



ABIM Certification Exam: Nephrology

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UCSF CME

Division of Nephrology
Department of Medicine

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NEPHROLOGY



Division of
Nephrology

Nephrology/Urology 6% of ABIM Exam

- Acute renal failure*
- Chronic kidney disease*
- Tubulointerstitial disease*
- Glomerular disorders*
- Hypertension*
- UTI
- Nephrolithiasis*
- Other kidney disorders*

Nephrology/Urology 6% of ABIM Exam

- **Urologic cancer**
- **Prostate disorders**
- **Other urology**
- **Urinary Incontinence**
- **Water and electrolyte balance***
- **Miscellaneous bladder and kidney disorders**

Acute Renal Failure/Kidney Injury

- **Pre-Renal = Decreased kidney perfusion**
- **Intra-Renal = Intrinsic kidney disease**
- **Post-Renal = Obstructive nephropathy**

Pre-Renal ARF: Kidney Hypoperfusion

- Dehydration, overdiuresis, hypovolemia
- Hemorrhage
- Hemodynamic effect: ACE/ARB and NSAIDs
- Heart failure
 - Cardiorenal syndrome
- Cirrhosis/End-stage liver disease
 - Hepatorenal syndrome

Pre-Renal ARF: 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 ARF: Hepatorenal Syndrome

- **Severe end-stage liver disease patients**
- **Intense renal vasoconstriction**
- **Diagnosis of exclusion**
 - Oliguria
 - Low urine sodium < 10 mEq/L, low FENa < 1%
 - Hyponatremia
 - Bland urine sediment
 - Normal US (no hydronephrosis)
 - No other identifiable cause
 - Lack of response to volume expansion

Pre-renal ARF: Hepatorenal Syndrome

- **Treatment**
 - Splanchnic vasoconstrictors (terlipressin, ornipressin), midodrine, octreotide
 - TIPS (transjugular intrahepatic portosystemic shunt)
 - Dialysis as bridge to liver transplant
 - Liver transplant

Post-Renal ARF: 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 ARF: Obstruction

- **Clinical**
 - Oliguric or non-oliguric
 - Can have type 4 RTA, metabolic acidosis
 - Foley does not definitively rule out obstructive nephropathy
 - Hydronephrosis on US, although negative US does not rule out obstructive nephropathy
- **Therapy**
 - Correct obstruction
 - Urology consultation
 - Interventional radiology consultation: nephrostomy tubes

Post-Renal ARF: Obstruction

■ Prognosis

- More rapid recovery with rapid correction of obstruction
- Can recover kidney function after prolonged obstruction
- Post-obstructive diuresis from urinary concentrating defect

Case

A 65 year-old woman is admitted to the hospital with newly diagnosed diffuse B cell lymphoma for induction chemotherapy. 24 hours after induction chemotherapy, she is noted to be oliguric.

Physical exam

T 38.4, BP 95/60, HR 94, RR 24

Heart is normal.

Lungs are clear, though she is mildly tachypneic

Trace-1+ pitting edema

Case

Labs

- Na 138
- K 6.0
- Cl 95
- HCO₃ 19
- BUN 43 mg/dL
- Creatinine 3.4 mg/dL
- Ionized Ca 0.79 mmol/L
- PO₄ 9.9 mg/dL
- Uric acid 11.1 mg/dL

Case Question

What is the most likely diagnosis?

- A.** Rhabdomyolysis
- B.** Tumor lysis syndrome
- C.** Cisplatin nephrotoxicity
- D.** Sepsis associated ATN

Intra-Renal ARF: Acute Tubular Necrosis (ATN)

■ Etiology

- Ischemic = hypotension, sepsis, shock, hemorrhage
- Toxic
 - Exogenous: intravascular radiocontrast, aminoglycosides, amphotericin, cisplatin, oxalate (ethylene glycol/anti-freeze 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 ARF: Acute Tubular Necrosis (ATN)

■ Prognosis

- Mortality: 40-70% in ICU ARF requiring dialysis
- 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

Intra-Renal ARF: 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

Intra-Renal ARF: Radiocontrast Nephropathy

■ 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

Intra-Renal ARF: Radiocontrast Nephropathy

■ Prevention

- Avoid radiocontrast (US, nuclear medicine)
- Minimize dose of radiocontrast
- Use iso-osmolar or hypo-osmolar contrast (as opposed to hyperosmolar contrast)
- N-Acetylcysteine
- IVF: Isotonic sodium bicarbonate vs. normal saline
- Hold diuretics peri-contrast, avoid hypovolemia
- No clear benefit of post-contrast dialysis

■ Recent reviews

- Barrett BJ, Parfrey PS. NEJM 2006.
- Pannu N et al. JAMA 2006.

Gadolinium based MRI agents – a word of caution

■ Nephrogenic systemic fibrosis

- Recently described syndrome associated with MRI based gadolinium administration
- Patients with acute renal failure/kidney injury and chronic kidney disease are at risk
- Studies to ascertain incidence are ongoing
- Rarer than radiocontrast nephropathy, but can be fatal

■ Recent reviews

- Perazella Clin Journal Amer Soci Neph 2009.

Intra-Renal ARF: Rhabdomyolysis

■ Etiology

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

Intra-Renal ARF: Rhabdomyolysis

■ Diagnosis

- High serum uric acid, phosphate, potassium
- Hypocalcemia
- Elevated serum CK (along with AST/ALT)
- Dipstick hematuria from myoglobinuria
- Negative microanalysis for RBCs
- ATN urine sediment, muddy brown casts

■ Treatment

- Aggressive and early hydration
- Alkalinization of urine vs. NS hydration alone?
- Stop offending medications

Intra-Renal ARF: Acute Interstitial Nephritis (AIN)

■ Etiology

- Medications = antibiotics, NSAIDs, diuretics, PPIs, others
- Infections = bacterial, fungal, viral, others
- Immune disorders = SLE, Sjogrens, sarcoidosis

■ Presentation

- Triad: Fever, drug rash, eosinophilia
- Minority of patients have complete triad
- Arthralgias
- NSAID-AIN may have proteinuria from concomitant minimal change disease
- AIN is often occult, should be suspected if no apparent etiology of ARF or new medication started

Intra-Renal ARF: 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 ARF: Atheroembolic Disease (AED)

■ Etiology

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

■ Presentation

- Stuttering, inexorable rise in serum creatinine
- Livedo reticularis, embolic stigmata
- Non-specific urine sediment
- Often occult, should be considered if no obvious etiology

Intra-Renal ARF: Atheroembolic Disease (AED)

■ 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

Diagnostics in ARF/AKI

Urine sediment

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

Fractional Excretion of Sodium (FENa)

