nephro 1

nephro 2

nephro cases

Nephrology 11

Diagnostic Tests in Nephrology

TIP

The "best initial test" in nephrology is a urinalysis and the blood urea nitrogen (BUN) and creatinine.

Urinalysis

The urinalysis (urine analysis or UA) measures chemical reactions associated with:

- Protein
- White cells (direct microscopic examination) or leukocyte esterase (dipstick)
- Red cells
- Specific gravity and pH
- Nitrites (indicates presence of Gram-negative bacteria on dipstick)

Urinalysis is two parts:

1. dipstick if positive

2. microscopic analysis

The dipstick gives some quantitative values as well. This means it is not just positive or negative, but can give an approximation of the quantity of the protein, white cells, and red cells. This can be described either as a direct number (e.g., 300 mg protein) or a scale: 0, 1+, 2+, 3+, or 4+.

TIP

Do not worry about knowing the precise scale. Every USMLE Step 2 CK test comes with the range of normal values attached so you will be able to assess severity.

Protein

It is normal to excrete a very tiny amount of protein. The tubules secrete slight amounts of protein normally known as **Tamm-Horsfall** protein. This should be less than 30 to 50 mg per 24 hours. Greater amounts of protein can be associated with either tubular disease or glomerular disease. Very **large amounts of protein** can only be excreted with **glomerular disease**.

Severe proteinuria means **glomerular damage**.

In terms of proteinuria, the problem with using the scale of "trace" through 4+ is that UA measures only the amount of protein excreted at a particular moment in the day. It does not give an average or total amount of protein excreted over 24 hours because renal function itself varies during the day based on bodily position and physical activity. It is like the difference between an EKG and a Holter monitor. **Transient proteinuria** is present in 2% to 10% of the population, with most of this being **benign** without representing pathology. If **proteinuria persists** and is not related to prolonged standing (**orthostatic proteinuria**), a **kidney biopsy** should be performed.

Standing and physical **activity** increase urinary **protein excretion**.

Assuming constant protein excretion throughout the day, 1+ protein is about one gram excreted per 24 hours, 2+ protein is about 2 grams per 24 hours, and so on. The 2 methods to assess the total amount of protein in a day are:

- Single protein to creatinine ratio
- 24-hour urine collection

Urine dipstick for protein detects only **albumin**.

These tests are considered **equal** in accuracy. However, since the 24-hour urine is much harder to collect, it is rarely performed. Normal protein is less than 300 mg per 24 hours.

Normal protein per 24 hour <300 mg.

TIP

To assess proteinuria:

- UA is the initial test.
- Protein-to-creatinine ratio is more accurate at determining the amount.

Protein-to-Creatinine Ratio

A protein-to-creatinine (P/Cr) ratio of one is equivalent to one gram of protein on a 24-hour urine. A P/Cr ratio of 2.5 is equivalent to 2.5 grams of protein found on a 24-hour urine. The **P/Cr ratio can be superior in accuracy to a 24-hour urine** because of technical difficulties in collecting a full day's worth of urine. If you collect a little less, it will *underestimate* the true excretion. If

you add a single extra urination, you might overestimate the protein excretion.

TIP

If both P/Cr ratio and 24-hour urine are in the choices, choose the P/Cr ratio. It is faster and technically easier to perform.

Biopsy determines the **cause** of proteinuria.

Microalbuminuria

Microalbuminuria = 30–300 mg/24 hours

The presence of **tiny amounts** of protein that are too small to detect on the UA is called **microalbuminuria**. This is very important to detect in diabetic patients. Long-term **microalbuminuria leads to worsening renal function** in a diabetic patient and should be treated.

A diabetic patient is evaluated with a UA that shows no protein. Microalbuminuria is detected (level between 30 and 300 mg per 24 hours).

What is the next best step in the management of this patient?

a. **Enalapril.**
b. **Kidney biopsy.**
c. **Hydralazine.**
d. **Renal consultation.**
e. **Low-protein diet.**
f. **Repeat UA annually and treat when trace protein is detected.**

Answer: A. An **ACE inhibitor or angiotensin receptor blocker** (e.g., losartan, valsartan) is the best initial **therapy** for any degree of proteinuria in a diabetic patient. They decrease the progression of proteinuria and delay the development of renal insufficiency in diabetic patients. Hydralazine is not as effective and has more adverse effects. Low-protein diets are less effective than ACE inhibitors. Do not consult for initiating medications like ACE inhibitors.

Kidney biopsy is especially important in kidney disease in a diabetic patient with no ophthalmic findings.

Bence-Jones protein in myeloma is **not detectable** on a dipstick. Use immunoelectrophoresis.

White Blood Cells

White blood cells detect inflammation, **infection**, or allergic **interstitial nephritis**. You cannot distinguish neutrophils from eosinophils on a UA. Neutrophils indicate infection. **Eosinophils** indicate allergic or acute **interstitial nephritis**. It is very useful if eosinophils are found because of their specificity. It is less important if they are absent, because the sensitivity of the test is limited. Microscopic examination gives a precise numerical count of the number of white cells present. Persistent WBC on UA with negative culture can be TB.

NSAID-induced renal disease does not show eosinophils.

TIP

Wright and Hansel stains detect eosinophils in the urine. They are the answer for allergic interstitial nephritis.

Hematuria

IgA nephropathy is common for mild recurrent hematuria.

Normal urinalysis has <5 RBCs per high power field. **Hematuria** is indicative of:

- **Stones** in bladder, ureter, or kidney
- Hematologic disorders that cause bleeding (**coagulopathy**)
- **Infection** (cystitis, pyelonephritis)
- **Cancer** of bladder, ureters, or kidney
- Treatments (cyclophosphamide gives hemorrhagic cystitis)
- **Trauma**; simply "banging" the kidney or bladder makes them shed red cells
- **Glomerulonephritis**

False positive tests for hematuria on dipstick are caused by **hemoglobin or myoglobin** in the urine.

A woman is admitted to the hospital with trauma and dark urine. The dipstick is markedly positive for blood.

What is the best initial test to confirm the etiology?

a. **Microscopic examination of the urine.**
b. **Cystoscopy.**
c. **Renal ultrasound.**
d. **Renal/bladder CT scan.**
e. **Abdominal x-ray.**
f. **Intravenous pyelogram.**

Answer: A. Hemoglobin and myoglobin make the dipstick positive for blood, but no red cells are seen on microscopic examination of the urine. Abdominal x-ray detects small bowel obstruction (ileus) but is very poor at detecting stones or cancer. **Renal CT** is the most accurate test for **stones**, but would not be done until the etiology of the positive dipstick had been confirmed as blood.

TIP

Intravenous pyelogram (IVP) is always wrong. It is slower and the contrast is renal toxic.

TIP

When "dysmorphic" red cells are described, the correct answer is

glomerulonephritis.

When Is Cystoscopy the Answer?

The answer is **cystoscopy** when there is **hematuria** without infection or prior trauma and:

- The renal ultrasound or CT does not show an etiology.
- **Bladder** sonography shows a **mass** for possible biopsy.

> **Cystoscopy** is the most accurate test of the **bladder**.

Casts

These are microscopic collections of material clogging up the tubules and being excreted in the urine.

Types of Urinary Casts and Their Significance

Type of cast	Association
Red cell	Glomerulonephritis
White cell	Pyelonephritis
Eosinophil	Acute (allergic) interstitial nephritis
Hyaline	Dehydration concentrates the urine and the normal Tamm-Horsfall protein precipitates or concentrates into a cast.
Broad, waxy	Chronic renal disease
Granular "muddy-brown"	Acute tubular necrosis; they are collections of dead tubular cells

Casts are very useful if found, but they are often not present.

TIP

The presence of a cast helps answer the "most likely diagnosis" question because they are specific.

Acute Kidney Injury

Definition

Acute kidney injury (AKI), formerly called acute renal failure (ARF), which you may encounter as a synonym, is defined as a decrease in creatinine clearance resulting in a sudden rise in BUN and creatinine. The definition is not based on a specific number of BUN and creatinine.

Etiology

AKI is categorized into 3 types:

- Prerenal azotemia (decreased perfusion)
- Postrenal azotemia (obstruction)
- Intrinsic renal disease (ischemia and toxins)

Prerenal azotemia: These are problems of **inadequate perfusion** of the kidney in which the kidney itself is normal. Any cause of hypoperfusion or hypovolemia will raise the BUN and creatinine, with the BUN rising more than the creatinine.

- **Hypotension** (systolic below 90 mm Hg) from sepsis, anaphylaxis, bleeding, dehydration
- **Hypovolemia:** diuretics, burns, pancreatitis
- Renal artery stenosis: Even though the blood pressure may be high, the

kidney is underperfused.

- Relative hypovolemia from decreased pump function: CHF, constrictive pericarditis, tamponade
- Hypoalbuminemia
- Cirrhosis
- **NSAIDs** constrict the afferent arteriole.
- **ACE inhibitors cause efferent arteriole vasodilation.**

Postrenal azotemia: Obstruction of any cause damages the kidney by blocking filtration at the glomerulus. Causes of postrenal azotemia include:

- **Prostate hypertrophy** or cancer
- **Stone** in the ureter
- Cervical **cancer**
- Urethral **stricture**
- Neurogenic (atonic) bladder
- Retroperitoneal **fibrosis** (look for bleomycin, methylsergide, or radiation in the history)

Prerenal and postrenal azotemia combined account for 80% of acute kidney. **The majority are reversible**.

> Management of prerenal and postrenal azotemia is based on correcting the underlying cause.

> You must obstruct **both** kidneys for the creatinine to rise.

The major force favoring filtration is the hydrostatic pressure in the glomerular capillary. If hydrostatic pressure in Bowman space rises, you cannot filter fluid. Unilateral obstruction causes renal failure if the person has only one kidney.

The kidney in prerenal and postrenal disease would function normally if transplanted into another person.

Intrinsic renal disease: The most common cause is **acute tubular necrosis** (ATN) from toxins or prolonged ischemia of the kidney. Glomerulonephritis is rarely acute, but when the kidney is injured from any cause, there is always a greater risk of AKI. For example, a few hours of hypotension might not damage a normal kidney at all, but with underlying renal damage, it may cause AKI. Other causes are:

- Acute (allergic) interstitial nephritis (commonly from medications such as penicillin)
- Rhabdomyolysis and hemoglobinuria
- Contrast agents, aminoglycosides, cisplatin, amphotericin, cyclosporine, and **NSAIDs**: most common toxins causing AKI from ATN
- Crystals such as hyperuricemia, hypercalcemia, or hyperoxaluria
- Proteins such as Bence-Jones protein from myeloma
- Poststreptococcal infection

Acute Kidney Injury Etiologies		
Prerenal	**Intrinsic renal**	**Postrenal**
Hypotension • Sepsis • Anaphylaxis • Bleeding • Dehydration Hypovolemia • Diuretics • Burns • Pancreatitis	Acute tubular necrosis • Toxins – NSAIDs – Aminoglycoside antibiotics, amphotericin – Cisplatin, cyclosporine • Prolonged ischemia AIN • Penicillin, sulfa drugs Rhabdomyolysis/hemoglobinuria	BPH/prostate cancer Ureteral stone Cervical cancer Urethral stone Neurogenic bladder Retroperitoneal fibrosis (chemotherapy or external-beam therapy)

• ↓ pump function • Low albumin • Cirrhosis Renal artery stenosis	Contrast Crystals Bence-Jones proteins Poststreptococcal infection	

Presentation

AKI may present with only an asymptomatic rise in BUN and creatinine. When symptomatic, the patient feels:

- **Nauseated** and **vomiting**
- Tired/**malaise**
- Weak
- Short of breath and has edema from fluid overload

Very **severe disease** presents with:

- **Confusion**
- Arrhythmia from hyperkalemia and acidosis
- Sharp, pleuritic chest pain from **pericarditis**

> There is no pathognomonic physical finding of AKI.

TIP

No symptoms are specific enough to answer the "most likely diagnosis" question without lab testing.

Presentation of Postrenal Azotemia

Enlargement (distention) of the **bladder** and massive diuresis after Foley (urinary) catheter placement are specific to urinary obstruction. This is the closest you will get to a specific presentation for any form of AKI.

Diagnostic Tests

The best initial test is the BUN and creatinine. With completely dead kidneys, the creatinine will rise about one point (1 mg/dL) a day. If the BUN:creatinine ratio is above 20:1, the etiology is either prerenal or postrenal damage of the kidney. Intrinsic renal disease has a ratio closer to 10:1. Renal sonogram is the best initial imaging test. Sonography does not need contrast. Contrast should be avoided in renal insufficiency.

