>	recurrent microscopic or gross hematuria, acute nephritis, nephrotic syndrome, chronic renal failure, HTN

<b>Henoch-Schonlein Purpura</b>	
<b>Epidemiology</b>	<b>Most common in children 3-8 years old</b> , onset often follows upper respiratory infection, most have excellent prognosis
<b>Pathophysiology</b>	<ul style="list-style-type: none"> <li>• <b>IgA deposited in glomerular mesangium</b> → IgA nephropathy &amp; Henoch-Schonlein Purpura are spectra of the same disease</li> <li>• Skin lesions = subepidermal hemorrhages, necrotizing vasculitis in dermis</li> </ul>
<b>Clinical Presentation</b>	<ul style="list-style-type: none"> <li>• <b>Purpuric skin lesions characteristically involving extensor surfaces of arms, legs, buttocks</b>; abdominal manifestations incl. pain, vomiting, GI bleeding; nonmigratory arthralgias renal abnormalities <ul style="list-style-type: none"> <li>➢ <i>Renal manifestations in ~30% of patients</i></li> <li>➢ <b>**think of this when there is a kid with a rash on legs and butt with abdominal pain!**</b></li> </ul> </li> </ul>
<b>Typical Outcome</b>	<ul style="list-style-type: none"> <li>• Recurrences of hematuria common</li> <li>• More diffuse lesions → poorer prognosis</li> </ul>

- **Bacterial Endocarditis** – immune complex nephritis initiated by complexes of bacterial Ag and Ab → hematuria, proteinuria, focal and segmental to diffuse glomerulonephritis

<b>Amyloidosis</b>	
<b>Pathophysiology</b>	Deposits of fibrillar amyloid (10-12 nm) w/in glomeruli → complete glomerulus obliteration
<b>Morphology</b>	
Gross Appearance	Normal or increased size
Histological	Light-chain (AL) or AA type amyloid deposits in mesangium and capillary walls – rarely localized to subepithelial space
<b>Clinical Presentation</b>	Nephrotic syndrome, uremia
<b>Typical Outcome</b>	Death from uremia due to glomerular destruction

- **Fibrillary Glomerulonephritis** – fibrillar deposits (18-24 nm) in mesangium and glomerular capillary walls (resemble amyloid but don't stain w/ Congo red) – glomerular lesions show selective deposition of IgG, C3, and Ig  $\kappa$  and  $\lambda$  light chains
  - **Clinical presentation** = nephrotic syndrome, hematuria, progressive renal insufficiency; recurs in kidney transplants
  - Occurs in 1% of cases in large renal biopsy series
- **Immunotactoid Glomerulopathy** – much rarer than fibrillary glomerulonephritis; microtubular (30-50 nm) and monoclonal Ig deposition in glomeruli
- **Goodpasture Syndrome** (chapter 15)– simultaneous lung and kidney lesions due to anti-GBM Ab cross-reacting w/ other basement membranes – see Alport Syndrome (above)
  - Ag is component of non-collagenous domain of  **$\alpha 3$  chain of collagen type IV** → **foci of glomerular necrosis and crescent formation** → **hematuria w/ mild decline in GFR**
- **Vasculitis** (microscopic polyarteritis/polyangiitis) – histologically similar to Goodpasture Syndrome
- **Wegener granulomatosis** (chapter 11)– histologically similar to Goodpasture Syndrome, c-ANCA
- **Essential mixed cryoglobulinemia** – IgG-IgM complexes induce cutaneous vasculitis, synovitis, proliferative glomerulonephritis (us. MPGN)
  - *Assoc. w/ HepC virus infection*
- **Plasma cell dyscrasias (i.e. Multiple myeloma)** – circulating monoclonal Ig assoc. w/ amyloidosis, deposition of monoclonal Ig or light chains in GMB, distinctive nodular glomerular lesions from deposition of nonfibrillar light chains
  - **Clinical presentation** – proteinuria, nephrotic syndrome, HTN, progressive azotemia

<b>Diabetic Glomerulosclerosis</b>	
<b>Etiology</b>	Diabetes mellitus, type I or type II <ul style="list-style-type: none"> <li>• Genetic predisposition to HTN → <math>\uparrow</math> risk of renal disease in type I diabetics, diabetic nephropathy w/ poor hyperglycemic control</li> </ul>
<b>Pathophysiology</b>	<ul style="list-style-type: none"> <li>• <b>Hyalinizing arteriolar sclerosis</b> → <math>\uparrow</math> susceptibility to development of pyelonephritis and <b>papillary necrosis</b></li> <li>• <b>Metabolic defect</b> (insulin deficiency) → hyperglycemia → <math>\uparrow</math> amount and synthesis of type IV collagen and fibronectin, <math>\downarrow</math> synthesis of heparan sulfate proteoglycan → <b>GBM thickening</b>, increased mesangial matrix</li> <li>• <b>Nonenzymatic glycosylation of proteins</b> → <b>Glomerulopathy</b></li> <li>• <b>Hemodynamic changes</b> → progression of diabetic glomerulosclerosis (<math>\uparrow</math> GFR, glomerular hypertrophy → proteinuria)</li> </ul>
<b>Histological</b>	<ul style="list-style-type: none"> <li>• <b>Capillary BM thickening</b></li> </ul>

<b>Morphology</b>	<ul style="list-style-type: none"> <li>• <b>Diffuse mesangial sclerosis</b></li> <li>• Intercapillary glomerulosclerosis (= <b>nodular glomerulosclerosis, Kimmelsteil-Wilson disease</b>)</li> </ul>
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Non-nephrotic proteinuria, nephrotic syndrome, chronic renal failure</li> <li>• Systemic HTN may precede proteinuria and renal insufficiency</li> <li>• Patients w/ end-stage diabetic nephropathy → long-term dialysis, renal transplant</li> <li>• Inhibition of angiotensin slows progression</li> </ul>
<b>Typical Outcome</b>	<ul style="list-style-type: none"> <li>• GFR → microalbuminuria (30-300 mg/day) → overt proteinuria (50% of patients) → progressive loss of GFR → end-stage renal failure w/in 5 years</li> <li>• Diabetic lesions may recur in renal allografts</li> </ul>
<b>Other</b>	<ul style="list-style-type: none"> <li>• Diabetes mellitus = major cause of renal morbidity and mortality</li> <li>• Diabetic neuropathy = one of the <b>MOST COMMON CAUSES</b> of chronic renal failure in US</li> <li>• Pancreatic transplant can reverse diabetic nephropathy if glycemic control is maintained for &gt;10 years</li> </ul>

### Diseases of Tubules and Interstitium

\*\* Know everything about ATN-- it shows up on the test and again on boards big time!\*\*

