ABIM CERTIFICATION EXAM: NEPHROLOGY
JULY 2016
UCSF CME

Disclosures
- I am site PI for the REPRISE study evaluating efficacy of tolvaptan in autosomal dominant polycystic kidney disease (Otsuka pharmaceuticals)

Roadmap for today
- Glomerular diseases (30 min)
  ------------------------ Scheduled 15 min break ------------------------
- Common electrolyte abnormalities (30 min)
- Acid-base (45 min)
- Acute kidney injury (20 min)
- Secondary hypertension (10 min)

GLOMERULAR DISEASES
Case

A 74 yo man is evaluated for a 5-month history of sinusitis and intermittent otitis media. He has lost 9 lbs (4.1 kg) and has occasional joint pains.

Physical exam: Afebrile
HEENT: crusting in right nares; opaque right tympanic membrane; bilateral maxillary sinus tenderness
CV: 2/6 systolic murmur
Lungs: rhonchi
Extremities: 2+ edema bilateral lower ext

Laboratory studies
- Hemoglobin 11.5 g/dl
- Leukocyte count 10.8x10^9 /L
- Blood urea nitrogen 28 mg/dl
- Creatinine 1.6 m/dl
- Albumin 3.8 g/dl
- C3 100 mg/dl
- C4 32 mg/dl
- Urinalysis: 18 dysmorphic erythrocytes and 1 erythrocyte cast/hpf
- CXR: nodule in RUL, hazy density in LLL

Case Question
Which one of the following studies is most appropriate?
A. Antinuclear antibody
B. Anti-glomerular basement membrane antibody
C. Myeloperoxidase antineutrophil cytoplasmic antibody
D. Proteinase-3 antineutrophil cytoplasmic antibody
E. Anti-double-stranded DNA antibody

Case answer review
A. Antinuclear antibody – lupus nephritis – wrong age / sex – low complements
B. Anti-glomerular basement membrane antibody – wrong history; usually younger men; no respiratory involvement
C. Myeloperoxidase ANCA – can exist in granulomatous polyangiitis (Wegener’s) but less specific
D. Proteinase-3 ANCA – right answer – granulomatous polyangiitis
E. Anti-double-stranded DNA antibody – lupus nephritis – wrong age / sex
**Granulomatous polyangiitis (GPA)**
- Formerly known as Wegener’s granulomatosis
- Granulomatous inflammation involving respiratory tract and necrotizing vasculitis affecting small to medium sized vessels
- Necrotizing glomerulonephritis is common

**Glomerular diseases: ‘nephritic’**
- Hematuria, tea-colored urine
- Hypertension (often acute)
- +/- Edema
- +/- Rapid loss of GFR
- Active urine sediment
  - Dysmorphic red blood cells
  - Red cell casts

**Glomerulonephritis: many ways to approach**
- Renal limited (mostly): IgA nephropathy, post-strep GN, anti-GBM antibody disease
- Pulmonary-renal: Goodpasture’s syndrome, microscopic polyangiitis, Churg-Strauss, granulomatous polyangiitis
- Renal-dermal: Henoch-Schonlein purpura; ANCA-associated vasculitis; cryoglobulinemia; systemic lupus erythematosus
- Systemic: systemic lupus erythematosus; HUS/TTP

- Rapidly progressive GN: 50% eGFR loss in <30 days

**Vasculitis approach**
- Small vessel: microscopic polyangiitis, GPA, Churg-Strauss, cryoglobulinemic, Henoch-Schonlein purpura—disease / leukocyte infiltration; crescentic glomerulonephritis
- Medium-vessel: Kawasaki’s disease, polyarteritis nodosa—renal infarctions / renovascular hypertension
- Large-vessel: giant cell arteritis, Takayasu’s arteritis—renal ischemia due to narrowed abdominal aorta / renal arteries
**Immunologic approach**

- Immune complex mediated: Henoch-Schönlein purpura; cryoglobulinemic vasculitis; lupus; serum sickness; rheumatoid; polyarteritis nodosa; infection-induced; viral (hep B/C), bacterial (strep); Goodpasture’s (anti-GBM antibodies)
- ANCA mediated (non-immune-complex mediated): GPA, MPA, Churg-Strauss
- Cell-mediated: allograft cellular vascular rejection; giant cell arteritis; Takayasu’s

**Immune complex GN**

- Post-streptococcal GN
  - Hematuria 2-3 weeks after pharyngitis or skin infection
  - Elevated ASO and anti-DNAse B antibody
  - Low C3 / low-normal C4
  - No direct therapy available
- IgA nephropathy
  - Sympharyngic gross hematuria
  - Henoch-Schönlein Purpura (HSP) = Abdominal pain, diarrhea, often seen in kids, rarely in adults
  - Rx: steroids, fish oil(?), ACE/ARB

**Immune complex GN**

- SLE nephritis
  - Usually occurs within first 3 years of SLE diagnosis
  - ANA, anti-dsDNA, anti-Smith antibodies
  - Immunosuppression:
    - Mycophenolate (CellCept) or cyclophosphamide
    - Steroids (combined with above)
### Immune complex GN

- Membranoproliferative glomerulonephritis (MPGN) type I
  - Secondary to cryoglobulinemia, neoplasms, or chronic infections (e.g., HCV)
  - Cryoglobulin deposits in vessels → mesangiocapillary GN
  - Low complements; + C3 nephritic factor (autoantibody against C3 convertase of alternative complement activation pathway)
  - Cryos: arthralgias, purpura, livedo reticularis
  - Rx: Underlying HCV → interferon and ribavirin

### Anti-GBM antibody disease

- Antibodies to noncollagenous portion of type IV collagen causes autoantigen response
- Renal limited: Anti-GBM Disease (older women)
- Pulmonary renal syndrome (hemoptysis / pulmonary hemorrhage + RPGN): Goodpasture’s Syndrome (young Caucasian men)
- Anti-GBM titer, kidney biopsy
- Rx: Plasmapheresis, steroids, cyclophosphamide

### ANCA

- Antineutrophil Cytoplasmic Antibodies
  - ANCA react with cytoplasmic antigens (PR3 and MPO) that are present at surface of cytokine-stimulated leukocytes, causing leukocytes to adhere to vessel walls, degranulate, and generate toxic oxygen metabolites
  - Specific for proteins within granules of neutrophils and monocytes
  - Cytoplasmic (c-ANCA) versus perinuclear (p-ANCA)
    - Cytoplasmic = PR3 (serine proteinase) = more common in GPA (Wegener)
    - Perinuclear = myeloperoxidase (MPO) = more common in MPA (microscopic polyangiitis)

### Pauci-Immune GN / ANCA Vasculitis

- Diagnosis: ANCA +, normal complements, no immunohistologic evidence for vascular immune complex localization on biopsy
- Microscopic polyangiitis (p-ANCA)
  - Necrotizing vasculitis; no granulomas
  - Granulomatosis with polyangiitis (c-ANCA)
    - Lung disease, upper airway disease, granulomas
- Churg-Strauss Disease (p-ANCA or ANCA neg)
  - Eosinophilia, asthma, sinus disease, peripheral neuropathy, granulomas
- Treatment: Steroids, cyclophosphamide (+/- plasmapheresis if hemoptysis, GPA)
**IgA and SLE: Chameleons**

Both IgA Nephropathy and SLE can be...
- Indolent or rapidly progressive
- Crescentic GN
- Nephritic and/or nephrotic

**IgA Nephropathy**
- More common in Asians and Hispanics
- Episodic macrohematuria

**SLE**
- More common in Asians, Hispanics, African-Americans
- Up to 75% with SLE have renal disease; usually presents with proteinuria

**Case**

A 67 yo man with a h/o osteoarthritis, BPH, hyperlipidemia is evaluated for new-onset joint pain in shoulders accompanied by lower extremity swelling. 3 months ago, baseline kidney function was normal. Meds include tamsulosin, simvastatin, naproxen. Physical examination reveals BP 132/68. HEENT: pale conjunctivae Cardiac: S3 gallop Pulmonary: decreased breath sounds at bases Ext: 3+ LE edema

**Case, continued**

* Labs  
  - Hemoglobin 8.2 g/dl  
  - Leukocyte count 8.1 x10^9/L  
  - Platelets 132K/mcL  
  - BUN 68 mg/dl, Creatinine 5.6 mg/dl  
  - Na 131 / K 3.5 / Cl 110 / Bicarb 18 / Albumin 3 / Anion gap 3  
  - Ca 10.5 / Phos 5.4  
  - UA: pH 5, SG 1.015, no blood, 2+ protein  
  - Urine protein:creatinine ratio 5 mg/g

**Case Question**

Which of the following studies is most likely to confirm the cause of this patient’s kidney failure?