Prerenal azotemia is usually a clear diagnosis with the question describing:

- **BUN:creatinine** ratio above **20**:**1**

and

- Clear history of **hypoperfusion or hypotension**

Postrenal azotemia is usually a clear diagnosis with the question describing:

- **BUN:creatinine** ratio above **20**:**1**

and

- **Distended bladder** or massive **release of urine** with catheter placement

and

- Bilateral or unilateral **hydronephrosis** on sonogram (ultrasound)

TIP

Kidney biopsy is rarely the right answer for AKI. Although the biopsy is the most accurate test of allergic interstitial nephritis or poststreptococcal glomerulonephritis, it is rare for either of these to actually need biopsy.

Tests for AKI of Unclear Etiology

When the cause of AKI is not clear, the “next best diagnostic step” is:

- Urinalysis
- Urine sodium (UNa)
- Fractional excretion of sodium (FENa)
- Urine osmolality

TIP

If all of these are choices, always go with urinalysis first.

Urine Sodium and Fractional Excretion of Sodium

Decreased blood pressure (or decreased intravascular volume) normally will increase aldosterone. Increased aldosterone increases sodium reabsorption. It is normal for urine sodium to decrease when there is decreased renal perfusion because aldosterone levels rise.

Prerenal azotemia: **low UNa** (<20) = **low FENa** (<1%)

Urine sodium and F_ENa give you the same information.

TIP

You can answer all the questions on USMLE Step 2 CK without knowing the mathematical formula for F_ENa.

Urine Osmolality

When **intravascular volume** is **low**, normally ADH levels should rise. A **healthy** kidney will **reabsorb more** water to fill the vasculature and increase renal perfusion.

When more water is reabsorbed from the urine, will the urine be more concentrated, or dilute? **Increased** water **reabsorption** leads to an **increase in urine osmolality**: more **concentrated** urine.

Normal tubule cells reabsorb water. In **ATN, the urine cannot be concentrated** because the tubule **cells are damaged**. The urine produced in ATN is similar in osmolality to the blood (about 300 mOsm/L). This is called **isosthenuria**. Urine osmolality in ATN is **inappropriately low**. Isosthenuria is

especially problematic when the patient is dehydrated.

Isosthenuria means the urine is the same (*iso*) strength (*sthenos*) as the blood. The term *isosthenuria* is used interchangeably with the phrase *renal tubular concentrating defect*.

Dehydration should **normally increase urine concentration** (osmolality). If there is damage to the tubular cells from ischemia or toxins, the kidney loses the ability to absorb sodium and water because a live, functioning cell is necessary to absorb sodium and water. In **ATN**, the body **inappropriately loses sodium** (UNa above 20) and water (UOsm below 300) into the urine.

Healthy person with **fluid overload → low urine osmolality** or dilute urine

Healthy person with **dehydration → high urine osmolality** or concentrated urine

A 20-year-old African American man comes for a screening test for sickle cell. He is found to be heterozygous (trait or AS) for sickle cell.

What is the best advice for him?

a. **Nothing needed until he has a painful crisis.**
b. **Avoid dehydration.**
c. **Hydroxyurea.**
d. **Folic acid supplementation.**
e. **Pneumococcal vaccination.**

Answer: B. The only significant manifestation of sickle cell trait is a defect in renal concentrating ability or isosthenuria. These patients will continue to produce inappropriately dilute, high-volume urine despite dehydration. Hydroxyurea is used to prevent painful crises when they occur more than 4 times a year. Painful crises rarely occur in sickle cell trait. They do not have hemolysis, so there is no need for additional folic acid supplementation. Splenic function is abnormal only in those who are homozygous, so pneumococcal vaccination is not routinely indicated.

Urine specific gravity correlates to urine osmolality.

High UOsm = high specific gravity

Classification of Acute Renal Failure by Laboratory Testing		
Test	**Prerenal azotemia**	**Acute tubular necrosis**
BUN:creatinine	>20:1	<20:1
Urine sodium (UNa)	<20 mEq/L	>20 mEq/L
Fractional excretion of sodium (FENa)	<1%	>1%
Urine osmolality (UOsm)	>500 mOsm/kg	<300 mOsm/kg

Acute Tubular Necrosis (ATN)

Definition

ATN is an injury to the kidneys from ischemia and/or toxins resulting in sloughing off of tubular cells into the urine. Sodium and water reabsorptive mechanisms are lost with the tubular cells. Proteinuria is not significant since protein, not tubules, spills into the urine when glomeruli are damaged.

Etiology

Knowing the causes of ATN is critical, since there is no specific diagnostic test to prove the etiology. You cannot do a blood level of a drug or a biopsy to prove that a particular toxin caused the renal failure.

TIP

Acute renal failure and a toxin in the history are your clues to the "What is the most likely diagnosis?" question for ATN.

Specific Causes of ATN

A patient comes with fever and acute, left lower quadrant abdominal pain. Blood cultures

on admission grow *E. coli* and *Candida albicans*. She is started on vancomycin, metronidazole and gentamicin, and amphotericin. She has a CT scan that identifies diverticulitis. After 36 hours, her creatinine rises dramatically.

Which of the following is most likely the cause of her renal insufficiency?

a. **Vancomycin.**
b. **Gentamicin.**
c. **Contrast media.**
d. **Metronidazole.**
e. **Amphotericin.**

Answer: C. Radiographic **contrast** media has a very **rapid onset of injury**. Creatinine rises the **next day. Vancomycin, gentamicin**, and **amphotericin** are all potentially nephrotoxic, but they would not cause renal failure with just 2 or 3 doses. They need 5 to 10 days to result in nephrotoxicity. Metronidazole is hepatically excreted and does not cause renal failure.

A 74-year-old blind man is admitted with obstructive uropathy and chest pain. He has a history of hypertension and diabetes. His creatinine drops from 10 mg/dL to 1.2 mg/dL 3 days after catheter placement. The stress test shows reversible ischemia.

What is the most appropriate management?

a. **Coronary artery calcium score on CT scan.**
b. **One to two liters of normal saline hydration prior and during angiography.**
c. **N-acetylcysteine prior to angiography.**
d. **Mannitol during angiography.**
e. **Furosemide during angiography.**
f. **Intravenous sodium bicarbonate before and during angiography.**

Answer: B. **Saline hydration** has the **most proven benefit** at preventing contrast-induced nephrotoxicity. Mannitol and furosemide may or may not prevent nephrotoxicity. There is minimal data to support their use. N-acetylcysteine and sodium bicarbonate have some benefit, but the evidence is not as clear as that with saline. **Calcium scoring on** CT scan is still **considered experimental**. It does not provide sufficient information to eliminate angiography.

How to Answer Questions Correctly When Your Real-life Experience Disagrees with What You Read Here

The last question may distress those of you who regularly see your attendings use N-acetylcysteine and bicarbonate to prevent renal failure from contrast. This is a case in which a person with no clinical experience in the area will do better than a person regularly in the hospital. They are using these substances because:

- The risk of precipitating worse renal failure is very real when using contrast.
- Contrast-enhanced procedures are often unavoidable.
- These are generally benign substances.
- We have nothing else to offer beyond hydration.

Extra-Difficult Question—How to Get a 280 on Step 2 CK

A patient with mild renal insufficiency undergoes angiography and develops a 2 mg/dL rise in creatinine from ATN despite the use of saline hydration before and after the procedure.

What do you expect to find on laboratory testing?

a. **Urine sodium 8 (low), FENa >1%, urine specific gravity 1.035 (high).**
b. **Urine sodium 58 (high), FENa >1%, urine specific gravity 1.005 (low).**
c. **Urine sodium 5 (very low), FENa <1%, urine specific gravity 1.040 (very high).**
d. **Urine sodium 45 (high), FENa >1% urine specific gravity 1.005 (low).**

Answer: C. Although **contrast-induced renal failure** is a form of **ATN**, the urinary **lab values are an exception** from the other forms of ATN. **Contrast causes spasm of the afferent arteriole** that leads to renal tubular dysfunction. There is tremendous reabsorption of sodium and water, leading the specific gravity of the urine to become very high. This results in profoundly low urine sodium. The usual finding in ATN from nephrotoxins would be UNa above 20, FENa greater than 1%, but a low specific gravity. Specific gravity correlates with urine osmolality.

A patient with extremely severe myeloma with a plasmacytoma is admitted for combination chemotherapy. Two days later, the creatinine rises.

What is the most likely cause?

a. **Cisplatin.**
b. **Hyperuricemia.**
c. **Bence-Jones proteinuria.**
d. **Hypercalcemia.**
e. **Hyperoxaluria.**

Answer: B. Two days after chemotherapy, the creatinine rises in a person with a hematologic malignancy. This is most likely from **tumor lysis syndrome** leading to **hyperuricemia**. Cisplatin, as with most **drug toxicities**, would not produce a **rise in creatinine for 5 to 10 days**. Bence-Jones protein and hypercalcemia both cause renal insufficiency, but it would not be rapid and it would not happen as a result of treatment. Treatment for myeloma would end up decreasing both the calcium

and Bence-Jones protein levels because they are produced from the leukemic cells. Cancer cells do not release oxalate.

What would have prevented this event? **Allopurinol, hydration, and rasburicase** should be given **prior to chemotherapy** to **prevent renal failure** from tumor lysis syndrome.

A patient who is suicidal ingests an unknown substance and develops renal failure 3 days later. Her calcium level is also low and the urinalysis shows an abnormality.

What did she take?

a. **Aspirin.**
b. **Acetaminophen.**
c. **Ethylene glycol.**
d. **Ibuprofen.**
e. **Opiates.**
f. **Methanol.**

Answer: **C**. **Ethylene glycol** is associated with acute kidney injury based on **oxalic acid** and **oxalate** precipitating within the **kidney tubules** causing ATN. Oxalate crystal appears as **envelope-shaped crystals**. The calcium level is low because it precipitates as calcium oxalate. Aspirin is renal toxic but does not lower calcium levels and has no abnormality on urinalysis. **Acetaminophen is hepatotoxic**. Ibuprofen and all **NSAIDS are renal toxic** by constricting the afferent arteriole, causing allergic interstitial nephritis and papillary necrosis. They have no impact on calcium levels and the only time something would be found in the urine is in the case of papillary necrosis. Papillary necrosis causes sudden flank pain and fever. **Methanol causes inflammation of the retina** and has no renal toxicity. **Opiates by injection are associated with focal-segmental glomerulonephritis**, not AKI. In addition, that is only with the impurities found with injection drug use, certainly not opiate medications.

Toxins Producing ATN

Toxins have an **increased likelihood** of developing ATN **if there is hypoperfusion** of the kidney and if there is **underlying renal insufficiency** such as from hypertension or diabetes. The risk of ATN is directly proportional to **increasing age** of the patient.

> The body loses 1% of renal function for every year past the age of 40.

Summary of Causes of ATN

- Nonoliguric renal injury is caused by aminoglycoside antibiotics, amphotericin, cisplatin, vancomycin, acyclovir, and cyclosporine. **Slower onset**: usually **5 to 10 days**. Dose dependent: the more administered, the sicker the patient gets. **Low magnesium level** may increase **risk of aminoglycoside** or cisplatin **toxicity**.
- **Contrast** media cause **immediate renal toxicity**. This can best be **prevented with saline hydration**. N-acetylcysteine and sodium bicarbonate are not consistently proven as beneficial.
- Hemoglobin and **myoglobin** (rhabdomyolysis)
- **Hyperuricemia** from tumor lysis syndrome acutely. Long-standing hyperuricemia from gout can cause chronic renal failure.
- **Precipitation of calcium oxalate in the renal cortex** from **ethylene glycol** overdose
- **Bence-Jones** protein is directly **toxic to renal tubules**.
- **NSAIDs**

Rhabdomyolysis

Rhabdomyolysis is caused by **trauma**, prolonged **immobility**, snake bites, seizures, and **crush injuries**. The best initial test to confirm the diagnosis is a urinalysis. The **UA** will be **positive only on dipstick** for large amounts of **blood**, but **no cells will be seen** on microscopic examination.

Urine dipstick cannot tell the difference between:

- Hemoglobin
- Myoglobin
- Red blood cells

Creatine phosphokinase (CPK) levels are **markedly elevated**, but it is the findings on UA that tell you myoglobin is spilling into the urine. The most **specific test** is a **urine test for myoglobin**. **Hyperkalemia** occurs from the

release of potassium from damaged cells because 95% of the potassium in the body is intracellular. **Hyperuricemia** occurs for the same reason it does in tumor lysis syndrome. When **cells break down**, **nucleic acids** are **released** from the cell's nuclei and are rapidly **metabolized to uric acid**. Damaged muscle releases phosphate. **Hypocalcemia** occurs from increased calcium binding to damaged muscle.

