Lec 1

Azotemia

- ↑ in blood urea nitrogen (BUN) & creatine levels due to ↓ glomerular filtration rate (GFR)

* brochemical aspect

Uremia

- progression of azotemia to clinical manifestations *

* Azotemia + clinical mainfestation = uremia

- characterized by : failure renal excretion, metobolic & endocrine alterations, & 2ndry GI neuromuscular & cardio vascular manifestations

So... what are the clinical manifestations?

Nephritic Syndrome

- acute
- Proteinuria (<3.5g)
- Hematuria
- Azotemia
- RBC casts (smoky urine)
- Oliguria
- Hypertension
- generalized edema

PHAROH

Nephrotic Syndrome

- heavy proteinuria (>3.5g) → hypoalbuminemia
- Severe generalized edema → puffy eyes, face, abdomen, limbs

- hyperlipidemia & lipiduria

Asymptomatic Hematuria / Proteinuria

- mild glomerular abnormalities
- accidently discovered on routine urinalysis
  - Pt is asymptomatic
- may progress if left untreated

Rapidly Progressive Glomerulonephritis

"Crescentic glomerulonephritis"

- Rapid loss of Renal function
- manifestid by: microscopic hematuria, RBC casts, & moderate proteinuria

Acute Renal failure

- needs presence of oliguria* or anuria*
- recent onset of Azotemia from: glomerular, interstitial, vascular injury or acute tubular necrosis

Chronic Renal failure

- prolonged uremia symptoms
- the end result of all types of chronic Renal disease

Urinary Tract Infection (UTI)

- Symptomatic / asymptomatic
- bacteriuria & pyuria
- Classified based on magnitude & level of infection:

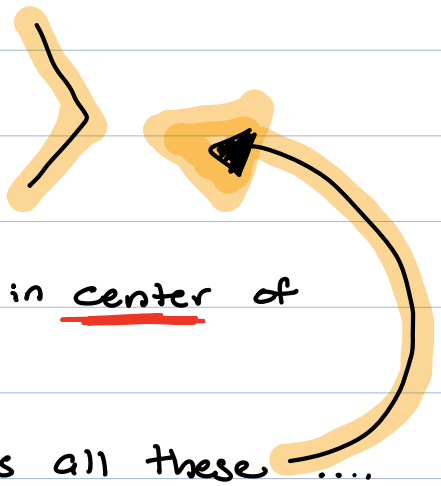
  Pyelonephritis → most severe or

  Cystitis → limited to bladder

Lec 2

Structure of Glomerulus

- Blood enters kidney through **Afferent arteriole** → then to **glomerulus** (anastomosing capillary network) → leaves through **efferent arteriole**
- The glomerulus sits in **Bowmans capsule**:
  1) internal layer made of **podocytes**
  2) outer layer made of **parietal epithelium**
  3) between the 2 layers is **bowmans space**
- the function of glomerulus is **filtration of blood** ... it sits in **bowmans space** where plasma ultra filtrate collects first
- in order for blood to get filtered, it must pass through the **filtration unit** → **glomerular capillary wall**:
  1) fenstrated endothelial cells
  2) basement membrane (GBM)
  3) podocyte foot processes
  4) mesangial cells → supportive cell in center of glomerular tufts btwn capillaries



- The **glomerular filtration membrane** has all these ... but the podocytes contain **nephrin** which form the **slit diaphragm** → regulates permiability of GBM
- foot processes are separated by **filtration slits**

Glomerular filtration characteristics

- highly permiable to water & small solutes
- not permiable to large or (-) charged molecules like albumin
- nephrin & podocin help maintain selective permiability of filtration barrier

Light Microscopy

- nth to say ... just lab image

Immunofluorescence Microscopy

- flourescein labled antibodies for Immunoglobulins (Ig G, M, A) compliment components (C3, C1q, C4), fibrin, kappa, & lambda light chains
- shows two patterns:
  - granular: antibody deposits as small or large dots
  - linear deposition

Electron Microscopy

- reveals presence of immune complexes that appear as electron dense deposits in one of 3 sites:
  1) mesangium
  2) subendothelial: btwn endothelium & GBM
  3) subepithelial: btwn outer GBM & podocytes

