45 y.o. male presents to ER with subjective weight gain, fatigue, and vomiting. He had a previously normal exam and serum chemistries 3 months prior to current presentation. Currently he has BP 150/110, perorbital edema. Labs include BUN 85, Scr 9.0; UA shows 2+ protein/blood, and cellular casts

What statement is least likely to be correct?

1. Renal biopsy is indicated
2. Post-strep GN is in the DDx
3. Spontaneous resolution of this particular AKI is likely
4. High-dose steroids are indicated
65 y.o. male presents 7 days following a diagnostic coronary angiogram; symptoms include abd pain and confusion.

PEx reveals diminished peripheral pulses, livedo reticularis, epigastric tenderness, and altered mental status.

Labs: BUN 131, SCr 5.2; UA shows 10-15 WBC, 5-10 RBC, one hyaline cast per HPF

The most likely diagnosis is:
1. AIN secondary to NSAIDS pt taking post-cath
2. Rhabdomyolysis with ATN
3. ATN secondary to radiocontrast exposure, nephropathy
4. Cholesterol embolization
5. Renal arterial dissection with prerenal azotemia
50 y.o male is receiving ampicillin and gentamicin for the past 2 weeks for treatment of enterococcal endocarditis. He has remained febrile.

Labs:
- Na 145, K 5.0, Cl 110, HCO3 20
- BUN 40, SCr 3.5
- UA 0-1 WBC, Urine Na 20, Cr 35

Which of the following is the most likely process implicated in this patient’s AKI?
1. Acute tubular necrosis
2. Insensible skin losses
3. Renal artery embolism
4. Decreased cardiac output/ CHF
5. Acute interstitial nephritis
Acute Renal Failure (ARF):

- Traditionally defined as the abrupt decrease of renal function sufficient to result in retention of nitrogenous waste products, as well as loss of regulation of extracellular volume and electrolytes.

- While consensus historically exists in this definition, none exists regarding the quantification of this decline in function to fully denote as ARF.
Acute Kidney Injury

- Creatinine (SCr): not sensitive in detecting the early decline in GFR in early stages of ARF
  - Non-steady-state of GFR vis-à-vis SCr; Creatinine accumulation lags behind
  - Rise in SCr usually a post-facto finding
- Oliguria/anuria: states may not exist even with significant decline in GFR
- Studies of ARF used different criteria for SCr, ΔSCr
  - Lack of consensus problematic also when studying the effects of intervention for ARF
  - Hou, et. al. 1983: used gradated SCr, ΔSCr in prospective study of hospital-acquired ARF
Acute Kidney Injury

• 2001: Acute Dialysis Quality Initiative (ADQI)
  - Risk: 1.5x inc in SCr, GFR dec 25%, UOP<0.5 ml/kg/h x 6h
  - Injury: 2x inc SCr, GFR dec 50%, UOP<0.5 ml/kg/h x 12h
  - Failure: 3x inc SCr, GFR dec 75%, UOP<0.5/kg/h x 24h
    - Also anuria x 12 hr
  - Loss: complete loss /dialysis
  - ESRD: complete loss (inc need for RRT) > 3 months

• 2007: Acute Kidney Injury Network (AKIN)
  - Modified RIFLE to include ΔSCr 0.3 mg/dL from baseline, within 48hr, based on 80% mortality risk (Chertow, JASN 2005)

• 2007: Acute Kidney Injury proposed by AKIN
Acute Kidney Injury

• AKI better represents the full spectrum of acute disorders of renal function, especially in regards to reversible injury (Palevsky, 2008)
  • Issue of prerenal, obstructive etiologies not entirely clear in AKI definition, but classically held to exist in this framework

• Despite these attempts, SCr, oliguria trends still suboptimal in outcomes, treatment measurement
  • Need “Troponin” analogue
Acute Kidney Injury

PRERENAL

AKI

INTRINSIC

POSTRENAL
Acute Kidney Injury: RIFLE

Risk
- Increased creatinine x 1.5 or GFR decrease > 50%
- Increased creatinine x 2 or GFR decrease > 50%
- Increase creatinine x 3 or GFR dec > 75% or creatinine ≥ 4mg/dl (acute rise of ≥ 20.6 mg/dl)