> Why doesn't **hemolysis** cause **hyperuricemia?** RBCs have no nuclei.

Treat with:

- **Saline** hydration
- **Mannitol** as an osmotic diuretic
- **Bicarbonate**, which drives potassium back into cells and may prevent precipitation of myoglobin in the kidney tubule

The concept is that myoglobin is a severe oxidant stress on the tubular cells. Saline and mannitol increase urine flow rates to decrease the amount of contact time between the myoglobin and the tubular cells.

> Don't treat hypocalcemia in rhabdomyolysis if asymptomatic. In recovery, the calcium will come back out of the muscles.

A man comes to the emergency department after a triathlon, followed by status epilepticus. He takes simvastatin at triple the recommended dose. His muscles are tender and the urine is dark. Intravenous fluids are started.

What is the next best step in the management of this patient?

a. **CPK level.**
b. **EKG.**
c. **Potassium replacement.**
d. **Urine dipstick.**
e. **Urine myoglobin.**

Answer: **B**. **EKG** is done to **detect life-threatening hyperkalemia**. Your question may have "potassium level" as the answer. CPK level, urine dipstick for blood and myoglobin should all be done, but the EKG will see if he is about to die of a fatal arrhythmia from hyperkalemia. Potassium replacement in a person with rhabdomyolysis would be fatal.

Treatment

There is **no therapy proven to benefit ATN**. Patients should be managed with hydration, if they are volume depleted, and correction of electrolyte abnormalities. **Diuretics increase urine output, but do not change overall outcome**.

> More urine output with diuretics does not mean renal failure is reversing.

TIP

Answering treatment questions for ATN is based on recognizing the most common wrong answers:

- **Low-dose dopamine**
- **Diuretics**
- **Mannitol**
- **Steroids**

All of these are ineffective in reversing ATN.

> Correct the underlying cause in ATN.

When Is Dialysis the Answer?

Dialysis is initiated if there is:

- Fluid overload
- Encephalopathy

- Pericarditis
- Metabolic acidosis
- Hyperkalemia

Initiating **dialysis** is **not based** on a specific level of **BUN or creatinine**. It is based on the development of **life-threatening conditions** like these that cannot be corrected another way.

Hypocalcemia, for example, is life-threatening (**seizures**, prolonged QT interval leading to **arrhythmia**) but you do not dialyze; you **give vitamin D and calcium**.

A patient develops ATN from gentamicin. She is vigorously hydrated and treated with high doses of diuretic, low-dose dopamine, and calcium acetate as a phosphate binder. Urine output increases but she still progresses to end-stage renal failure. She also becomes deaf.

What caused her hearing loss?

a. **Hydrochlorothiazide.**
b. **Dopamine.**
c. **Furosemide.**
d. **Chlorthalidone.**
e. **Calcium acetate.**

Answer: C. Furosemide causes ototoxicity by damaging the hair cells of the cochlea, resulting in sensorineural hearing loss. This is related not only to the **total dose**, but **how fast** it is injected. It essentially "burns" the inner ear. Aminoglycoside antibiotics also cause hearing loss. **Furosemide** in ATN adds **no proven overall benefit**. It does add ototoxicity to the gentamicin.

Hepatorenal Syndrome

Hepatorenal syndrome is renal failure developing secondary to liver disease. The kidneys are intrinsically normal. Look for:

- Severe liver disease (**cirrhosis**)
- New-onset renal failure with no other explanation
- Very **low urine sodium** (less than 10–15 mEq/dL)
- FENa below 1%
- **Elevated BUN:creatinine ratio (greater than 20:1)**

Treatment is with:

- Midodrine
- Octreotide

> Lab values in hepatorenal syndrome fit in with prerenal azotemia.

- Albumin (albumin is less clear)

Atheroemboli

Etiology

Cholesterol plaques in the aorta or near the coronary arteries are sometimes large and fragile enough that they can be "**broken off**" when these vessels are manipulated during **catheter procedures**. **Cholesterol emboli** lodge in the kidney, leading to AKI. Look for **blue/purplish skin lesions** in fingers and toes, **livedo reticularis**, and ocular lesions.

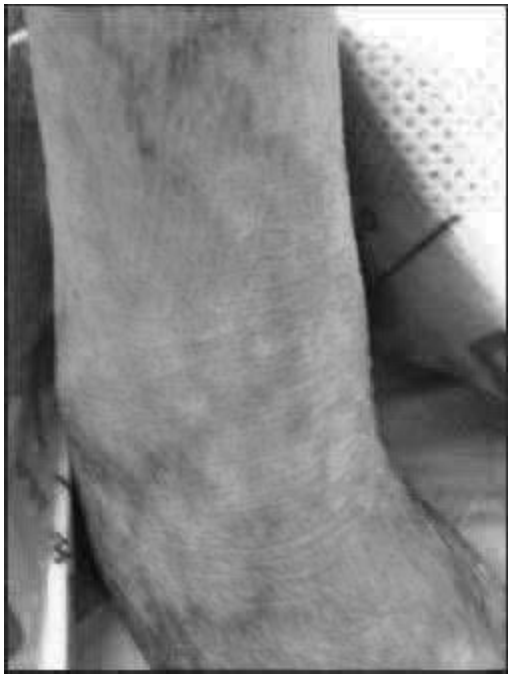


Figure 11.1: Livedo Reticularis. *Source: Farshad Bagheri, MD.*

Peripheral **pulses are normal** in atheroemboli. They are too small to occlude vessels such as the radial or brachial artery.

Diagnostic Tests

Look for:

- Eosinophilia
- Low complement levels
- **Eosinophiluria**
- Elevated ESR

Biopsy of one of the **purplish skin lesions** is the **most accurate diagnostic test**. It shows cholesterol crystals, but this result **does not change management** because there is **no specific therapy** to reverse atheroembolic disease.

Acute (Allergic) Interstitial Nephritis

Definition

Acute (allergic) interstitial nephritis (AIN) is a form of acute renal failure that damages the tubules occurring on an idiosyncratic (idiopathic) basis. Antibodies and **eosinophils attack the cells lining the tubules** as a reaction to **drugs (70%)**, infection, and autoimmune disorders.

Etiology

Although any medication can cause AIN, certain medications are more allergenic (allergy-inducing) than others. The most common medications are:

- **Penicillins** and cephalosporins
- **Sulfa drugs** (including diuretics like furosemide and thiazides, which are sulfa derivatives)
- Phenytoin
- Rifampin

- Quinolones
- Allopurinol
- Proton pump inhibitors

Some medications are just not allergenic. For example, it is extremely rare to have a rash from calcium channel blockers, SSRIs, or beta blockers. These drugs are also almost never associated with AIN, toxic epidermal necrolysis, or hemolysis.

The medications that cause AIN are the same as those that cause:

- Drug allergy and rash
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Hemolysis

TIP

Why learn these allergies as separate diseases? They are the same process, with different target organs affected.

Allergenic substances affect:

- Skin
- Kidney
- Red cells

In addition to drugs, AIN is also caused by infections and autoimmune disease like systemic lupus erythematosus (SLE), Sjögren, and sarcoidosis.

Presentation/"What Is the Most Likely Diagnosis?"

Look for acute renal failure (rising BUN and creatinine) with:

- **Fever** (80%)
- **Rash** (50%)
- Arthralgias
- Eosinophilia and **eosinophiluria** (80%)

Diagnostic Tests

- Elevated BUN and creatinine with ratio below 20:1
- White and red cells in the urine

> Eosinophils are not found in the urine with AKI from NSAIDs.

The **most accurate test is the Hansel** or **Wright stain**, which is how you determine whether **eosinophils** are present. The UA is able to detect only WBCs, RBCs, and protein; **it is not sufficiently accurate to determine that they are eosinophils**.

> Urine sodium and osmolality are not uniformly up or down in AIN. They cannot help establish the diagnosis.

Treatment

AIN usually resolves spontaneously with stopping the drug or controlling the infection. Severe disease is managed with dialysis, which may be temporary. When the creatinine continues to rise after stopping the drug, giving glucocorticoids (prednisone, hydrocortisone, methylprednisolone) is the answer.

Analgesic Nephropathy

Analgesic nephropathy presents with:

- **ATN** from direct toxicity to the tubules
- **AIN**
- **Membranous glomerulonephritis**
- **Vascular insufficiency** of the kidney from **inhibiting prostaglandins**. Prostaglandins dilate the afferent arteriole. **NSAIDs constrict the afferent arteriole** and decrease renal perfusion. This is asymptomatic in healthy patients. When patients are older and have underlying renal insufficiency from diabetes and/or hypertension, then NSAIDs can tip them over into clinically apparent renal insufficiency.
- **Papillary necrosis**

There is no specific diagnostic test to determine NSAIDs caused the disease previously described. **Exclude other causes and look for NSAIDs in the** history.

Papillary Necrosis

Definition/Etiology

Papillary necrosis is a **sloughing off of the renal papillae**. It is caused by toxins such as **NSAIDs**, or sudden vascular insufficiency leading to death of the cells in the papillae and their dropping off the internal structure of the kidney.

Patients who are otherwise healthy don't get papillary necrosis. The case must describe a reason for underlying renal damage, even if the baseline BUN and creatinine levels are normal. Remember that a patient must lose at least 60% to 70% of renal function before the creatinine even begins to rise. Look for **extra NSAID use** with a history of:

- **Sickle cell disease**
- Diabetes
- Urinary obstruction
- Chronic pyelonephritis

Presentation

Papillary necrosis can be very hard to distinguish from pyelonephritis. Look for **the sudden onset of flank pain**, fever, and hematuria in a patient with one of the diseases previously listed.

> Papillary necrosis can give grossly visible **necrotic material** passed **in the urine**. These are the renal papillae.

Diagnostic Tests

The best initial test is a UA that shows red and white cells and may show necrotic kidney tissue. The urine culture will be normal (no growth). The **most accurate test is a CT scan** that shows the abnormal internal structures of the kidney from the loss of the papillae.

Treatment

There is **no specific therapy**. You cannot reattach the sloughed-off part of the kidney.

Differences between Pyelonephritis and Papillary Necrosis

	Pyelonephritis	Papillary necrosis
Onset	Few days	Few hours
Symptoms	Dysuria	Necrotic material in urine
Urine culture	Positive	Negative
CT scan	Diffusely swollen kidney	“Bumpy” contour of interior where papillae were lost
Treatment	Antibiotics such as	No treatment

	ampicillin/gentamicin or fluoroquinolones	

Summary of Tubular Disease

- Generally, tubular diseases are **acute**.
- Tubular diseases are caused by **toxins** (drugs, myoglobin, hemoglobin, oxalate, urate, NSAIDS, contrast).
- **None of them ever cause nephrotic syndrome** or give massive proteinuria.
- **Biopsy is not needed** to establish a diagnosis.
- They are **not treated with steroids** (like all drug allergies, AIN usually resolves spontaneously).
- Additional **immunosuppressive medications** (cyclophosphamide, mycophenolate) are **not used**.
- Treat tubular diseases by **correcting hypoperfusion** and **removing the toxin**.

Tubular Diseases

- Acute
- Toxins
- None nephrotic
- No biopsy usually
- No steroids
- Never additional immunosuppressive agents

Acute = **T**ubular = **T**oxin

Glomerular Diseases

General Answers to Glomerular Disease Questions

- Glomerular diseases are generally **chronic**.
- Glomerular diseases are generally **not caused by toxins or hypoperfusion**.
- **All of them** can cause **nephrotic syndrome**.
- **Biopsy is the most accurate test** to establish a diagnosis (though not always needed).
- They are **often treated with steroids** (several resolve spontaneously).
- **Additional immunosuppressive** medications (cyclophosphamide, mycophenolate) are **frequently used**.

Glomerular Diseases

- Chronic
- **Not from toxins/drugs**
- All potentially **nephrotic**
- **Biopsy** sample
- **Steroids** often

Glomerular = **S**low = **S**ample = **S**teroids = Immuno**suppressives**

Diagnostic Tests

All forms of glomerulonephritis have:

- UA with **hematuria**

- **"Dysmorphic"** red cells (deformed as they "squeeze" through an abnormal glomerulus)
- **Red cell casts**
- Urine sodium and FENa are low
- **Proteinuria**

> The degree or **amount** of proteinuria is the main difference between **glomerulonephritis** and **nephrotic** syndrome.

