Acute Renal Failure

Introduction

- Incidence can range from 7% to 50% of ICU patients
- Abrupt decline in kidney function (hours to weeks)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum Creatinine Criteria</th>
<th>Urine Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cr inc by 1.5-2x or Cr inc by 0.3 mg/dL</td>
<td>&lt;0.5 mL/kg/hr for 6 h</td>
</tr>
<tr>
<td>2</td>
<td>Cr inc by 2-3x</td>
<td>&lt;0.5 mL/kg/hr for 12 h</td>
</tr>
<tr>
<td>3</td>
<td>Cr inc by more than 3x or Cr inc of 0.5 with baseline Cr ≥4 mg/dL</td>
<td>&lt;0.3 mL/kg/hr for 24 hr (or anuria for 12 h)</td>
</tr>
</tbody>
</table>

- Use criteria after fluid challenge in most cases

Causes

- Pre-renal
  - Volume depletion
  - Cardiac
  - Redistribution
  - Hepatorenal syndrome
    - Cirrhosis with ascites
    - Serum creatinine > 1.5 mg/dL
    - Not improved by holding diuretics and giving albumin challenge (1g/kg for 2 days)
    - Absence of shock and nephrotoxins
    - No intrinsic renal disease i.e. no proteinuria (<500 mg/day) or microhematuria (< 50 RBCs)
  - NSAIDS
  - ACE-inhibitor

- Post-renal
  - Consider obstruction in every patient with ARF
  - Sites of obstruction
    - Bladder neck obstruction
    - Bilateral ureters
  - Urine volume is variable. Patients can be asymptomatic and with no change in urine output.
  - Diagnose with renal USG, straight catherization, or bladder scan
- **Intrinsic**
  - **Vascular**
    - Vascular occlusion
    - Atheroembolic disease
      - Eosinophilia, low complement
      - Can see multi-organ dysfunction, livedo reticularis, blue toes
      - Generally irreversible
    - Thrombotic microangiopathy
      - Fibrin deposition in the microvasculature, intravascular hemolysis, thrombocytopenia, organ dysfunction
      - Associated disorders: Malignant HTN, HUS/TTP, Scleroderma renal crises, HELLP, drugs (tacrolimus, cyclosporine, mitomycin, Plavix)
  - **Glomerular:** RPGN
    - Systemic findings
    - Proteinuria, RBC, RBC casts
    - Need renal biopsy
  - **Interstitital**
    - Fever, rash, eosinophilia (<10% of patients)
    - Drugs: PCN, cephalosporins, diuretics, NSAIDS, Dilantin
    - Usually reversible upon withdrawal of the offending agent
    - Consider steroids if prolonged and severe
  - **Tubular**
    - Crystal induced
      - Uric acid in tumor lysis
      - Oxalate (ethylene glycol)
      - Methotrexate
      - Acyclovir
      - Sulfonamides
      - Indinavir
    - Osmotic nephrosis
      - Sucrose
      - Mannitol
      - Dextran
      - IVIG
    - Radiocontrast agents
      - Onset of oliguria within 24 hrs
      - PEARL: peak creatinine in 4-5 days followed by recovery in the majority
      - Differential diagnosis: atheroembolic disease
      - Prevent with hydration
    - **ATN**
• Ischemic: all pre-renal causes
• Endogenous toxins:
  o Heme Pigment Induced
    ▪ Rhabdomyolysis
    ▪ Intravascular hemolysis
    ▪ Dipstick +++ for blood with no RBCs
  o Myeloma (cast) nephropathy
    ▪ Light chains form complexes with Tamm-Horsfall mucoprotein, leaving to tubular casts
    ▪ PEARL: urine dipstick negative for protein (no albumin) but high protein-to-creatinine ratio
    ▪ Diagnosed with SPEP, UPEP, serum free light chains
    ▪ Treat with hydration, chemo, plasmapheresis
    ▪ Other forms of myeloma kidney disease include hypercalcemia causing a drop in GFR and glomerular disease resulting from light chain deposition (MPGN, cryoglobulinemia, and amyloidosis)
• Exogenous:
  o Antibiotics
  o Contrast
  o Chemotherapy
  o Org. solvents, heavy metals