A. ANCA antibodies  
B. Serum protein electrophoresis / urine protein electrophoresis  
C. Urine eosinophil measurement  
D. Hepatitis C antibody assay  
E. Kidney ultrasonography
Case answer review

A. ANCA antibodies – no hematuria
B. Serum protein electrophoresis / urine protein electrophoresis – right answer – amyloidosis, multiple myeloma – low anion gap (increase in unmeasured cations including immunoglobulins)
C. Urine eosinophil measurement – wrong history; test no longer favored even in AIN
D. Hepatitis C antibody assay – MPGN can be nephrotic and associated with RPGN, but no hematuria
E. Kidney ultrasonography – dx obstructive uropathy in older man with BPH, but more going on here

Nephrotic disease: Amyloidosis

- Pathology
  - β pleated structure that forms 8-10 nm fibrils
  - Congo Red stain has apple-green birefringence with polarized light
- Classification
  - ~ 20 unique amyloidoses
  - AL (primary) amyloidosis
    - myeloma and monoclonal gammopathies
  - AA (secondary) amyloidosis
    - chronic infections, inflammatory states (inflammatory bowel disease, rheumatoid arthritis, familial Mediterranean fever)

- Clinical findings
  - Large kidneys and massive proteinuria
  - Multi-organ involvement
    - Periorbital hemorrhage (raccoon sign), macroglossia
    - Cardiac deposits
    - GI involvement, hepatomegaly
    - Carpal tunnel syndrome, neuropathy
    - Shoulder pad sign = amyloid deposits in deltoids
  - Cardiac and kidney disease are poor prognostic signs

- Treatment
  - AA Amyloidosis: Treat underlying infection or inflammation, colchicine for Familial Mediterranean Fever
  - AL Amyloidosis: Treat underlying myeloma, melphalan, prednisone, stem-cell transplant
  - Adjuvant therapy: ACEi/ARB, blood pressure control, diuretics, sodium/water restriction
Glomerular Disease: ‘nephrotic’

- Proteinuria > 3 g/day
- Dyslipidemia
- Edema
- Hypoalbuminemia
- Lipiduria (oval fat bodies in urine, Maltese cross with polarized light)
- Associated Feature: Hypercoagulability

Caveat: Many patients do not have all 5 features, i.e. nephrotic-range proteinuria without nephrotic “syndrome”

Nephrotic Diseases: DDx

- Focal Segmental Glomerulosclerosis (FSGS)
  - More common in African-Americans, age < 40 y/o
  - Membranous Nephropathy (MN)
    - Tend to be Caucasian, age > 40 y/o
  - Minimal Change Disease (MCD)
    - Age < 15 y/o, BUT 10% adults (second peak age 60-70)
  - Amyloidosis
  - Diabetic nephropathy
  - Others: SLE, IgA nephropathy, MPGN

Nephrotic Disease: Focal Segmental Glomerulosclerosis (FSGS)

- Primary
  - Can be treated with steroids
  - Can recur rapidly post-kidney transplant
- Secondary
  - HIV-associated nephropathy (HIVAN): from uncontrolled HIV; almost exclusively in African-Americans
  - Chronic kidney disease, reduced nephron mass, hyperfiltration injury
  - Morbid obesity
  - Heroin, drugs (lithium, pamidronate)
  - Sickle cell disease
  - Typically not steroid responsive

Nephrotic Disease: Membranous Nephropathy

- Idiopathic/Primary
- Secondary
  - Malignancy
    - Typically solid (colon, lung, breast), also non-Hodgkin’s
    - 5-10% have malignancy, but <1-2% are occult
  - Chronic infections, HBV > HCV, syphilis
  - SLE (10-20% of lupus nephritis) and autoimmune/connective tissue diseases
  - Drugs: NSAIDs, gold, penicillamine (think of this in pts with RA treated with these agents)
Nephrotic Disease: Membranous Nephropathy
- Clinical
  - Renal vein thrombosis and hypercoagulability
  - Secondary prophylaxis with warfarin
  - Malignancy and age-appropriate cancer screening
- Prognosis: Mixed
  - Third get better, third stay same, third get worse
- Treatment:
  - Carefully selected patients with poor prognostic features (older age, men, chronic kidney disease, symptomatic proteinuria/nephrotic syndrome)
  - Immunosuppression: steroids AND (cyclophosphamide or chlorambucil)

Nephrotic Disease: Minimal Change Disease (MCD)
- Idiopathic/Primary
  - Second peak in 60-70 year old patients
  - More steroid resistance/dependence and higher relapse rate in adults than in children
- Secondary
  - Drugs
    - NSAID-induced AIN with MCD, pyuria with proteinuria
  - Infections
    - Neoplasms, Hodgkin’s and others
  - Allergy and toxins (bee stings, mercury, lead)
  - Rx: Steroids typically first-line

Kidney Disease in Multiple Myeloma
- Amyloidosis
  - Lambda > kappa light chains
- Light chain deposition disease
  - Kappa > lambda light chains
- Cast nephropathy
- Hypercalcemia and vasoconstrictive AKI
- Hypercalcemia and nephrogenic DI with pre-renal AKI

Diabetic Nephropathy
- Common cause of nephrotic-range proteinuria
- Unusual cause of nephrotic syndrome
- Early hyperfiltration phase usually with preserved creatinine and large kidneys
- Diagnosis
  - Usually clinical diagnosis without kidney biopsy
  - Compatible clinical history
    - Duration and severity of DM
    - Evidence of end-organ disease from DM (retinopathy, neuropathy)
  - No suspicious features for alternative diagnosis
DDx Enlarged Kidneys

- Obstruction / hydronephrosis
- Polycystic kidney disease
- Infiltrative disease (lymphoma)
- Amyloidosis
- Diabetic nephropathy (early stage)
- HIV-associated nephropathy

Adjuvant Rx in nephrotic syndrome

- Blood pressure control
- Proteinuria suppression
  - ACE inhibitors / ARB
  - Goal urine protein/creatinine ratio < 0.5
  - Dietary protein restriction → controversial
- Loop diuretics for edema
- Sodium/fluid restriction
- Primary prophylaxis with anticoagulation for hypercoagulability somewhat controversial

Interstitial kidney disease

- Affect vascular / interstitial compartments of kidney with relative sparing of glomeruli
- Often asymptomatic
  - May not have the fever, rash, and arthralgias of acute interstitial nephritis
- Minimal proteinuria/hematuria
- Sterile pyuria
- Urine sediment: +/- WBC, WBC casts

TUBULOINTERSTITIAL DISEASES
Chronic tubulointerstitial diseases

- Toxic
  - Occupational exposures, lead and heavy metals
  - Medications: analgesics, lithium, cisplatin, calcineurin inhibitors
  - Traditional medicines: aristolochic acid nephropathy
- Medical
  - Metabolic: hyperCa, hypoK, oxalosis
  - Immune disorders: SLE, Sjogren’s, sarcoidosis
  - Lymphoproliferative disease
  - Hypertensive nephropathy
  - Atheroemboli
- Genetic: Alport’s, cystinosis, medullary cystic kidney disease, polycystic kidney disease
- Chronic urinary tract obstruction