Individual Glomerular Diseases

Every type of glomerulonephritis causes proteinuria, red cells, red cell casts in urine, hypertension, and edema, so you will need to know what is different or unique about each disease. It is like an IQ test: Which of these is different from the others?

Goodpasture Syndrome

Goodpasture also presents with **lung and kidney** involvement, but unlike Wegener granulomatosis (WG), there is **no upper respiratory tract involvement**. Goodpasture is also limited to just the lung and kidney, so signs of systemic vasculitis are absent. There is **no skin**, **joint**, **GI**, **eye**, **or neurological involvement**.

Diagnostic Tests/Treatment

The best initial test is antiglomerular basement membrane antibodies. The most accurate test is a lung or kidney biopsy. **Anemia is often present** from chronic blood loss from hemoptysis. The chest x-ray will be abnormal but is insufficient to confirm the diagnosis.

Treat with **plasmapheresis and steroids**. Cyclophosphamide can be helpful.

> Kidney biopsy in Goodpasture syndrome shows "**linear deposits**."

IgA Nephropathy (Berger Disease)

IgA nephropathy is the **most common cause of acute glomerulonephritis** in the United States. Look for an Asian patient with recurrent episodes of **gross hematuria** 1 to 2 **days** after an upper respiratory tract infection (**synpharyngitic**). This actually helps, because IgA disease is the most common cause of glomerulonephritis and all the other causes have some specific physical findings.

Poststreptococcal glomerulonephritis follows pharyngitis by 1 to 2 **weeks**.

TIP

There are no unique physical findings in IgA nephropathy to allow you to answer the "most likely diagnosis" question.

Diagnostic Tests

IgA levels are increased in only 50%. The **most accurate test is a kidney biopsy**.

> Proteinuria levels correspond to severity of disease and likelihood of progression.
>
> More proteinuria = worse progression

Treatment

There is **no treatment proven to reverse the disease**. Thirty percent will completely resolve. Between 40% and 50% will slowly progress to end-stage renal disease.

Severe **proteinuria** is treated with **ACE inhibitors and steroids**. Fish oil is of uncertain benefit.

Postinfectious Glomerulonephritis

The most common organism leading to postinfectious glomerulonephritis (PIGN) is *Streptococcus*, but almost any infection can lead to abnormal activation of the immune system and PIGN. Poststreptococcal glomerulonephritis (PSGN) **follows throat infection or skin infection (impetigo) by 1 to 3 weeks**.

Presentation

Patients present with:

- **Dark (cola-colored) urine**
- Edema that is often **periorbital**
- **Hypertension**
- Oliguria

Diagnostic Tests

A UA with **proteinuria**, red cells, and **red cell casts** tells you that glomerulonephritis is present. PSGN from group A beta hemolytic streptococci (pyogenes) is confirmed first by antistreptolysin O (ASO) titers and anti-DNase antibody titers. Biopsy is the most accurate test, but you should **not routinely do a kidney biopsy** because the blood test is sufficiently accurate and the disorder usually resolves spontaneously.

> Complement levels are low in PSGN.

Treatment

Management of PSGN does not reverse the glomerulonephritis. Use supportive therapies such as:

- **Antibiotics**
- **Diuretics** to control fluid overload

> Less than 5% of those with PSGN will progress.

Alport Syndrome

Alport syndrome is a congenital **defect of collagen** that results in glomerular disease combined with:

- Sensorineural **hearing loss**
- **Visual disturbance** from loss of the collagen fibers that hold the **lens of the eye** in place

There is **no specific therapy** to reverse this defect of type IV collagen.

Polyarteritis Nodosa

Definition

Polyarteritis nodosa (PAN) is a **systemic vasculitis** of small and medium-sized arteries that most commonly affects the kidney. Virtually every organ in the body can be affected, but it tends to **spare the lung**. Although it is of unknown etiology, it can be **associated with hepatitis** B and all patients with PAN should be tested.

Presentation

Besides the presentation of **glomerulonephritis**, PAN presents with nonspecific symptoms of **fever**, **malaise**, **weight loss**, **myalgias**, **and arthralgia** developing over weeks to months—as does almost every type of vasculitis. The most common organ systems involved are:

Gastrointestinal: Abdominal pain, bleeding, nausea, and vomiting occur. **Pain can be worsened by eating** because of mesenteric vasculitis.

> PAN spares the lungs.

Neurologic: Vasculitis damages the blood vessels surrounding larger peripheral nerves such as the peroneal, ulnar, radial, and brachial nerves. When more than one large peripheral nerve is involved, it is called

"**mononeuritis multiplex**." When presented with **stroke in a young person**, you should look for vasculitis.

> Damage to small blood vessels around nerves starves them into neuropathy.

Skin: Vasculitis of any cause leads to purpura (large) and petechiae (small). PAN also gives ulcers, **digital gangrene**, **and livedo reticularis**.

> PAN is nonspecific. There is no single finding that allows you to answer the "most likely diagnosis" question.

Cardiac disease is present in about one-third of patients.

> Stroke or MI in a young person suggests PAN.

Diagnostic Tests

Blood tests will show:

- Anemia and leukocytosis
- Elevated ESR and C-reactive protein
- **ANCA: not present in most cases**
- ANA and rheumatoid factor: sometimes present in low titer

Angiography of the renal, mesenteric, or hepatic artery showing aneurysmal dilation in association with new-onset hypertension and characteristic symptoms is the best initial test that has specificity for PAN. Angiography is a clear answer as a diagnostic test when the most involved organ is not easily accessible for a biopsy (such as the kidney).

The **most accurate diagnostic test is a biopsy** of a symptomatic site such as skin, nerves, or muscles.

There is no blood test to confirm PAN.

Treatment

Prednisone and cyclophosphamide are the standard of care and they lower mortality.

Treat hepatitis B when it is found.

Any form of glomerular disease can produce nephrotic syndrome.

Lupus Nephritis

SLE can give **any degree of renal involvement**. The kidneys in SLE can be normal or present with **mild**, **asymptomatic proteinuria**. Severe disease presents with **membranous glomerulonephritis**. Long-standing SLE may simply "scar" the kidneys and biopsy will **show glomerulosclerosis**, which has no active inflammatory component but may lead to such damage as to require dialysis.

Biopsy is the most accurate test of lupus nephritis. **Biopsy is indispensable in determining therapy based on the stage.** Mild inflammatory changes may respond to glucocorticoids. Severe, proliferative disease such as membranous nephropathy is treated with **glucocorticoids combined with either cyclophosphamide or mycophenolate**.

Biopsy is not performed to diagnose lupus, but rather to guide intensity of therapy.

Amyloidosis

Amyloid is an **abnormal protein** produced in association with:

- **Myeloma**
- Chronic inflammatory diseases
- Rheumatoid arthritis
- Inflammatory bowel disease
- Chronic infections

There is also a primary form of amyloidosis in which the protein is produced for unknown reasons. The kidney is the primary target of the protein.

> Amyloid, HIV nephropathy, polycystic kidneys, and diabetes give **large kidneys** on sonogram and CT scan.

Biopsy is the most accurate test. You will see **green birefringence with Congo red staining**.

Treat amyloidosis by trying to control the underlying disease. When this is unsuccessful or there is no primary disease to control, the treatment of amyloidosis is with **melphalan and prednisone**.

Nephrotic Syndrome

Definition

Nephrotic syndrome is a measure of the **severity** of proteinuria in association with any form of glomerular disease. Nephrotic syndrome occurs when proteinuria is so massive that the liver can no longer increase the production of albumin to compensate for urinary losses. Massive proteinuria leads to:

- **Edema**
- **Hyperlipidemia**
- Thrombosis: from urinary loss of the natural anticoagulants protein C, protein S, and antithrombin

> Nephrotic syndrome is not based on the etiology; it is based on the severity.

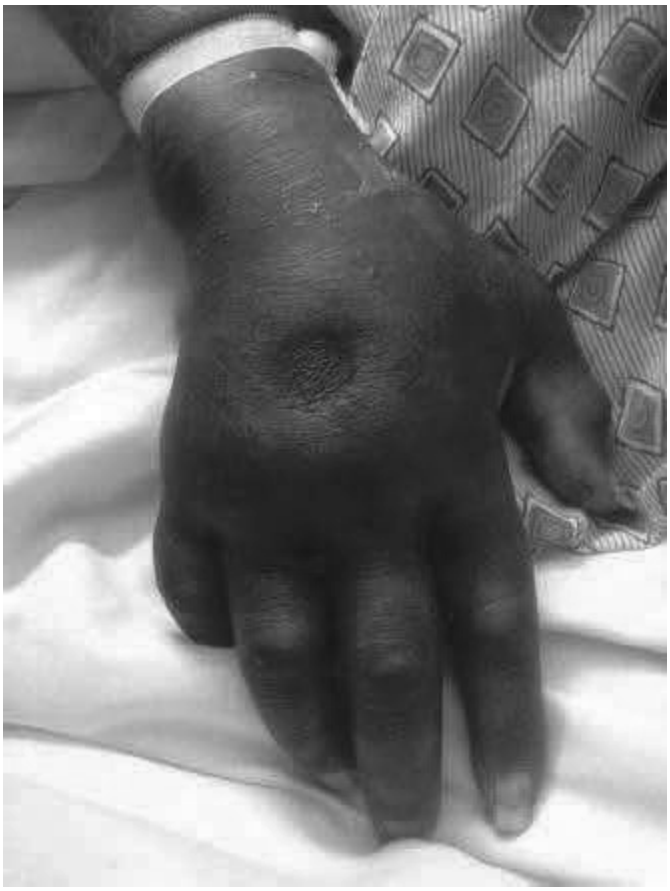


Figure 11.2: Pitting Edema. *Source: Pramod Theetha Kariyanna, MD.*

Etiology

Overall, diabetes and hypertension are the most common causes of nephrotic syndrome. Any of the glomerular diseases just described may lead to such massive protein loss that nephrotic syndrome develops.

> The major difference between “nephritic” and “nephrotic” is the amount of proteinuria.

In addition to systemic disease, there are a number of diseases limited to the kidney that produce nephrotic syndrome. It is better to describe “associations” rather than “causes,” since we do not know what causes nephrotic syndrome.

The associations are:

Cancer (solid organ): membranous

Children: minimal change disease

Injection drug use and AIDS: focal-segmental

NSAIDs: minimal change disease and membranous

SLE: any of them

Presentation

Nephrotic syndrome presents with generalized **edema**. **Infections are more frequent** because of increased urinary loss of immunoglobulins and complement. **Clots are more common** from loss of antithrombin, protein C, and protein S.

> CHF leads to edema of dependent areas like the legs. Nephrotic patients are edematous everywhere.

Diagnostic Tests

The **best initial test is a urinalysis**.

Protein levels on a UA roughly correspond to the amount of protein excreted over 24 hours; however, since renal function varies with the time of day, as well as posture (flat or upright), the **UA is not sufficiently accurate**. You can have trace proteinuria on one UA and 2+ protein on another.

> UA only detects albumin as a protein.

The urine **albumin/creatinine ratio** gives a measure of the average protein produced over 24 hours. A ratio of 2:1 means 2 grams of protein excreted over 24 hours. A ratio of 5.4 to 1 means 5.4 grams excreted over 24 hours.

Periorbital edema is characteristic of nephrotic syndrome.

The **urine albumin/creatinine spot urine ratio is equal to a 24-hour urine** in terms of accuracy and is much easier to obtain.

UA shows Maltese crosses, which are lipid deposits in sloughed-off tubular cells.

Renal biopsy is the most accurate test of the cause of nephrotic syndrome. Although there are certain associations with each form of nephrotic syndrome, only the biopsy can distinguish between the forms:

- Focal-segmental
- Membranous
- Membranoproliferative
- Minimal change
- Mesangial

By definition, nephrotic syndrome is:

- **Hyperproteinuria (more than 3.5 grams per 24 hours)**
- **Hypoproteinemia**
- **Hyperlipidemia**
- **Edema**

Anything with a carrier protein can be lost in urine.

Lipid levels rise because the lipoprotein signals that turn off the production of circulating lipid are now lost in the urine. With loss of these lipoproteins that surround chylomicrons and VLDLs, all lipid levels in the blood will rise. Iron,

copper, and zinc are low because their carrier protein is lost in the urine.

Treatment

The best **initial therapy** for nephrotic syndrome is **glucocorticoids**. If there is no response after several weeks of therapy, other immunosuppressive medications such as **cyclophosphamide** are used.