Injury
- Persistent ARF** = complete loss of renal function > 4 weeks
- End Stage Renal Disease

Failure
- Urine output criteria:
  - UO < 0.5ml/kg/h x 6 hr
  - UO < 0.5ml/kg/h x 12 hr
  - UO < 0.3ml/kg/h x 24 hr or Anuria x 12 hrs

Loss
- High Sensitivity
- High Specificity

ESRD

Acute Dialysis Quality Initiative Consensus Group
Acute Kidney Injury

• PRERENAL: 40-80%
  • Volume loss
  • Impaired Cardiac Output
  • Cirrhosis

• Net result: glomerular hypoperfusion
Acute Kidney Injury

- RENAL/INTRINSIC: 10-30%
  - Vascular disorders:
    - small vessel
    - large vessel
  - Glomerulonephritis
  - Interstitial disorders:
    - Inflammation

- Tubular necrosis:
  - Ischemia
  - Toxin
  - Pigmenturia
Acute Kidney Injury

- **POSTRENAL**: 5-15%
  - Intrarenal
    - Crystals
    - Proteins
  - Extrarenal
    - Pelvis/Ureter
    - Bladder/Urethra
Acute Kidney Injury

- Prerenal and ATN encountered most often in the hospital setting: 70-75% in many studies
- Most common diagnostic consideration is therefore between these two conditions

**Prerenal:**
1. Intravascular volume depletion
2. Hypotension
3. Edematous states
4. Localized renal ischemia

**ATN:**
1. All causes for prerenal, leading to post-ischemic ATN
2. Toxins
AKI: Diagnostic studies-urine

- Urinalysis for sediment, casts
- Response to volume repletion with return to baseline SCr 24-72 hr c/w prerenal event
- Urine Na; FENa
  \[ \text{FENa} (%) = \frac{\text{UNa} \times \text{SCr}}{\text{SNa} \times \text{UCr}} \times 100 \]
  - FENa < 1\%: Prerenal
  - FENa 1-2\%: Mixed
  - FENa > 2\%: ATN
Urinalysis in Acute Kidney Injury

Normal/bland
- Prerenal
  - Postrenal
  - Oncotic
  - AKI

Abnormal sediment
- Hematuria
  - RBC casts
  - Proteinuria
- WBC
  - WBC casts
- Eosinophils
- RTE cells
  - Pigmented casts
- Crystalluria
- Myoglobin
- Uric acid
  - Toxins
- Plasma cell dyscrasia
- Athero-embolic AKI
  - AIN
- Interstitial nephritis
- Pyelonephritis
- Glomerulopathy
- Vasculitis
- Thrombotic MA
- Thrombotic
- MA

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- MA
Acute Kidney Injury

LABORATORY DATA
- Creatinine; also BUN/Cr ratio
- CBC: anemia, thrombocytopenia
- $\text{HCO}_3^{-}$: anion gap, lactic acid, ketones
- $K$
- CPK/LDH/Uric acid/liver panel
- Serologies:
  - Complement
  - ESR, RF, ANA, ANCA, AntiGBM, hepatitis
  - Electrophoresis
- Toxicology studies
Acute Kidney Injury

IMAGING STUDIES

- Ultrasound: evaluates renal size, able to detect masses, obstruction, stones
- CT: detects masses, stones Caution with IV dye
- MRI/MRA: can detect RAS; use of Gadolinium carries uncertain R/B ratio in AKI 2° potential hemodynamic changes similar to IVCD, and NFD

In the AKI setting, U/S provides most information with the most favorable R/B ratio
Acute Kidney Injury

- **Prerenal Azotemia**: fall in GFR secondary to renal hypoperfusion that potentially has rapid reversible component
- Restoration of effective intravascular volume, perfusion pressure
- By current detectable methods, AKI reverses with minimal evidence of tubular ischemia
AKI: Acute Tubular Necrosis

- Non-oliguric vs. Oliguric
  - Prognosis worse with **oliguric** ATN in most series

- Ischemic insult: medulla most susceptible to hypoxic event, cellular ATP depletion, oxidative injury

- AKI/ARF phase of ATN: 7-21 days on average

- Recovery phase of ATN: also known as diuretic phase
  - High urine output (>3-4 L)
  - K, Mg, PO4 wasting

