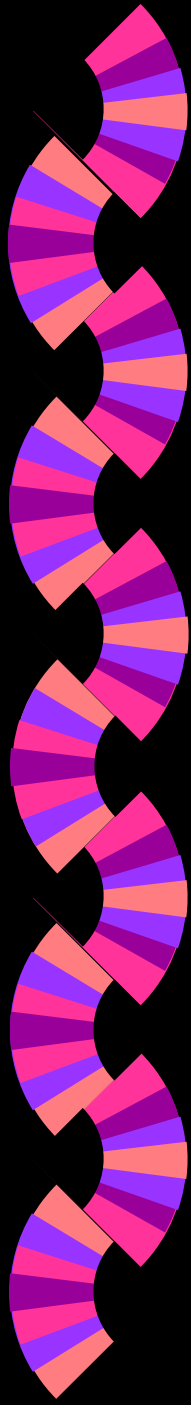


# Acute Renal Failure

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# Functional Classification of Acute Renal Failure (ARF)

- Hemodynamic ARF ( $\approx 30\%$ )
- Parenchymal ARF (65%)
  - Acute tubular necrosis (55%)
  - Acute glomerulonephritis ( $\approx 5\%$ )
  - Vasculopathy (3%)
  - Acute interstitial nephritis ( $\approx 2\%$ )
- Obstruction ( $\approx 5\%$ )



# Differentiating ARF vs. Chronic Renal Failure (CRF)

- 1) History
- 2) Oliguria = ARF; acute CRF decompensation
- 3) Renal ultrasound
  - Normal or large = acute
  - CRF – small (unless PKD, diabetes, amyloid)
- 4) ARF = Unstable azotemia ( $\uparrow$  or  $\downarrow$  over days)
- 5) Anemia – unreliable for ARF vs. CRF
- 6)  $\uparrow$ PO<sub>4</sub>,  $\uparrow$ K<sup>+</sup>, metabolic acidosis,  $\uparrow$ uric acid – little diagnostic value
- 7) Urinalysis – no value unless normal suggesting pre-renal azotemia



# Pre-Renal Azotemia

## Definition:

A reduction in glomerular filtration rate (GFR) due to a ↓ glomerular capillary pressure

## Diagnosis:

Characteristic clinical setting and urinary findings

Response to the correction of the presumptive pre-renal state



# Pre-Renal Azotemia: Causes

- 1) ↓ cardiac output
  - CHF
  - Intravascular volume depletion
- 2) Normal Cardiac Output
  - Selective renal vasoconstriction (NSAIDs, ↑Ca<sup>++</sup>)
  - ACE (-) in patients with pre-existent renal vascular disease
  - Hepatorenal syndrome
- 3) ↑ cardiac output
  - Hepatorenal syndrome
  - Sepsis syndrome



# Pre-Renal Azotemia: Renal Manifestations

- 1)  $\text{Na}^+$  avidity
- 2) Relatively normal urinalysis
- 3) Relatively normal serum bicarbonate
- 4) High BUN/creatinine ratio (not always)
- 5) High urine osmolality (typically  $>600$  mosm/kg)



# Pre-Renal Azotemia: Confounding Diagnostic Variables

- 1) A low urine  $\text{Na}^+$  is not unique – Found in:
  - Non-oliguric ATN, especially contrast-induced
  - Early urinary tract obstruction
  - Acute glomerulonephritis
- 2) Diuretic use can obfuscate the urine  $\text{Na}^+$  and urine osmolality
- 3) Jaundice – muddy brown granular casts
- 4) Poor dietary intake lowers the BUN/Cr ratio



# Hepatorenal Syndrome (HRS)

Definition: “Irreversible” pre-renal azotemia in the setting of end-stage hepatic disease

Pathogenesis:

- 1) Unrelenting renal vasoconstriction induced by unknown mediators
- 2) Renin/angiotensin, endothelin, NO, prostanooids, endotoxin, ↑sympathetic tone all implicated; none proven and may reflect secondary phenomena





# HRS: Differential Diagnosis

- 1) Rule out volume depletion by volume challenge
- 2) Rule out combined hepatic and renal epithelial injury
- 3) Rule out ATN (which is common in the HRS patients)



# HRS: Therapy

- 1) Portal-systemic shunts: acute, but not long-term benefits
- 2) Paracentesis: no proven benefit; may precipitate ARF
- 3) Vasodilator therapy: no proven benefit
- 4) Dialysis:
  - IF a possibility of hepatic functional recovery
  - IF there is a likelihood of ATN (high urine Na<sup>+</sup>; urine sediment not helpful)
- 5) Hepatic transplantation