- Only useful in oliguric patients
- The FENa asks, "Why is this patient oliguric?"
- FENa < 1%, pre-renal
- FENa > 1-2%, intra-renal/post-renal
- Many causes of intrinsic ARF with low FENa (rhabdomyolysis, contrast nephropathy, acute GN)
- FENa does not replace a good history/physical

Diagnostics in ARF/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 (ARF on CKD vs. CKD)

Diagnostics in ARF/AKI

- **24 Hour Urine for CrCl and Proteinuria**
 - Not helpful, serum creatinine not stable
 - Estimate proteinuria with spot urine protein:creatinine
- **Predictive Formulas:**
 - Cockcroft-Gault for CrCl
 - MDRD for eGFR
 - Not helpful, serum creatinine not stable
 - Should only be used in CKD patients

Diagnostics in ARF/AKI

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

Case

A 65 year-old man admitted to the hospital for ARF and palpable purpura. He has a history of recurrent enterococcal UTIs. Over the past two weeks, he noticed a lower extremity rash.

Physical exam

T 38.4, BP 170/98, HR 82.

Heart and chest are normal.

No hepatosplenomegaly.

Petechial purpuric rash on lower extremities

No edema.

Case

Labs

- CBC Normal
- Electrolytes Normal
- BUN 68 mg/dL
- Creatinine 3.4 mg/dL
- HCV, cryos Negative
- C3 ↓ 75 mg/dL (normal 88-252 mg/dL)
- C4 ↓ 10 mg/dL (normal 12-72 mg/dL)
- UA 2+ proteinuria, many dysmorphic RBCs
occasional RBC casts

Case Question

Which one of the following studies is most appropriate?

- A. ANCA
- B. Anti-GBM antibodies
- C. Echocardiogram and blood cultures
- D. Spiral CT scan

Glomerulonephritis: Signs and Symptoms

- Hematuria, tea-colored urine
- HTN
- +/- Edema
- +/- Rapid loss of GFR
- Active urine sediment
 - Dysmorphic red blood cells
 - Red cell casts

Non-glomerular Hematuria

- **Bloody/pink urine**
- **Blood clots**
- **Complete absence of proteinuria**
- **Bland urine sediment**
 - Non-dysmorphic red cells
 - No red cells
 - No red cell casts

Chronic Hematuria

- **Benign Familial Hematuria**
- **Alport Syndrome/Hereditary Nephritis**
- **IgA nephropathy**
- **SLE**
- **Nephrolithiasis**

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
- Treatment: Steroids, fish oil(?) in selected patients with more severe disease

Rapidly Progressive Glomerulonephritis (RPGN)

- **Diagnosis**
 - Clinical diagnosis = Loss of 50% GFR in less than one month from glomerular disease
 - Not a pathological diagnosis, does not always correlate with crescents on kidney biopsy.
 - Red cell dysmorphism and RBC casts
- **3 major categories**
 - Immune-Complex Disease
 - Anti-GBM Disease
 - Pauci-immune disease/ANCA Disease

RPGN: Immune Complex (Hypocomplementemic) Disease

■ Post-infectious/Strep GN

- 2-3 weeks after pharyngitis or skin infection
- Strep: elevated ASO and anti-DNase B antibody
- No direct therapy available

■ SLE nephritis

- ANA, anti-dsDNA, anti-Smith antibodies
- Immunosuppression:
 - Steroids
 - Mycophenolate (CellCept) or cyclophosphamide
 - +/- Plasmapheresis

RPGN: Immune Complex (Hypocomplementemic) Disease

■ IgA nephropathy (normal complements)

- Henoch-Schonlein Purpura (HSP) = Abdominal pain, diarrhea, often seen in kids, rarely in adults
- Synpharyngitic hematuria (simultaneous URI with hematuria, compared to post-infectious GN where hematuria occurs 1-2 weeks after URI sxs)

■ MPGN/cryoglobulinemia

- Highly associated with HCV infection
- Cryos: arthralgias, purpura, livedo reticularis
- Rx: Underlying HCV → interferon and ribavirin

RPGN: Anti-GBM Disease

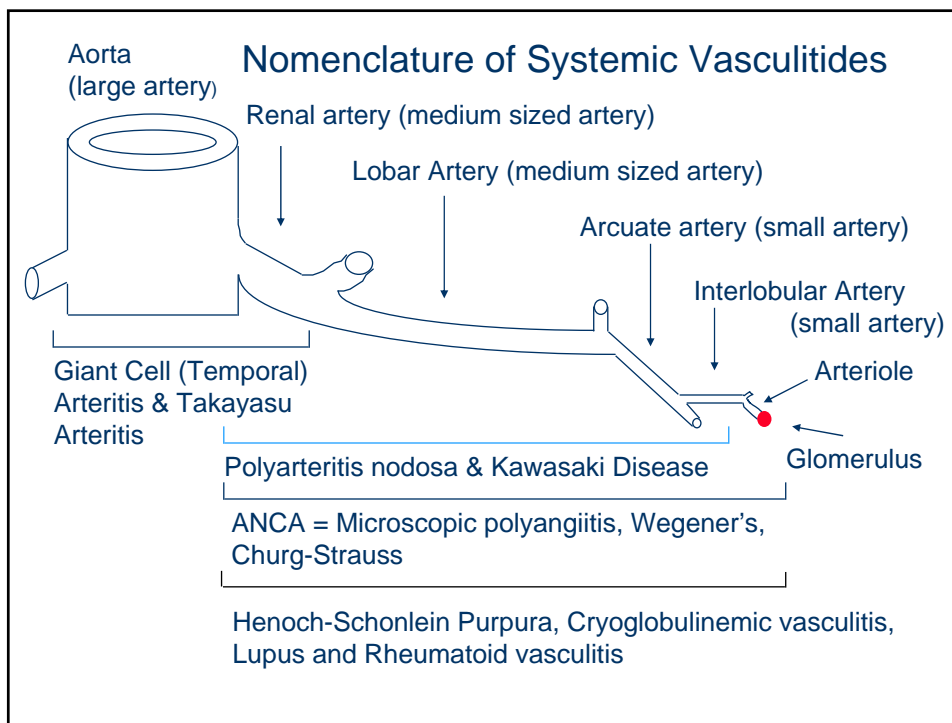
- **Autoimmune disease**
 - Auto-antigen on type IV collagen
 - Renal limited: Anti-GBM Disease
 - Pulmonary renal syndrome: Goodpasture's Syndrome
- **Clinical Features**
 - RPGN +/- hemoptysis/pulmonary hemorrhage
 - Young Caucasian men, recent URI or smoking hx
- **Diagnosis: Anti-GBM titer, kidney biopsy**
- **Rx: Pheresis, steroids, cyclophosphamide**