ACE inhibitors or ARBs (angiotensin receptor blockers) are used to try to control proteinuria.

Edema is managed with **salt restriction and diuretics**. **Hyperlipidemia is managed with statins** as you would any form of hyperlipidemia.

End-Stage Renal Disease

Definition

End-stage renal disease (ESRD), or chronic renal failure, is defined as that form of kidney failure **so severe as to need dialysis** or renal transplantation. **ESRD is not defined as a particular BUN or creatinine**. ESRD is defined as the loss of renal function leading to a collection of symptoms and laboratory abnormalities also known as **uremia**. Uremia is a term interchangeable with the conditions for which dialysis is the answer as therapy.

Etiology

Any form of tubular or glomerular damage can cause ESRD. Overall, diabetes and hypertension are, by far, more common than all the other causes of renal failure combined. ESRD usually implies disease that has been present for years; however, rapidly progressive glomerulonephritis is so named because it can lead to ESRD over weeks.

> Diabetes and hypertension are the most common causes of ESRD.

Presentation

Uremia is defined as the presence of:

- Metabolic **acidosis**
- **Fluid** overload
- **Encephalopathy**
- **Hyperkalemia**
- **Pericarditis**

Each of these is an indication for dialysis. Although pericarditis is the least common, these events usually occur at the same time when creatinine clearance drops below the level at which acids, fluid, and potassium can be excreted.

> Peritoneal dialysis and hemodialysis are equally effective at removing wastes from the body.

Manifestations of Renal Failure

Anemia: Loss of erythropoietin leads to normochromic, normocytic anemia.

Hypocalcemia: The kidney transforms the less active 25-hydroxy-vitamin D into the much more active 1,25-dihydroxy-vitamin D. Without the 1,25 dihydroxy form of vitamin D, the body will not absorb enough calcium from the gut.

> Patiromer binds potassium, allowing longer of ACEIs to decrease progression.

Osteodystrophy: Low calcium leads to **secondary hyperparathyroidism**. High parathyroid hormone levels remove calcium from bones, making them soft and weak.

Bleeding: Platelets do not work normally in a uremic environment. They do not degranulate. If a platelet does not release the contents of its granules, it

will not work.

Infection: The same defect occurs with neutrophils. Without degranulation, neutrophils will not effectively combat infection.

Pruritus: Unclear reasoning; urea accumulating in skin causes itching.

Hyperphosphatemia: Phosphate is normally excreted through kidneys. **High parathyroid hormone levels release phosphate from bones**, but the body is unable to excrete it.

Hypermagnesemia: from loss of excretory ability

Accelerated atherosclerosis and hypertension: The immune system (lymphocytes) helps keep arteries clear of lipid accumulation. White cells don't work normally in a uremic environment. This is the most common cause of death in those on dialysis.

Endocrinopathy: Women are **anovulatory**. Men have **low testosterone**. **Erectile dysfunction** is common. Insulin levels tend to go up because insulin is excreted renally. However, insulin resistance also increases. Glucose levels therefore can be up or down.

> Cardiac disease kills triple the number that infection does in ESRD.

Treatment of the Manifestations of ESRD

Manifestation	Treatment
Anemia	Erythropoietin replacement and iron supplementation
Hypocalcemia and osteomalacia	Replace vitamin D and calcium
Bleeding	DDAVP increases platelet function; use only when bleeding

Pruritus	Dialysis and ultraviolet light
Hyperphosphatemia	Oral binders: see “Treatment of Hyperphosphatemia”
Hypermagnesemia	Restriction of high-magnesium foods, laxatives, and antacids
Atherosclerosis	Dialysis
Endocrinopathy	Dialysis, estrogen and testosterone replacement

Anemia from ESRD is the only time erythropoietin is always used.

Treatment of Hyperphosphatemia

Oral phosphate binders will prevent phosphate absorption from the bowel. Treatment of hypocalcemia will also help because it is the hyperparathyroidism that causes increased phosphate release from bone. When vitamin D is replaced to control hypocalcemia, it is critical to also give phosphate binders; otherwise vitamin D will increase GI absorption of phosphate.

Use:

- Calcium acetate
- Calcium carbonate
- Sevelamer
- Lanthanum

Never use aluminum-containing phosphate binders. **Aluminum causes dementia**.

Use sevelamer and lanthanum to bind phosphate when the calcium level is high.

Kidney Transplantation

Only 50% of ESRD patients will be suitable for transplantation. The donor does not have to be alive or related, although these are both better.

HLA-identical, related donor kidneys last 24 years on average.

Survival by Method			
	1 year	**3 years**	**5 years**
Living, related donor	95%	88%	72%
Deceased donor	90%	78%	58%
Dialysis alone	Variable	Variable	30%–40%
Diabetics on dialysis	Variable	Variable	20%

Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are different variants of what is probably the same disease. TTP is associated with HIV, cancer, and drugs such as cyclosporine, ticlopidine, and clopidogrel. HUS is more common in children and the most frequently tested association is *E. coli* 0157:H7 and *Shigella*. Both TTP and HUS are

associated with:

- Intravascular hemolysis
- Renal insufficiency
- Thrombocytopenia

The hemolysis is visible on smear with **schistocytes**, helmet cells, and **fragmented red cells**.

TTP is associated with:

- Neurological symptoms
- Fever

> PT and aPTT are normal in HUS/TTP.

TTP does not have to have all 5 manifestations to establish a diagnosis. In fact, **the only indispensable finding to establish the diagnosis is the intravascular hemolysis**. A low ADAMTS 13 level supports the diagnosis of TTP.

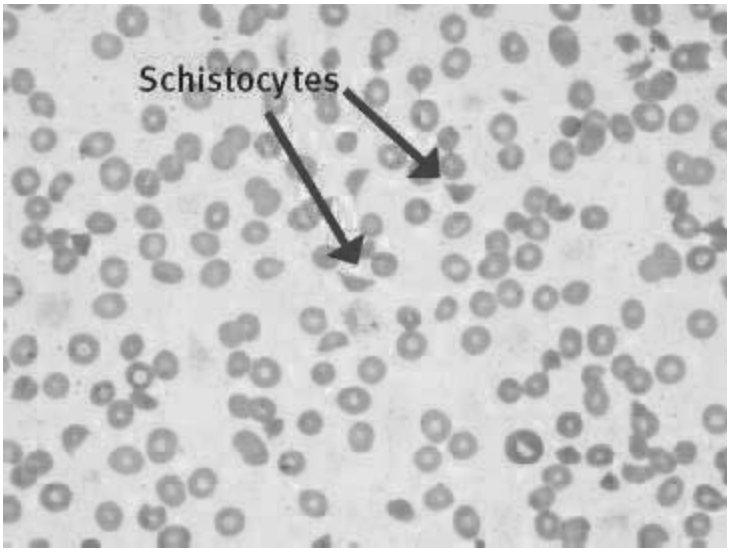


Figure 11.3: Fragmented red cells, or schistocytes, are characteristic of intravascular hemolysis. *Source: Abhay Vakil, MD.*

Most cases of **HUS from *E. coli* will resolve spontaneously**. Plasmapheresis

is generally urgent in TTP. Severe HUS also needs urgent plasmapheresis. If plasmapheresis is not one of the choices, use **infusions of fresh frozen plasma (FFP)**. Steroids do **not** help.

TIP

Platelet transfusion is never the correct choice for TTP or HUS.

Cystic Disease

The single most important point in cystic disease is how to recognize a cyst that is potentially malignant and needs to be aspirated. If any of the qualities of a complex cyst are found, it should be aspirated to exclude malignancy.

Comparing Benign (Simple) Cysts and Potentially Malignant Cysts		
	Simple cyst	**Complex cysts (potential malignancy)**
Echogenicity	Echo free	Mixed echogenicity
Walls	Smooth, thin	Irregular, thick
Demarcation	Sharp	Lower density on back wall
Transmission	Good through to back	Debris in cyst

Polycystic Kidney Disease

Polycystic kidney disease (PCKD) presents with:

- Pain
- Hematuria
- Stones

- Infection
- Hypertension

What is the most common cause of death from PCKD?

a. **Intracerebral hemorrhage.**
b. **Stones.**
c. **Infection.**
d. **Malignancy.**
e. **Renal failure.**

Answer: **E**. Renal failure occurs in PCKD from recurrent episodes of pyelonephritis and nephrolithiasis causing progressive scarring and loss of renal function. PCKD does not have malignant potential. Only 10% to 15% of affected people have cerebral aneurysms, most of which do not rupture. Connective tissue is weak throughout the body. These patients may have:

- *Liver cysts (most common site outside the kidney)*
- *Ovarian cysts*
- *Mitral valve prolapse*
- *Diverticulosis*

> No therapy exists to prevent or reverse cysts of any type.

Sodium Disorders

Hypernatremia

Etiology

Hypernatremia occurs when there is **loss of free water**. Examples are:

- **Sweating**
- Burns
- Fever

- **Pneumonia:** from insensible losses from hyperventilation
- Diarrhea
- Diuretics

Diabetes insipidus (DI) leads to **high-volume water loss** from **insufficient** or **ineffective antidiuretic hormone (ADH)**. Any CNS disorder (stroke, tumor, trauma, hypoxia, infection) can damage the production of ADH in the hypothalamus or storage in the posterior pituitary, leading to central diabetes insipidus (CDI).

Nephrogenic DI is a **loss of ADH effect** on the collecting duct of the kidney. This is much less common. Nephrogenic DI is caused by **lithium** or demeclocycline, **chronic kidney disease**, **hypokalemia**, **or hypercalcemia**. They make **ADH ineffective** at the tubule.

Presentation

DI and hypernatremia of any cause presents with **neurological** symptoms such as **confusion**, **disorientation**, **lethargy**, and **seizures**. If uncorrected, severe hypernatremia causes **coma** and irreversible **brain damage**.

> High-volume **nocturia** is the first clue to the **presence of DI**.

> **Sodium** disorders cause **CNS** problems.

TIP

Polyuria is high urine volume. Frequency just means increased attempts at voiding. The volume in urinary frequency might be very small (such as in urethritis or cystitis).

Diagnostic Tests

High serum sodium is nearly equivalent to hyperosmolality since the majority

of osmolality is sodium. Fluid losses from the skin, kidneys, or stool generally lead to:

- Decreased urine volume (high urine volume in DI)
- Increased urine osmolality (decreased urine osmolality in DI)
- Decreased urine sodium

> Increased urine volume despite dehydration and hyperosmolality of the blood suggests DI.

Water Deprivation Test

The best initial test for DI is preventing the patient from drinking, then observing urine output and urine osmolality. With **DI**, urine **volume stays high** and urine **osmolality** stays **low** despite vigorous urine production and despite developing dehydration.

Response to ADH administration:

- **CDI: sharp decrease in urine volume**, increase in osmolality
- NDI: no change in urine volume or osmolality with ADH administration

The **ADH level is low in CDI**, and markedly **elevated in NDI**.

Comparison of Central versus Nephrogenic Diabetes Insipidus

	CDI	NDI
Polyuria and nocturia	Yes	Yes
Urine osmolality and sodium	Low	Low
Positive water deprivation test	Yes	Yes
Response to ADH	Yes	No

ADH level	Low	High

A “positive” water deprivation test means urine volume stays high despite withholding water.

Treatment

1. Fluid loss: **Correct the underlying cause** of fluid loss.
2. **CDI: Replace ADH** (vasopressin also known as DDAVP).
3. **NDI:**
   - Correct **potassium and calcium**.
   - Stop lithium or demeclocycline.
   - Give hydrochlorothiazide or NSAIDs for those still having NDI despite these interventions.

Complications of Therapy

If sodium levels are brought down too rapidly, cerebral edema will occur. This is from the shift of fluids from the vascular space into the cells of the brain. Cerebral edema presents with worsening confusion and seizures.