<b>Acute Tubular Necrosis (ATN)</b>	
<b>Etiology</b>	<ul style="list-style-type: none"> <li>➢ <i>Ischemic ATN</i> → period of inadequate blood flow to peripheral organs, us. accompanied by hypotension and shock</li> <li>➢ <i>Nephrotoxic ATN</i> = direct toxic injury to tubules</li> <li>➢ Acute tubulointerstitial nephritis (hypersensitivity rxn to drugs)</li> <li>➢ DIC</li> <li>➢ Urinary obstruction</li> </ul>
<b>Epidemiology</b>	Accounts for 50% of cases of acute renal failure in hospital
<b>Pathophysiology</b>	<ul style="list-style-type: none"> <li>➢ <i>Tubule cell injury</i> <ul style="list-style-type: none"> <li>○ loss of cell polarity → ↑ sodium delivery to distal tubules, tubuloglomerular feedback → endothelin release, ↓ production of vasodilators NO and PGI<sub>2</sub> → vasoconstriction</li> <li>○ detachment from BM → luminal tubule obstruction, ↑ intratubular pressure, ↓ <b>GFR</b></li> <li>○ leakage of fluid from damaged tubules → interstitial edema</li> </ul> </li> <li>➢ <i>Persistent and severe disturbances in blood flow</i> <ul style="list-style-type: none"> <li>○ Intrarenal vasoconstriction → ↓ glomerular plasma flow, ↓ O<sub>2</sub> delivery to thick ascending limb and straight segment of proximal tubule → ↓ <b>GFR</b></li> </ul> </li> </ul>
<b>Histological Morphology</b>	<ul style="list-style-type: none"> <li>➢ Focal destruction of tubular epithelial cells (necrosis) at various discontinuous points along the nephron</li> <li>➢ <i>Ischemic ATN</i> <ul style="list-style-type: none"> <li>○ <i>Tubulorrhexis</i> = rupture of BM</li> <li>○ Thick ascending limb and straight segment of PT most vulnerable</li> </ul> </li> </ul>

	<ul style="list-style-type: none"> <li>○ Loss of PT brush borders, cell swelling, vacuolization</li> <li>○ Eosinophilic hyaline casts common in DT and CD = <i>Tamm-Horsfall protein</i> (urinary glycoprotein secreted in ascending thick limb and distal tubules)</li> <li>○ Interstitial edema</li> <li>○ Accumulations of leukocytes w/in dilated vasa recta</li> <li>➤ <b>Toxic ATN</b> <ul style="list-style-type: none"> <li>○ Most obvious in PCT</li> <li>○ Mercuric chloride poisoning → large acidophilic inclusions in dying cells → total necrosis, desquamation, calcification</li> <li>○ Carbon tetrachloride poisoning → accumulation of neutral lipids in dying cells → necrosis</li> <li>○ Ethylene glycol → marked ballooning, hydropic or vacuolar degeneration of PCT, calcium oxalate crystals in lumen</li> </ul> </li> </ul>
--	--

<b>Acute Tubular Necrosis (ATN)</b>	
<b>Clinical Presentation</b>	<ul style="list-style-type: none"> <li>➤ Acute diminution or loss of renal function</li> <li>➤ <b>Initiation phase</b> – 36 hours duration; inciting medical, surgical, or obstetric event → ischemic ATN → slight decline in urine output w/ rise in BUN</li> <li>➤ <b>Maintenance phase</b> – <b>sustained decreases in urine output (40-400 mL/day), salt &amp; water overload, rising BUN, hyperkalemia, metabolic acidosis, uremia</b></li> <li>➤ <b>Recovery phase</b> – steady increase in urine volume up to 3L/day; loss of large amt's of water, sodium, and potassium in urine due to damaged tubules; hypokalemia, increased vulnerability to infection; BUN and creatinine levels return to normal</li> </ul>
<b>Typical Outcome</b>	<ul style="list-style-type: none"> <li>• Remove precipitating cause → re-epithelialization possible (need growth factors like EGF, TGF<math>\alpha</math>, etc.)</li> <li>• 95% chance of recovery for those who do not succumb to precipitating cause</li> </ul>
<b>Other</b>	<ul style="list-style-type: none"> <li>➤ the MOST COMMON CAUSE of <i>acute renal failure</i></li> <li>➤ <b>Non-oliguric ATN</b> = normal or increased urine volumes, assoc. w/ nephrotoxins, follows more benign clinical course, 50% of patients w/ ATN</li> </ul>

**Pyelonephritis = one of the MOST COMMON diseases of the kidney**

- *Acute pyelonephritis* – caused by bacterial infection, assoc. w/ UTI
- *Chronic pyelonephritis* – bacterial infection and other factors (VUR, obstruction)

<b>Acute Pyelonephritis &amp; UTI</b>	
<b>Etiology</b>	G(-) bacilli, normal inhabitants of GI tract, endogenous infection <ol style="list-style-type: none"> <li>1) <b><i>E. coli</i></b>- MOST COMMON</li> <li>2) <i>Proteus</i></li> <li>3) <i>Klebsiella</i></li> <li>4) <i>Enterobacter</i></li> </ol>

	<p>5) <i>Streptococcus faecalis</i></p> <p>6) Adenovirus, cytomegalovirus, polyoma virus in immunocompromised pts. w/ transplanted organs</p>
<b>Epidemiology</b>	<ul style="list-style-type: none"> <li>• Assoc. w/ pregnancy</li> <li>• Females age 1-40 more susceptible than males</li> <li>• Assoc. w/ diabetes mellitus</li> </ul>
<b>Pathophysiology</b>	<ul style="list-style-type: none"> <li>• <b>Ascending infection</b> – MOST COMMON CAUSE of <i>clinical pyelonephritis</i> <ul style="list-style-type: none"> <li>➢ Colonization of distal urethra and introitus → instrumentation (catheter) → bladder → multiplication → VUR → intrarenal reflux</li> </ul> </li> <li>• <b>Hematogenous infection</b> – more common w/ ureteral obstruction and nonenteric organisms</li> </ul>
<b>Morphology</b>	<ul style="list-style-type: none"> <li>• Patchy interstitial suppurative inflammation, intratubular aggregates of neutrophils, tubular necrosis</li> <li>• <b>Papillary necrosis</b> – mainly seen in diabetics and w/ urinary tract obstruction – us. bilateral – distal 2/3 of pyramids show coagulative necrosis</li> <li>• <b>Pyonephrosis</b> – total obstruction; suppurative exudate unable to drain → fills renal pelvis, calyces, and ureters</li> </ul>
<b>Clinical Presentation</b>	<ul style="list-style-type: none"> <li>➢ Sudden onset of <b>pain at costovertebral angle and systemic evidence of infection (fever, malaise)</b></li> <li>➢ Dysuria, frequency, urgency</li> <li>➢ Pyuria, <b>white blood cell casts</b></li> </ul>

