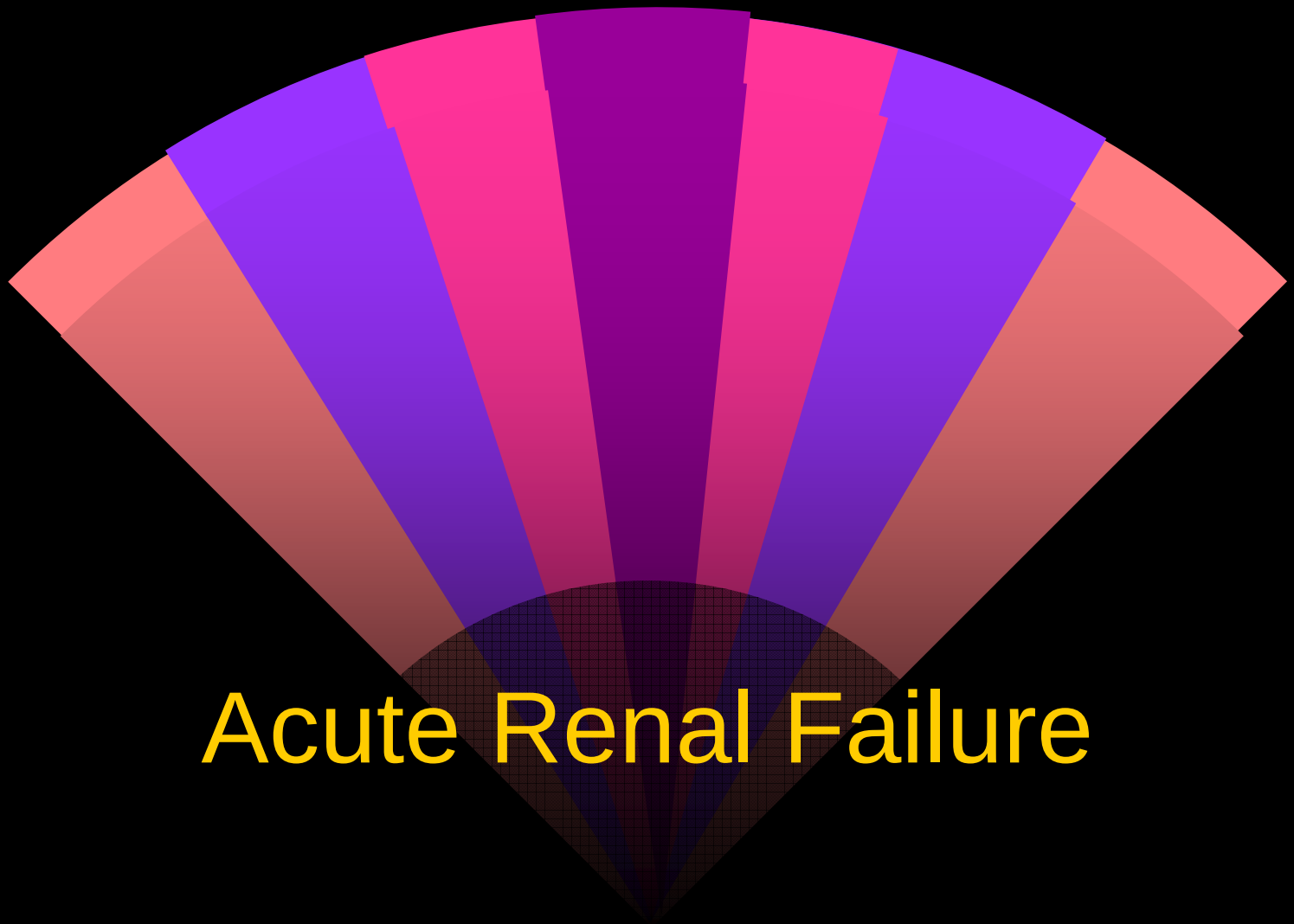

Acute Renal Failure

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Functional Classification of Acute Renal Failure (ARF)

- Hemodynamic ARF (≈30%)
- Parenchymal ARF (65%)
  - Acute tubular necrosis (55%)
  - Acute glomerulonephritis (≈5%)
  - Vasculopathy (3%)
  - Acute interstitial nephritis (≈2%)
- Obstruction (≈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 (↑ or ↓ over days)
5) Anemia – unreliable for ARF vs. CRF
6) ↑PO4, ↑K^+, metabolic acidosis, ↑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++)
   - ACE (-) in patients with pre-existent renal vascular disease
   - Hepatorenal syndrome
3) ↑ cardiac output
   - Hepatorenal syndrome
   - Sepsis syndrome

Pre-Renal Azotemia: Renal Manifestations

1) 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 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 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/angiotensis, endothelin, NO, prostanoids, 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^+; urine sediment not helpful)
5) Hepatic transplantation

Obstructive Nephropathy

1) Incidence: ≈ 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 ↑ in intraluminal pressure
   - 2° renal vasoconstriction (TXAII)
   - "Disuse atrophy"
   - Inflammatory cell mediated tubulointerstitial injury
4) Symptoms:
   - Pain (> common if acute; ↑ 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^+: 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 calcyeal 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: ≈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
     - ± 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: ± 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) Treament:
   - 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 lympocytes, 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, especialy 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 InterstitialNephritis 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 real 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 progresive real dysfunction
   - May $\rightarrow$ irrevesible 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 > 18mg/dL due to overproduction, not uderexcretion
- Correct clinical setting
  - Chemotherapy
  - Spontaneous tumr 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
   - $\downarrow Mg^{++}$, $\downarrow K^{+}$, glycosuria
3) Mechanisms: Proximal tubular active transport$\rightarrow$lysosomal overload $\rightarrow$phospholipidosis altered phospholipase signallingmechanisms: *Proximal tubule necrosis*

Aminoglycoside Nephrotoxicity

4) Risk factors:
   - Dose and duration
   - Volume depletion/ ↓GFR (prior renal disease; old age)
   - Oter 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 arteriolopathy/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 ± 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)