* deposition & pattern helps distinguish btwn different glomerulonephritis (GN)

Pathogenesis of Glomerular Disease

Antibody associated Injury

- detected by immunoflourescence

- injury to glomerulus by:
  1) deposition of circulating Ag-Ab complex in glomerulus
  2) Ab reacting w/ Ag in situ w/in glomerulus
  3) Ab against all glomerular cell components
- Granular immunofluorescence:
  1) deposition of Ag-Ab complex
  2) in situ Ab binding to Ag podocyte
- Linear immunofluoresence:
  1) in situ binding to Ag GBM

Non-Immune mechanism of glomerular injury

- Podocyte injury: effacement of foot processes that leads to proteinuria
  → direct mechanical injury to podocyte by toxins, inflimation, genetic mutations
- Nephron loss: progressive loss of functional volume of kidney
  → leads to partial or global sclerosis = ↓ in nephron mass = progressive glomerularsclerosis cycle

Lec 3

Nephrotic Syndrome

- Massive Proteinuria is hallmark (>3.5 gm/day), causes almost all other manifestations
- Hypoalbuminemia
- Generalized edema due to ↓ colloidal osmotic pressure from ↓ Albumin

- hyperlipidemia & lipiduria
- little to no Azotemia, no hypertension*, no hematuria

Pathogenesis

- injury to podocyte or GBM

Causes of Nephrotic Syndrome

Primary glomerular disease

- Minimal change disease, focal segmental glomerulosclerosis (FSGS), membranous nephropathy, membranoproliferative glomerulonephritis type 2
- varrying prevelence depending on age group
  - Minimal change 65% in children
  - FSGS 35% in Adults

Secondary Systemic disease w/ Renal manifestations

- diabetes, Amyloidosis, Systemic lupus, drugs (heroin), infection, malignancy, Miscellaneous
  - Bee sting

Minimal Change Disease (Lipoid Nephrosis)

- Benign, minimal changes to glomeruli apearance
- children
- unclear pathogenisis → maybe T-cell derived factors cause effacement of foot processes of podocytes

Morphology

LM: normal glomeruli, delicate BM

If: negative (immunoflouresceree)

EM: diffuse/uniform defacement of foot processes, no immune

deposite

Clinically

- good prognosis → 95% recover
- treatment w/ corticosteroids
- preserved renal function, selective proteinuria (albumin)
- Adults respond to treatment slower & get more relapse

Focal Segmental Glomerulosclerosis (FSGS)

- usually causes nephrotic syndrome
- is primary in 20-30% of NS
- 2ndry to AIDS, heroin abuse, nephron loss, mutations in nephrin protein

Pathogenesis

- unclear, maybe from podocyte injury, ↑ in GFR, or mutation in nephrin protein
- plasma proteins & lipids get trapped in foci of injury where sclerosis develops

Clinically

- poor prognosis & poor response to corticosteroids
- worse in adults

morphology

LM: Sclerosis in some* glomeruli & in segments*, collagen deposites stain blue

IF: negative

EM: effacement of foot processes

Collapsing glomerulopathy

- type of FSGS w/ poor prognosis
- Collapse of glomerular tufts & podocyte hyperplasia *
- can be idiopathic, associated w/ HIV, or drug induced

Membranous Nephropathy

- Subepithelial deposites of immune complexes w/ spikes * of basement membrane material between them
- 85% idiopathic w/ Ab's against podocyte antigen PLA2R

morphology

LM: diffuse thickining of GBM *, characteristic spikes around capillary loops

IF: postive * → IgG & compliment deposites

EM: Subepithelial deposites (spikes & dome) *

Clinically

- poor response to corticosteroids
- persistent proteinuria
- progresses to renal failure
- partial / complete remission of proteinuria 30% of cases

Lec 4

Nephritic Syndrome

Proteinuria < 3.5 gm

Hematuria

Azotemia

RBC casts

Oliguria

Hypertension

- inflimation of glomerulus → leukocyte infiltration → proliferation of glomerular cells → damage to capillary walls → ↓ GFR → oliguria, edema, Azotemia, hypertension

now lets talk about glomerular diseases that usually present as nephritic...

