DISEASES OF THE TUBULES AND INTERSTITIUM

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Mechanisms of Tubulointerstitial Disease

- 2 general categories:
  - Ischemic/toxic (non-inflammatory)
    - Acute tubular necrosis
  - Inflammatory
    - Tubulointerstitial nephritis
    - Infection, allergic/drug-induced, systemic disease (eg. Sarcoid), etc.
Acute Tubular Necrosis

- Clinical-pathologic entity:
  - Clinical: ARF (#1 cause)
  - Oliguria / anuria
  - Minimal proteinuria & bland sediment
  - Increased FE Na
  - Pathology: tubular epithelial injury
    - Not necrosis

Ischemic ATN

- Occurs in setting of decreased renal blood flow / hypotension
  - Trauma/severe blood loss, CHF, septic shock
- Pathology
  - Gross: P & S
  - Degenerative changes
  - Subsequent regenerative changes
  - Most severe changes in proximal tub and mTAL (makes sense)

Clinical Phases of ATN

- Initiation
  - First 36 hours, dominated by initial event
- Maintenance
  - Up to 3 weeks, oliguric, dialysis required
- Recovery ("diuretic phase")
  - Increasing urine output – often substantial, electrolyte abnormalities
- Prognosis: > 90% recovery if survive initiating event
Nephrotoxic ATN

- Many toxins implicated
  - Heavy metals: Hg, Pb, gold, arsenic, ...
  - Organic solvents: CCl₄, ethylene glycol
  - Therapeutics
    - Antibiotics: gentamicin
    - Antifungals: amphotericin B
    - Chemotherapeutic agents: cisplatin
    - Bisphosphonate: zoledronate
    - Radiation & radiocontrast
    - Pigments: Hgb, Mgb
    - Abnormal levels of physiologic substances
    - Osmotic agents: mannitol

Nephrotoxic ATN

- Similar pathology to ischemic ATN
- Additional, toxin-specific findings:
  - Ethylene glycol
  - Osmotic agents/radiocontrast
  - Light chains
  - Hemoglobin/Myoglobin
- How does GFR decrease?
**Tubulointerstitial Diseases**

- Predominantly interstitial and tubular
  - secondarily involve glomeruli and vessels
  - low grade proteinuria
- A.K.A. Interstitial Nephritis
- Acute forms
  - inflammation, edema and tubular injury
- Chronic forms
  - inflammation, fibrosis, and atrophy
- Etiology: mainly infection or drug-induced

**Drug-Induced Interstitial Nephritis**

- Clinical: fever, eosinophilia, rash, & RI
  - Occurs 1-2 weeks following exposure
  - sterile pyuria (with eosinophils)
- Hypersensitivity reaction to drug
  - not dose related
- Resolves within weeks of withdrawal
  - Definitive proof: recurs with re-exposure

**Drug-Induced Interstitial Nephritis**

- Causative agents:
  - Antibiotics: synthetic penicillins, i.e. methicillin, ampicillin
  - Other antibiotics: i.e. rifampin, sulfonamides, vancomycin
  - NSAIDs
  - Diuretics: i.e. thiazides
  - Phenytoin
  - Others...

**Drug-Induced Interstitial Nephritis**

- Pathogenesis: cell-mediated hypersensitivity reaction (T’s)
- Pathology
  - interstitial inflammation & edema
  - EOSINOPHLS
  - Tubulitis
  - +/- granulomas
**NSAIDs**
- Inhibit COX
- Multiple patterns of renal disease
  - Acute interstitial nephritis
  - Acute tubular necrosis
    - Loss of PG vasodilation / precip ATN in the setting of volume depletion
  - Minimal change disease (rarely MG)
  - Papillary necrosis
  - Same nephrotoxicity for Cox-2 inhibitors

**Acute Pyelonephritis**
- Acute suppurative infection of kidney
- Clinical: back pain, fever, pyuria, +/- RI
  - Urine cultures: confirmation / Ab sensitivity
- Route of infection
  - ascending > hematogenous
  - ascending starts in bladder as UTI (F>M)
  - hematog: septic emboli, bacteremia (F=M)
- Organisms
  - 85% gram negative bacilli (#1 E. coli)
  - fecal flora

**Acute Pyelonephritis**
- Increased risk of ascending infection in three clinical settings
  - Obstruction: BPH, tumors, pregnancy, neurogenic bladder (DM)
  - Instrumentation
  - Vesicoureteral reflux
    - 50% UTI’s in 1st year of life
    - congenital anomaly: intravesical portion of ureter lacks normal oblique course that prevents reflux

**Acute Pyelonephritis**
- Gross: normal size, +/- coalescent abscesses
- Micro: severe inflammation, PMN's
  - Microabscesses
  - PMN casts & tubulitis
- Distribution:
  - Ascending: originates near medulla
  - Hematogenous: cortical
Chronic Pyelonephritis

**Definition:** chronic renal disorder with scarring, inflammation, and deformity of calyces/pelvis (ascending*)

**Gross:** shrunken
- Irregular, asymmetric broad/flat scars (U*)
- Papillary blunting and calyceal deformity

**Micro:**
- Disproportionate tubulointerstitial scarring
- Atrophic tubules with colloid casts (*"thyroidization"*)
- Chronic inflammation (not PMN's)

**Clinical**
- Insidious onset of RI
- +/- HTN, mild proteinuria, decreased urinary concentration, culture neg
- Rarely follows "usual" acute pyelo
- More common with persistent obstruction or VUR
- +/- awareness of acute episodes
- Rx: relieve obstruction / correct VUR, antibiotics as indicated
Voiding cystourethrogram

Vesicoureteral reflux (VUR):
- Congenital
- 50% UTIs < 1 yo
Tubulointerstitial nephritis in systemic disease

- Sjogren’s syndrome
  - Systemic autoimmune disease
  - Frequent overlap with SLE or RA
  - Keratoconjunctivitis (dry eyes)
  - Xerostomia (dry mouth)
- Sarcoidosis
  - Multisystem granulomatous disease
  - Lungs, LNs, less commonly kidneys

Papillary Necrosis

- Obstructive pyelonephritis
- Sickle Cell Anemia
  - medulla leads to sickling
  - sickling leads to medullary ischemia
- Analgesic abuse (phenacetin*)
  - increased risk with combinations
  - direct toxicity and ASA-induced PG deficiency
- Diabetes Mellitus
Cystic Diseases of Kidney

- Simple cysts
  - common post-mortem finding
  - as with all cysts, r/o RCC
- Dialysis-associated renal cysts
- Autosomal Dominant Polycystic kidney disease (mainly adults)
- Autosomal Recessive Polycystic kidney disease (children)

Autosomal Dominant Polycystic Kidney Disease

- Common: 1/500-1/1000 live births
- Genes: Pkd1 on 16p; Pkd2 on 4
- Clinical:
  - typical onset at 20-40 years
  - HTN, RI, hematuria, and pain
  - 10% U.S. ESRD population
- Polycystic liver disease in 40%
- Cerebral artery berry aneurysms

Autosomal Dominant Polycystic Kidney Disease

- Gross: massively enlarged & cystic
- Micro: numerous cysts
  - predominantly distal tubular origin
- Etiology:
  - two-hit hypothesis
  - dysregulated, clonal tubular cell growth
### Autosomal Dominant Polycystic Kidney Disease

- Rare
- Perinatal presentation (most)
- Typically rapid progression to ESRD
- Bilateral (like ADPKD)
- Liver involvement in majority
  - liver cysts & bile duct proliferation
  - if survive infancy: congenital hepatic fibrosis (cirrhosis)