RPGN: Pauci-Immune/ANCA Disease

- **ANCA: anti-neutrophil cytoplasmic Ab**
 - p-ANCA/myeloperoxidase, MPO
 - c-ANCA/proteinase 3, PR3
- **Normal complements**
- **Immunofluorescence: Few immune complexes**

RPGN: Pauci-Immune/ANCA Disease

- **Microscopic polyangiitis (p-ANCA)**
 - Steroids/cyclophosphamide
- **Wegener's granulomatosis (c-ANCA)**
 - Lung disease, upper airway disease
 - Granulomas
 - Steroids/cyclophosphamide, +/- pheresis if severe
- **Churg-Strauss Disease (p-ANCA)**
 - Eosinophilia, asthma, sinus disease, peripheral neuropathy
 - Granulomas
 - Steroids/cyclophosphamide



ARF: Disease Associations

Pulmonary Renal Syndromes

- **Pneumonia with ATN**
- **Vasculitis**
- **SLE**
- **Anti-GBM Disease/Goodpasture's Syndrome**

ARF: Disease Associations

- **ARF with thrombocytopenia**
 - Common: ATN with DIC/sepsis
 - SLE nephritis
 - HUS/TTP (thrombotic microangiopathy)
- **Renal-Dermatological Syndrome**
 - SLE nephritis
 - Henoch-Schonlein Purpura/IgA nephropathy
 - HCV-related cryoglobulinemia
 - ANCA vasculitis



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ARF: AEIOU Indications for Dialysis

- **Acidemia**
 - Refractory to medical therapy
- **Electrolytes**
 - Refractory or life-threatening hyperkalemia
- **Ingestions**
 - Lithium, ethylene glycol, methanol
- **Overload**
 - Hypervolemia refractory to diuretics
- **Uremia**
 - Signs and symptoms of kidney failure



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Dialysis Dose in ARF: Is More Better?

- **Yes = Continuous dialysis CRRT**
 - High dose vs. low dose hemofiltration
 - Ronco C et al. Lancet 2000.
- **Yes = Intermittent hemodialysis**
 - Daily HD is better than qOD dialysis
 - Schiff H et al. NEJM 2002.
- **No = CRRT or HD**
 - ATN Study NEJM 2008.
 - Largest randomized trial of ARF/ATN
 - Intensive Dose vs. Conventional Dose dialysis

ARF: Unknowns in Dialysis

- **Continuous vs. intermittent dialysis?**
 - Conventional wisdom = continuous is better
 - No evidence
 - Several trials showing lack of benefit
- **Early vs. late initiation of dialysis?**

Chronic Kidney Disease (CKD)

- **National Kidney Foundation (NKF) classification**
 - Chronic defined as 3 months or longer
 - Disease defined as abnormal...
 - kidney structure (imaging)
 - function (blood and urine tests)
 - pathology
- **CKD replaces “chronic renal insufficiency”**

NKF Classification of CKD

GFR mL/min/1.73 m ²	NKF CKD Stage	ICD9 Code
≥ 90	1	585.1
60-89	2	585.2
30-59	3	585.3
15-29	4	585.4
< 15 or dialysis	5	585.5
		585.6 if dialysis
		585.9 CKD NOS

Predictive formulas for kidney function

- **Cockcroft-Gault Formula**

- Estimates Creatinine Clearance (mL/min)

$$eCrCl = \frac{140 - \text{age} \times \text{mass (kg)} \times 0.85 \text{ (female)}}{72}$$

- Inaccurate for non-whites, women, patients at extremes of age/weight?

- **MDRD Formula**

- Estimates GFR (mL/min/1.73 m²)

- **CKD-EPI Formula**

- More accurate at higher eGFR than MDRD?

Levey, AS et al Ann Int Med 2009; Stevens LA et al. NEJM 2006; Cockcroft DW, Gault MH. Nephron 1976.



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MDRD estimated GFR (eGFR)

- **Modification of Diet in Renal Disease Study**
- **4 variables predict GFR, weight not needed**
- **Recommended by NKF and NIDDK**

- Reported by clinical labs
- PDA calculators or Google “MDRD”

$$\text{eGFR (mL/min/1.73 m}^2\text{)} =$$

$$186 \times (\text{SCr})^{-1.154} \times \text{age}^{-0.203}$$

$$\times 0.742 \text{ (female)} \times 1.210 \text{ (black)}$$

Klahr S et al. NEJM 1994.

Levey AS et al. Ann Intern Med 1999.



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Estimating Proteinuria

- **24-hour urine collection**
 - Time consuming, inconvenient
 - Inaccurate/inadequate urine collections
 - Difficult to follow serially
- **Spot Urine Protein:Creatinine ratio**
 - Ratio correlates to grams/day/1.73 m² of proteinuria
 - Quick, easy to follow serially
 - Assess response to therapy, e.g. ACE inhibitors/ARB
 - Recommended by NKF

Albuminuria in DM Nephropathy

- **Normal urinary albumin excretion (UAE)**
 - < 30 mg/24hr or < 20 µg/min
 - < 30 mg/gram creatinine (albumin:creatinine ratio)
- **Microalbuminuria**
 - 30-300 mg/day or 20-200 µg/min
 - 30-300 mg/gram creatinine (albumin:creatinine ratio)
 - Incipient diabetic nephropathy
- **Macroalbuminuria**
 - > 300 mg/day or > 200 µg/min
 - > 300 mg/gram creatinine (albumin:creatinine ratio)
 - Overt diabetic nephropathy

Renoprotective Therapy in CKD

- **HTN control**
 - Goal BP < 130/80 mm Hg
- **Proteinuria suppression**
 - ACE inhibitors ± ARB
 - Goal urine protein:creatinine ratio < 0.5
 - Dietary protein restriction → controversial
- **Glycemic/metabolic control**
 - HbA1c < 7%
- **Smoking cessation**
- **Avoid nephrotoxins**

Adjuvant Therapy in CKD

- **Lipid management**
 - LDL < 100 mg/dL and triglycerides < 200
 - Cardiovascular risk reduction
 - Emerging evidence for kidney function preservation
- **Primary CV prophylaxis with ASA**
- **Independent cardiovascular risk factors**
 - Kidney disease
 - Proteinuria/albuminuria
 - Elevated cystatin C

HTN Definitions and Goals

- **JNC 7 (2003)**
 - Normal BP < 120/80
 - Pre-hypertension 120-139/80-89
 - Stage 1 140-159/90-99
 - Stage 2 >160/100
- **BP Goals for patients on therapy**
 - < 140/90 (JNC 7)
 - < 130/80 CKD or DM (JNC 7, ADA, NKF)
 - < 125/75 for proteinuric CKD (MDRD, AASK)?