<b>Chronic Pyelonephritis</b>	
<b>Pathophysiology</b>	<p>Chronic tubulointerstitial inflammation and renal scarring assoc. w/ pathologic involvement of calyces and pelvis</p> <ol style="list-style-type: none"> <li>1) <b>Reflux nephropathy</b> – MOST COMMON FORM of chronic pyelonephritis; occurs in childhood w/ UTI superimposed on congenital VUR or intrarenal reflux; may be unilateral or bilateral; can lead to chronic renal insufficiency</li> <li>2) <b>Chronic obstructive pyelonephritis</b> – recurrent bouts of renal inflammation and scarring; parenchymal atrophy bilateral diseases causes renal insufficiency</li> <li>3) <b>Xanthogranulomatous pyelonephritis</b> – rare; accumulation of foamy macrophages; assoc. w/ <i>Proteus</i> infections</li> </ol>
<b>Morphology</b>	
<b>Gross Appearance</b>	<ul style="list-style-type: none"> <li>➢ Kidneys irregularly scarred – asymmetric if bilateral</li> <li>➢ Hallmark = coarse, discrete, <b>corticomedullary scar overlying dilated, blunted, or deformed calyx = “POLAR SCARS”</b></li> </ul>
<b>Histological</b>	<ul style="list-style-type: none"> <li>• Alternating atrophy and hypertrophy of tubules</li> <li>• <b>Dilated tubules w/ flattened epithelium filled w/ colloid</b></li> </ul>

	<p><b>casts (thyroidization)</b></p> <ul style="list-style-type: none"> <li>• Interstitial inflammation and fibrosis</li> <li>• Obliterative intimal sclerosis of arcuate and interlobular vessels</li> <li>• Hyaline arteriosclerosis in entire kidney in presence of HTN</li> <li>• <i>Focal segmental glomerulosclerosis</i> w/ significant proteinuria can develop in advanced stages, may be due to renal ablation theory (→ poor prognosis)</li> </ul>
<b>Clinical Presentation</b>	<ul style="list-style-type: none"> <li>➢ May be insidious or may present like acute recurrent pyelonephritis w/ back pain, fever, pyuria, frequency, bacteriuria</li> <li>➢ Reflux nephropathy often discovered when etiology of HTN in children is investigated</li> <li>➢ Loss of tubular function → polyuria, nocturia</li> </ul>
<b>Other</b>	<ul style="list-style-type: none"> <li>➢ IMPORTANT CAUSE of <i>end-stage kidney disease</i></li> <li>➢ IMPORTANT CAUSE of kidney destruction in kids w/ severe lower urinary tract abnormalities</li> </ul>

<b>Acute Drug Induced Tubulointerstitial Nephritis</b>	
<b>Etiology</b>	Rxn to sulfonamides, synthetic penicillins (methicillin, ampicillin), rifampin, diuretics, NSAIDs
<b>Pathophysiology</b>	<ul style="list-style-type: none"> <li>• <b>NOT dose related – drugs act as haptens &amp; covalently bind some cytoplasmic or extracellular component of tubular cells</b></li> <li>• ↑ serum IgE suggests late-phase rxn of IgE-mediated (<i>type I hypersensitivity</i>)</li> <li>• mononuclear or granulomatous infiltrate w/ (+) skin tests to drug haptens suggests <i>delayed hypersensitivity type rxn (type IV)</i></li> </ul>
<b>Histological Morphology</b>	<ul style="list-style-type: none"> <li>• Interstitial edema, infiltration by mononuclear cells (lymphocytes and macrophages)</li> <li>• Interstitial granulomas w/ giant cells may be seen</li> <li>• <i>Tubulitis</i> = infiltration of tubules by lymphocytes</li> <li>• Variable degrees of tubular necrosis and regeneration</li> <li>• Glomeruli are normal – may exhibit some <i>minimal change disease w/ concurrent nephrotic syndrome</i> (common w/ NSAIDs)</li> </ul>
<b>Clinical Presentation</b>	<ul style="list-style-type: none"> <li>• Begins ~ 15 days after drug exposure w/ fever, eosinophilia, rash, renal abnormalities (hematuria, mild proteinuria, leukocyturia)</li> <li>• Rising serum creatinine level or acute renal failure w/ oliguria develops in 50% of cases</li> <li>• Withdrawal of offending drug → recovery</li> </ul>
<b>Other</b>	Drugs are the LEADING IDENTIFIABLE CAUSE of <i>acute interstitial nephritis</i>

<b>Analgesic Nephropathy</b>	
<b>Etiology</b>	Aspirin, caffeine, acetaminophen (metabolite of phenacetin), codeine

<b><i>Epidemiology</i></b>	<ul style="list-style-type: none"> <li>• More common in women than men</li> <li>• Prevalent in individuals w/ recurrent headaches and muscle pain, in psychoneurotic patients, and in factory workers</li> </ul>
<b><i>Pathophysiology</i></b>	<ul style="list-style-type: none"> <li>• Drugs damage cells by covalent binding &amp; oxidative damage → papillary necrosis → cortical tubulointerstitial nephritis → chronic renal insufficiency</li> <li>• Aspirin inhibits vasodilatory effects of prostaglandins → ischemia</li> </ul>
<b><i>Morphology</i></b>	
<b><i>Gross Appearance</i></b>	Normal or slightly small kidneys
<b><i>Histological</i></b>	<ul style="list-style-type: none"> <li>• Chronic tubulointerstitial nephritis w/ renal papillary necrosis – papillae at various stages of necrosis, calcification, fragmentation, sloughing</li> <li>• Loss and atrophy of tubules, interstitial fibrosis in cortex</li> </ul>
<b><i>Clinical Presentation</i></b>	<ul style="list-style-type: none"> <li>• Polyuria, renal stones, headache, anemia, GI symptoms, HTN</li> <li>• UTI in 50% of cases</li> <li>• Gross hematuria or renal colic if entire tips of necrotic papillae are excreted (obstruction of ureter)</li> </ul>
<b><i>Typical Outcome</i></b>	<ul style="list-style-type: none"> <li>➢ Progressive impairment of renal function → chronic renal failure</li> <li>➢ Drug withdrawal → renal function may stabilize or improve</li> </ul>
<b><i>Other</i></b>	<b><i>Transitional papillary carcinoma of the renal pelvis</i></b> = carcinogenic effect of analgesic phenacetin

<b><i>NSAID Nephropathy</i></b>	
<b><i>Etiology</i></b>	COX-2 inhibitors, nonsteroidal anti-inflammatory drugs
<b><i>Pathophysiology</i></b>	<ul style="list-style-type: none"> <li>• Inhibition of vasodilatory prostaglandin synthesis → acute renal failure</li> <li>• Acute hypersensitivity interstitial nephritis → acute renal failure</li> <li>• Hypersensitivity rxn affecting interstitium and glomeruli → acute interstitial nephritis AND minimal change disease → acute renal failure w/ nephrotic syndrome</li> <li>• Membranous glomerulonephritis w/ nephrotic syndrome (pathogenesis unclear)</li> </ul>

***Chinese Herbs Nephropathy*** – chronic tubulointerstitial nephritis caused by aristolochic acid (herbal remedies); assoc. w/ ↑ incidence of carcinoma in kidney and urinary tract

**Other Tubulointerstitial Diseases**

**Urate Nephropathy** – 3 types:

- 1) ***acute uric acid nephropathy*** = precipitation of uric acid crystals in renal tubules (principally CD) → obstruction of nephrons → acute renal failure
  - likely in patients undergoing ***chemotherapy for leukemia/lymphoma (d/t rapid turn over of cells)***