Interstitial kidney disease

- Tubular abnormalities
  - Urinary concentrating defects and nephrogenic diabetes insipidus
    - polyuria, nocturia
  - Fanconi syndrome
    - Impaired tubular reabsorption: amino acids, bicarbonate, phosphate, glucose in urine
    - Glucosuria with normal serum glucose
    - Proximal (type 2) RTA/metabolic acidosis from bicarbonate spilling
    - Distal (type 1) RTA/metabolic acidosis from inability to acidify urine

NSAIDs and kidney disease

- AKI: Hemodynamic acute renal failure
  - Prostaglandins vasodilate afferent arteriole
- AKI: Acute interstitial nephritis +/- minimal change disease
  - Sterile pyuria with proteinuria
- CKD: Analgesic nephropathy
  - Cumulative nephrotoxicity, high doses over years
  - Sometimes associated with papillary necrosis
- CKD: Membranous nephropathy
- Heavy proteinuria, nephrotic syndrome
- Hypercoagulability

ELECTROLYTE ABNORMALITIES
Case

54 yo man was hospitalized for shortness of breath. Found to have pleural effusion, dx'd with metastatic small-cell lung ca. Long h/o cigarette smoking. Now seen in follow-up a few weeks later.
Medications include ACEI
Exam: BP 126/84, pulse 84, afebrile, RR 18
  Fatigued, cachectic, but alert/oriented
  CV reg
  Lungs diminished breath sounds right base
  No edema

Case, continued

Labs
- Glucose 114 mg/dl
- BUN 10 mg/dl, Cr 0.6 mg/dl
- Sodium 112 / K 3.2 / Cl 84 / Bicarb 21 / Phos 3.1
- Albumin 3.2 g/dl
- Serum Osm 243 mmol/kg
- Urine Na 120 mmol/L
- Urine K 24 mmol/L
- Urine Osm 542 mmol/kg

Case Question

Which of the following is the most appropriate therapy at this time?

A. 3% saline via infusion pump
B. Tolvaptan
C. Fluid restriction < 1 L/day
D. Sodium chloride tablets, 2g three times daily
E. Hydrochlorothiazide

Case answer review

A. 3% saline via infusion pump – chronic hyponatremia – do not want to correct aggressively; no symptoms
B. Tolvaptan – right answer – need to increase free water excretion
C. Fluid restriction < 1 L/day – insufficient due to electrolyte-free water clearance
D. Sodium chloride tablets, 2g three times daily – not getting at problem of water out of proportion to salt
E. Hydrochlorothiazide – impairs diluting capacity – can be a cause of hyponatremia
Sodium: Key physiology

- Think about water, not salt!
- Water and sodium balance are interrelated, but regulated by separate mechanisms
  - ADH regulates osmolality (water balance)
  - Aldosterone regulates sodium balance

Hyponatremia

- Serum Osmolality
  - High: Transloational, mannitol and glucose
  - Normal: Pseudohyponatremia, triglycerides and paraproteinemias
  - Low: Majority of hyponatremia cases
- Volume status can be confusing
  - Appropriate ADH release: normovolemic states of ADH excess due to non-osmotic stimuli: postop, pain, nausea
  - States of effective circulating volume depletion: heart failure, cirrhosis, diuretics
  - Inappropriate ADH release: SIADH, cortisol deficiency, hypothyroidism

Review case

Labs
- Glucose 114 mg/dl
- BUN 10 mg/dl, Cr 0.6 mg/dl
- Sodium 112 / K 3.2 / Cl 84 / Bicarb 21 / Phos 3.1
- Albumin 3.2 g/dl
- Serum Osm 243 mmol/kg
- Urine Na 120 mmol/L / Urine K 24 mmol/L
- Urine Osm 542 mmol/kg

- Electrolyte-free water clearance: (UNa + UK) > (Serum Na + Serum K) means free water is being RETAINED rather than excreted – only ADH antagonism will help
- Same concept as UOsm > SOsm but more accurate; UOsm that is not maximally dilute could still be inappropriate for the low POsm – does not necessarily have to be greater than SOsm
**Case**

- A 23 yo man with HIV infection comes for a follow-up after being hospitalized with pneumocystis jiroveci pneumonia, which is being treated with trimethoprim-sulfamethoxazole and pred taper.
- Exam: Temp 97.8°F, pulse 84, respirations 12, BP 110/60
- Thin, in no apparent distress
- Cardiac exam normal
- Lungs clear
- No peripheral edema

**Laboratory studies**

- CD4 cell count 87 / mcl
- Glucose 182 mg/dl
- BUN 12 mg/dl
- Cr 0.7 mg/dl
- Sodium 111 mmol/L
- Potassium 3.6 mmol/L
- Chloride 98 mmol/L
- Bicarb 22 mmol/L
- Albumin 3.3 g/dL
- Phos 2.6 mg/dl
- Serum Osm 246 mOsm/kg H2O
- Urine sodium 117 mmol/L
- Urine potassium 24 mmol/L
- Urine Osm 453 mosm/kg

**Case Question**

- Which of the following is the most likely cause of this patient’s hyponatremia?
  - A. Syndrome of inappropriate antidiuretic hormone secretion
  - B. Volume Depletion
  - C. Adrenal insufficiency
  - D. Pseudohyponatremia
  - E. Psychogenic polydipsia.

**Case answer review**

- A. Syndrome of inappropriate antidiuretic hormone secretion – correct answer – hypotonic (hypoosmolal) hyponatremia with excess free water retention / abnormal free water excretion
- B. Volume Depletion – history not suggestive; would have a lower urine sodium
- C. Adrenal insufficiency – common cause of hyponatremia including in HIV but no evidence of mineralocorticoid deficiency
- D. Pseudohyponatremia – in pseudohyponatremia, osmolality is normal
- E. Psychogenic polydipsia – would have very low urine Osm and low urine electrolytes
Review laboratory studies

- Serum Osm 246 mM/kg H₂O
- Urine sodium 117 mmol/L
- Urine potassium 24 mmol/L
- Urine Osm 453 mosm/kg

(Urine sodium + urine potassium) > (serum sodium + serum potassium)

Urine Osm > Serum Osm

SIADH: Syndrome of Inappropriate Antidiuretic Hormone

- Common cause of hyponatremia
- Low serum osmolality
- Clinically euovolemic
- DDx
  - CNS: head trauma, infection, CVA, tumors, others
  - Pulmonary: Small cell lung cancer, pneumonia, lung abscess, pneumothorax
  - Drugs: Chlorpropamide, tricyclic antidepressants, haloperidol, SSRIs
  - Neoplasm
  - Pain, nausea

SIADH: Syndrome of Inappropriate Antidiuretic Hormone

- Findings
  - Urine osms > Serum osms
  - Urine Na > 20 mEq/L
- Diagnosis of exclusion
  - Rule-out hypothyroidism and adrenal insufficiency
- Treatment more specific for SIADH
  - Sodium tablets and water restriction
  - Demeclocycline no longer used, nephrotoxic (induces nephrogenic diabetes insipidus)
  - Vasopressin receptor antagonists (vaptans) = liberalize fluid intake if on vaptan!