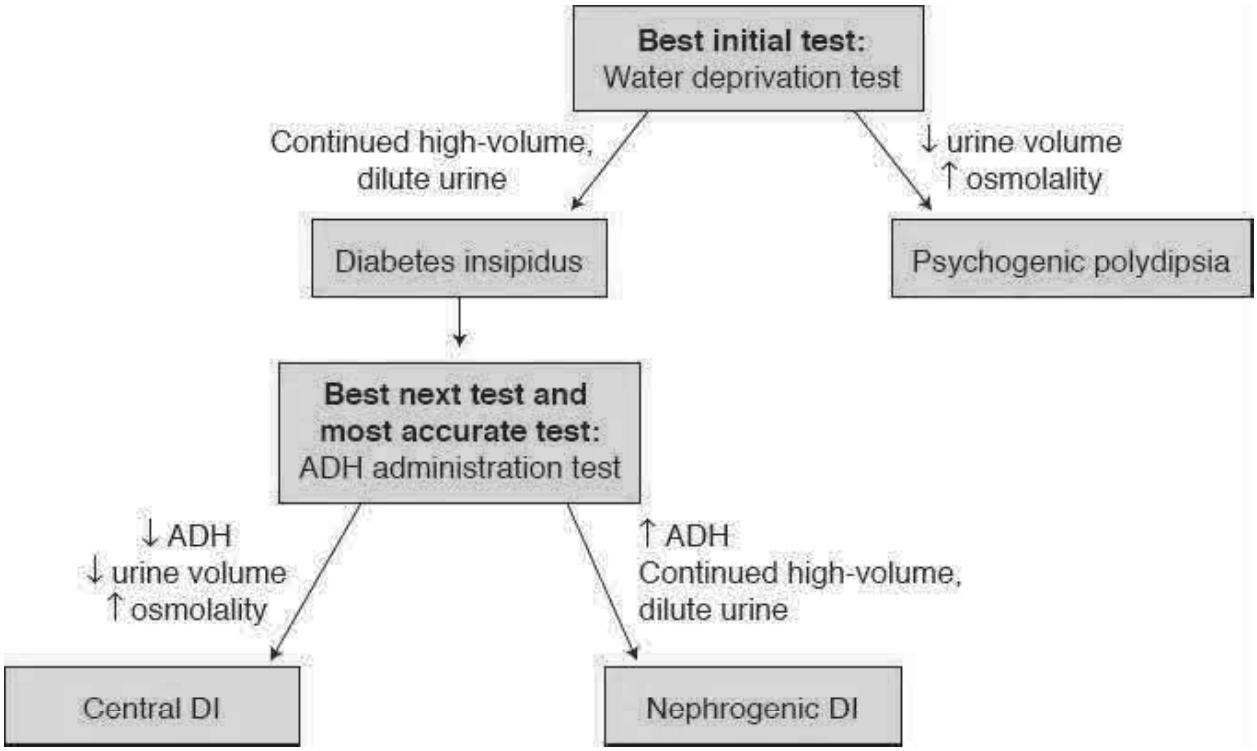


Figure 11.4: Diagnosing Diabetes Insipidus

Hyponatremia

Etiology

Hyponatremia is characterized according to overall **volume status** of the body.

Hypervolemia

The most common causes of hyponatremia with a hypervolemic state are:

- **CHF**
- **Nephrotic syndrome**
- **Cirrhosis**

These are cases in which **intravascular volume depletion** leads to **increased ADH levels**. Pressure receptors in the **atria and carotids sense the decrease in volume and stimulate ADH production** and release. Although the sodium level drops, it is more important to maintain vascular volume and organ perfusion.

> Perfusion is more important than normal sodium.

Hypovolemia

- **Sweating**
- Burns
- Fever
- **Pneumonia:** from insensible losses from hyperventilation
- Diarrhea
- Diuretics

All of these are also causes of hypernatremia; however, they cause hyponatremia if there is **chronic replacement with free water**. A little sodium and a lot of water are lost in urine, which is then replaced with free water that has no sodium. Over time, this process **depletes the body of sodium** and the serum sodium level drops.

Addison disease or loss of adrenal function also causes hyponatremia because of loss of aldosterone. Aldosterone causes sodium reabsorption. If the body **loses aldosterone**, **it loses sodium**.

Euvolemia

The most common causes of hyponatremia with euvolemia (normal volume status) are:

- Pseudohyponatremia (hyperglycemia)
- Psychogenic polydipsia
- Hypothyroidism
- Syndrome of inappropriate ADH release (SIADH)

Hyperglycemia: Very **high glucose** levels lead to a **decrease in sodium levels**. Hyperglycemia acts as an osmotic draw on fluid inside the cells. Free water leaves the cells to correct the hyperosmolar serum. This drops the sodium level. The management is to correct the glucose level.

For every 100 mg/dL of glucose above normal, there is a 1.6 mEq/L decrease

in sodium.

Psychogenic polydipsia: Massive ingestion of free water above 12 to 24 liters a day will overwhelm the kidney's ability to excrete water. The minimum urine osmolality is 50 mOsm/kg. The body can produce 12 to 24 liters of urine a day, depending on whether you can get the urine osmolality down to 50 or 100 mOsm/kg.

TIP

Look for a history of bipolar disorder to suggest psychogenic polydipsia.

Hypothyroidism: Thyroid hormone is needed to excrete water. If the thyroid hormone level is low, free water excretion is decreased.

SIADH: Any **lung** or **brain disease** can cause **SIADH** for unclear reasons. Certain drugs such as SSRIs, sulfonylureas, vincristine, cyclophosphamide, or tricyclic antidepressants can cause SIADH. Certain cancers, especially small-cell cancer of the lung, produce ADH. Pain causes SIADH.

Presentation

Hyponatremia presents entirely with **CNS symptoms**:

- Confusion
- Lethargy
- Disorientation
- Seizures
- Coma

If the sodium levels drop very fast, the patient can immediately seize. **Slow drops** may be entirely **asymptomatic** even if the level is very low.

> Symptoms of hyponatremia are dependent on how fast it occurs.

Sodium means **CNS** symptoms.

Diagnostic Tests

In SIADH, the urine is inappropriately concentrated (**high urine osmolality**). The urine sodium is inappropriately high in SIADH. The uric acid level and BUN are low in SIADH.

The most accurate test is a high ADH level.

Response to Hyponatremia		
	Normal levels	**SIADH**
Urine osmolality	Low (<100 mOsm/kg)	High
Urine sodium	Low (<20 mEq/L)	High (>40 mEq/L)

Treatment

Clinical Manifestations of Hyponatremia by Severity		
Degree of hyponatremia	**Specific manifestation**	**Management**
Mild hyponatremia	No symptoms	Restrict fluids
Moderate	Minimal confusion	Saline and loop diuretic
Severe	Lethargy, seizures, coma	Hypertonic saline, conivaptan, tolvaptan

TIP

The treatment answer is not based on the sodium level; it is based on the symptoms.

> In SIADH, saline without a diuretic makes it worse.

ADH antagonists: Tolvaptan and conivaptan are antagonists of ADH. They are the answer as part of urgent therapy for severe, symptomatic SIADH. They are only for urgent treatment in hospital. No oral version is available.

Chronic SIADH: SIADH can be from an underlying disorder that cannot be corrected such as metastatic cancer. **Demeclocycline treats chronic SIADH**. **Demeclocycline blocks** the action of **ADH** at the collecting duct of the kidney tubule.

Complications of Treatment

Correction of sodium must occur slowly. "Slowly" is defined as under 0.5 to 1 mEq per hour or 12 to 24 mEq per day. If the sodium level is brought up to normal too rapidly, the neurological disorder known as **central pontine myelinolysis** or **osmotic demyelinization** occurs.

Potassium Disorders

Hyperkalemia

High potassium levels (hyperkalemia) are an absolutely indispensable portion of your knowledge because of the **life-threatening nature of potassium disorders**.

> Severe hyperkalemia can stop the heart in seconds if the level is high enough.

Etiology

Pseudohyperkalemia (falsely elevated levels):

- **Hemolysis**
- Repeated fist clenching with tourniquet in place
- **Thrombocytosis** or **leukocytosis** will leak out of cells in the lab specimen

None of these causes of hyperkalemia needs further treatment or investigation beyond repeating the sample.

Decreased excretion:

- **Renal failure**
- **Aldosterone decrease:**
  - **ACE inhibitors**/ARBs
  - Type IV renal tubular acidosis (hyporeninemic, hypoaldosteronism)
  - Spironolactone and eplerenone (aldosterone inhibitors)
  - Triamterene and amiloride (potassium-sparing diuretics)
  - Addison disease

Release of potassium from tissues:

- Any **tissue destruction**, such as hemolysis, **rhabdomyolysis**, or **tumor lysis** syndrome, can release potassium.
- **Decreased insulin:** Insulin normally drives potassium into cells.
- **Acidosis:** Cells will pick up hydrogen ions (acid) and release potassium in exchange.
- Beta blockers and digoxin: These drugs inhibit the sodium/potassium ATPase that normally brings potassium into the cells.
- Heparin increases potassium levels, presumably through increased tissue release.

> Since 95% of potassium in the body is intracellular, shifting potassium out of cells can easily be fatal.

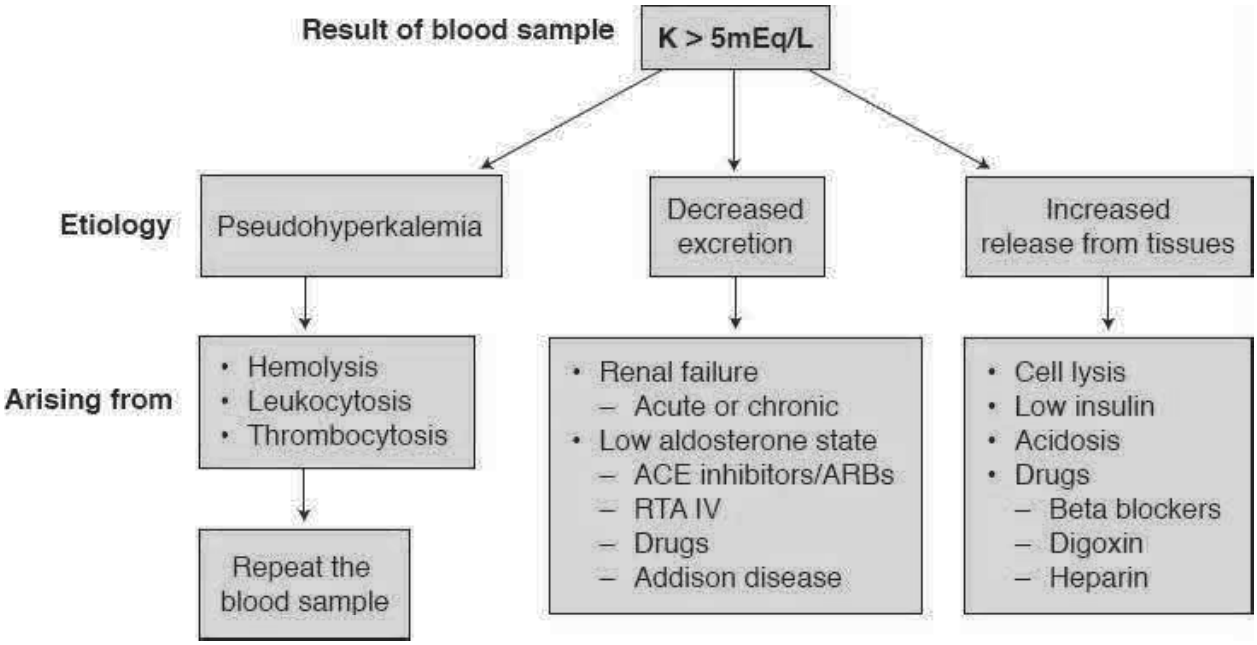


Figure 11.5: Hyperkalemia Etiology

Presentation

Potassium disorders interfere with muscle contraction and cardiac conductance. Look for:

- Weakness
- **Paralysis** when severe
- **Ileus** (paralyzes gut muscles)
- Cardiac rhythm disorders

> Hyperkalemia does not cause seizures.

Diagnostic Tests

> Sodium = CNS symptoms
>
> Hyperkalemia = muscular and cardiac symptoms

Besides a potassium level, testing is aimed at looking for the causes previously described. **The most urgent test in severe hyperkalemia is an EKG**.

The EKG in severe hyperkalemia shows:

- **Peaked T waves**
- Wide QRS
- PR interval prolongation

Treatment

Life-Threatening Hyperkalemia (Abnormal EKG)

1. Calcium chloride or calcium gluconate
2. Insulin and glucose to drive potassium back into cells
3. Bicarbonate: drives potassium into cells but should be used most when acidosis causes hyperkalemia

Removing Potassium from the Body

Sodium polystyrene sulfonate (**Kayexalate**) **removes potassium from the body** through the bowel. The patient ingests Kayexalate orally and over several hours it will bind potassium in the gut and remove it from the body.

> Calcium is only used if the EKG is abnormal to protect the heart. It does not lower the potassium level.

Insulin and bicarbonate lower the potassium level through redistribution into the cells.