# Obstructive Nephropathy

- 1) Incidence:  $\approx$  5-10% ARF cases
- 2) Causes: in part segregates according to age:
  - Children: anatomic (urethral valves, ureteral-vesicle or ureteral-pelvic stenoses)
  - Young adults: stones; retroperitoneal processes (tumor, infections)
  - Elderly: GU tumors (bladder, cervical); BPH



# Obstructive Nephropathy

## 3) Pathogenesis:

- Acute  $\uparrow$  in intraluminal pressure
- 2° renal vasoconstriction (TXAII)
- “Disuse atrophy”
- Inflammatory cell mediated tubulointerstitial injury

## 4) Symptoms:

- Pain (> common if acute;  $\uparrow$  with solute load)
- Abnormal urine flow – absolute anuria (R/O acute GN, cortical necrosis), oliguria, or non-oliguria
- Hematuria



# Urinary Tract Obstruction Diagnosis

History: most often suggests the diagnosis

- 1) Urinalysis
  - RBCs, minimal proteinuria, pyuria, bacteriuria
  - Urine Na<sup>+</sup>: low (early); high (late)
- 2) Foley catheter (excludes only bladder outlet obstruction)



# Urinary Tract Obstruction Diagnosis

## 3) Renal Ultrasound (95% accurate)

### ✓ Possible false negatives:

- Early obstruction (<48 hours)
- Retroperitoneal fibrosis (prevents calyceal dilation)
- Concomitant acute tubular necrosis

### ✓ Possible false positives:

- Vesicoureteral reflux
- Long-standing, physiologically insignificant urinary obstruction



# Urinary Tract Obstruction Diagnosis

## 4) Renal CT:

- Obtain if high index of suspicion with dubious ultrasound
- Can help localize the site of obstruction

## 5) Retrograde pyelogram:

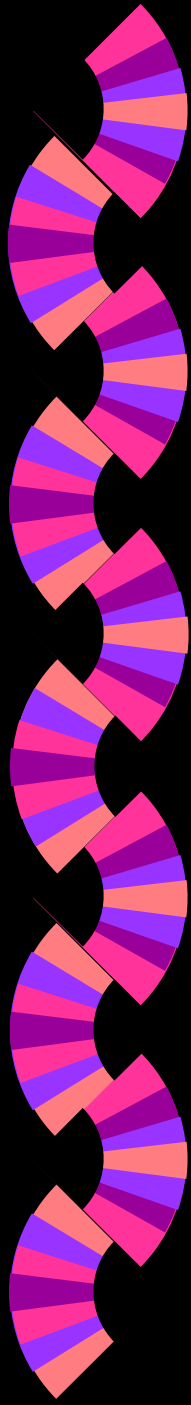
The gold standard: diagnostic and often leads to immediate therapy (i.e., stints)



# Urinary Tract Obstruction: Treatment and Prognosis

- 1) Drainage
  - Foley catheter
  - Retrograde pyelography/stints
  - Percutaneous nephrostomy
- 2) Treat Underlying Disease
- 3) Prognosis depends on:
  - Chronicity (relatively good if < 1 week; little if > 12 weeks; but highly variable)
  - Coincidental diseases (e.g., UTI)
- 4) Rate of recovery
  - Much within 48-72 hours
  - Most within 2 weeks





# Acute Glomerulonephritis (GN) / Glomerulopathy

- 1) Incidence:  $\approx$ 5-10% of cases of ARF
- 2) Setting:
  - Idiopathic
  - Post-infectious
  - Collagen vascular disease
  - Flair of chronic GN (e.g., IgA nephropathy)



# Acute GN

## 3) Pathogenesis

- Direct interference with glomerular capillary function
- Altered tubular function
  - Protein cast formation
  - Tubular injury 2° glomerular bleeding
  - Potential hemodynamic component to the ARF (diuretics, NSAIDs, ACE inhibitors)
- “Nephrosarca”: ARF in minimal change disease



# Acute GN

## 4) Diagnosis:

- RBC casts (not always)
- Heavy proteinuria (not always, e.g. IgA nephropathy)
- Lack of other compelling diagnoses
- Renal biopsy