Hyponatremia

- Treatment
  - Free water restriction; increase solute intake
  - Hypovolemic: Saline IVF, suppress ADH excretion
  - Euvolemic: Free H₂O restriction
  - Hypervolemic: Diuretics and/or dialysis
  - Hypertonic Saline (3% NaCl)
    - Rarely indicated
    - Risk of osmotic demyelination/pontine myelinolysis
    - Used for severely symptomatic patients
    - Infusion rate typically 0.5 to 1 mL/kg/hour
- Correction rate
  - Approximately 10-12 mEq/L per day
Hypernatremia

- Clinical
  - CNS symptoms: lethargy, weakness, irritability, altered mental status, seizures, coma
  - Thirst usually protects against hypernatremia; impaired access to free water
- DDx
  - Renal water loss: DM and glucosuria, diabetes insipidus (central or nephrogenic), post-obstructive or post-ATN diuresis
  - Extra-renal water loss: insensible losses, GI losses
  - Excess Na⁺ retention: AKI

\[ \text{Free water deficit} = 0.5 \times \text{Wt (kg)} \times \left(\frac{\text{plasma Na} - 140}{140}\right) \]

- Free water deficit typically at least 2 L
- Intravenous D5W vs. water NG/PO
- If hypovolemic, resuscitate with NS first or simultaneously with free water
- Correction rate: 12 mEq/L per 24 hours (approx)

Hyperkalemia: Work-up

- Transtubular Potassium Gradient (TTKG)
  - TTKG = (\text{U}_K/\text{P}_K) / (\text{U}_{\text{osm}}/\text{P}_{\text{osm}})
  - Normal range is 6-8
  - TTKG < 6 → renal hyperkalemia
  - TTKG > 10 → appropriate renal response

Potassium

- Primarily intracellular compartment (98%)
- Shifts (from one compartment to another) versus absolute excess / deficiency of total body potassium
- 90% of regulation in kidney (trivial amounts in sweat / GI tract)
- Daily excretion in urine 120-140 mEq/24 hours
- Aldosterone is primarily responsible for activity of Na/K ATPase in collecting duct, which stimulates excretion of K⁺
- TTKG can assess aldosterone effect
- Hyperkalemia generally asymptomatic
- Symptoms of hypokalemia: Weakness, rhabdomyolysis, arrhythmias, cramps
Hyperkalemia: Etiology

- Dietary ingestion - salt substitutes, K supplementation
- Decreased excretion
  - AKI/CKD
  - Decreased RAAS (ACEi/ARB, NSAIDs, heparin)
  - Hypoaldosteronism (Addison’s disease) or lack of aldosterone effect (type 4 RTA)
  - Block tubular K handling (trimethoprim, pentamidine, amiloride, calcineurin inhibitors)
- Extracellular K shift: metabolic acidosis, insulin deficiency, beta-blockers, tumor lysis, digoxin overdose, succinylcholine, hyperkalemic periodic paralysis

Hyperkalemia Treatment

- Stabilization of membrane = Fast
  - Calcium gluconate IV
- Shift potassium = Fast
  - Beta-agonists (albuterol)
  - Insulin/glucose
  - NaHCO₃ (may not work in ESRD)
- Removal of potassium = Slow
  - Diuretics, Dialysis
  - Cation exchange resins (sodium polystyrene - avoid in peri-operative pts, ileus/SBO)

EKG findings in hyperkalemia

- Loss of P waves, QRS widening, T wave peaking, Ventricular tach/flip
- Correlate poorly with severity of hyperkalemia

Hypokalemia: Etiology

- Low dietary intake – not really a problem on Western diet
- Increased excretion
  - GI: diarrhea, vomiting (TTKG <2)
  - Kidney (TTKG >4): diuretics, hypomagnesemia, mineralocorticoid excess (primary aldosteronism, Cushing’s, European licorice, hyperreninemia, syndrome of apparent mineralocorticoid excess), Bartter, Gitelman
- Shift: alkalemia, increased insulin, increased beta-activity, periodic paralysis (classically with thyrotoxicosis)
### Phosphorus
- Excreted through kidneys, reabsorbed in proximal tubule
- 5-20% of filtered load excreted, except in malnutrition
- Regulated by parathyroid hormone and calcitriol (1,25 \( \text{vitD} \)), which stimulates phosphate absorption in gut
- Hypophosphatemia: malnutrition, alcoholism
- Hyperphosphatemia: renal failure

### Calcium
- Intracellular levels are low – stored in bone
- PTH regulates vitamin D, urinary Ca excretion and reabsorption
- Vitamin D regulates gut absorption
- Hypocalcemia: vitamin D deficiency, hyperphos / renal failure, hypoparathyroidism
- Hypercalcemia: hyperparathyroidism, malignancy, increased vitamin D (granulomatous production)

### Case
68 year-old man with chronic kidney disease due to type 2 diabetes is evaluated in clinic for nausea, vomiting, and fatigue for the past several weeks. His symptoms started several days after a cardiac catheterization which demonstrated two-vessel coronary artery disease. Physical examination is remarkable for bibasilar crackles, a regular cardiac rhythm, and 2+ peripheral edema.
Case

- Laboratory studies:
  - BUN 110 mg/dL
  - Serum Cr 14.0 mg/dL
  - Serum sodium 135 mEq/L
  - Serum potassium 5.5 mEq/L
  - Serum chloride 80 mEq/L
  - Serum bicarbonate 23 mEq/L
- Arterial blood gas (room air):
  - pH 7.39
  - PCO₂ 39 mmHg
  - PO₂ 72 mmHg
  - Bicarbonate 23 mEq/L

Case Question

Which of the following describes this patient’s acid-base status?
A. No acid-base abnormality
B. Metabolic acidosis and respiratory alkalosis
C. Metabolic acidosis with respiratory compensation
D. Metabolic acidosis and metabolic alkalosis

Acid base disorders: systematic approach is key!
- Identify Primary Disorder
- Calculate the anion gap and learn the use of delta gap
- Know 1 set of compensation methods and apply
- Finalize the acid base disturbance and generate a differential diagnosis for each problem identified

Acid base formulas – expected compensation for primary metabolic disturbance
- Metabolic Acidosis
  - Winter's formula – predicts PCO₂ = (1.5 x HCO₃⁻) + 8 +/- 2
- Metabolic Alkalosis
  - 0.6 mmHg rise in PCO₂ per 1 meq/L elevation in plasma [HCO₃⁻]
Expected compensation for primary respiratory disturbance

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<thead>
<tr>
<th>Acute respiratory acidosis</th>
<th>Acute respiratory alkalosis</th>
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<tbody>
<tr>
<td>1 meq/L increase in plasma [HCO₃⁻] per 10 mmHg rise in PCO₂</td>
<td>2 meq/L decrease in plasma [HCO₃⁻] per 10 mmHg decrease in PCO₂</td>
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<tr>
<th>Chronic respiratory acidosis</th>
<th>Chronic respiratory alkalosis</th>
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<tbody>
<tr>
<td>3.5 meq/L elevation in plasma [HCO₃⁻] per 10 mmHg increase in PCO₂</td>
<td>4 meq/L decrease in plasma [HCO₃⁻] per 10 mmHg decrease in PCO₂</td>
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Case: Laboratory studies

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  - PO₂ 72 mmHg
  - Bicarbonate 23 mEq/L

Primary disorder: difficult to tell from ABG!