- 2) **chronic urate nephropathy (gouty nephropathy)** = deposition of **monosodium urate crystals (not uric acid crystals)** in distal tubules and CD as well as interstitium; due to more protracted forms of hyperuricemia
  - **birefringent needle-like crystals** in tubular lumina or interstitium
  - **tophus** = foreign body giant cells, fibrotic reaction
  - tubular obstruction → cortical atrophy and scarring
  - arterial and arteriolar thickening common
- 3) **nephrolithiasis** = uric acid stones; present in 22% of gout patients and 42% of patients w/ secondary hyperuricemia

### Multiple Myeloma

50% of patients develop over renal insufficiency

- **Bence Jones proteinuria** – good correlation w/ renal failure
  - Some **light chains directly toxic to epithelial cells**
  - Combine w/ **Tamm-Horsfall protein** under acidic conditions to form large casts that obstruct tubular lumina and cause inflammatory rxn (= **cast nephropathy**)
- **Amyloidosis** – accumulations of light chains in fibrillar deposits
- **Light-chain deposition disease** – light chain deposition in GBM and mesangium in nonfibrillar forms causes glomerulopathy; deposition in tubular BM causes tubulointerstitial nephritis
- **Hypercalcemia, hyperuricemia** – common
- **Morphology** = concentrically laminated Bence Jones tubular casts surrounded by multinucleate giant cells
- **Clinically** –
  - MOST COMMON form is *insidious chronic renal failure*
  - Acute renal failure w/ oliguria is less common
  - Lytic bone lesions

### Diseases of Blood Vessels

*Nearly all diseases of the kidney involve the renal blood vessels secondarily.*

<b>Benign Nephrosclerosis</b>	
<b>Pathophysiology</b>	<b>Medial and intimal thickening</b> (response to hemodynamic changes, aging, genetic defects) + <b>Hyaline deposition in arterioles</b> (extravasation of plasma proteins through injured endothelium, ↑ deposition of BM matrix) → <i>sclerosis of renal arterioles and small arteries</i>
<b>Morphology</b>	
<b>Gross Appearance</b>	<ul style="list-style-type: none"> <li>• Normal or slightly small kidneys</li> <li>• Cortical surfaces have fine granularity (leathery appearance)</li> </ul>
<b>Histological</b>	<ul style="list-style-type: none"> <li>➤ <b>Hyaline arteriolosclerosis</b> in arterioles and small arteries</li> <li>➤ <b>Fibroelastic hyperplasia</b> (medial hypertrophy, reduplication of elastic lamina, ↑ myofibroblastic tissue in intima) of interlobular and arcuate arteries → narrow lumens</li> <li>➤ <b>Ischemic atrophy</b> – foci of tubular atrophy and interstitial fibrosis w/ variety of glomerular alterations</li> </ul>
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Moderate reductions in renal plasma flow, GFR normal or slightly</li> </ul>

<b>Presentation</b>	<p>reduced</p> <ul style="list-style-type: none"> <li>• Mild proteinuria sometimes</li> <li>• <b>3 groups w/ HTN &amp; benign nephrosclerosis at risk for developing renal failure = blacks, patients w/ severe HTN, patients w/ second underlying disease (esp. diabetes)</b></li> </ul>
<b>Typical Outcome</b>	Focal ischemia of parenchyma supplied by vessels w/ thickened walls and narrowed lumens

<b>Malignant HTN &amp; Accelerated Nephrosclerosis</b>	
<b>Epidemiology</b>	<ul style="list-style-type: none"> <li>➢ 1-5% of all patients w/ HTN</li> <li>➢ Us. affects younger black men</li> </ul>
<b>Pathophysiology</b>	<p>Vascular damage to kidneys → ↑ permeability of small vessels to fibrinogen, endothelial injury, focal death of cells of vascular wall, platelet deposition → fibrinoid necrosis of arterioles → intravascular thrombosis → mitogenic factors released → <b>hyperplastic arteriolosclerosis</b> → marked ischemia → <b>renin-angiotensin system</b> → self-perpetuating cycle</p>
<b>Morphology</b>	
<b>Gross Appearance</b>	Petechial hemorrhages on cortical surface
<b>Histological</b>	<p>Fibrinoid necrosis of arterioles = eosinophilic granular change in blood vessel wall</p> <p><b>Onion-skinning of interlobular arteries and arterioles</b></p>
<b>Clinical Presentation</b>	Diastolic pressure > 130 mmHg, <b>papilledema retinopathy</b> , encephalopathy, CV abnormalities, renal failure
<b>Typical Outcome</b>	75% survival at 5 years
<b>Other</b>	Frequent cause of death from uremia in patients w/ scleroderma

<b>Renal Artery Stenosis</b>	
<b>Etiology</b>	<ul style="list-style-type: none"> <li>• 70% of cases caused by <b>atheromatous plaque occlusion</b> at origin of renal artery – more frequent in men than women, increases with age and diabetes</li> <li>• <b>fibromuscular dysplasia</b> of renal artery – more common in women, occurs in younger age groups (3<sup>rd</sup> and 4<sup>th</sup> decades)</li> </ul>
<b>Pathophysiology</b>	<ul style="list-style-type: none"> <li>• Kidney w/ renal artery stenosis thinks it's getting low perfusion → juxtaglomerular apparatus begins producing renin → renin-angiotensin system kicks in → vasoconstriction</li> <li>• Can cause malignant HTN</li> </ul>
<b>Morphology</b>	
<b>Gross Appearance</b>	<ul style="list-style-type: none"> <li>➢ <b>Small kidney, diffuse ischemic atrophy</b></li> <li>➢ Fibromuscular dysplasia of renal artery – intimal, <i>medial (most common)</i>, or adventitial</li> </ul>
<b>Histological</b>	Crowded glomeruli, atrophic tubules, interstitial fibrosis, focal inflammatory infiltrates
<b>Clinical Presentation</b>	<ul style="list-style-type: none"> <li>➢ <b>High serum or renal vein renin levels</b></li> <li>➢ Pts. show reduction in bp when given competitive antagonist of angiotensin II</li> </ul>

<b>Typical Outcome</b>	Surgical treatment successful in 70-80% of cases of unilateral renal artery stenosis
------------------------	--

**Thrombotic Microangiopathies** = thrombosis in capillaries and arterioles throughout the body; *characterized clinically by microangiopathic hemolytic anemia (will see schistocytes), thrombocytopenia, renal failure* (assoc. w/ platelet or platelet-fibrin thrombi in interlobular renal arteries, arterioles, glomeruli)