> Insulin does not remove potassium from the body.

Other methods to lower potassium are:

- Inhaled beta agonists (albuterol)
- Loop diuretics
- Dialysis

> Patiromer allows use of ACEI/ARB despite rising potassium levels.

- Oral potassium binder (patiromer)

TIP

When there is hyperkalemia and an abnormal EKG, the "most appropriate next step" is clearly calcium chloride or gluconate.

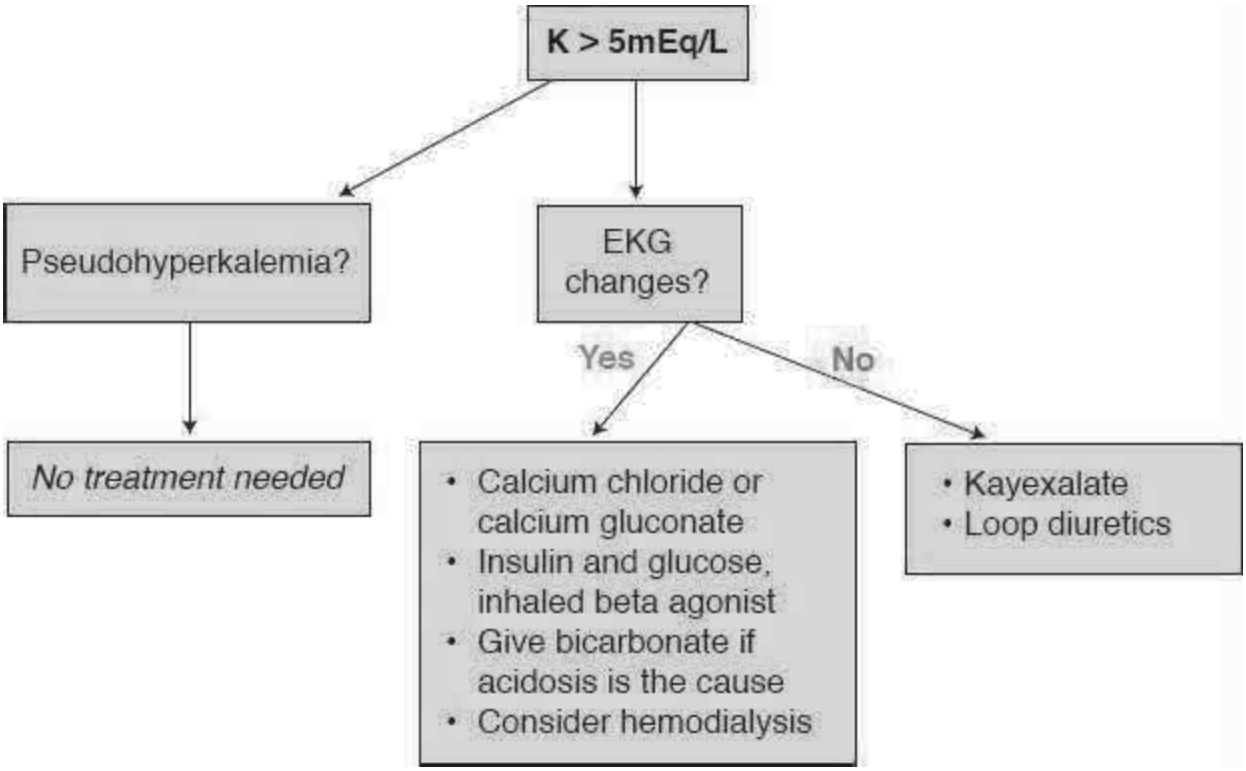


Figure 11.6: Hyperkalemia Treatment

Hypokalemia

Etiology

Decreased intake: This is unusual because the kidney can decrease potassium excretion to extremely small amounts.

Shift into cells:

- Alkalosis (hydrogen ions come out of the cell in exchange for potassium entering)
- Increased insulin
- Beta adrenergic stimulation (accelerates sodium/potassium ATPase)

Renal loss:

- Loop diuretics
- Increased aldosterone
  - Primary hyperaldosteronism (Conn syndrome)
  - Volume depletion raises aldosterone
  - Cushing syndrome
  - Bartter syndrome (genetic disease causing salt loss in loop of Henle)
  - Licorice
- Hypomagnesemia: There are magnesium-dependent potassium channels. When magnesium is low, they open and spill potassium into the urine.
- Renal tubular acidosis (RTA) both proximal and distal

Gastrointestinal loss:

- Vomiting
- Diarrhea
- Laxative abuse

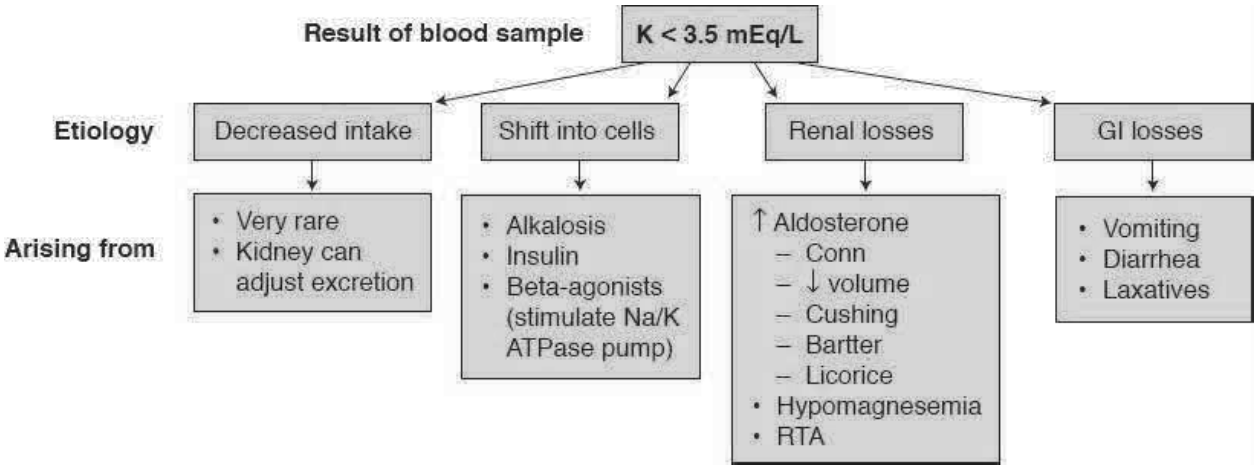


Figure 11.7: Hypokalemia Etiology

Presentation

Hypokalemia leads to problems with muscular contraction and cardiac conduction. Potassium is essential for proper neuromuscular contraction. Hypokalemia presents with:

- Weakness
- Paralysis
- Loss of reflexes

> Muscular abnormalities may be so severe as to cause rhabdomyolysis.

EKG Findings

U waves are the most characteristic finding of hypokalemia.

Other findings are ventricular ectopy (PVCs), flattened T waves, and ST depression.

> Hypokalemia does **not** cause seizures.

Treatment

There is no **maximum rate of oral potassium replacement**. The gastrointestinal system cannot absorb potassium faster than the kidneys can excrete it, so you cannot go too far too fast. **Intravenous potassium replacement**, **however**, **can cause a fatal arrhythmia** if it is done too fast. You must allow time for potassium to equilibrate into the cells.

> Intravenous potassium replacement must be very slow.

A patient is admitted with vomiting and diarrhea from gastroenteritis. His volume status is corrected with intravenous fluids and the diarrhea resolves. His pH is 7.40 and his serum bicarbonate has normalized. Despite vigorous oral and intravenous replacement, his potassium level fails to rise.

What should you do?

a. **Consult nephrology.**
b. **Magnesium level.**
c. **Parathyroid hormone level.**
d. **Intracellular pH level.**
e. **24-hour urine potassium level.**

Answer: B. Hypomagnesemia can lead to increased urinary loss of potassium. If magnesium is replaced, it will close up the magnesium-dependent potassium channels and stop urinary loss. Although magnesium is necessary for parathyroid hormone release, this would have nothing to do with potassium levels. Try not to consult on Step 2. You are supposed to handle anything that is based on knowledge. Consultations are generally indicated only for procedures such as catheterization or endoscopy. Although there will be increased potassium on a 24-hour urine with hypomagnesemia, there is no point in performing this test because you still have to detect and treat hypomagnesemia.

A woman with ESRD and glucose 6-phosphate dehydrogenase deficiency skips dialysis for a few weeks and then is crushed in a motor vehicle accident. She is taking dapsone and has recently eaten fava beans. What is the most urgent step?

a. **Initiate dialysis.**
b. **EKG.**
c. **Bicarbonate administration.**
d. **Insulin administration.**
e. **Kayexalate.**
f. **Urine dipstick.**

g. CPK levels.
h. Urine myoglobin.

Answer: B. All of these interventions may be helpful in a person with life-threatening hyperkalemia. The most important step is to determine if there are EKG changes from hyperkalemia. If the EKG is abnormal, she needs calcium chloride or gluconate in order to protect her heart while the other interventions are performed. Kayexalate and dialysis take hours to remove potassium from the body. Bicarbonate and insulin work in 15 to 20 minutes, but they are not as instantaneous in effect as giving calcium.

TIP

Protect the heart first in potassium disorders.

Acid-Base Disturbances

Renal Tubular Acidosis

Definition

Renal tubular acidosis (RTA) is a metabolic acidosis with a normal anion gap. The anion gap is defined as sodium minus chloride plus bicarbonate.

$$(Na^+) \text{ minus } (Cl^- \text{ and } HCO_3^-)$$

A normal anion gap is between 6 and 12. The difference between the cations and the anions is predominantly from negative charges that are on albumin. The 2 most important causes of a metabolic acidosis with a normal anion gap are:

- RTA
- Diarrhea

The anion gap is normal in both of these because the chloride level rises. Hence, they are also referred to as hyperchloremic metabolic acidosis. The anion gap increases from ingested substances such as ethylene glycol or methanol, or organic acids such as lactate that are anionic and drive down the chloride level.

Distal RTA (Type I)

The **distal tubule** is responsible for **generating new bicarbonate** under the influence of aldosterone. Drugs such as **amphotericin** and **autoimmune diseases** such as SLE or Sjögren syndrome can damage the distal tubule. If new bicarbonate cannot be generated at the distal tubule, then acid cannot be excreted into the tubule, raising the pH of the urine.

> No acid into the tubule makes the urine basic.

In an alkaline urine, there is **increased formation of kidney stones** from calcium oxalate.

> Distal RTA calcifies the kidney parenchyma (nephrocalcinosis).

Diagnostic Tests

The best initial test is a UA looking for an abnormally **high pH above 5.5.** The most accurate test is to infuse acid into the blood with ammonium chloride. A healthy person will be able to excrete the acid and will decrease the urine pH. Those with distal RTA cannot excrete the acid and the urine pH will remain basic (over 5.5) despite an increasingly acidic serum.

Treatment

Replace bicarbonate that will be absorbed at the proximal tubule. Since the majority of bicarbonate is absorbed at the proximal tubule, distal RTA is relatively easy to correct. Just give more bicarbonate and the proximal tubule will absorb it and correct the acidosis.

> RTA does not mean the tubule is always acidic.

Proximal RTA (Type II)

Normally 85% to 90% of filtered bicarbonate is reabsorbed at the proximal tubule. Damage to the proximal tubule from amyloidosis, myeloma, Fanconi syndrome, acetazolamide, or heavy metals **decreases the ability of the kidney to reabsorb most of filtered bicarbonate**. Bicarbonate is lost in the urine until the body is so depleted of bicarbonate that the distal tubule can absorb the rest. When this happens, the urine pH will become low (at or below 5.5). Chronic metabolic acidosis leaches calcium out of the bones and they become soft (osteomalacia).

Diagnostic Tests

The **urine pH is variable in proximal RTA**. First it is basic (above 5.5) until most bicarbonate is lost from the body, then it is low (below 5.5). The most accurate test is to evaluate bicarbonate malabsorption in the kidney by giving bicarbonate and testing the urine pH. Because the kidney cannot absorb bicarbonate, the urine pH will rise.

> Both proximal and distal RTA are hypokalemic. Potassium is lost in the urine.

Treatment

Because bicarbonate is not absorbed well in proximal RTA, it is difficult to treat it with bicarbonate replacement and massive doses are necessary. **Thiazide diuretics cause volume depletion. Volume depletion will enhance bicarbonate reabsorption.**

Hyporeninemia, Hypoaldosteronism (Type IV RTA)

Type IV RTA occurs most often in diabetes. There is a decreased amount or effect of aldosterone at the kidney tubule. This leads to loss of sodium and retention of potassium and hydrogen ions. Test for type IV RTA by finding a persistently high urine sodium despite a sodium-depleted diet. In addition, hyperkalemia is a main clue to answering “What is the most likely diagnosis?”