# Vasculopathy: Unexplained MULTISYSTEM Disease

## 1) Causes:

- Thrombotic microangiopathy (HUS/TTP)
  - Idiopathic HUS/TTP
  - Collagen vascular disease (e.g., SLE)
  - Chemotherapy/radiation therapy (particularly bone marrow transplants)
  - Cyclosporine: renal transplant rejection
  - Infectious (E.coli, Shigella enterocolitis, HIV)
- Polyarteritis nodosa
- Atheroembolic renal disease



# Vasculopathy: Unexplained MULTISYSTEM Disease

## 1) Diagnosis:

- HUS/TTP:
  - Schistocytes on peripheral smear
  - Absent/low haptoglobin
  - High LDH
  - $\pm$  low platelets
- Polyarteritis: arteriography, biopsy  
[U/A in both may show hematuria, RBC casts, proteinuria]
- Atheroemboli: characteristic clinical presentation



# Atheroembolic Renal Disease

- 1) Setting: Diffuse, erosive atherosclerosis
- 2) Triggers:
  - Aortic manipulation (angiography, surgery, blunt trauma)
  - Anticoagulation (prevents healing of ulcerative plaques)
- 3) Pathogenesis
  - Microscopic atheromatous plaques shower renal vasculature
  - Incites progressive obliterative arteropathy (intimal proliferation, giant cells, eosinophils)



# Atheroembolic Renal Disease

## 4) Renal manifestations (early, can mimic contrast-induced ATN)

- Acute renal failure
- Mild acute renal dysfunction → ESRD over weeks/months
- U/A:  $\pm$  RBCs, mild proteinuria, occ. eosinophils

## 5) Systemic Manifestations:

- Livedo reticularis; cutaneous infarcts
- Multiorgan injury (eyes, mesentary, etc.)
- Hypocomplementemia
- eosinophilia



# Atheroembolic Renal Disease

## 6) Diagnosis:

- Clinical presentation usually sufficient
- Renal biopsy: 75% yield diagnosis
- Biopsy involved skin

## 7) Treatment:

- Supportive only





# Acute Interstitial Nephritis

## Causes

- 1) Allergic (drugs)
- 2) Infectious
  - Bacterial (Legionella, leptospirosis, scarlet fever, diphtheria)
  - Viral (CMV, hantavirus, infectious mononucleosis, measles, HIV)
  - Protozoan (toxoplasmosis)
- 3) Autoimmune
  - Sarcoidosis, SLE, Sjogren's syndrome, idiopathic
- 4) Toxins – Chinese herb nephropathy
- 5) Infiltrative – leukemia, lymphoma



# Acute Interstitial Nephritis

## Clinical Presentation

- 1) Incremental azotemia (ARF) temporally related to offending agent (drug, infection, toxin exposure)
- 2) Fever: Allergic and infection-related cases
- 3) Rash (Allergic: selected infectious and autoimmune cases)
- 4) Eosinophilic (Allergic)



# Acute Interstitial Nephritis

## Clinical Presentation

### 5) Urinalysis

- Leukocytes/WBC casts
- Eosinophiluria (allergic)
- Hematuria (micro or gross)
- Minimal/mild proteinuria (rarely nephrotic range, except with NSAIDs)

### 6) + Gallium scan



# Causes of Drug-Induced AIN

- 1) NSAIDs (all classes, cross reactions possible)
- 2) Antibiotics
  - Penicillins
    - Methicillin (1-20% patients)
    - Ampicillin, amoxicillin, carbenicillin, etc.
    - Cephalosporins – cephalothin, cephalexin, cefoxitin (cross reactions possible, rare)



# Causes of Drug-Induced AIN

- Quinolones (ciprofloxacin)
- Anti-tuberculous agents – rifampin, INH, ethambutol
- Sulfonamides: antibiotics (Bactrim); diuretics (furosemide, thiazides)
- Miscellaneous: over 200 drugs implicated; most not proven
  - Allopurinol, cimetidine, dilantin (proven)



# NSAID-Associated Interstitial Nephritis

- 1) Onset: Days to months after initiating therapy
- 2) Presentation:
  - Heavy proteinuria/nephrotic syndrome (85% ARF cases)
  - ARF without heavy proteinuria
  - Fever, rash, eosinophilia uncommon



# NSAID-Associated Interstitial Nephritis

## 3) Diagnosis:

- Characteristic presentation
- Consider other NSAID associated renal syndromes (hemodynamic and ischemic ARF)
- Consider trial of drug withdrawal prior to biopsy
- Biopsy
  - Interstitial edema, infiltration with lymphocytes, rarely granulomas
  - Negative immunofluorescence
  - Foci of ATN