Workup

• Every patient should have a history, physical, urine analysis, and kidney ultrasound
• Urinalysis and urine chemistries

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Dipstick</th>
<th>Micro</th>
<th>Uosm</th>
<th>FeNa+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-renal</td>
<td>Minimal protein</td>
<td>Negative</td>
<td>&gt;500</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>ATN</td>
<td>Tubular protein</td>
<td>Granular casts</td>
<td>&lt;350</td>
<td>&gt;1%</td>
</tr>
<tr>
<td>AIN</td>
<td>Tubular protein</td>
<td>WBC&gt;RBC</td>
<td>&lt;350</td>
<td>&gt;1%</td>
</tr>
<tr>
<td>GN</td>
<td>Protein and blood</td>
<td>RBC +casts</td>
<td>&gt;500</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Post-renal</td>
<td>Minimal protein</td>
<td>Varies</td>
<td>Varies</td>
<td>Varies</td>
</tr>
</tbody>
</table>
• Urinary indices in oliguric ARF

<table>
<thead>
<tr>
<th>Urinary Index</th>
<th>Pre Renal</th>
<th>ATN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmolality (mOsm/kg)</td>
<td>&gt;500</td>
<td>&lt;450 (&lt;350)</td>
</tr>
<tr>
<td>Sodium (meq/L)</td>
<td>&lt;20</td>
<td>&gt;40</td>
</tr>
<tr>
<td>FeNa</td>
<td>&lt;1%</td>
<td>&gt;2%*</td>
</tr>
<tr>
<td>FE urea</td>
<td>&lt;35%</td>
<td>50-65%</td>
</tr>
</tbody>
</table>

*Except: contrast, heme-pigment ATN, AGN

Glomerulonephritis
• Scope of the Problem
• Definitions
  ○ Overlap in terminology; nephritic and nephrotic syndromes not dichotomous
  ○ Key criterion is intraglomerular inflammation, suggested by an active urinary sediment containing red cells (particularly dysmorphic cells), +/- white cells
  ○ Clinical syndromes vary widely
• GN: Clinical Presentations
  ○ Asymptomatic Hematuria
    ■ Can be micro or macroscopic
    ■ Often proteinuric (< 1.5 g / day)
    ■ Common presentation of IgA nephropathy, the most common cause of GN worldwide (hematuria in setting of concomitant respiratory / GI infection), 20-40% of which progress to ESRD
  ○ Acute Glomerulonephritis
    ■ Macroscopic hematuria, oliguria, AKI, and fluid retention (edema / hypertension)
    ■ Common presentation of post-infectious glomerulonephritis; symptoms develop 1-12 weeks after infection, 0-20% progress to ESRD
  ○ Rapidly Progressive Glomerulonephritis
    ■ Hematuria, proteinuria, red-cell casts and acute decline in GFR progressing to ESRD within days to weeks
    ■ Often insidious onset with nonspecific symptoms / signs (fatigue, edema)
    ■ 4 major types
      • I: Anti-GBM disease
      • II: Immune complex mediated
- III: Pauci-immune
- IV: Idiopathic
  - Empiric glucocorticoids are mainstay of therapy while searching for underlying etiology
  - Nephrotic Syndrome
    - Discussed in more detail in separate talk, however, several forms of glomerulonephritis (e.g., postinfectious GN, MPGN, IgA nephropathy) can lead to the nephrotic-range proteinuria and the nephrotic syndrome (accompanying edema / hyperlipidemia)
  - Chronic Glomerulonephritis
    - Progressive renal insufficiency with intermittently active urinary sediment, often with hypertension
    - Common manifestation of SLE renal involvement