Calculate anion gap = 135-80-23 = 32; there is DEFINITELY an anion gap metabolic acidosis

Case: Laboratory studies

- Is there a secondary disorder?
  - BUN 110 mg/dL
  - Serum Cr 14.0 mg/dL
  - Serum sodium 135 mEq/L
  - Serum potassium 5.5 mEq/L
  - Serum chloride 80 mEq/L
  - Serum bicarbonate 23 mEq/L
  - Arterial blood gas (room air):
    - pH 7.39
    - PCO₂ 39 mmHg
    - PO₂ 72 mmHg
    - Bicarbonate 23 mEq/L

Calculate delta delta = 32 – 12 = 20; there is a superimposed metabolic alkalosis!
Case: Mixed disorder

- How do we know there is a superimposed metabolic alkalosis?
- BUN 110 mg/dL
- Serum creatinine 14.0 mg/dL
- Serum sodium 135 mEq/L
- Serum potassium 5.5 mEq/L
- Serum chloride 80 mEq/L
- Serum bicarbonate 23 mEq/L + 20 = 43 higher than normal serum bicarb of 24 = metabolic alkalosis – change in bicarb ascended by change in anion gap – see diagram

- Arterial blood gas (room air):
  - pH 7.39
  - PCO2 39 mmHg
  - PO2 72 mmHg
  - Bicarbonate 23 mEq/L

Case: Laboratory studies

- Is there a third disorder?
- BUN 110 mg/dL
- Serum Cr 14.0 mg/dL
- Serum sodium 135 mEq/L
- Serum potassium 5.5 mEq/L
- Serum chloride 80 mEq/L
- Serum bicarbonate 23 mEq/L

Arterial blood gas (room air):
  - pH 7.39
  - PCO2 39 mmHg
  - PO2 72 mmHg
  - Bicarbonate 23 mEq/L

Calculate expected respiratory compensation. Winter's formula predicts pCO2 should be 43 +/- 2. pCO2 of 39 close enough to predicted pCO2 of 43 +/- 2. No third disorder.

Case Question

Which of the following describes this patient’s acid-base status?
A. No acid-base abnormality – not true although the ABG is deceiving!
B. Metabolic acidosis and respiratory alkalosis
C. Metabolic acidosis with respiratory compensation – examples on subsequent slides
D. Metabolic acidosis and metabolic alkalosis

Correct answer is D. Metabolic (gap) acidosis from DKA / renal failure plus metabolic alkalosis from vomiting.
Example: metabolic acidosis and respiratory alkalosis (choice B)

- Na 140 K 5.0 Cl 105 HCO3 15
- pH 7.4 pCO2 25
- AG 140-105-15 = 20
- Predicted pCO2 = 22.5+ 8 +/- 2 = 30.5 +/- 2
- 25 is less than 30 = superimposed respiratory alkalosis (mild)

- What if pH were 7.5, pCO2 20?
- More severe superimposed respiratory alkalosis

Example: metabolic gap acidosis with respiratory compensation (choice C)

- Na 140 K 4.5 Cl 105 HCO3 12
- pCO2 26 pH 7.29
- AG = 140-105-12 = 23
- Predicted pCO2 = 18 + 8 +/- 2 = 26 +/- 2

Metabolic disturbances

1) Metabolic acidosis
2) Metabolic alkalosis
3) Gap metabolic acidosis
4) Gap metabolic acidosis AND nongap metabolic acidosis (!!!) ≠ 2 completely different disorders
5) Gap metabolic acidosis AND metabolic alkalosis

Anion gap metabolic acidosis

- Increased Anion Gap
- MUDPILES (methanol, uremia, DKA, paraldehyde, isoniazid, lactic acidosis, ethylene glycol, salicylate)
- AG > 20 implies metabolic acidosis regardless of serum bicarbonate or pH

Serum Anion Gap = Na – Cl – HCO3
Normal AG < 12
Aside: DDx Decreased Anion Gap

- Extra Positive (+) charges
  - Immunoglobulins (myeloma)
  - Lithium
  - Potassium
  - Magnesium
  - Calcium
- Decreased Negative (-) charges
  - Albumin
- Corrected AG = add 2.5 to the AG for every 1 g/dL drop in albumin

Case

- A 56 yo man with h/o alcoholism is found lying on the street with impaired consciousness. On arrival at ED, he is unresponsive and is intubated.
- Exam: Temp 97°F, pulse 70, BP 126/80
- Funduscopic exam: no papilledema
- Cardiac, pulmonary, abdominal exams normal. No edema.

Laboratory studies

- Glucose 86 mg/dl
- Blood urea nitrogen 45 mg/dl
- Creatinine 2.8 mg/dl
- Sodium 138 mmol/L
- Potassium 5.4 mmol/L
- Chloride 94 mmol/L
- Bicarb 14 mmol/L
- Plasma osmolality 316 mosm/kg H2O
- ABG pH 7.28 / pCO2 29 / PO2 108
- UA calcium oxalate crystals

Case Question

Which of the following is the most appropriate treatment for this patient?
A. Fomepizole and hemodialysis
B. Bicarbonate supplementation
C. Ethanol drip
D. Hemodialysis
E. Fomepizole and ethanol drip
Case answer review

A. Fomepizole and hemodialysis – correct answer – ethylene glycol poisoning – block metabolism with fomepizole and remove / treat severe acidosis with dialysis
B. Bicarbonate supplementation – could be a temporizing measure, but is inadequate on its own
C. Ethanol drip – ethanol can also be used but more toxic – sometimes fomepizole is not available
D. Hemodialysis – on its own insufficient because does not block ethylene glycol metabolism
E. Fomepizole and ethanol drip – do not use both concurrently because fomepizole prolongs ethanol half-life

Osmolar Gap

Osmolar Gap =

\[ \text{Estimated Osms} = 2\text{Na} + \frac{\text{BUN}}{2.8} + \frac{\text{glucose}}{18} + \frac{\text{EtOH}}{4.6} \]

Normal Osmolar Gap < 10

Osmolar Gap

Major conditions with increased osmolar gap
- Same as for Anion gap (MUDPILES)
- Conditions = uremia, DKA, alcoholic ketoacidosis, lactic acidosis
- PLUS ingestions = methanol, paraldehyde, formaldehyde, ethylene glycol
- Normal AG, no metabolic acidosis
- Exogenous = isopropanol, diethyl ether, mannitol
- Artifact = hyperproteinemia, hypertglycemia (artificial lowering of serum sodium concentration)

Metabolic acidosis: Non-anion gap

- Normal gap (non-gap) metabolic acidosis
- Also called hyperchloremic metabolic acidosis
- Primary decrease in serum bicarb with increase in serum chloride
- GI: Diarrhea with bicarbonate loss
- Negative urine anion gap
- Renal: Renal tubular acidosis (RTA)
- Positive urine anion gap (think, “if it’s the kidney, it’s positive!”)
Urine anion gap

- Unmeasured anions + measured anions = unmeasured cations + measured cations
- Rearrange equation:
  - Unmeasured anions - unmeasured cations = urine AG = measured cations - measured anions
  
  Urine Anion Gap = Na + K - Cl

Normal UAG in acidosis is negative (because unmeasured cation term is LARGE from ammonium ions – which is the normal renal response to acidosis)

RTA = Urine K is high = UAG becomes positive

Diarrhea = GI losses of bicarb -> low urine bicarb (lower unmeasured anions) = negative UAG = “neGUTive”

Case

- A 22 yo woman with a history of Sjogren’s syndrome presents with a 1 week history of progressive weakness
- Physical Exam: Diffuse muscle weakness, normal DTRs

Laboratory studies:
- BUN 20 mg/dL
- Serum Cr 0.7 mg/dL
- Serum sodium 140 mEq/L
- Serum potassium 2.2 mEq/L
- Serum chloride 120 mEq/L
- Serum bicarbonate 12 mEq/L
- Arterial blood gas (room air): pH 7.1
  - PCO2 40 mmHg
  - PO2 72 mmHg
- Urine pH 6.5
- Urine Na 95 K 32 Cl 90 (UAG = 37)

Case Question

Which of the following describes this patient’s acid-base status?
A. No acid-base abnormality
B. Metabolic acidosis and respiratory acidosis
C. Metabolic acidosis with respiratory compensation
D. Metabolic acidosis and metabolic alkalosis
Case

• Laboratory studies:
  • BUN 20 mg/dL
  • Serum Cr 0.7 mg/dL
  • Serum sodium 140 mEq/L
  • Serum potassium 2.2 mEq/L
  • Serum chloride 120 mEq/L
  • Serum bicarbonate 12 mEq/L
  • Arterial blood gas (room air):
    • pH 7.1
    • PCO2 40 mmHg
    • PO2 72 mmHg
  • Urine pH 6.5
  • Urine Na 95 K 32 Cl 90 (UAG = 37)

Calculate anion gap. 140 - 120 - 12 = 8. No anion gap.
Calculate predicted respiratory compensation. 18 + 8 +/- 2 = 26 +/- 2

Case answer review

Which of the following describes this patient’s acid-base status?