- **Pathophysiology** – endothelial injury/activation and platelet aggregation → vascular obstruction, vasoconstriction → distal ischemia
  - Endothelial denudation → exposure of potentially thrombogenic subendothelial connective tissue
  - Reduced production of prostaglandin I<sub>2</sub> and NO → platelet aggregation, vasoconstriction
  - Elaboration of vWF → platelet aggregation
- **Classic (Childhood) Hemolytic-Uremic Syndrome (HUS)** – assoc. w/ bloody diarrhea caused by intestinal infection by verocytotoxin
  - **75% of cases** occur in children after infection w/ *E. coli* O157:H7 (**so think of this when the case presentation is a kid that just ate a hamburger and then gets bloody diarrhea and renal problems**)
  - **one of the MAIN CAUSES of acute renal failure in children**
  - sudden onset of hematemesis and melena, severe oliguria, hematuria, neurologic changes, microangiopathic hemolytic anemia, HTN
  - **Kidney morphology** = patchy or diffuse renal cortical necrosis; thickened glomeruli; deposits of fibrin-related materials in capillary lumen, subendothelial, and in mesangium; mesangiolysis is common; interlobular and afferent arterioles show fibrinoid necrosis and intimal hyperplasia
- **Idiopathic thrombotic thrombocytopenic purpura (TTP)** – **manifested by fever, neurologic symptoms- MAJOR Sx, hemolytic anemia, thrombocytopenia, renal thrombi**
  - Acquired or congenital loss of **ADAMTS-13** (vWF-cleaving metalloprotease)
  - More common in **women** than men, more prevalent in women < 40 y.o.
  - Renal involvement in only ~ 50% → eosinophilic granular thrombi in interlobular arteries, afferent arterioles, glomerular capillaries

### Other Vascular Disorders

- **Atherosclerotic Ischemic Renal Disease** – bilateral disease causes chronic ischemia w/ renal insufficiency in older patients, sometimes in absence of HTN
  - Surgical revascularization → reverses further decline in renal function
- **Atheroembolic Renal Disease** – embolization of atheromatous plaques from aorta or renal artery → acute renal failure following abdominal surgery on atherosclerotic aneurysms
- **Sickle Cell Disease Nephropathy** – hematuria, diminished concentrating ability, patchy **papillary necrosis**, mild to moderate proteinuria (nephrotic syndrome can arise assoc. w/ sclerosing glomerular lesions)
  - **4 things cause Papillary necrosis: diabetes, acute pyelonephritis, sickle cell disease and chronic phenacetin use**
- **Diffuse Cortical Necrosis** – rare, occurs most frequently after obstetric emergency

- Bilateral and symmetric → can be fatal (sudden anuria, uremic death)
- Ischemic necrosis of cortex and columns of Bertin, glomerular and arteriolar microthombi
- **Renal Infarcts – most infarcts due to embolism (major source = mural thrombosis in L atrium and ventricle as result of myocardial infarction)**
  - Less frequent = vegetative endocarditis, thrombosis in aortic aneurysms, aortic atherosclerosis
  - White, anemic, sharply demarcated wedge-shaped areas of coagulative necrosis, us. ringed by zone of intense hyperemia

**Urinary Tract Obstruction (Obstructive Uropathy)**

- *Obstruction increases susceptibility to infection and to stone formation.*
- *Unrelieved obstruction almost always leads to permanent renal atrophy = hydronephrosis, obstructive uropathy*
- **Hydronephrosis** = dilation of renal pelvis and calyces assoc. w/ progressive atrophy of kidney due to obstruction to outflow of urine
- **Pathophysiology:**
  - Complete obstruction → filtrate diffuses back into renal interstitium and perirenal spaces → returns to lymphatic and venous systems → continued filtration causes calyces and pelvis to become dilated → high pressure in pelvis transmitted back through CD into cortex → **renal atrophy**, compression of renal vasculature of medulla → less inner medullary plasma flow → medullary functional disturbances → impaired concentrating ability → **eventual ↓ GFR**
  - Obstruction → interstitial inflammatory rxn → *interstitial fibrosis*
- **Morphology:**
  - Intermittent obstruction – normal GFR, progressive dilation
  - Slight to massive enlargement of kidneys
  - Chronic cases – cortical tubular atrophy w/ diffuse interstitial fibrosis
  - Progressive blunting of apices of pyramids
  - Advanced cases – thin-walled cystic kidneys, striking parenchymal atrophy, total obliteration of pyramids, thin cortex
- **Clinical:**
  - **Acute obstruction – flank pain, renal colic**, prostatic enlargements
  - Bilateral partial obstruction – earliest manifestation is inability to concentrate urine (polyuria, nocturia); some patients have acquired distal tubular acidosis, renal salt wasting, secondary renal calculi, tubulointerstitial nephritis, HTN
  - Complete bilateral obstruction – oliguria or anuria, incompatible w/ long survival unless obstruction is relieved
    - *Postobstructive diuresis* = kidney excretes large amts. of urine rich in NaCl

<b><i>Urolithiasis (renal calculi, stones)</i></b>	
<b><i>Etiology</i></b>	
<b><i>Genetic Factors</i></b>	Familial and hereditary predisposition Inborn errors of metabolism (gout, cystinuria, primary hyperoxaluria)
<b><i>Epidemiology</i></b>	➤ 5-10% of Americans in their lifetime ➤ <b>Men</b> affected more often than women

	➤ Peak age 20-30 years
<b>Pathophysiology</b>	<ul style="list-style-type: none"> <li>• <b>Calcium containing stones (70%)</b> – calcium oxalate, calcium phosphate, radio-opaque stones <ul style="list-style-type: none"> <li>➤ Assoc. w/ hypercalcemia, hypercalciuria caused by hyperparathyroidism, diffuse bone disease, sarcoidosis</li> <li>➤ 5% assoc. w/ <b>hyperoxaluria</b> (vegetarians)</li> <li>➤ <b>Hypocitraturia</b> assoc. w/ acidosis, chronic diarrhea</li> </ul> </li> <li>• <b>Triple or struvite stones (15%)</b> – <b>magnesium ammonium phosphate</b> <ul style="list-style-type: none"> <li>➤ Form following infection w/ urea-splitting bacteria (<i>Ureaplasma urealytica</i>, <i>Proteus</i>)</li> <li>➤ Alkaline urine causes precipitation of magnesium ammonium phosphate salts → large stones (= <b>staghorn calculi</b>)</li> </ul> </li> <li>• <b>Uric acid stones (5-10%)</b> – <b>radiolucent</b> stones <ul style="list-style-type: none"> <li>➤ Common in pts. w/ hyperuricemia (gout) and diseases w/ rapid cell turnover (leukemia)</li> </ul> </li> <li>• <b>Cystine stones (1-2%)</b> – form at low urinary pH <ul style="list-style-type: none"> <li>➤ Caused by genetic defects in renal reabsorption of aa (including cystine)</li> </ul> </li> </ul>
<b>Morphology</b>	Unilateral in 80% of patients Favored sites = renal calyces and pelves and bladder
<b>Clinical</b>	<ul style="list-style-type: none"> <li>➤ <b>Smaller stones most hazardous → pass into ureters → colic, ureteral obstruction</b></li> <li>➤ Larger stones cannot enter ureters → hematuria</li> <li>➤ Predisposed to superimposed infection</li> </ul>
<b>Other</b>	<b>Stone formation enhanced by deficiency in inhibitors of crystal formation in urine by pyrophosphate, diphosphonate, citrate, glycosaminoglycans, osteopontin, nephrocalcin, etc.</b>