ACE inhibitors/ARB in Diabetes

Preferred Rx in DM patients

- HTN
- Diabetic nephropathy +/- HTN
- Prevention of microalbuminuria in hypertensive DM pts
 - Ruggenenti P et al. NEJM 2004.
- Regression of microalbuminuria in DM1
 - Perkins BA et al. NEJM 2003.
- **Unknown: prevention of microalbuminuria in non-HTN diabetic patients?**

ACE inhibitors/ARB in Diabetes

Strongest evidence

- **Type 1 DM pts → ACE inhibitors**
 - Lewis EJ et al. NEJM 1993.
- **Type 2 DM pts → ARB**
 - NEJM 2001; IDNT, RENAAL, IRMA 2.

Preliminary Data

- **ACE and ARB clinically equivalent**
 - Barnett AH et al. NEJM 2004; 351:1952-1961.
- **Combination of ACE and ARB may be superior to either alone**
 - Blood pressure and proteinuria, unknown clinical endpoints

Anemia in CKD

Early manifestation of CKD, GFR < 60 mL/min

Evaluation

- Rule-out GI bleed
- Check iron status (iron sat > 20%, ferritin > 100)
- Reticulocyte index
- Serum/urine protein electrophoresis
- Should you check Epo levels? No.

Treatment

- Epoetin alfa or Darbepoetin if Hb < 10 g/dL
- Goal Hb < 10-12 g/dL
- Increased CV events in CHOIR Study, NEJM 2006

Renal Osteodystrophy

Renal osteodystrophy includes a variety of different bone diseases in CKD

- Adynamic bone disease
- Osteomalacia (often assoc. with aluminum toxicity)
- Osteitis fibrosa cystica

Need bone biopsy to differentiate bone diseases

- Rarely done
- Not widely available

Vitamin D Deficiency

25-OH Vit D (ng/mL) [nmol/L]	Definition	Ergocalciferol (Vitamin D ₂)	Follow-up
< 5 [12]	Severe deficiency	50,000 units weekly x 12, then monthly	Treat 6 months then repeat 25-OH Vit D
5-15 [12-37]	Mild deficiency	50,000 units weekly x 4, then monthly	Treat 6 months then repeat 25-OH Vit D
16-30 [40-75]	Insufficiency	50,000 units monthly	Treat 6 months then repeat 25-OH Vit D

NKF KDOQI Guidelines, Am J. Kidney Diseases 2004.

Screening for 2° Hyperparathyroidism

GFR mL/min/1.73 m ²	CKD Stage	Serum PTH	Ca and PO ₄
30-59	3	Annual	Annual
15-29	4	Quarterly	Quarterly
< 15 or dialysis	5	Quarterly	Monthly

NKF KDOQI Guidelines, Am J. Kidney Diseases 2004.

Secondary Hyperparathyroidism

Intact PTH (pg/mL)	Calcitriol Initial oral dose	Doxercalciferol Initial oral dose
> 70 Stage 3 > 110 Stage 4	0.25 mcg daily	2.5 mcg three times weekly

- Calcium < 9.5, PO₄ < 4.6, and 25-OH vitamin D > 30 at initiation
- Opinion based recommendations
- Goal intact PTH for stage 5 CKD/ESRD: 150-300 pg/mL

NKF KDOQI Guidelines, Am J. Kidney Diseases 2004.

Osteoporosis in CKD

- **Avoid bisphosphonates**
 - Prolonged half-life in CKD
 - Unclear dosing with GFR < 30-60 mL/min
 - Avoid osteoporosis treatment dose
 - E.g. alendronate 70 mg weekly
 - Consider osteoporosis prevention dose
 - E.g., alendronate 35 mg weekly
- **Safety of long acting bisphosphonates?**
 - Low bone turnover and adynamic bone disease?

Case

A 60 year-old woman with chronic low back pain has an elevated creatinine on routine annual evaluation. She has had polyuria and nocturia over the past few years.

She has no other medical history. She does not use any prescription medications.

Physical exam is unremarkable.

Case, continued

Labs

- CBC normal
- Electrolytes normal
- BUN 35 mg/dL
- Creatinine 2.9 mg/dL
- UA 5-10 WBC/hpf, no protein or blood

Renal US small kidneys
possible papillary necrosis

Case Question

What is the next step in management?

- A.** Nephrology referral for renal biopsy.
- B.** Ophthalmology referral for retinal exam.
- C.** Ask the patient about over-the-counter medications.
- D.** Urine culture for *Mycobacterium tuberculosis*.

DDx Non-proteinuric CKD

- Urinary tract obstruction
- Polycystic kidney disease
- Hypertensive nephropathy
- Chronic tubulointerstitial diseases
- Proteinuric kidney disease with suppressed proteinuria from ACE/ARB

CKD: Tubulointerstitial Diseases

■ Acute Interstitial Nephritis

- Medications = antibiotics, NSAIDs, diuretics, others
 - Old and new medications can cause AIN
- Infections = bacterial, fungal, viral, others
- Immune disorders = SLE, Sjogrens, sarcoidosis

CKD: Tubulointerstitial Diseases

■ Chronic Interstitial Nephritis

- Occupational exposures, lead and heavy metals
- Medications = analgesics, lithium
- Traditional medicines: Chinese herbal nephropathy
- Metabolic = hypercalcemia, hypokalemia, oxalosis, cystinosis
- Medullary cystic kidney disease
- Immune disorders = SLE, Sjogrens, sarcoidosis
- Myeloma and lymphoproliferative disease

CKD: Interstitial Disease

- **Often asymptomatic**
 - May not have the fever, rash, and arthralgias of acute interstitial nephritis
- **Minimal proteinuria/hematuria**
- **Sterile pyuria**
- **Urine sediment: +/- WBC, WBC casts**
- **Late manifestations: hypertension and anemia**

CKD: Interstitial 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

CKD: Interstitial Disease

- **Definitive diagnosis by kidney biopsy**
 - Diagnosis often made clinically
 - Biopsy may not alter therapy

- **Therapy**
 - Eliminate or treat underlying cause
 - Mainly supportive therapy
 - Steroids for AIN? Controversial, lack of good trials
 - Steroids NOT used for chronic interstitial nephritis

CKD: Analgesic Nephropathy (AN)

- **Phenacetin**
 - Previously widely available outside United States
 - Incidence of AN dropped after taken off market

- **Acetaminophen**
 - Metabolite of phenacetin
 - Conflicting data on nephrotoxicity

- **Aspirin**
 - Potentiates toxicity of phenacetin and acetaminophen

CKD: Analgesic Nephropathy (AN)

- **Usually seen in women**
- **History of chronic back pain or headaches**
- **Radiology findings**
 - IVP: Papillary necrosis in severe cases
 - Ultrasound: Atrophic kidneys
 - CT: Papillary calcifications, atrophic kidneys with “bumpy” or lobulated/irregular contours

NSAIDs and Kidney Disease

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

Case

A 32 year-old African-American man with a recent diagnosis of HIV presents with nausea and vomiting for 2 months. He notes frothy urine for 6 months.