- Associated with high FENa
AKI: Acute Tubular Necrosis

- Saline loading effective in lowering ATN risk from drugs/pigments/toxins; sometimes limited in post-ischemic ATN, particularly if CO/CI compromised
- Maintenance of CO, BP, avoid new insults
- Preventative agents have shown promise in animal models, but poorly translated to clinical situations
  - Dopamine, fenoldopam, mannitol, statins, loop diuretics
- Identification of high risk AKI patients is essential to prevention: DM, CKD, ASCVD, poor nutrition
AKI: Rhabdomyolysis

- Precipitated by trauma/crush injury, extreme exertion, statins, cocaine, envenomation, hypoK, hypoPO4

- Multifold injury, with volume depletion, direct tubular toxicity, and obstructing pigment casts

- UA: granular casts, (+) bld on dipstick but (-) microscopy due to myoglobin pigment

- CK levels not always consistent in predicting AKI, but general consensus is that low likelihood exists with CK levels less than 5k-10k
Rhabdomyolysis

- Endotoxin cascade
- Hypovolemia, CV suppression due to hi K, lo Ca, Met Acidosis
- Activation of ET NO scavenging
- Muscular vasodilatation and uptake of ECF in damaged muscles
- Myoglobinemia
- Hyperuricemia
- Increased load of PO4 and urate
- Pigment nephrotoxicity
- Myoglobinuria
- Uricosuria
- Renal vasoconstriction, ischemia
- Depletion of ATP stores, synergistic tubular damage
- Tubular cast formation and stasis
- ATN

AKI: Rhabdomyolysis

- Treatment is via forced saline diuresis: goal of UOP > 200-300 mL/hr

- Early hydration: in crush victims, IV begun in field, advised even before full extrication (Turkey earthquake, 1999)

- Urinary alkanization

- Treatment for symptomatic hypocalcemia only: watch for hyperK
AKI: Radiocontrast Nephrotoxicity

- Well-recognized adverse outcome, but incidence varies widely, because of problems in defining AKI historically, as well as competing factors in pathogenesis
- Improved with iso-osmolar agents
- Onset of rise in SCr occurs within 24 hr; peak/fall within 3-5 days
- Ddx of embolic AKI, ATN from other causes
- Many studies with diuretics, osmolar agents, dopaminergic agents, etc.: recent improvements with saline/HCO3 pre/post at 1mL/kg/hr
- Mucomyst has recent equivocal benefit, but harmless
Atheroembolic (AE) AKI

- Renal and systemic AE occur in patients with diffuse atherosclerotic disease

- Risk factors include manipulation of the aorta or other large arteries during angiography or CV surgery

- Also can occur spontaneously with ulcerated plaques

- Destabilization of plaque may be enhanced in the setting of anticoagulation or thrombolytic therapy
Atheroembolic AKI

- Clinical Manifestations
  - AKI days to weeks after manipulation, anticoagulation
  - Systemic signs, signals of inflammation
    - Rash
    - Livedo reticularis
    - Decreased complement due to activation by exposed atheromata
    - Eosinophilia/eosinophiliuria
  - Occlusion of distal arteriolar beds
    - AKI
    - Visual field deficits
    - Gangrenous digits, palpable pulses
    - Pancreatitis
    - GI bleeding
Acute Kidney Injury

Clinical features of Acute Interstitial Nephritis

- Onset usually 3-5 days with most drugs, but may be sooner with rifampin, or much later with NSAIDS
- Rising SCr which resolves upon d/c of offending drug
- Fever, hematuria, **pyuria**: Urine eosinophils
- Mild to moderate proteinuria; much higher to NS in NSAIDS
- **Eosinophilia** and morbilliform rash also s/sx in AIN
- Occasionally see hyperkalemia and distal RTA
- Bx not usually necessary for dx, assuming reversal of sx’s; may be needed for complicated cases
- Prednisone 40 mg PO x 2 wks sometimes utilized to shorten AKI interval
Acute Kidney Injury: AIN causes

**DRUGS**
- ACEI
- Allopurinol
- Cephalosporins
- Cimetidine
- Fluoroquinolones
- Loop diuretics
- NSAIDS
- PCN
- Phenytoin
- Rifampin
- Sulfonamides
- Tegretol
- Thiazides