Membranoproliferative Glomerulonephritis (MPGN)

- abnormal **proliferation** & inflimation of glomerular cells
- can be nephritic, or combined nephritic-nephrotic

MPGN Type 1 (80% of cases)

- **deposition** of circulating immune complexes in the glomeruli leading to inflimation
- associated w/ hep B & C, Lupus, infected A-V shunts

MPGN Type 2 (dense deposite disease DDD)

- caused by excessive **compliment activation**
- **C3 nephritic factor** against C3 convertase resulting in C3 compliment consumption & **hypocomplimentemia**

morphology of both MPGN

LM: large globular glomeruli w/ inflimation in mesangial & endothelial cells w/ leukocytes. Thickened GBM called "**double contour or Tram track**" *
↳ caused by splitting of GBM

IF: type 1 - subendothelial IgG, C1q, C4 deposit
type 2 - C3 alone in GBM

EM: dense black deposit of C_3 in GBM of type 2

Clinically

- poor prognosis, no remission
- DDD has worse prognosis & recurs in renal transplant pts.
- progression to end stage renal failure

Acute Postinfectious Glomerulonephritis (PSGN)

- deposition of immune complex w/ inflimation & proliferation of glomerular cells & leukocytes

* not direct infection of kidney → post infectious

Pathogenesis

- immune mediated rxn against previous skin or pharynx infection
- Post streptoccocal GN (most common), also by pneumoccoci, & staphylococci
- Clinical manifestations of glomerular inflimation appear 1-4 weeks after recovery
- binding of antibodies to bacterial antigens implanted in GBM leading to inflamitory cascade

Morphology

LM: proliferation of endo/epithelium & mesangial cells w/ *neutrophils around capillary loops

IF: positive, IgG & C_3 within capillary walls

EM: characteristic Sub epithelial humps* in GBM

Clinically

- Acute ... mostly children

- gross hematuria & proteinuria
- low C3 serum levels during active phase
- anti streptolysin O ... if high, this means previous streptococci infection
- Recovery mainly in children

IgA Nephropathy

- most common cause of recurrent gross or microscopic hematuria
- Children & young adults
- hematuria 1-2 days after non specific URI, last several days, & recur every few months

pathogenesis

- abnormal IgA production or clearance

morphology

LM:

IF: mesangial IgA & C3 deposites
↳ characteristic & diagnostic

EM: deposites in mesangium

Lec 5

Cystic Kidney Diseases

- fluid filled space w/ wide range of clinical significance
- we will talk about 5 types

Simple Renal Cysts

- multiple or single lesion (1-5 cm)
- in Cortex *

- no clinical significance *
- discovered incidently b/c of hemorrhage & pain

Dialysis associated Cysts

- numerous * in cortex & medulla
- in pts w/ renal failure * & prolonged dialysis
- hematuria, flank pain, ↑ risk of carcinoma

how does it develop ?

Chronic inflimation / irritation → abnormal cell division → ↑ mutations → malignant cells

Autosomal Dominant Adult Polycystic Disease

- multiple bilateral * large cysts in cortex & medulla
- replaces renal parenchyma destroy all & function

etiology

- mutation in PKD1 * (most common) or PKD2 * both code for polycystin 1 or 2 respectively

mutation → cell division in Renal tubules → multiple cysts that move to cystic space

Clinically

- asymptomatic until 4th decade *
- flank pain, heavy dragging feeling *, mass, hemmorhage, obsruction by stones, hematuria

Complications

- Renal failure at age 50 (most common)
- hypertension, urinary infection, ancurysim in circle of willis

Autosomal Recessive Childhood polycystic Kidney

- tiny fusiform* cysts in medulla & cortex
- *early life: perinatal, neonatal, infintile, juvinile

* associated w/ liver cysts

- mutation in PKHD1* that codes fibrocystin*
- parenchyma replaced by white spaces & full of cysts from abnormal Renal tubule
- progress to chronic Renal failure