- Algorithm:
  - Common indications for biopsy:
    - Acute glomerulonephritis that is not compellingly post-infectious; consider biopsy in post-infectious if persistent hypocomplementemia or recurrent hematuria
    - Unexplained acute renal failure
    - Nephrotic range proteinuria + GN
Usually not necessary in isolated hematuria, isolated proteinuria; often deferred if renal ultrasound shows small, chronically diseased kidneys (less likelihood of recovery / increased rate of complications)

- **Work-up**
  - Evaluate for SLE with ANA, anti-dsDNA, and complement levels
  - ANCA to screen for granulomatosis with polyangiitis (AKA Wegener’s), microscopic polyangiitis, Churg-Strauss, renal vasculitis
  - Check ASO / streptozyme to evaluate for post-streptococcal GN
  - Consider culturing to evaluate for infectious causes of MPGN
  - Anti-GBM antibodies (can present with isolated renal disease without pulmonary hemorrhage)
  - Consider checking cryoglobulins (particularly if associated with palpable purpura, arthralgias, hypocomplementemia
  - Screen for hepatitis B and C (associated with MPGN directly as well as with cryoglobulinemia in the case of hep C)
  - HIV Ag/Ab screen to evaluate for HIVAN

- **Management**
  - Varies widely based on underlying etiology
  - See KDIGO 2012 guidelines for recommended approaches to specific diagnoses


**The Nephrotic Syndrome**

- **Definitions**
  - Proteinuria can represent a failure in any of several portions of the nephron, however, tubular proteinuria, overflow proteinuria, and post-renal proteinuria rarely significant. Most clinically relevant proteinuria = glomerular in origin, and represents a failure of the
filtrative barrier in either charge selectivity (MCD) or size selectivity (MPGN)
  ○ “Nephrotic-range proteinuria” = Marked proteinuria ( > 3.5g / day in a 24-hour urine collection or a spot protein:creatinine ratio of > 3.5)
  ○ Heavy proteinuria alone insufficient for diagnosis: other hallmarks include hypoalbuminemia and edema (+/- hyperlipidemia and other sequelae)

● Etiologies
  ○ Broadly divided into systemic causes (with secondary renal involvement) and primary glomerulopathies.
  ○ Approximately 30% of cases attributable to systemic illness (DM most common, SLE / amyloidosis less so; in patients over 65, amyloidosis relatively more common, SLE less common)
  ○ Among patients ages 15-65, most common primary renal causes include FSGS, minimal change disease, and membranous nephropathy. Keep in mind that these patterns can all also be secondary disorders
  ○ MPGN, post-infectious glomerulonephritis, and IgA nephropathy can also cause nephrotic range proteinuria, though they typically present with a more active sediment
  ○ Common pathologic denominator is podocyte foot process effacement / podocyte loss

● Sequelae
  ○ Major sequelae include edema and thrombosis (the pathophysiology of which will be discussed below), hyperlipidemia (secondary to increased hepatic lipoprotein synthesis in response to decrease in oncotic pressure) as well as infection (potentially due to loss of IgG)
  ○ Minor sequelae include loss of endocrine binding proteins (thyroglobulin, vitamin D-binding protein, and cortisol-binding globulin, thus low total hormonal levels but clinically euthyroid, etc.), hypocalcemia (mediated through both hypoalbuminemia and less commonly hypovitaminosis D)

● Pathophysiology
  ○ Edema:
    ■ Classic understanding: Albuminuria → Loss of plasma oncotic pressure → Intravascular hypovolemia → Increased sodium avidity and fluid retention → Edema
    ■ This breaks down at several steps:
      • Most adult patients with nephrotic syndrome (A) actually have increased plasma volume when measured, (B) have increased ANP levels, suggesting circulatory
overload, and (C) do not manifest a natriuretic response to RAAS inhibition, suggesting hypovolemic sodium avidity is not the underlying mechanism for fluid retention. These suggest a primary rather than compensatory role for renal sodium retention.