### Benign Tumors of the Kidney

<b>Renal papillary adenoma</b>	
<b>Epidemiology</b>	Present in 7-22% of autopsy patients
<b>Pathophysiology</b>	Small, discrete adenomas arising from renal tubular epithelium
<b>Morphology</b>	
<b>Gross Appearance</b>	<ul style="list-style-type: none"> <li>➤ Small tumors, &lt;5mm in diameter</li> <li>➤ Pale yellow-gray, discrete, well-circumscribed nodules in cortex</li> </ul>
<b>Histological</b>	<ul style="list-style-type: none"> <li>• Complex, branching, papillomatous structures w/ numerous fronds</li> <li>• Cells are cuboidal to polygonal w/ regular, small central nuclei, scanty cytoplasm, no atypia</li> <li>• Do not differ from low-grade papillary renal cell adenocarcinoma, share trisomies 7 and 17 w/ papillary cancers</li> </ul>

**Renal Fibroma or Hamartoma (renomedullary interstitial cell tumor)** – small foci of gray-white firm tissue, us. <1cm in diameter w/in pyramids

- Tumors consist of fibroblast-like cells (w/ features of renal interstitial cells) and collagenous tissue

**Angiomyolipoma** – consists of vessels, smooth muscle, fat

- Present in 25-50% of patients w/ **tuberous sclerosis (disease characterized by lesions of cerebral cortex, epilepsy, mental retardation, skin abnormalities)**

**Oncocytoma** – epithelial tumor

- Tumors are **tan or mahogany brown**, relatively homogeneous, well encapsulated, can be up to 12 cm in diameter
- Cells are large and eosinophilic w/ small, round, benign-appearing nuclei, large nucleoli, **and numerous mitochondria; thought to arise from intercalated cells of CD**

### Malignant Tumors of the Kidney

<b><i>Urothelial Carcinomas of the renal pelvis</i></b>	
<b><i>Epidemiology</i></b>	<ul style="list-style-type: none"> <li>➤ 5-10% of primary renal tumors originate from urothelium of renal pelvis</li> <li>➤ 50% of pts. have preexisting or concomitant bladder urothelial tumor</li> <li>➤ Increased incidence of urothelial carcinomas of renal pelvis and bladder in pts. w/ analgesic nephropathy</li> </ul>
<b><i>Pathophysiology &amp; Morphology</i></b>	Same as urothelial tumors of the bladder
<b><i>Clinical Presentation</i></b>	Hematuria, palpable hydronephrosis, flank pain
<b><i>Typical Outcome</i></b>	5-year survival rates vary from 50-70% for low-grade to 10% for high-grade infiltrating tumors (infiltration of wall of pelvis and calyces is common)

<b><i>Renal cell carcinoma (adenocarcinoma of the kidney)</i></b>	
<b><i>Etiology</i></b>	
<b><i>Genetic Factors</i></b>	<ul style="list-style-type: none"> <li>• Most cases are sporadic</li> <li>• Unusual forms of autosomal-dominant familial cancers occur in younger individuals               <ol style="list-style-type: none"> <li>1) <b><i>von Hippel-Lindau syndrome (VHL)</i></b> – hemangioblastomas of cerebellum and retina, renal cysts, bilateral renal cell carcinomas; <i>VHL</i> gene on chromosome 3p is a tumor suppressor gene</li> <li>2) <b><i>Hereditary (familial) clear cell carcinoma</i></b> – confined to kidney but has abnormalities involving same gene as VHL</li> <li>3) <b><i>Hereditary papillary carcinoma</i></b> – multiple bilateral tumors, mutations in <i>MET</i> protooncogene</li> </ol> </li> </ul>
<b><i>Environmental Factors</i></b>	Tobacco is the most significant risk factor

<b>Epidemiology</b>	<ul style="list-style-type: none"> <li>➤ Male predominance in 6<sup>th</sup> and 7<sup>th</sup> decades of life</li> </ul>
<b>Pathophysiology</b>	<ul style="list-style-type: none"> <li>• Arise from tubular epithelium</li> <li>• <b>Clear cell carcinoma = most common type</b>, accounts for 70-80% of renal cell cancers; 95% are sporadic <ul style="list-style-type: none"> <li>➤ 98% show loss of part of <b>chromosome 3p</b> which harbors <i>VHL</i> gene; 80% show mutated or hypermethylation-induced inactivation of other nondeleted allele of <i>VHL</i> gene</li> <li>➤ <b>Mutated <i>VHL</i> → ↑ levels of hypoxia-inducible factor (HIF-1) → ↑ trxn and production of VEGF, TGFβ, insulin-like growth factor → cell growth and angiogenesis stimulated</b></li> <li>➤ Tumors are usually solitary, unilateral lesions</li> </ul> </li> <li>• <b>Papillary carcinoma = 10-15% of renal cancers</b> <ul style="list-style-type: none"> <li>➤ Assoc. w/ trisomies 7, 16, 17; loss of Y in male patients in sporadic form; trisomy 7 in familial form</li> <li>➤ <i>MET</i> gene on chromosome 7 = protooncogene, tyrosine kinase receptor for hepatocyte growth factor (scatter factor, HGF) which mediates growth, cell mobility, invasion, differentiation</li> <li>➤ <i>PRCC</i> gene on chromosome 1 = implicated in sporadic tumors in children; t(X;1) translocation causes fusion of <i>PRCC</i> w/ <i>TFE-3</i> gene on X chromosome → fusion protein dysregulates mitotic checkpoints</li> <li>➤ Tumors are frequently multifocal</li> </ul> </li> <li>• <b>Chromophobe renal carcinoma = 5% of renal cell cancers</b> <ul style="list-style-type: none"> <li>➤ Tumors exhibit multiple chromosome losses, extreme hypodiploidy</li> <li>➤ Thought to grow from intercalated cells of CD like benign oncocytomas</li> </ul> </li> <li>• <b>Bellini duct carcinoma = 1% of renal epithelial neoplasms</b> <ul style="list-style-type: none"> <li>➤ Arise from CD cells in medulla</li> <li>➤ Variety of chromosomal losses and deletions</li> </ul> </li> </ul>
<b>Gross Appearance</b>	<ul style="list-style-type: none"> <li>• Renal vein invasion → solid column of cells extending into inferior vena cava and right heart</li> <li>• <b>Clear cell carcinomas = Yellow color</b> (prominent lipid accumulations), us. at upper pole</li> <li>• <b>Papillary tumors = hemorrhagic, cystic</b></li> </ul>
<b>Histological</b>	<ul style="list-style-type: none"> <li>➤ <b>Clear cell carcinoma</b> – cells resemble clear cells of adrenal cortex; cells are round or polygonal w/ abundant clear or granular cytoplasm; most are well-differentiated but some show marked nuclear atypia</li> <li>➤ <b>Papillary carcinoma</b> – cuboidal or low columnar cells in papillary formations; interstitial foam cells common; <i>psammoma bodies</i> (concentric whorls of cells in various</li> </ul>