A. No acid-base abnormality
B. Metabolic acidosis and respiratory acidosis – right answer – metabolic acidosis from type I RTA, respiratory acidosis from poor muscle function
C. Metabolic acidosis with respiratory compensation
D. Metabolic acidosis and metabolic alkalosis

Renal tubular acidosis – non gap met acid

<table>
<thead>
<tr>
<th>Type</th>
<th>Defect</th>
<th>Urine pH</th>
<th>Plasma K</th>
<th>Dose of bicarbonate</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 Distal</td>
<td>↓ distal acidification</td>
<td>&gt; 5.3</td>
<td>Low or normal, can be high</td>
<td>Low</td>
<td>Nephrocalcinosis and nephrolithiasis</td>
</tr>
<tr>
<td>Type 2 Proximal</td>
<td>↓ proximal HCO3 reabsorption</td>
<td>&gt; 5.3 early &lt; 5.3 late</td>
<td>Low or normal, can be high</td>
<td>High</td>
<td>Renal tubular acidosis or osteomalacia</td>
</tr>
<tr>
<td>Type 4</td>
<td>Aldosterone deficiency or resistance</td>
<td>Usually &lt; 5.3</td>
<td>High</td>
<td>Low</td>
<td>None</td>
</tr>
</tbody>
</table>

Non-gap Metabolic Acidosis: Stepwise Analysis

• Examine serum K
  - If high, then type 4 RTA
  - If normal, then type 1 or type 2
• Urine pH
  - If urine pH > 5.5, then Type 1 (Distal)
  - If urine pH < 5.0, then Type 2 (Proximal)
  - If type 2 Proximal RTA
    - Confirm with evidence of proximal tubular dysfunction
      - Glycosuria, low-grade proteinuria, phosphaturia
Case

A 22 year-old woman comes to the emergency room with paresthesias and generalized weakness.

She has no significant medical history and does not take any medications.

Her blood pressure is 120/72 and physical exam is unremarkable.

Case Question

Which of the following is the most likely diagnosis?
A. Surreptitious vomiting
B. Surreptitious active diuretic use
C. Gitelman syndrome
D. Bartter syndrome
E. Liddle syndrome

Case, continued

<table>
<thead>
<tr>
<th>Labs</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>pH 6.0</td>
</tr>
<tr>
<td>K</td>
<td>&lt;5 mEq/L</td>
</tr>
<tr>
<td>Cl</td>
<td>16 mEq/L</td>
</tr>
<tr>
<td>Ca</td>
<td>20 mEq/L</td>
</tr>
<tr>
<td>Mg</td>
<td>14 mg/dL</td>
</tr>
<tr>
<td>Ca</td>
<td>1.0 mg/dL</td>
</tr>
<tr>
<td>Ca</td>
<td>1.9 mg/dL</td>
</tr>
<tr>
<td>Ca</td>
<td>9.0 mg/dL</td>
</tr>
</tbody>
</table>

Calculate urine anion gap. 16+20-5 = 31. Positive UAG.
Case answer review

A. Surreptitious vomiting – right answer – extracellular volume depletion – chloride retention by kidney - lots of urine bicarb (high unmeasured anion makes UAG pos – remember “neGUTive” is only in met ACIDOSIS)

B. Surreptitious active diuretic use – would expect higher urine chloride

C. Gitelman syndrome – autosomal recessive – mimics thiazide diuretics - hypocalciuria

D. Bartter syndrome – autosomal recessive, mimics loop diuretics

E. Liddle syndrome – autosomal dominant gain of function of epithelial sodium channel – associated with elevated BP, hypokalemic metabolic alkalosis, low renin, low aldo – low urine chloride but history not supportive

Pathogenesis of Metabolic Alkalosis

- Generation, then maintenance
- Generation: net gain of bicarb versus net loss of hydrogen
  - Exogenous HCO₃⁻ loads: acute alkali administration, Milk-alkali syndrome, pica
  - ECV contraction with high renin and high aldo
    - GI losses: vomiting, gastric aspiration
    - Renal origin: diuretics (thiazide / loop)

- Hypokalemia
- Bartter, Gitelman
- ECV expansion with hypermineralocorticidism
  - High renin: RAS
  - Low renin: primary aldosteronism

Maintenance of Metabolic Alkalosis

Reduced renal bicarbonate excretion due to:

- Effective circulating volume depletion
  - Reduction in the filtered load of HCO₃⁻
  - Secondary aldosteronism (paradoxic aciduria)
- Chloride depletion
  - Vomiting and diuretics
- Hypokalemia
  - Intracellular shifting of potassium and hydrogen ions

Urine Chloride in Metabolic Alkalosis

- Vomiting and long term diuretic use
  - Depleted body chloride stores
  - Kidneys will conserve/reabsorb chloride
  - Urine Cl < 15 mEq/L
  - Urine Cl will be elevated with ACTIVE diuretic use
- Primary aldosteronism
  - Volume expanded
  - Urine Cl > 20 mEq/L
Saline and Alkalosis

- **Saline Responsive** = Low urine Cl < 15
  - Vomiting or nasogastric suction
  - Diuretics
  - Post-hypercapnic alkalosis
  - Low dietary chloride intake

- **Saline Unresponsive** = High urine Cl > 20
  - Mineralocorticoid excess
  - Severe hypokalemia
  - Edematous disorders, e.g. CHF
  - Bartter / Gitelman

Example: post-hypercapnic metabolic alkalosis

- Na 140 K 5 Cl 100 HCO3 31 (AG 9)
- pCO2 55 pH 7.37

  - pH is low, pCO2 is HIGH = respiratory acidosis
  - Calculate expected metabolic compensation
    - Delta pCO2 = 15
    - Divide 15 by 10, then multiply by 3.5 (for chronic compensation since pH relatively normal)
    - Expected serum HCO3 = 24 + 5.25 = 29.25

  - If you intubated this person, serum bicarb would remain elevated until volume status corrects

Example

- Na 140 K 3.5 Cl 92 HCO3 34 AG 12
- pCO2 55 pH 7.41

  - pCO2 high = respiratory acidosis
  - Predicted bicarb 30 (24 + 1.5 * 3.5)
  - Actual bicarb higher = concomitant metabolic alkalosis (which explains pH > 7.4)

  - OR start with metabolic alkalosis
  - Predicted pCO2 = 0.7 * 34 = 23.8 + 20 = 43.8 +/- 5
  - Actual pCO2 higher = concomitant respiratory acidosis

Acid base formulas

- **Metabolic Acidosis**
  - Winter's formula pCO2 = (1.5 x HCO3) + 8 +/- 2
  - If you don't like Winter's formula: expected pCO2 is [HCO3] + 15

- **Metabolic Alkalosis**
  - 0.6 mmHg rise in pCO2 per 1 meq/L elevation in plasma [HCO3-]
  - pCO2 = 0.7 [HCO3-] + 20 +/- 5
Acid base formulas

Respiratory Acidosis
- **Acute:**
  - 1 meq/L increase in plasma \([HCO_3^-]\) per 10 mmHg rise in PCO2
  - \(\Delta[H^+] = 0.8 \Delta PCO2\)
- **Chronic:**
  - 3.5 meq/L elevation in plasma \([HCO_3^-]\) per 10 mmHg increase in PCO2
  - \(\Delta[H^+] = 0.3 \Delta PCO2\)