# NSAID-Associated Interstitial Nephritis

## 4) Treatment:

- Stop agents
- ?? Benefit of steroids

## 5) Prognosis:

- Generally reversible after weeks (up to a year)
- May cause chronic renal insufficiency/ESRD (unlike NSAID-induced hemodynamic ARF)





# Urinary Eosinophils: Diagnostic Utility

- 1) Suggestive of allergic interstitial nephritis
- 2) False Negatives
  - NSAID associated AIN
  - Use of Wright stain, not Hansel stain
- 3) False Positives
  - UTI, especially prostatitis
  - RPGN – RBCs, heavy proteinuria
  - Atheroembolic renal disease
- 4) Significance
  - 1-5% considered positive
  - Consistent with but not diagnostic of AIN
  - Interpret in context of clinical setting



# Acute Interstitial Nephritis

## Treatment

- 1) Treat underlying disease
  - Infections
  - Withdraw offending agent
- 2) Trial of corticosteroids, particularly for allergic interstitial nephritis
  - 1mg/kg/day or 2mg/kg/day QOD
  - If no response in 1-2 weeks, biopsy
  - If no response in 4-6 weeks, cyclophosphamide
- 3) Results
  - Reversal of renal failure
  - No randomized trials proving steroid efficacy



# Chinese Herb Nephropathy

- 1) Chinese herbs for weight reduction
  - Aristolochic acid has been implicated in some, not all cases
  - Some contain NSAIDs
- 2) Only some users affected
  - Women > Men
  - Batch to batch variation
  - Individual variations in metabolism?
- 3) Presentation/course
  - Often rapidly progressive renal dysfunction
  - May → irreversible renal failure even after withdrawal



# Chinese Herb Nephropathy

## 4) Diagnosis:

- Clinical setting
- Typical tubulointerstitial disease presentation (little proteinuria, no RBC casts)
- Biopsy: tubular destruction, interstitial inflammation/fibrosis: glomerulosclerosis

## 5) Therapy:

- Withdraw agents
- Steroids may be efficacious (1mg/kg x 1 month; followed by taper)



# Intratubular Obstruction Associated ARF

## A. Crystalluria associated ARF

### 1) Ethylene glycol (oxalate crystals)

- Osmolar gap: measured – calculated >10-15
- Oxalate crystals in urine
- Severe anion gap metabolic acidosis
- Encephalopathy (drunk)
- Pulmonary infiltrates/CHF
- Confirm by blood level (start treatment with a presumptive diagnosis alcohol/dialysis)



# Intratubular Obstruction Associated ARF

## A. Crystalluria associated ARF

### 2) Acute urate nephropathy

- Diagnosis: urate  $> 18\text{mg/dL}$  due to overproduction, not underexcretion
- Correct clinical setting
  - Chemotherapy
  - Spontaneous tumor lysis syndrome (HIV-associated Burkitt's)

### 3) Medication-induced intratubular precipitation

- Acyclovir (high dose)
- Methotrexate (high dose)
- Sulfonamides (rare; more likely to cause AIN)



# Intratubular Obstruction Associated ARF

## B. Cast associated ARF

- Multiple myeloma (light chain-proteinuria-associated ARF)

## C. Pathogenesis of tubular “obstruction” associated ARF

- Intratubular destruction
- Nephrotoxic proximal tubular necrosis (e.g., ethylene glycol: tumor lysis products, light chains)



# Ischemic Acute Renal Failure

- 1) Definition: Onset of ARF in the aftermath of relatively modest hypertensive events
- 2) Morphology
  - Sporadic foci of tubular necrosis (<10% cells)
  - May involve late proximal tubule, or Henle's thick ascending limb
  - Sloughing of viable cells into the tubular lumen
  - Vascular congestion/neutrophil accumulation





# Ischemic Acute Renal Failure

## 3) Pathogenesis of filtration failure:

- Tubular obstruction
- Backleak
- Renal vasoconstriction (2° obstruction)

## 4) Course: Reversibility is its hallmark

## 5) Treatment

- Re-establish hemodynamic stability
- Early renal vasodilator/diuretic therapy to abort ARF
- Supportive management/ early or “prophylactic” dialysis



# Common Nephrotoxins

## 1) Endogenous Nephrotoxins

- Myoglobin/hemoglobin
- Light chains
- Tumor lysis syndrome

## 2) Exogenous Nephrotoxins

- Antimicrobial agents
  - Aminoglycosides
  - Amphotericin B
  - Acyclovir
  - Foscarnet
  - ?? Pentamidine; vancomycin