	<p>stages of hyaline change and mineralization)- MOST COMMON type of renal cancer in pts. w/ <i>dialysis-assoc. cystic disease</i></p> <ul style="list-style-type: none"> <li>➤ <b>Chromophobe renal carcinoma</b> – histologic distinction from oncocytoma is difficult; cells have prominent cell membranes, pale eosinophilic cytoplasm, us. w/ halo around nucleus- excellent prognosis</li> <li>➤ <b>Bellini duct carcinoma</b> – nests of malignant cells enmeshed w/in prominent fibrotic stroma in medulla; hobnail pattern of highly atypical epithelium</li> </ul>
<b>Clinical Presentation</b>	<ul style="list-style-type: none"> <li>• 10% of pts. have CVA pain, palpable mass, hematuria</li> <li>• <b>One of the few SOLID TUMORS that presents w/ fever</b></li> <li>• Assoc. w/ several <b>paraneoplastic syndromes</b> = <b>polycythemia</b>, hypercalcemia, HTN, hepatic dysfunction, feminization or masculinization, Cushing syndrome, eosinophilia, leukemoid rxns, amyloidosis</li> <li>• Tends to metastasize widely before giving rise to local symptoms – <b>most common sites of metastasis incl. lungs (&gt;50%)</b>, bones (33%), regional lymph nodes, liver, adrenals, brain</li> </ul>

### Lower Urinary Tract Pathology Notes

**Normal – transitional epithelium throughout. Surface layer consists of umbrella cells possessing apical plaques composed of uroplakins**

- Brunn nests – nests of urothelium or inbudding of surface epithelium in mucosa.
- Ureters – course retroperitoneally- pass under uterine artery and under ductus deferens
- Sites predisposed to obstruction (due to anatomic narrowing) – renal calculi may impact, etc
  - Ureteropelvic jxn
  - Where ureter enters bladder – oblique course allows for sphincteric valvular action – prevents retrograde flow of urine.
  - Where ureter crosses iliac vessels
- Trigone – made up by orifices of ureters and urethra
- Vesicoureteral reflux - results defect in intravesical portion of ureter

### Congenital anomalies of the ureter

- Double and bifid ureters – derived from double or split ureteral bud
- Ureteropelvic jxn obstruction → hydronephrosis. More common in boys during infancy. More common in women if it presents in adulthood
  - Abn organization of smooth mm or excess stromal deposition of collagen
- Diverticula – saccular outpouchings of the ureteral wall → stasis → infection
- Hydroureter – dilation, elongation and tortuosity of the ureter
- Megaloureter – due to functional defect of ureteral mm

**Ureteral inflammation** – ureteritis can be component of UTI.

- Morph – aggregation of lymphocytes in subepithelial region
  - Ureteritis follicularis – fine granular mucosal surface
  - **Ureteritis cystica** – mucosa sprinkled with fine cysts
    - Cysts may aggregate to form grape-like clusters

#### **Tumors and tumor-like lesions of the ureter** – primary neoplasia is rare

- Leiomyoma
- Fibroepithelial polyp – small mass protruding into the lumen. More common in ureter than rest of UT. More often on left. Loose, vascularized connective tissue mass.
- TCC – cause obstruction. 60s-70s.

#### **Obstructive lesions** – results of obstruction = hydroureter, hydronephrosis, pyelonephritis

- Intrinsic causes = calculi, strictures, tumors, blood clots, neurogenic cz
- Extrinsic causes = prego, periureteral inflammation, endometriosis, tumors
- Sclerosing retroperitoneal fibrosis – fibrous proliferative inflammatory process encasing retroperitoneal structures → hydronephrosis.
  - Occurs in mid to late age.
  - May be assoc with chronic inflamm process in the vicinity, e.g. Crohn dz
  - Assoc with mediastinal fibrosis, sclerosing cholangitis and Riedel fibrosing thyroiditis.
  - Inflamm infiltrate – germinal ctrs, plasma cells and eosinophils

#### **Congenital anomalies of the urinary bladder.**

- Diverticula – pouchlike eversion or evagination of bladder wall
  - Acquired – most often seen with prostatic enlargement, which → ↑ intravesical pressure
  - Create areas of urinary stasis → infection and calculi.
  - May also predispose to vesicoureteral reflux
- Exstrophy – developmental failure in **anterior wall of abdomen and bladder**. ↑risk for infection
  - Bladder mucosa may → colonic glandular metaplasia → ↑risk for adenocarcinoma
- Vesicoureteral reflux – most common and serious anomaly → renal infection and scarring
- Congenital vesicouterine fistulas – abn communication b/w tubes, e.g. bladder and vagina
- Patent urachus – bladder connected with umbilicus → urachal cysts → adenocarcinoma of the bladder (resembling colonic variety)

#### **Inflammation of the bladder**

- Bacterial pyelonephritis is commonly preceded by infection of bladder with retrograde spread to kidney.
- *E. coli* > *Proteus*, *Klebsiella*, and *Enterobacter*
- *Schistosoma haematobium* in Egypt and Sudan → chronic inflamm → SCC of bladder
- Rads, adenovirus and cyclophosphamide → hemorrhagic cystitis
- Triad = frequency, suprapubic pain, dysuria

- Can obviously be secondary complication of obstruction, e.g. BPH (prostatic enlargement)
- Interstitial cystitis (Hunner ulcer) – severe frequency, urgency, dysuria, abdominal pain with hematuria
  - Hunner ulcers – on mucosal surface
  - Assoc with SLE and other autoimmune dz
- Malacoplakia – soft, slightly raised mucosal plaques. Large foamy macs, multinucleate giant cells, lymphocytes
  - Laminated, mineralized concretions = **Michaelis-Gutmann bodies**
  - related to bacterial infection – *E. coli* > *Proteus*
- Cystitis glandularis and cystitis cystica – **Brunn nests** grow downward into the lamina propria → glandlike structures or cystic structures
  - more prominent in inflamed and chronically irritated bladders
  - lesions exhibit intestinal metaplasia → ↑risk for adenocarcinoma

### **Neoplasms of the Bladder – vast majority of epithelial origin. TCC most common.**

- Often multifocal at presentation
- Low-grade urothelial tumors – always papillary. Recapitulate normal transitional epithelium
- High-grade urothelial tumors – considerable pleomorphism and anaplasia. Always aneuploid. High freq of gene and chrom abnormalities. Lack blood group Ags (presence of Ags → better prognosis)
  - Metastatic potential
- Papillomas and low grade lesions nearly always papillary.
- Higher grade lesions may be flat
- Met to regional nodes. Hematogenous dissemination → liver, lungs and marrow
- CIS – confined to bladder. Commonly multifocal
- **SCC – schistosomiasis. Always assoc with chronic inflamm of bladder.**
- Adenocarcinomas – rare. Urachal remnants or in assoc with intestinal metaplasia.
- **Epidemiology and pathogenesis**
  - Cigarette smoking – most bladder cancer among men assoc with smoking cigs
  - Exposure to arylamines – e.g. **2-naphthylamine** → ↑risk for bladder CA
  - **Schistosoma haematobium** – SCC in Egypt and Sudan
  - **Long-term analgesic use** → ↑risk for TCC
  - **Cyclophosphamide** → hemorrhagic cystitis → ↑risk for bladder CA
  - **Chrom 9 deletions** – present in papillary and noninvasive tumors
    - 9p deletion → ↓p16 (tumor suppressor that encodes inhibitor of cyclin-dependent kinase)
  - 17p deletions – often exhibited by invasive CA of the bladder
  - **chrom 9 deletions** → loss of suppressor gene → superficial flat or papillary noninvasive lesions → loss of p53 → progression to invasion
  - initial loss of p53 also implicated in pathogenesis of invasive lesions.
- **Clinical – painless hematuria is hallmark of bladder CA.** Inflammation triad may occasionally accompany hematuria.
  - Recurrence common with all grade tumors
  - Papillomas and grade I have excellent survival rates
  - Grade III – horrible prognosis – mortality very high