Respiratory Alkalosis
- **Acute:**
  - 2 meq/L decrease in plasma \([HCO_3^-]\) per 10 mmHg decrease in PCO2
  - \(\Delta[H^+] = 0.8 \Delta PCO2\)
- **Chronic:**
  - 4 meq/L decrease in plasma \([HCO_3^-]\) per 10 mmHg decrease in PCO2
  - \(\Delta[H^+] = 0.4 \Delta PCO2\)

ACUTE KIDNEY INJURY

Case

A 57-yr-old man is admitted after a motor vehicle accident. He has sustained multiple fractures and blunt chest and abdominal trauma. A left hemothorax is treated with a chest tube, an abdominal lavage reveals only minimal blood, and a noncontrast computed tomography (CT) scan of the abdomen is negative. He is volume-resuscitated with approximately 15 L of crystalloid. Twenty-four hours after admission, he is noted to have marked abdominal distension and low urine output.
### Case

**Physical Exam:**
- Tm 37.2 BP 135/86 HR 86 RR 16 UOP 100 cc/12h
- CVP 18 Bladder pressure 28
- Intubated, sedated
- Decreased breath sounds at bases
- Regular heart sounds, no m/r/g
- Abdomen distended and firm, hypoactive BS

**Labs:**
- Na 135
- K 5.8
- Cl 103
- HCO3 24
- BUN 46
- Cr 2.3
- Imaging: Small retroperitoneal hematoma, normal sized kidneys without hydronephrosis, marked ascites.

### Case Question

Which of the following would be the most appropriate next step?

A. Abdominal decompression
B. Fluid resuscitation
C. Placement of bilateral ureteral stents
D. Initiation of renal replacement therapy

### Case answer review

A. Abdominal decompression - correct answer - Intraabdominal hypertension (IAH) is defined as a sustained intraabdominal pressure >12 mmHg. Abdominal compartment syndrome (ACS) is defined as a sustained intraabdominal pressure >20 mmHg that is associated with new organ dysfunction

B. Fluid resuscitation – correct answer for AKI from hypovolemia / some cases of pre-renal azotemia

C. Placement of bilateral ureteral stents – sometimes indicated for obstruction

D. Initiation of renal replacement therapy – indicated for emergencies including acidosis, electrolyte abnormalities, ingestions, volume overload, and uremia
### Acute Renal Failure / Acute Kidney Injury
- **Pre-Renal** = Decreased kidney perfusion
- **Intra-Renal** = Intrinsic kidney injury
- **Post-Renal** = Obstruction

### Fractional Excretion of Sodium (FeNa)
- Percent of filtered sodium that is excreted in the urine
- \[ \text{FeNa} = \frac{(U_{Na} \times P_{Cr})}{(P_{Na} \times U_{Cr})} \times 100 \]
- \(<1\%\) consistent with pre-renal state
- Only useful when patient is oliguric (< 400 cc urine output/24 hours)
- Confounded by use of diuretics

### Pre-Renal: Kidney Hypoperfusion
- Dehydration, overdiuresis, hypovolemia
- Abdominal compartment syndrome: Typically occurs after massive volume resuscitation
- Hemorrhage
- Hemodynamic effect: ACE/ARB and NSAIDs
- Heart failure
  - Cardiorenal syndrome
- Cirrhosis/End-stage liver disease
  - Hepatorenal syndrome

### Pre-Renal: Kidney Hypoperfusion
- Diagnosis
  - +/- Oliguria
  - High BUN:Creatinine ratio > 20
  - Bland urine sediment, normal kidney US
  - Low FENa < 1% and low urine Na <10 mEq/L
  - High specific gravity, high urine osmolality
  - Rapid renal recovery with resuscitation
- Therapy: Restore renal perfusion
- Prognosis: Good, often rapid renal recovery
  - Exceptions: Cardiorenal and hepatorenal syndromes
Pre-renal: Hepatorenal Syndrome
- Severe end-stage liver disease patients
- Intense renal vasoconstriction
- Diagnosis of exclusion
  - Oliguria
  - Low urine sodium < 10 mEq/L, low FENa < 1%
  - Hypernatremia
  - Bland urine sediment
  - Normal US (no hydronephrosis)
  - No other identifiable cause
- Treatment
  - Splanchnic vasoconstrictors (terlipressin, ornipressin), midodrine, octreotide; TIPS controversial; liver transplant

Post-Renal: Obstruction
- Urinary tract obstruction
  - Renal pelvis, ureters, bladder, prostate, urethra
  - Congenital and acquired lesions, BPH
  - Neurogenic bladder, medication effects
  - Nephrolithiasis
  - Malignancy
  - GI cancers
  - Prostate cancers
  - Uterine, cervical, ovarian cancers
  - Lymphadenopathy
  - Retroperitoneal fibrosis

Post-Renal: Obstruction
- Clinical
  - Oliguric or non-oliguric
  - Can have type 4 RTA, metabolic acidosis
  - Foley does not definitively rule out obstructive nephropathy
  - Hydronephrosis, although negative ultrasound does not rule out obstructive nephropathy
- Therapy
  - Correct obstruction; can see post-obstructive diuresis from urinary concentrating defect
  - Urology consultation
  - Interventional radiology consultation: nephrostomy tubes

Intra-Renal: Acute Tubular Necrosis (ATN)
- Etiology
  - Ischemic = hypotension, sepsis, shock, hemorrhage
  - Toxic
    - Exogenous: intravascular radioccontrast, aminoglycosides, amphotericin, cisplatin, oxalate (ethylene glycol/antifreeze ingestion)
    - Endogenous: rhabdomyolysis (myoglobin), hemolysis (hemoglobin), tumor lysis (urate)
- Diagnosis
  - Muddy brown/pigmented casts in urine sediment
  - Elevated FENa > 1-2%
  - High urine Na > 20 mEq/L
**Intra-Renal:**

**Acute Tubular Necrosis (ATN)**

- **Prognosis**
  - Mortality: 40-70% in ICU if dialysis-requiring AKI
  - Slower recovery
- **Therapy**
  - Supportive care
  - Dialysis as needed
  - Fluid and electrolyte management
  - Medication dosing adjustment for GFR
  - No proven therapies
  - No benefit: mannitol, furosemide, dopamine, ANP, thyroxine

**Radiocontrast Nephropathy**

- **Etiology**
  - Iodine-based radiocontrast
  - Intravenous or intraarterial injection
  - CT, angiography, cardiac catheterization
- **Risk factors**
  - Pre-existing chronic kidney disease
  - Proteinuria
  - Age
  - Diabetes mellitus
  - Multiple myeloma
  - Dehydration

**Presentation**

- Rise in creatinine 24-48 hours post-exposure
- Patient with risk factors
- Low FENa < 1%
- Bland sediment (mild forms with vasoconstriction) or muddy brown casts of ATN (severe forms with toxic injury)
- **Prognosis**
  - Mild cases resolve within 2-5 days, likely vasoconstriction mediated ARF
  - Severe cases resolve slowly over days to weeks, require dialysis, and may be irreversible due to toxin-induced ATN

**Prevention**

- Avoid radiocontrast (US, nuclear medicine)
- Minimize dose of radiocontrast
- Use iso-osmolar or hypo-osmolar contrast (as opposed to hyperosmolar contrast)
- IVF: Isotonic sodium bicarbonate vs. normal saline
- N-Acetylcysteine (KDIGO yes, AHA no)
- Hold diuretics peri-contrast, avoid hypovolemia
- No clear benefit of post-contrast dialysis
- Many meta-analyses
  - Brar, CJASN 2009
  - Kshirsagar, JASN 2004
Gadolinium based MRI agents – a word of caution

- Nephrogenic systemic fibrosis
  - Syndrome associated with MRI-based gadolinium administration
  - Patients with both acute renal failure/kidney injury and chronic kidney disease (especially) are at risk
  - Studies to ascertain incidence are ongoing
  - Rarer than radiocontrast nephropathy, but can be debilitating and fatal
  - Post-contrast hemodialysis is recommended
- Recent reviews