He is afebrile with blood pressure 100/62 and heart rate 72. Physical exam is normal without pedal edema.

Case, continued

Labs

- Hematocrit 32%
- BUN 104 mg/dL
- Serum Cr 14.2 mg/dL
- CD4 132/mm³
- U/A 3+ protein, no hematuria
- 24-hr urine 12 gm protein

Renal US large kidneys with marked echogenicity

He starts hemodialysis and has a kidney biopsy.

Case Question

Kidney biopsy shows focal segmental glomerulosclerosis of the collapsing variant, interstitial inflammation, and tubular microcyst formation.

Which of the following is the most appropriate therapy for this patient's disease?

- A. Pulse IV methylprednisolone**
- B. Cyclophosphamide**
- C. Cyclosporine**
- D. Highly active antiretroviral therapy (HAART)**

Case

A 72 year-old woman is admitted to the hospital for new onset nephrotic syndrome. She had been healthy until the past year when she noticed a decrease in appetite, constipation, and a ten pound weight loss. Over the past month, she has noticed face, arm, and leg swelling.

Physical examination reveals a chronically ill-appearing woman with anasarca.

Case, continued

Labs

- Hematocrit 29% with MCV 72 fL
- BUN 54 mg/dL
- Creatinine 3.1 mg/dL
- HBV, HCV, cryo negative
- Complements normal
- UA 4+ protein, no hematuria
- 24-hr urine 4.5 g protein

Renal US: Normal sized kidneys with mild echogenicity.

Renal Bx: Thickened glomerular capillary walls with subepithelial deposits consistent with membranous nephropathy.

Case Question

Which of the following studies are most appropriate in light of the renal biopsy results?

- A. ANCA antibodies
- B. Anti-GBM antibodies
- C. ANA and double-stranded DNA antibodies
- D. Echocardiogram
- E. Colonoscopy

Nephrotic Syndrome

- Proteinuria > 3.5 g/day
- Dyslipidemia
- Edema
- Hypoalbuminemia
- Lipiduria (oval fat bodies in urine, Maltese cross with polarized light)

Caveat:

- Many patients do not have all 5 features; nephrotic proteinuria without nephrotic syndrome

Associated Feature: Hypercoagulability

Nephrotic Diseases

- Focal Segmental Glomerulosclerosis (FSGS)
- Membranous Nephropathy (MN)
- Minimal Change Disease (MCD)
- Amyloidosis
- Diabetic nephropathy
- Others = SLE, IgA nephropathy, MPGN

Nephrotic Disease: Focal Segmental Glomerulosclerosis (FSGS)

- **Idiopathic/Primary**
 - African-Americans and patients < 40 years
 - Can be treated with steroids
 - Can recur explosively post-kidney transplant
- **Secondary**
 - HIV-associated nephropathy (HIVAN), almost exclusively in African-Americans, large kidneys
 - Chronic kidney disease, reduced nephron mass, hyperfiltration injury
 - Heroin, morbid obesity, drugs (lithium, pamidronate)
 - Sickle cell disease
 - Typically not steroid responsive

Nephrotic Disease: Membranous Nephropathy

- **Idiopathic/Primary**
 - Caucasians, most common cause of nephrotic syndrome by a primary glomerular disease
- **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, leprosy, schistosomiasis
 - SLE and autoimmune/connective tissue diseases
 - Drugs: NSAIDs, gold, penicillamine
 - Sickle cell disease

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
- Neoplasm, Hodgkin's and others
- Allergy and toxins (bee stings, mercury, lead)

■ Rx: Steroids typically first-line

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)

Nephrotic Disease: Amyloidosis

■ Clinical findings

- Renal involvement is common in amyloidoses
- 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

Nephrotic Disease: Amyloidosis

■ 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: ACE/ARB, blood pressure control, diuretics, sodium/water restriction

Kidney Disease in Multiple Myeloma

■ Amyloidosis

- Lambda > kappa light chains

■ Light chain deposition disease

- Kappa > lambda light chains

■ Cast nephropathy

■ Hypercalcemia and vasoconstrictive ARF

■ Hypercalcemia and nephrogenic DI with pre-renal ARF

■ ATN from sepsis

Diabetic Nephropathy

- **Common cause of proteinuria**
- **Unusual cause of massive proteinuria and nephrotic syndrome.**
- **Early hyperfiltration phase 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

Diabetic Nephropathy

- **Untreated DM patients will lose GFR at rate of 1 mL/min/month or 12 mL/min/year**
- **Rapid deterioration of function and/or unexplained rise in proteinuria suggest non-diabetic disease**

Serologies for Secondary Causes of Nephrotic Syndrome

- **FSGS**
 - HIV
- **Membranous Nephropathy**
 - HBV, HCV, VDRL/RPR, ANA, RF
- **Minimal change disease**
 - None
- **Amyloidosis**
 - SPEP/UPEP/IFE for primary/AL amyloidosis
- **Diabetic Nephropathy**
 - None, HbA1c for glycemic control

3 Approaches to Nephrotic Proteinuria

- 1. All serologies on all patients**
 - Expensive, time-consuming, low yield
- 2. Biopsy first, ask questions later**
 - Serologies based on pathology to r/o 2° causes
- 3. Some serologies on all patients**
 - C3 C4: low vs. normal complements
 - ANA: vaguely rheumatologic vs. non-rheumatologic
 - SPEP/UPEP/IFE: multiple myeloma and MGUS
 - Other serologies based on clinical suspicion
 - Low threshold for kidney biopsy

Serologies in Nephrotic Syndrome

- Serologies are suggestive, not definitive
- Still require kidney biopsy for diagnosis

Nephritic Diseases

- Serologies and clinical hx can be definitive
 - SLE (ANA, anti-DS DNA)
 - ANCA-related disease (ANCA)
 - Anti-GBM disease (anti-GBM)
 - Post-infectious (ASO/antiDNase)
- Kidney bx for prognosis

DDx Enlarged Kidneys

- Hydronephrosis/Obstruction
- Polycystic kidney disease
- Infiltrative disease (lymphoma)
- HIVAN
- Amyloidosis
- Early diabetic nephropathy