Medullary Cystic Disease

- cysts at cortico medullary junction* & begins in childhood
- 2 types:
  1) medullary sponge Kidney: common, innocent
  2) nephronophthisis medullary cystic disease complex: least common, worst variant
     - associated w/ Renal dysfunction & failure
     - polyuria & polydipsia, positive family history, progress to renal failure during childhood or early adult

Lec 6

Urinary Outflow Obstruction

Renal Stones (Urolithiasis)

- most common cause of obstruction outflow from stone formation at any level, most commonly in kidney
- common medical issue, can be asymptomatic (usually symptomatic in men)
- some familial tendency

- usually unilateral w/ variable sizes made of inorganic salt & organic matrix
- classified according to inorganic composition, each w/ different colors & morphologies

Types of stones

- Calcium oxalate (most common): Ca oxalate + Ca phosphate
- Struvite: magnesium amonium phosphate, large & smooth
- uric Acid stones
- Cystine stones (least common)

Causes

- Supersaturation* of constituents in urine
  - hypercalcuria → supersaturation of urine → precipitation → Calcium stones

* pt w/ calcium stones usually have hypercalcuria w/out hypercalcemia

- Presence of nidus* → central part of stone made of organic material provided by urates to incourage stone formation
- ↑ in PH* = struvite stones, ↓ in PH = uric acid stones
- bacterial infections* split urea into CO_2 & NH_3 to form NH_4 = ↑ PH

Hydronephrosis

- sudden dilation at any level proximal to the site of obstruction
- marked dilation of calyces or renal pelvis

- Atrophy (thin & small) parenchyma & cortex

Congenital Causes

- Atresia, valve formation, renal artery compression, renal ptosis & torsion of ureter

Acquired Causes

- foreign body, tumors, inflamation, neurogenic

Tubulointerstitial Nephritis

- inflammation of tubules & interstitium due to drugs, infection, metobolic disorder, injury, immune rxn
- can be acute or chronic w/ inflamitory infiltrates (eosinophils, neutrophils, macrophages, & lymphocytes)

Acute Drug Induced Interstitial nephritis

- associated w/ Synthetic penicillins & antibiotics, NSAID's, & diuretics that cause either type 1 or 4 hypersensitivity (T-cell mediated)
- leukocytes mentioned above invade interstitium & tubules, but not glomeruli
- symptoms (fever, eosinophillia, rash, hematuria) begin 2-40 days after drug exposure
- recovery develops after stopping the drug that caused the problem

Chronic (Analgesic) Drug Induced nephropathy

- Caused by taking large amount of analgesics over a long period of time leading to chronic interstitial nephritis w/ papillary necrosis

- Aspirin & Acetaminophen can cause damage by:
  1) Direct toxicity by covalent binding & causing oxidative damage leading to papillary necrosis & interstitial fibrosis
  2) inhibition of prostaglandin synthesis → vasoconstriction → ↓ medullar blood flow → capillary sclerosis → ischemia → & production of reactive Oxygen species causing necrosis & fibrosis
- clinical variability → progressive renal imparement & failure, hypertension, transitional cell carcinoma*

Acute Tubular Necrosis (ATN/ATI)

- a * reversible condition characterized morphologically by tubular epithelial damage and Clinically by ↓ Renal function

* most common cause of Renal failure

- acidosis, uremia, oliguria, & electrolyte abnormality
- 2 causes:

Toxic injury (nephrotoxic)

- by medication or poisons (heavy metal, gentamicin, organic solvents) leading to tubular necrosis & interstitial inflamation
- Sloughed cells caus obstruction of tubule → lack of basement membrane → backflow of toxic substances in tubular bed → ↓ GFR & urine output

Ischemic Injury (most common)

- associated w/ shock, trauma, septecemia, pancreatitis, blood transfusion ....

- Ischemia → vasoconstriction → ↓ GFR → acute Renal failure

morphology

- Sloughed & flattened epithelial cells w/ blebbing
- detachment from basement membrane

management

- Reversible w/ proper care
- repair & tubular regeneration → gradual improvement
- Supportive care
- pts w/ preexisting kidney disease dont fully recover