- SCC – death within a yr of dx
- Mesenchymal tumors
  - Leiomyoma = most common
  - Rhabdomyosarcoma
    - Adult variant = histology similar to tumors of striated mm
    - **Embryonal rhabdomyosarcoma (sarcoma botryoides) – infancy and childhood**
- Secondary tumors – cervix > uterus > prostate > rectum = sources of secondary lesions

**Bladder obstruction** – deleterious effect on kidney.

- Male – enlargement of prostate = most common cause
- Female – cystocele of the bladder = most common cz
- Morph – hypertrophy of smooth mm secondary to ↑intravesical pressure

**Inflammation of the urethra**

- Urethritis –
  - Gonococcal – early manifestation of VD (*Neisseria*)
  - Non-gonococcal - *E. coli* = common cz
    - *Chlamydia* and *Mycoplasma* also causative
  - Accompanied by cystitis in women and prostatitis in men
  - **Reiter syndrome – urethritis, arthritis and conjunctivitis-** (can't see, pee, or climb a tree)
  - Early sx = local pain, itching and frequency

**Tumors of the urethra**

- Caruncle – small, red, painful mass about the external urethral meatus. More common in later life.
  - Extremely friable – the slightest trauma can → ulceration and bleeding
  - Highly vascularized, fibroblastic connective tissue with leukocytic infiltrate.
- Papilloma – viral origin
- Carcinoma – older women. Lesion begins about external meatus, glans or introitus
  - Warty, papillary growths. Sessile papillary carcinoma progresses → fungating ulcerating lesion
  - Most are SCC
  - More aggressive than bladder CA
    - Very invasive and difficult to eradicate even though they generally don't metastasize.

**Dr. Dubins Material**

**Hypertensive Urgency vs. Emergency**

**Urgency:** A systolic BP > 180 or a diastolic BP > 130 and NO evidence of end organ damage.

**Emergency:** May occur at any BP, but involves DAMAGE to at least one organ system.

**Atherosclerosis vs. Fibromuscular Dysplasia**

Feature	Atherosclerosis	Fibromuscular dysplasia
Age	>50	<40
Sex	Male	Female
Bilaterality	33%	60%
Progressive	+++	+
Response to Angioplasty	+	+++
Associated risks – tobacco, lipids, diabetes, etc...	+++	+

**Fibromuscular Dysplasia** (important to look at age and sex in case presentation)

1. **Medial fibromuscular dysplasia: Most common**, 85% of all stenosis, 9/1 **Females** to males, **ages 25-45**, Can be seen in carotids and iliac arteries. 70% of lesions are bilateral. May appear as solitary mid and distal stenotic lesions or multiple constrictions with intervening aneurysmal dilations.
2. Perifibromuscular dysplasia: 10-25% of cases. Usually **mid-distal portion of renal artery**.
3. Intimal fibromuscular dysplasia: 5%, **Males = Females**, Infants and young adults more freq.

**Coarctation of Aorta**

- Narrowing of medial layer of aorta.
- Commonly at ligamentum arteriosum- can be preductal (infant) or post ductal (adults)
- Differences in upper and lower extremities- HTN in upper etremities and weak pulse in lower extremities
- Blood Pressure
  - systolic hypertension in an infant
  - 20mm hg between arms
- Heart Sounds – if isolated a systolic ejection murmur in the aortic outlet and between scapulae.
- Radiology : Cardiomegaly and Rib notching (d/t collateral circulation)

**Contraindications for ACE inhibitors**

1. Bilateral renal artery stenosis
2. Unilateral renal artery stenosis with solitary kidney
3. Pregnancy
4. Known angioneurotic edema with prior ACE administration.

### Cardio/Pulmonary Choice of Drugs

CONDITION	AGENT	CAUTION
After MI	Beta Blocker, ACE Inhibitor	Direct Vasodilators (may worsen coronary insufficiency)
CHF	ACE Inhibitor, Diuretics; Beta blockers (no pulm edema)	Beta Blockers, CCB
Hypertrophic Cardiomyopathy	Beta Blockers, CCB	Diuretics, ACE Inhibitors, direct vasodilators
Bradycardia, Heart Block		Beta Blockers, CCB
Tachyarrhythmias	Beta Blockers, verapamil	
Angina	Beta Blockers, CCB, Nitroglycerin,	Direct Vasodilators (<afterload may < coronary perfusion)
COPD/ROAD	CCB	Beta Blockers
Aortic Dissection	Nitroprusside, Beta Blocker	Drugs that > cardiac output (Increased shear stress)
Bilateral Renal Artery Stenosis		Ace Inhibitors, Angiotensin Blockers (May worsen renal function)
Chronic Renal Insufficiency	Ace Inhibitors (With serum creatinine <2.5), Loop diuretics, CCB	ACE Inhibitors, Angiotensin blockers (may worsen renal function)
Renal Transplants		ACE Inhibitors (may worsen renal function)
Diabetes	ACE inhibitor (delay renal failure; decrease proteinuria)	
Pregnancy (preeclampsia, eclampsia)	Methyldopa, Hydralazine; Beta blockers with caution	ACE Inhibitors, Angiotensin blockers, (may cause renal agenesis) Diuretics
Gout		Diuretics (worsen joint pain or precipitate gout)

Cocaine Use	Labetalol, Clonidine	Selective B-blockers (unopposed cocaine induced Alpha agonism)
GI Bleed	Non-selective Beta Blocker (lower portal blood pressure)	Beta Blockers (may mask signs of acute bleeding)
Pheochromocytoma	Alpha Blocker – then – Beta blockade	Selective Beta Blocker (unopposed alpha agonism)
Benign Prostatic hypertrophy	Alpha-1 antagonist	Selective Beta Blocker (unopposed alpha agonism)

\*\*\*\*This review is NOT meant to be used instead of going to class or reading Robbins. I have bolded some things that are high yield and I remember being important concepts, but that in no way means that everything is included in here. Use this to help pick out what the important details out of Robbins are.

Other things to look out for in renal 2:

There are lots of drugs to know so don't put them off. Look at the charts. Acid/Base lecture, there are no power points and lots of reading assigned, however she goes over the main points that you need to know in the CIL- if you don't understand then go back and read in the book. If you don't plan on reading the chapters at all it is worth your time to flip through and look at charts within the chapters- there were questions from there.  
DO WEB PATH QUESTIONS!!