Adjuvant Rx in Nephrotic Disease

- **HTN control**
 - Goal BP < 130/80 mm Hg or even 125/75
- **Proteinuria suppression**
 - ACE inhibitors ± ARB
 - Goal urine protein:creatinine ratio < 0.5
 - Dietary protein restriction → controversial
- **Loop diuretics for edema**
- **Sodium/fluid restriction**
- **No clear role for primary prophylaxis with anticoagulation for hypercoagulability**

Secondary HTN: When to Suspect

- **Clinical Features**
 - Age at onset < 30 yrs (unless + family history)
 - Age at onset > 50 yrs
 - Rapid onset of severe HTN
 - Refractory HTN
 - Worsening of previously well controlled HTN
 - Hypokalemia

Secondary HTN: DDx

■ Kidney

- Renovascular disease, Liddle syndrome

■ Endocrine

- Hyper/hypothyroidism
- Aldosteronism (plasma aldo:renin ratio, 24 hr urine aldosterone)
- Cushing Syndrome (dexamethasone suppression test, 24 hr urine cortisol)
- Pheochromocytoma (24 hr urine catecholamines and metanephrines)
- Congenital adrenal hyperplasia
- Hypercalcemia
- Syndrome apparent mineralocorticoid excess

Secondary HTN: DDx

■ Drugs

- Prescription: estrogen, cyclosporine, steroids
- Over the counter: NSAIDs, pseudoephedrine
- Smoking, ethanol, cocaine

■ Neurogenic

- Increased intracranial pressure, spinal cord injury

■ Miscellaneous

- Aortic coarctation
- Obstructive sleep apnea
- Polycythemia vera

Renal Artery Stenosis/Disease

■ Clinical Features

- Secondary HTN
- Flash pulmonary edema
- Hypokalemia
- Kidney size asymmetry > 1.5 cm
- ARF after initiation of ACE inhibitor/ARB

■ Diagnosis

- CTA, MRA, conventional angiograph
- Ultrasound: highly operator/institution dependent

Renal Artery Stenosis/Disease

■ Atherosclerosis

- 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

HIV and Kidney Disease

■ ARF/ATN

- Immunodeficiency and sepsis
- Drug nephrotoxicity
 - Tenofovir, foscarnet, pentamidine
 - Acyclovir, aminoglycosides, amphotericin B

■ AIN

- NSAIDs, rifampin, trimethoprim-sulfamethoxazole

■ Nephrolithiasis

- Indinavir, acyclovir, sulfadiazine
- Drug crystals on urine sediment

HIV and Kidney Disease

■ HIV associated diseases

- HIVAN (African-Americans)
- Immune complex GN (all others)
- HUS/TTP/Thrombotic Microangiopathy
- IgA Nephropathy

■ Other co-morbidities causing kidney disease

- HBV: Membranous > MPGN
- HCV: MPGN, cryoglobulinemia > Membranous

HIV-Associated Nephropathy (HIVAN)

- **African-Americans, unusual in Caucasians**
 - Other HIV kidney diseases (immune-complex glomerulonephritis, IgA nephropathy)
- **Usually late manifestation of AIDS**
 - Low CD4 count
- **Often asymptomatic**
- **Lack of hypertension and edema**
- **Nephrotic proteinuria**
- **Bland urine sediment**
- **Normal or enlarged kidneys**
- **Often rapid deterioration of renal function**

Treatment of HIVAN

- **Highly active antiretroviral therapy (HAART)**
- **ACE inhibitors and/or ARBs**
- **Lack of randomized controlled trials**

Case

A 21 year-old woman in the third trimester of her first pregnancy comes to the ED after a minor car collision.

Medical history is unremarkable.

On physical examination, she is anxious. Respiratory rate is 18/min, and blood pressure is 110/70 mmHg. Otherwise her exam is unremarkable.

Case, continued

Labs

- Hematocrit 33%
- WBC 9000/uL
- Platelet count 122,000/uL
- Serum sodium 132 mEq/L
- Serum potassium 3.8 mEq/L
- Serum chloride 100 mEq/L
- Serum bicarbonate 20 mEq/L
- BUN 5 mg/dL
- Creatinine 0.4 mg/dL
- UA pH 6.0, SG 1.020, no proteinuria or hematuria

Case Question

Which of the following is the most likely explanation for her serum electrolytes?

- A.** Acute respiratory alkalosis due to a possible pneumothorax
- B.** Normal electrolyte values in a pregnant woman
- C.** Metabolic acidosis from hypoperfusion and tissue hypoxia
- D.** Renal tubular acidosis

Kidney Physiology during Pregnancy

- Kidney length increases by 1 cm
- Dilatation of the calyces, pelves, ureters
- During 1st trimester, renal plasma flow increases 50-80%, GFR increases 50%
- Creatinine decreases from 0.8 mg/dL non-pregnant to 0.5 mg/dL in 3rd trimester
- Slight increase in urine protein excretion, upper limit of normal increases from 150 to 300 mg/day

Kidney Physiology during Pregnancy

- **Chronic respiratory alkalosis**
 - Progesterone-induced hyperventilation, pCO₂ 30 mmHg
 - Serum bicarbonate drops to 22 mmol/L
- **Reset osmostat**
 - Decreased serum osmolality by 5-10 mosm/kg
 - Increased total body water by 6-8 liters
 - Plasma volume increases 50%
- **Lower blood pressure and vasodilation**
 - Diastolic pressure 10 mmHg less by midpregnancy
 - Increased cardiac output, decreased SVR
- **Transient diabetes insipidus**
 - Placental vasopressinases metabolize ADH

Pregnancy and ACE/ARB

- **Avoid ACE inhibitors during all 3 trimesters**
 - Fetal malformations
 - Previously thought to be safe during first trimester
 - Cooper WO et al. NEJM 2006.
- **Stop ACE/ARB prior to conception**

HTN and Pregnancy

■ Chronic hypertension

- Elevated BP prior to pregnancy
- Documented before 20 weeks of pregnancy
- Persists 12 weeks after pregnancy

■ Gestational hypertension

- Elevated BP without proteinuria after 20 weeks
- BP returns to normal within 12 weeks after pregnancy
- 25% progress to preeclampsia (develop proteinuria)
- Increased risk for developing HTN postpartum

Preeclampsia: Definition and Risk Factors

■ Hypertension and proteinuria after 20 weeks

- BP > 140/90 mmHg in pts with previously normal BP
- Proteinuria > 0.3 g/day (roughly 1+ dipstick protein)
- Unusual in first trimester/20 weeks

■ Risk factors

- Age > 35 or < 20 years, African-American, family/pt hx preeclampsia, nulliparity, gestational DM, type 1 DM, obesity, chronic HTN, kidney disease, thrombophilias, vascular and connective tissue disease, antiphospholipid antibody syndrome, elevated serum uric acid