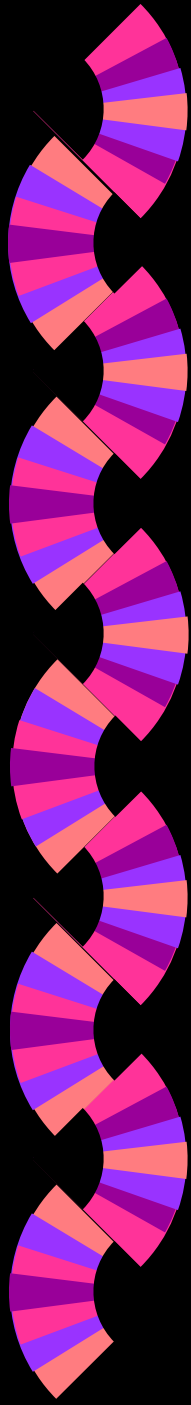
# Common Nephrotoxins

## 2) Exogenous Nephrotoxins

- Chemotherapeutic agents
  - Cisplatin
  - High dose methotrexate
  - Streptozocin
  - Mitomycin C
- Heavy metals
- Radiocontrast agents
- Ethylene Glycol

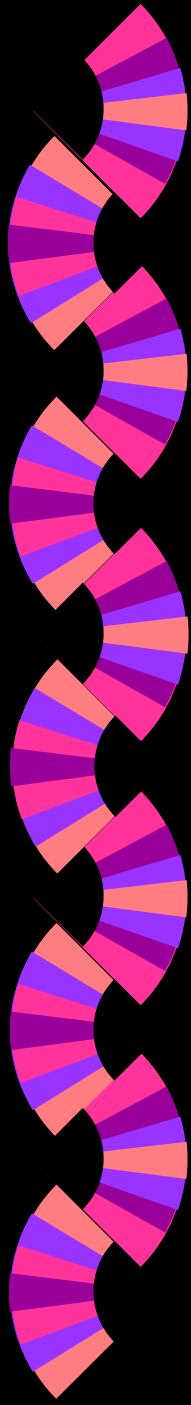
## 3) Vasoactive ARF

- ACE inhibitors, NSAIDs, CSA/ FK-506, IL-2, endotoxin



# Aminoglycoside Nephrotoxicity

- 1) Incidence: Dependent on duration of treatment (10% and 40% after 7 and 14 days, respectively)
- 2) Clinical manifestations
  - Generally non-oliguric ARF
  - $\downarrow\text{Mg}^{++}$ ,  $\downarrow\text{K}^{+}$ , glycosuria
- 3) Mechanisms: Proximal tubular active transport  $\rightarrow$  lysosomal overload  $\rightarrow$  phospholipidosis altered phospholipase signalling mechanisms: *Proximal tubule necrosis*



# Aminoglycoside Nephrotoxicity

## 4) Risk factors:

- Dose and duration
- Volume depletion/  $\downarrow$ GFR (prior renal disease; old age)
- Other nephrotoxins, concomitant ischemia

## 5) Prevention

- Appropriate dosing for GFR
- Remove reversible factors
- QD dosing if possible
- Stop ASAP
- Monitor trough levels (but may only represent insipient renal failure, rather than prevent it)



# Cyclosporine Nephrotoxicity

## 1) Spectrum

- Acute vasomotor nephropathy
- Hemolytic Uremic Syndrome
- Chronic obliterative arteriopathy/stripped interstitial fibrosis

## 2) Diagnosis

- Nothing definitive other than clinical setting and response to dose/withdrawal
- Drug levels only help to support the diagnosis

## 3) Prevention

- Watch drugs that ↑ cyclosporine level
- Monitor drug trough levels (weak guide)
- Possible benefit of calcium channel blockers



# Management of ARF

## 1) Attempt to prevent ARF:

- Reverse volume depletion/renal ischemia
- Stop nephrotoxic agents if possible

## 2) Attempt to abort ARF:

- Usually only possible with ischemia
- Vasodilator therapy (dopamine  $\pm$  ANF)
- Diuretic therapy



# Management of ARF

## 3) Conservative management:

- Avoid nephrotoxins
- Fluid/electrolyte balance
- Treat underlying illness (the prime determinant of recovery)
- Nutritional support

## 4) Dialysis:

- Prophylactic treatment (BUN<120)
- Biocompatible membranes may be preferable
- Intermittent vs. continuous (no compelling evidence favoring one; individualize treatment)