Intra-Renal: Rhabdomyolysis

- Etiology
  - Crush injury, muscle trauma/ischemia/inflammation
  - Prolonged immobilization: coma, ethanol, earthquake victims
  - Fevers/ripgs, seizures
  - Toxic injury: statins, cocaine, reverse transcriptase inhibitors
  - Metabolic: Hypokalemia, hypophosphatemia
  - Genetic: McArdle disease

Intra-Renal: Rhabdomyolysis

- Diagnosis
  - High serum uric acid, phosphate, potassium
  - Hypocalcemia
  - Elevated serum CK (along with AST/ALT)
  - Dipstick heme+ from myoglobinuria
  - UA negative for RBCs
  - Urine sediment with ATN, muddy brown casts
- Treatment
  - Aggressive and early hydration
  - Alkalization of urine vs. NS hydration alone?
  - Stop offending medications

Intra-Renal: Acute Interstitial Nephritis (AIN)

- Etiology
  - Medications = antibiotics (beta lactams), NSAIDs, diuretics, PPIs, others
  - Infections = bacterial, fungal, viral, others
  - Immune disorders = SLE, Sjogren’s, sarcoidosis
- Presentation
  - Fever (27%), drug rash (15%), eosinophilia (23%)
  - Minority of patients have complete triad (10%)
  - Arthralgias
  - NSAID-AIN may have proteinuria from concomitant minimal change disease
  - AIN is often occult, should be suspected if no other apparent etiology of AKI or if new medication started – time frame very variable
Intra-Renal: Acute Interstitial Nephritis (AIN)

- **Diagnosis**
  - Sterile pyuria, WBC casts, eosinophilia
  - Clinical diagnosis: kidneys improve after stopping offending drug (which may be a chronic medication or one tolerated safely in the past)
  - Kidney biopsy
  - Skin biopsy (leukocytoclastic vasculitis)

- **Therapy**
  - Stop offending drugs
  - Treat underlying infection
  - Consider oral steroids (e.g., prednisone 60 mg PO daily), lack of large randomized controlled trials showing efficacy

Intra-Renal: Atheroembolic Disease

- **Etiology**
  - Spontaneous/idiopathic
  - Anticoagulation
  - Instrumentation: aortic surgery/cross-clamping, CABG, angiography, cardiac catheterization

- **Presentation**
  - Stuttering, inexorable rise in serum creatinine
  - Livedo reticularis, stigmata of embolism
  - Triad: precipitating event, subacute/acute AKI, skin findings
  - Non-specific urine sediment
  - Often occult, should be considered if no obvious etiology

- **Diagnosis**
  - Often clinical diagnosis, embolic skin findings
  - Low complements C3 and C4
  - Eosinophilia and eosinophiluria
  - Retinal embolization (Hollenhorst plaques)
  - Skin biopsy, kidney biopsy

- **Therapy**
  - Supportive. Stop anticoagulation?

- **Prognosis**
  - Poor, generally irreversible
  - Heavy burden of cardiovascular disease

Intra-Renal: Thrombotic Microangiopathy

- Can be associated with albuminuria and dysmorphic hematuria
- Spectrum: renal-limited to thrombotic thrombocytopenic purpura (fever, microangiopathic hemolytic anemia, thrombocytopenia, renal failure, neurologic manifestations)
- Causes: drugs, diarrheal syndromes, antiphospholipid antibodies, lupus, HIV, hematopoietic stem cell transplantation
- Associated with scleroderma renal crisis, malignant hypertension, calcineurin inhibitors
Common Etiologies of Kidney Injury in HIV-infected Patients

**Pre-renal**
- Dehydration
- NSAID

**Obstruction**
- Acute Tubular Necrosis
  - (RBC, casts, edema)
- Glomerular lesion
  - HIVAN
- Acute Interstitial Nephritis
  - (Proteinuria, +/− RBC)
  - (Pyuria, WBC casts)
- Hypotension/Sepsis
  - HIVAN
- Acyclovir
- Indinavir

**Renal**
- Muddy brown casts → ATN
- Red cell casts and/or dysmorphic RBCs → GN
- White cell casts → AIN, pyelonephritis

**HUS**
- Sulfadiazine
- NSAID
- HUS
- Acyclovir
- Indinavir

**HIV AN**
- Trimethoprim-
  - Sulfamethoxazole
- NSAID (proteinuria)
- Rifampin

HIV may be coincident with:
- HBV: Membranous > MPGN
- HCV: MPGN, cryoglobulinemia
  > Membranous

Diagnostics in AKI

- **BUN:Creatinine Ratio**
  - BUN/Cr > 20 pre-renal
  - Many causes of azotemia/elevated BUN (steroids, hypercatabolic states, total parenteral nutrition)
  - Overused

- **Renal Ultrasound**
  - Never wrong to R/O obstruction
  - Safe, fast, and cheap
  - Small kidneys suggest element of chronic kidney disease (AKI on CKD vs. CKD)

Diagnostics in AKI

- **24 Hour Urine for CrCl and Proteinuria**
  - Not helpful if serum creatinine not stable
  - Predictive formulas (CrCl, eGFR) should not be used if Cr is not at steady state!

- **Serologies and Kidney Biopsy**
  - Usually not necessary with careful history, physical, and urine sediment exam
  - Serologies are low yield: ANA, ANCA, anti-GBM, ASO, cryoglobulins, HIV, HCV, HBV
  - Biopsy will often find occult atheroembolic disease or AIN
SECONDARY HYPERTENSION

Case
- 68 yo lady with h/o poorly controlled hypertension is evaluated for primary aldosteronism.
- Blood pressure is 176/105 mmHg
- CV exam S3 gallop
- Lungs clear
- Plasma renin activity 0.06 ng/ml
- 24 hour urine aldosterone 18 mcg per day
- Adrenal CT scan reveals 1.5 cm solitary nodule in left adrenal gland. Right adrenal gland appears normal to slightly enlarged.

Case Question
Which of the following is the most appropriate next step in this patient's management?
A. Laparoscopic left adrenalectomy
B. Adrenal vein sampling for aldosterone and cortisol
C. Renal arteriography
D. Dexamethasone suppression test

Case answer review
A. Laparoscopic left adrenalectomy – Conn’s syndrome = aldosterone-producing adenoma – cure rate from resection only in 50-60% because of smaller functioning nodules
B. Adrenal vein sampling for aldosterone and cortisol – correct answer – document unilateral secretion of aldosterone and suppression from contralateral gland, esp if age >40; cortisol shows that sample obtained from adrenal vein (rather than IVC)
C. Renal arteriography – treatment will be aldosterone blockade – even in renal artery stenosis, med mgt favored over intervention
D. Dexamethasone suppression test – diagnose glucocorticoid-remediable hyperaldosteronism
Renovascular hypertension

- Clinical Features
  - Secondary HTN
  - Flash pulmonary edema
  -Kidney size asymmetry > 1.5 cm
  - AKI after initiation of ACE inhibitor/ARB
- Diagnosis
  - CTA, MRA, conventional angiography
  - Ultrasound: highly operator/institution dependent

Renal Artery Stenosis

- Atherosclerosis - #1 cause
  - Men and women, age > 50
  - Proximal/ostial lesions
  - Complete occlusion and renal atrophy are common
  - Medical management

- Fibromuscular Dysplasia
  - Women, younger, 15-40
  - Mid-vessel disease, can affect multiple vessels
  - String of beads appearance on angiography
  - Complete occlusion and renal atrophy are rare
  - Often reversible with angioplasty

Classic “string of beads” – medial fibroplasia
Lesions occur in mid to distal vessel
(Atherosclerotic disease – more proximal - closer to origin)

References

- Primer on Kidney Diseases, 5th Edition
- American College of Physicians Medical Knowledge Self-Assessment Program, Nephrology section

- THANK YOU FOR YOUR ATTENTION