Preeclampsia: Clinical Features

- **May develop before, during, or after delivery**
- **Insidious or fulminant**
- **+/- Symptoms (visual disturbances, headache, upper abdominal pain)**
- **5-15% with HELLP (worse prognosis)**
- **Complications**
 - Eclampsia, intrauterine growth retardation (IUGR)
 - Placental abruption, DIC, acute renal failure
 - CVA and cardiovascular complications
 - Maternal death

Preeclampsia: Treatment

- **Delivery, vaginal preferred over Cesarean**
- **Seizure prophylaxis – magnesium sulfate**
- **Hospitalization for non-compliant patients, poor access to medical care, progressive or severe preeclampsia**
- **Tertiary center and/or high-risk obstetrician**

Pregnancy and CKD

- **High-risk CKD patients**
 - Baseline creatinine > 1.4 mg/dL
 - Pre-existing hypertension
- **Pregnancy effects on CKD**
 - Worsening HTN and proteinuria
 - Temporary or permanent decline in kidney function
- **CKD effects on Pregnancy**
 - Intrauterine growth retardation, prematurity, fetal loss
 - Increased risk for preeclampsia, eclampsia

Case

83 year-old woman falls and fractures her right hip. Medical history includes hypertension and diabetes.

Medications include an ACE inhibitor.

On physical exam, she is slightly confused. BP 140/90, HR 80. JVP is 8 cm, normal heart sounds, and clear chest exam. No hepatosplenomegaly. No pedal edema. Deep tendon reflexes are normal.

Case, continued

Labs

- WBC 5000/uL
- Hematocrit 39%
- Platelets 122,000/uL
- Sodium 115 mEq/L
- Potassium 3.8 mEq/L
- Chloride 85 mEq/L
- Bicarbonate 23 mEq/L
- BUN 12 mg/dL
- Creatinine 1.0 mg/dL
- Serum osms 240 mosm/kg
- Urine Na 42 mEq/L
- Urine osms 680 mosm/kg

CXR

Normal

Case Question

Which of the following is the most likely cause of hyponatremia in this patient?

- A.** Extracellular fluid volume depletion
- B.** Congestive heart failure
- C.** Syndrome of inappropriate antidiuretic hormone (SIADH)
- D.** Addison's disease
- E.** Cirrhosis

Hyponatremia

■ Serum Osmolality

- High: Translocational, mannitol and glucose
- Normal: Pseudohyponatremia, triglycerides and paraproteinemias
- Low: Majority of hyponatremia cases

■ Volume Status for hypo-osmolar patients

- High: Heart failure, cirrhosis, nephrotic syndrome
- Normal: SIADH, SIADH-mediated (hypothyroid, adrenal insufficiency, pain, nausea), polydipsia
- Low: Losses of fluid (kidneys, GI, insensible) with hypotonic fluid replacement, kidneys sacrifice osmolality for volume

Hyponatremia

■ Treatment

- Free water restriction for all patients
- 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

- Controversial, approximately 10-12 mEq/L per day

SIADH: Syndrome of Inappropriate Antidiuretic Hormone

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

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**
 - Water restriction
 - Sodium tablets
 - Demeclocycline is rarely used, nephrotoxic (induces nephrogenic diabetes insipidus)

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

Hypernatremia

Free water deficit =

$$0.5 \times Wt \text{ (kg)} \times [(plasma \text{ Na} - 140)/140]$$

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

■ Hypervolemic hypernatremia

- Often iatrogenic/nosocomial
- May require diuretics and free water replacement
- May require dialysis

Hyperkalemia: Etiology

- **Dietary ingestion**
- **Decreased excretion**
 - ARF/CKD
 - Decreased RAAS (ACE/ARB, NSAIDs, cyclosporine, type 4 RTA)
 - Hypoaldosteronism (Addison's disease)
 - Aldosterone resistance (trimethoprim, pentamidine, amiloride)
- **Extracellular K shift: metabolic acidosis, insulin deficiency, beta-blockers, tumor lysis, digoxin overdose, succinylcholine, hyperkalemic periodic paralysis**

Hyperkalemia: Work-up

- **EKG findings**
 - Loss of P waves, QRS widening, T wave peaking, V tach/fib
 - EKG findings correlate poorly with severity of hyperkalemia
- **Transtubular Potassium Gradient (TTKG)**
 - $TTKG = (U_K/P_K) / (U_{osm}/P_{osm})$
 - $TTKG < 6 \rightarrow$ renal hyperkalemia
 - $TTKG > 10 \rightarrow$ appropriate renal response
- **Tumor lysis syndrome**
 - High LDH, uric acid, phosphate, potassium,
 - Low calcium

Hyperkalemia Treatment

- **Stabilization of membrane = Fast**
 - Calcium gluconate IV
- **Shift potassium = Fast**
 - Beta-agonists, high dose albuterol NMT
 - Insulin/glucose
 - NaHCO₃ (may not work in ESRD)
- **Removal of potassium = Slow**
 - Diuretics, Dialysis
 - Sodium polystyrene (Kayexalate – avoid in peri-operative pts, ileus/SBO)

Hypokalemia

- **Clinical, typically K < 2.5-3 mEq/L**
 - Weakness, rhabdomyolysis, arrhythmias
- **DDx**
 - Low dietary K intake
 - Intracellular shift: alkalemia, increased insulin, increased beta-activity, periodic paralysis (classically with thyrotoxicosis)
 - Increased excretion:
 - GI: diarrhea, vomiting
 - Kidney: diuretics, hypomagnesemia, mineralocorticoid excess (aldosteronism, Cushing's, European licorice, hyperreninemia, syndrome of apparent mineralocorticoid excess), Bartter, Gitelman

Hypokalemia

Diagnostics

- **Transtubular Potassium Gradient (TTKG)**
 - TTKG < 2 → GI losses, TTKG > 4 renal loss
- **24 hr urine**
 - < 25 mEq/day → extrarenal loss
 - > 25 mEq/day → renal losses

Treatment

- **Potassium**
 - Difficult to estimate deficit, usually at least 200 mEq
 - IV: 10 mEq/hr peripherally, 20 mEq/hr centrally

Metabolic Acidosis: Increased Anion Gap

- **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

$$\text{Serum Anion Gap} = \text{Na} - \text{Cl} - \text{HCO}_3$$

Normal AG < 12

- Add 2.5 to the AG for every 1 g/dL drop in albumin

Aside: DDx Decreased Anion Gap

- **Extra Positive (+) charges**
 - Immunoglobulins (myeloma)
 - Lithium
 - Potassium
 - Magnesium
 - Calcium
- **Decreased Negative (-) charges**
 - Albumin