**INFECTION**
- Bacterial
  - Agents causing pyelonephritis
  - Legionella
  - Brucella
  - Yersinia
- Viral
  - Hantavirus
  - HIV
  - CMV, EBV, HSV
AKI: Glomerulonephritis (RPGN)/Systemic Vasculitis

- **Immune-Complex Mediated**
  - SLE
  - Cryoglobulinemic vasculitis
  - Henoch-Schönlein purpura
  - Post-strep GN

- **Direct Ab attack**
  - Anti-GBM disease
  - Goodpasture’s syndrome

- **Pauci-immune vasculitis**
  - Microscopic polyangiitis
  - Wegener’s granulomatosis
  - Churg-Strauss syndrome

- **Thrombotic Microangiopathy**
  - TTP
  - HUS
  - Scleroderma renal crisis
  - Preeclampsia
  - Malignant hypertension
Acute Glomerulonephritis (RPGN)

- Accounts for a minority of AKI: ~5%
- May have severe morbidity, mortality
- Extra-renal manifestations may be present
  - Pulmonary
  - Dermal
  - GI
  - Hematologic
- HTN may be present, especially in absence of prior Hx
- UA: differentiates from ATN, AIN
  - Dysmorphic RBC, RBC casts, proteinuria > 0.5gm/24h
- Serologies, complement activation
- Need for specific therapy to reduce Ab critical towards attenuating/reversing AKI
Systemic Lupus Erythematosus (SLE)

• SLE nephritis diagnosis based on pathology, serology, extrarenal manifestations: 4/11 criteria by ARA
• WHO Class I-V of SLE nephritis: histopathology
• Variable s/sx of renal disease, but Class IV (diffuse proliferative GN) most often seen in AKI
• ANA, anti-DNA Ab, hypocomplementemia
• Role of Bx to guide therapy
• Immunosuppression
  • Steroids
  • cyclophosphamide
Anti-GBM disease/Goodpasture’s

- Pulmonary hemorrhage distinguishes Goodpasture’s from anti-GBM disease
- Bimodal peak incidence
  - 3rd decade: men, pulmonary hemorrhage with AKI (Goodpasture’s)
  - 6th-7th decade: women, anti-GBM Ab AKI, no pulm involvement
- Ab targets type IV collagen
- Aggressive course of AKI typically seen; pulm hemorrhage seen more often in smokers, exposure
- Anti-GBM present in >95% cases
- Predisone plus cyclophosphamide; TPEx indicated daily until circulating Ab titers undetectable
Pauci-immune vasculitis

- Microscopic polyangiitis, Wegener’s granulomatosis, Churg-Strauss syndrome
- RBC casts with proteinuria, ESR elevated; crescentic GN on Bx
- Respiratory tract involvement may vary
  - Alveolar hemorrhage
  - Sinusitis, nodular lesions (Wegener’s)
  - Asthma, eosinophilia (Churg-Strauss)
- ANCA hallmark of disease spectrum (90 %)
- MPO (+) in microscopic polyangiitis, Churg-Strauss
- PR3 (+) in Wegener’s
- Prednisone/Cytoxan; TPEx used in pulm hemorrhage
- Renal survival associated with entry-level SCr
Thrombotic Microangiopathy

**Hemolytic-uremic Syndrome**

- Predominately occurs in children
- Associated with diarrheal prodrome, Shigatoxin (verotoxin): *E. coli* O157:H7
- Predominance of uremic signs/symptoms
- Hallmark of endothelial damage from verotoxin
- Supportive care

**Thrombotic thrombocytopenic purpura**

- Predominately in adults
- No inciting pathogen, GI prodrome
- Predominance of CNS signs, symptoms
- Hallmark of circulating von Willebrand factor-induced damage: defect in protease
- Plasma exchange
Acute Kidney injury

Crystal-induced AKI:
- Common factors include high excretion in urine, and low solubility in acidic urine; exacerbated by hypovolemia; examination of urine critical to Dx

Common agents
- Uric acid
- Acyclovir
- Sulfa
- Methotrexate
- Ethylene glycol

Pre-exposure hydration, Urinary alkalinization
Acute Kidney Injury

Indications for Renal Biopsy in AKI:

- Tissue examination via LM/EM/IF
- Acute nephritic syndrome
  - Hematuria, cellular casts, proteinuria in setting of new-onset or exacerbation of HTN, rising SCr
  - May also have serologic (+) i.e. ANA, ANCA, aGBM that tissue dx also provides treatment options and prognosis
- Unexplained AKI
  - Uncertain or multiple competing ddx, of which treatment differs greatly with definitive dx; AIN vs ATN considerations are seen not uncommonly in hospitalized pts
  - Young pts with AKI often are considered based on long-term renal survival outcomes maximized with definitive dx
- Renal TPL: Acute Rejection
Acute Kidney Injury

INDICATIONS FOR RENAL REPLACEMENT THERAPY

- Consensus generally includes:
  1. Refractory volume overload
  2. Severe metabolic acidosis; HCO₃ may be variable, but declining level of factor; also falling pH to 7.1-7.2
  3. Hyperkalemia, with levels > 6.5, or documented rapid rise refractory to medical therapy
  4. Major uremic target organ manifestations i.e. pericarditis, progressive neuropathy, seizure, or unexplained AMS
  5. Platelet dysfunction, bleeding diasthesis
  6. AKI in setting of dialyzable drug/toxin
Acute Kidney Injury

INDICATIONS FOR RENAL REPLACEMENT THERAPY

- Despite modalities available (IHD, CRRT) mortality remains 50% for AKI in critically ill patients
- Clinicians will generally opt for RRT induction prior to development of the above symptoms; BUN of 80-100 in absence of other sx’s sometimes is a indication, but practices vary
- While concept of prophylactic RRT has been around since 1950-60’s, its benefit remains uncertain, whether due to dose, timing, modality
  - Studies based on BUN criteria
  - Studies based on volume removal/ultrafiltration in cardiac patients rather than high-dose diuretics
- No benefit proven of IHD vs CRRT
AKI Case #1

45 y.o. male presents to ER with subjective weight gain, fatigue, and vomiting. He had a previously normal PEx, serum chemistries 3 months prior to current presentation. Currently he has BP 150/110, perorbital edema. Labs include BUN 85, SCr 9.0; UA shows 2+protein/blood, and cellular casts

What statement is least likely to be correct?
1. Renal biopsy is indicated
2. Post-strep GN is in the DDx
3. Extracapillary cell proliferation is likely
4. Spontaneous resolution of this particular AKI is likely
5. High-dose steroids are indicated
65 y.o. male presents 7 days following a diagnostic coronary angiogram; symptoms include abd pain and confusion.

PEx reveals diminished peripheral pulses, livedo reticularis, epigastric tenderness, and altered mental status.

Labs: BUN 131, SCr 5.2; UA shows 10-15 WBC, 5-10 RBC, one hyaline cast per HPF

The most likely diagnosis is:
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2. Rhabdomyolysis with ATN
3. ATN secondary to radiocontrast exposure, nephropathy
4. Cholesterol embolization
5. Renal arterial dissection with prerenal azotemia
AKI Case #3

50 y.o male is receiving ampicillin and gentamicin for the past 2 weeks for treatment of enterococcal endocarditis. He has remained febrile.

Labs:
1. Na 145, K 5.0, Cl 110, HCO3 20
2. BUN 40, SCr 3.5
3. UA 0-1 WBC, Urine Na 20, Cr 35

Which of the following is the most likely process implicated in this patient’s AKI?
1. Acute tubular necrosis
2. Insensible skin losses
3. Renal artery embolism
4. Decreased cardiac output/ CHF
5. Acute interstitial nephritis
Acute Kidney Injury: conclusions

- Major advances in understanding AKI, but no clear definition that guides research on prophylaxis, prognosis
- AKI still carries high M/M risk, especially in ICU setting
- Improving volume status, hemodynamics rapidly aids in minimizing ischemic AKI risk; volume resuscitation, relief of urinary obstruction can be done concurrently
- Patient history, hosp chart review, PEx coupled with routine labs, UA may establish cause in 40-60% of AKI
- Serologies and consideration of Bx are also adjuncts
- Advent of urinary biomarkers of ischemic tubular injury i.e. urine NGAL, will be next front in redefining AKI