- Albuminuria alone is insufficient to explain the hypoalbuminemia, as the liver is capable of producing albumin in amounts sufficient to overcome their measured losses (e.g., in peritoneal dialysis patients)
- Patients usually exhibit a decrease in interstitial oncotic pressure concomitant with the fall in plasma oncotic pressure, thus do not produce a significant transcapillary oncotic gradient. In other words, the hypoalbuminemia cannot explain their edema.

Thus although classic mechanism likely plays a role, the primary etiology lies elsewhere. Mechanisms invoked include increased catabolism of albumin by tubular cells to explain the discrepancy between albuminuria and hypoalbuminemia, and a relative insensitivity of the affected kidney to ANP to explain the volume retention. Notably, delivery of sodium to the distal tubule is unchanged, and sodium reabsorption is actually reduced in the PCT, suggesting that increased distal reabsorption is the end-response.

- Thrombosis
  - Multifactorial due to loss of anticoagulant factors (ATIII, proteins C/S), an increase in procoagulant proteins (particularly hyperfibrinogenemia in response to hypoalbuminemia, but also factors V, VIII, VWF, and a2-macroglobulin), and an increase in platelet reactivity (due to coagulant factors above as well as hypercholesterolemia increasing platelet reactivity; moreover, hypoalbuminemia increases arachidonic acid bioavailability)

- Work-up
  - History: Too many associations to list, however, a thorough medication history is key (bisphosphonates associated with FSGS, NSAID’s associated with both MCD and membranous nephropathy; membranous nephropathy in turn also associated with gold, penicillamine, captopril, etc.
  - Labs: Screen for SLE (ANA, anti-dsDNA), amyloidosis (SPEP, UPEP, serum free light chains / K:L ratio), HBV / HCV (HBsAg, anti-HBs, anti-
HBc, anti-HCV), HIV (Ag/AB screen). Also consider RPR if patient’s history suggestive (or if patient unreliable)
- Not much of a role for RVT screening, as it will rarely change management, however keep RVT / renal infarction in mind if patient develops flank pain / hematuria, +/- an increase in LDH
- Many patients will require a biopsy, even if an explanatory disease is present; may be deferred if ultrasound shows small kidneys consistent with irreversible chronic process

- Management
  - Disease-modifying
    - Treatment of idiopathic nephrotic syndrome revolves around immunosuppression, particularly with glucocorticoids; the regimen and recommendation varies based on pathologic subtype
    - Treatment of secondary nephrotic syndromes is aimed at the underlying etiology
  - Symptomatic Management
    - Proteinuria: ACE-I / ARB shown to reduce proteinuria, which may slow disease progression. Note that the anti-proteinuric effects are significantly delayed (approximately 4 weeks) compared to the antihypertensive effects
    - Edema: Sodium restriction (< 2g / day) and loop diuresis are the foundation of volume management, though this must be performed slowly as these patients are at a high risk for precipitation of hypovolemia and/or acute renal failure
    - Thrombophilia: No clear role for empiric anticoagulation, however it may be a consideration in high-risk patients. Interestingly, more severe hypoalbuminemia but not more severe proteinuria was associated with increased thrombotic risk; albumin < 2.8 g/dl had increased thromboembolic events as compared with counterparts (RR 2.5) and this risk increases approximately two-fold per additional 1 g/dl decrement; the usual decision point seems to be around 2g/dl in clinical practice. Rates also relatively increased in membranous nephropathy, particularly if associated with SLE. Notably no good trial data to support the prophylactic use of aspirin, though it makes mechanistic sense.
    - Hyperlipidemia: Statins commonly used if hyperlipidemia develops, though no good clinically relevant outcome data available
1998 NEJM Review -

2001 Archives Review of GN + Nephrotic Syndrome -

2013 VTE in Nephrotic Syndrome -