Metabolic acidosis: Normal Gap


- **Normal anion gap metabolic acidosis**
 - Also called hyperchloremic met. acidosis
 - GI: Diarrhea with bicarbonate loss
 - Negative urine anion gap
 - Renal: Renal tubular acidosis (RTA)
 - Positive urine anion gap

$$\text{Urine Anion Gap} = \text{Na} + \text{K} - \text{Cl}$$

Normal UAG is negative

Metabolic acidosis			
	Type 1 Distal	Type 2 Proximal	Type 4
Defect	↓ distal acidification	↓ proximal HCO ₃ reabsorption	Aldosterone deficiency or resistance
Urine pH	> 5.3	> 5.3 early < 5.3 late	Usually < 5.3
Plasma K	Low or normal, can be high	Low or normal	High
Dose of bicarbonate	Low	High	Low
Complications	Nephrocalcinosis Nephrolithiasis	Rickets or osteomalacia	None

NEPHROLOGY



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Division of
Nephrology

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
 - Glucosuria, 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, continued

Labs

- Sodium 138 mEq/L
- Potassium 2.4 mEq/L
- Chloride 90 mEq/L
- Bicarbonate 36 mEq/L
- BUN 14 mg/dL
- Creatinine 1.0 mg/dL
- Magnesium 1.9 mg/dL
- Calcium 9.0 mg/dL

Urine

- pH 6.0
- Na 16 mEq/L
- K 20 mEq/L
- Cl < 5 mEq/L

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

Metabolic Alkalosis

- What caused the metabolic alkalosis?
- What is preventing the renal excretion of the excess bicarbonate?

Major Causes of Metabolic Alkalosis

- **GI hydrogen loss**
 - NG suction, vomiting
 - Chloride-losing diarrhea (villous adenoma, laxatives)
- **Renal hydrogen loss**
 - Aldosteronism
 - Loop and thiazide diuretics, Bartter and Gitelman
 - Post-hypercapnic alkalosis
 - Milk-alkali syndrome (calcium carbonate loading)
- **Intracellular shift of hydrogen (hypokalemia)**
- **Administration of bicarbonate**
- **Contraction alkalosis**

Maintenance of Metabolic Alkalosis

Reduced renal bicarbonate excretion

- **Effective circulating volume depletion**
 - Reduction in the filtered load of HCO_3
 - Secondary aldosteronism (paradoxical 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

Osmolar Gap

**Osmolar Gap =
Measured Osms – Estimated Osms**

**Estimated osms =
2Na + BUN/2.8 + glucose/18 + EtOH/4.6**

Normal Osmolar Gap < 10

DDx High Osmolar Gap

- **Increased anion gap metabolic acidosis**
- **Normal anion gap, no metabolic acidosis**

Osmolar Gap

Major Conditions with increased osmolar gap

- **Increased AG metabolic acidosis (MUDPILES)**
 - Conditions = uremia, DKA, alcoholic ketoacidosis, lactic acidosis
 - Ingestions = methanol, paraldehyde, formaldehyde, ethylene glycol
- **Normal AG, no metabolic acidosis**
 - Exogenous = isopropanol, diethyl ether, mannitol
 - Artifact = hyperproteinemia, hypertriglyceridemia (artificial lowering of serum sodium concentration)

Case

A 42 year-old woman has had 2 episodes of nephrolithiasis over the past year. Stone analysis reveals calcium oxalate.

24-hour urine collection showed the following:

Sodium	↑ 250 mEq/day	normal < 150 mEq
Calcium	↑ 380 mg/day	normal < 250 mEq
Oxalate	↑ 82 mg/day	normal < 45 mg
Citrate	↓ 220 mg/day	normal > 320 mg
Urine pH	5.34	normal 5.5 – 6.0
Volume	1250 mL/day	

Case Question

Which of the following would NOT be helpful in preventing future episodes of nephrolithiasis?

- A. Starting hydrochlorothiazide
- B. Starting furosemide
- C. Starting potassium citrate
- D. Reducing animal protein intake
- E. Reducing sodium intake
- F. Increasing urine output > 2 L/day

Nephrolithiasis

- **Common**
- **80% stones contain calcium (usually Ca-oxalate)**
- **Assessment**
 - Stone: analysis (if stone available)
 - Blood: routine electrolytes, calcium, uric acid, PTH if hypercalcemic
 - Urine: UA, sediment exam for crystals
 - 24 hour urine: metabolic analysis for volume, sodium, calcium, uric acid, citrate, oxalate, creatinine, pH

Nephrolithiasis: Risk Factors

- **Hypercalciuria (50%)**
 - Absorptive hypercalciuria
 - Most common
 - Increase in intestinal calcium absorption
 - Fasting hypercalciuria
 - Renal hypercalciuria
 - Defect in renal tubular calcium reabsorption
- **Hyperoxaluria (15-60%)**
 - Low calcium diet
 - Increased intestinal calcium absorption
 - Small bowel disease (enteric hyperoxaluria)

Nephrolithiasis: Risk Factors

- **Hypocitraturia**
 - Urinary citrate inhibits crystal formation
- **Hyperuricosuria**
 - Nidus for calcium oxalate precipitation
 - High purine diet
- **Dietary factors**
 - Vitamin D supplements (increase risk)
 - High calcium intake (reduces risk)
 - High fluid intake (reduces risk)
 - High sodium intake (increases risk)
 - High protein intake (increases risk)

Nephrolithiasis: Treatment

- **Dietary Modification**
 - Increase urine output to >2 liters/day
 - Reduce protein intake to 1 g/kg/day
 - Reduce sodium intake to 80-100 mEq/day
 - Avoid low calcium intake
- **Drug therapy**
 - Thiazides for hypercalciuria
 - Potassium citrate and allopurinol for hyperuricosuria
 - Potassium citrate for hypocitraturia
 - Calcium carbonate for enteric hyperoxaluria

Genetic Diseases

■ Autosomal Dominant Polycystic Kidney

- PKD1/polycystin 1
- PKD2/polycystin 2
- Enlarged kidneys
- Mitral valve prolapse, polycystic liver disease
- Intracranial aneurysms, screen with MRA if affected family members with CVA, sudden death
- No direct therapy, ACE/ARB for HTN/LVH
- Kidney transplantation

Genetic Diseases

■ Alport's Syndrome

- Type IV collagen of kidney, lens, cochlea
- Findings
 - Hematuria in female carriers and men
 - ESRD/CKD in men
 - Sensorineural hearing loss
 - Ocular defects, anterior lenticonus
- Treatment
 - Kidney transplant
 - Anti-GBM disease can occur in transplant kidney