TIP

Just because RTA is difficult does not mean it isn't tested. RTA is tested. Learn it.

> Fludrocortisone is the steroid with the highest mineralocorticoid or "aldosteronelike" effect.

Types of Renal Tubular Acidosis (RTA)			
	Proximal (type II)	**Distal (type I)**	**Type IV**
Urine pH	Variable	High >5.5	<5.5
Blood potassium level	Low	Low	High
Nephrolithiasis	No	Yes	No
Diagnostic test	Administer bicarbonate	Administer acid	Urine salt loss
Treatment	Thiazides	Bicarbonate	Fludrocortisone

Urine Anion Gap

Definition

The **urine anion gap (UAG) is a way to distinguish between diarrhea and RTA** as causes of normal anion gap metabolic acidosis.

$$\text{UAG} = \text{sodium minus chloride}$$

or

$$Na^+ \text{ minus } Cl^-$$

Acid excreted by the kidney is buffered off as NH_4Cl or ammonium chloride. The more acid excreted, the greater the amount of chloride found in the urine. In RTA there is a defect in acid excretion into the urine, so the amount of chloride in the urine is diminished. This gives a positive number when calculating Na^+ minus Cl^-.

RTA has a positive UAG.

In diarrhea, the ability to excrete acid through the kidney remains intact. Because diarrhea is associated with metabolic acidosis, the kidney tries to compensate by increasing acid excretion. Hence, in diarrhea there is more acid in the urine. Acid (H^+) is excreted with chloride. So, in diarrhea, more acid in the urine means more chloride in the urine. Na^+ minus Cl^- will become a negative number in diarrhea.

Diarrhea has a negative UAG.

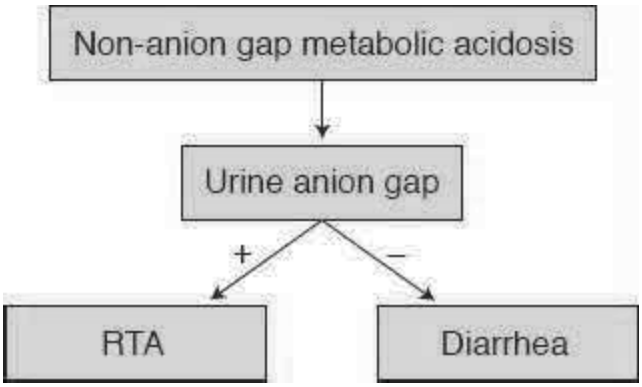


Figure 11.8: Urine Anion Gap: Definition

Metabolic Acidosis

Normal anion gap (6–12): RTA and diarrhea

Elevated anion gap (above 12): The anion gap is increased if there are

unmeasured anions driving the bicarbonate level down. Examples are found in the following table.

> Respiratory alkalosis from hyperventilation compensates for all forms of metabolic acidosis.

Causes of Metabolic Acidosis with an Increased Anion Gap			
	Cause	**Test**	**Treatment**
Lactate	Hypotension or hypoperfusion	Blood lactate level	Correct hypoperfusion
Ketoacids	DKA, starvation	Acetone level	Insulin and fluids
Oxalic acid	Ethylene glycol overdose	Crystals on UA	Fomepizole, dialysis
Formic acid	Methanol overdose	Inflamed retina	Fomepizole, dialysis
Uremia	Renal failure	BUN, creatinine	Dialysis
Salicylates	Aspirin overdose	Aspirin level	Alkalinize urine

Arterial Blood Gas in Metabolic Acidosis

The arterial blood gas (ABG) in metabolic acidosis will always have:

- Decreased pH below 7.4
- Decreased pCO_2 indicating respiratory alkalosis as compensation
- Decreased bicarbonate

TIP

You cannot determine the etiology of metabolic acidosis from the ABG.

> Metabolic problems always show compensation.

Metabolic Alkalosis

By definition, **metabolic alkalosis** has an **elevated serum bicarbonate** level. The compensation for metabolic alkalosis is respiratory acidosis. There will be a **relative hypoventilation** that will increase the pCO_2 to compensate for metabolic alkalosis.

Etiology

- GI loss: **vomiting** or nasogastric suction
- Increased **aldosterone**: primary hyperaldosteronism, Cushing syndrome, ectopic ACTH, volume contraction, licorice
- **Diuretics**
- Milk-alkali syndrome: high-volume liquid antacids
- Hypokalemia: hydrogen ions move into cells so potassium can be released

Arterial Blood Gas in Metabolic Alkalosis

The ABG in metabolic alkalosis will always have:

- **Increased** pH >7.40
- **Increased** pCO_2 indicating respiratory acidosis as compensation
- **Increased** bicarbonate

TIP

You cannot determine the etiology of metabolic alkalosis from the ABG.

Metabolic derangements kill patients with cardiac arrhythmia. They also alter potassium levels.

Respiratory Acidosis and Alkalosis

Respiratory acid/base disturbances are easy to understand because they come down to the single pathway of the effect on minute ventilation.

Minute ventilation = respiratory rate × tidal volume

Minute ventilation is more precise than respiratory rate.

Hyperventilation may occur with a tiny tidal volume. This does not increase minute ventilation.

Etiology

Causes of Respiratory Acidosis and Alkalosis	
Respiratory alkalosis	**Respiratory acidosis**
Decreased pCO_2	Increased pCO_2
Increased minute ventilation	Decreased minute ventilation
Metabolic acidosis as compensation	Metabolic alkalosis as compensation
• Anemia • Anxiety • Pain	• COPD/emphysema • Drowning • Opiate overdose

• Fever • Interstitial lung disease • Pulmonary emboli	• Alpha 1-antitrypsin deficiency • Kyphoscoliosis • Sleep apnea/morbid obesity

Nephrolithiasis

The most common cause of kidney stones (nephrolithiasis) is **calcium oxalate**, which forms more frequently in an **alkaline urine**. The most common risk factor is the **overexcretion of calcium** in the urine.

A 46-year-old man comes to the emergency department with excruciating pain in his left flank radiating to the groin. He has some blood in his urine.

What is the most appropriate next step in the management of this patient?

a. **Ketorolac.**
b. **X-ray.**
c. **Sonography.**
d. **Urinalysis.**
e. **Serum calcium level.**

Answer: A. Ketorolac is an NSAID that is available orally and intravenously. It provides a level of analgesia similar to opiate medications. When the presentation of nephrolithiasis is clear, it is more important to provide relief for this excruciating form of pain than to obtain specific diagnostic tests.

Crohn disease causes kidney stones because of increased oxalate absorption.

What is the most accurate diagnostic test for nephrolithiasis?

a. **CT scan.**
b. **X-ray.**
c. **Sonography.**
d. **Urinalysis.**
e. **Intravenous pyelogram.**

Answer: **A**. The CT scan for nephrolithiasis does not need contrast and is more accurate (sensitive) than an x-ray or sonogram. Intravenous pyelogram (IVP) needs intravenous contrast and takes several hours to perform. Urinalysis and straining the urine may show blood or the passage of a stone, but will not help manage acute renal colic. X-ray has a false negative rate between 10% and 20%. X-rays of the abdomen are useful only in detecting an ileus.

TIP

IVP is always a wrong answer for nephrolithiasis.

Treatment

The best initial therapy for acute renal colic is with:

- Analgesics and hydration
- CT and sonography to detect obstruction such as hydronephrosis

Uric acid stones are **not detectable on x-ray but are visualized on CT**.

- Stones <5 mm pass spontaneously
- Stones 5–7 mm get nifedipine and tamsulosin to help them pass

The etiology of the stone is determined with:

- Stone analysis
- Serum calcium, sodium, uric acid, PTH, magnesium, and phosphate levels
- 24-hour urine for volume, calcium, oxalate, citrate, cystine, pH, uric acid, phosphate, and magnesium

Cystine stones are managed with surgical removal, **alkalinizing the urine**.

Fat malabsorption increases stone formation.

Stones 5–7 mm get nifedipine + tamsulosin to help them pass.

A woman with her first episode of renal colic is found to have a 1.8 cm stone in the left renal pelvis. She has no obstruction and her renal function is normal (normal BUN and creatinine).

What is the most appropriate next step in the management of this patient?

a. **Wait for it to pass; hydrate and observe.**
b. **Lithotripsy.**
c. **Surgical removal.**
d. **Hydrochlorothiazide.**
e. **Stent placement.**

Answer: B. Lithotripsy is used to manage stones between 0.5 and 2 to 3 centimeters. Small stones (less than 5 mm) will spontaneously pass. Stones larger than 2 centimeters are not well-managed with lithotripsy because the fragments will get caught in the ureters. These large stones are best managed surgically. **Stent placement relieves hydronephrosis** from stones caught in the distal ureters. Stones halfway up the ureters are treated with lithotripsy. Those halfway down the ureter are removed from below with a basket.

Urinary tract infection gives struvite stones (magnesium/ammonium/phosphate). Remove them surgically.

Long-Term Management of Nephrolithiasis

Fifty percent of those with kidney stones will have a recurrence over the next 5 years.

A man with a calcium oxalate stone is managed with lithotripsy and the stone is destroyed and passes. His urinary calcium level is increased.

Besides increasing hydration, which of the following is most likely to benefit this patient?

a. **Calcium restriction.**
b. **Hydrochlorothiazide.**
c. **Furosemide.**

d. **Stent placement.**

e. **Increased dietary oxalate.**

Answer: **B. Hydrochlorothiazide removes calcium from the urine** by increasing distal tubular reabsorption of calcium. Furosemide increases calcium excretion into the urine and can make it worse. Calcium restriction actually does not help decrease overexcretion of calcium into the urine. In fact, it can make it more likely to form a stone. This is because calcium binds oxalate in the bowel. When calcium ingestion is low, there is increased oxalate absorption in the gut because there is no calcium to bind it in the gut. Stent placement is done when there is an obstruction in the ureters, especially at the ureteropelvic junction. Hydrochlorothiazide desaturates the urine of calcium. The risk of stone formation is increased if there is a dietary decrease in calcium, increase in oxalate, or decrease in citrate.

Metabolic Acidosis and Stone Formation

Metabolic acidosis removes calcium from bones and increases stone formation. In addition, metabolic acidosis decreases citrate levels. Citrate binds calcium, making it unavailable for stone formation.

Urinary Incontinence		
	Stress incontinence	**Urge incontinence**
Symptoms	Older woman with painless urinary leakage with coughing, laughing, or lifting heavy objects	Sudden pain in the bladder followed immediately by the overwhelming urge to urinate
Test	Have patient stand and cough; observe for leakage	Pressure measurement in half-full bladder; manometry
Treatment	1. Kegel exercises 2. Local estrogen cream 3. Surgical tightening of urethra	1. Bladder training exercises 2. Local anticholinergic therapy • Oxybutynin • Tolterodine • Solifenacin • Darifenancin 3. Surgical tightening of urethra

Hypertension

Definition

- **Systolic pressure above 140 mm Hg**
- **Diastolic pressure above 90 mm Hg**

> JNC 8 says:
>
> In diabetes, goal is 140/90.
>
> Thiazides are not better than CCBs, ACEIs, or ARBs.
>
> BP 150/90 over age 60.

In order to establish the diagnosis of hypertension, blood pressure measurements must be repeated in a calm state over time. The precise interval between measurements over what period of time is not clear.

A **diabetic** patient with blood pressure **above 140/90 mm Hg** is hypertensive.

Hypertension is:

- The most common disease in the United States
- The most common risk factor for the most common cause of death: myocardial infarction

Etiology

Ninety-five percent of hypertension has no clear etiology and can be called "essential hypertension." Known causes of hypertension are:

- **Renal artery stenosis**
- Glomerulonephritis
- Coarctation of the aorta

- Acromegaly
- Obstructive sleep apnea
- Pheochromocytoma
- Hyperaldosteronism
- Cushing syndrome or any cause of hypercortisolism including therapeutic use of glucocorticoids
- Congenital adrenal hyperplasia

Presentation

The vast majority of cases are found on **routine screening of asymptomatic patients**. When hypertension does have symptoms, they are from end organ damage from atherosclerosis such as:

- Coronary artery disease
- Cerebrovascular disease
- CHF
- Visual disturbance
- Renal insufficiency
- Peripheral artery disease

Presentation of Secondary Hypertension

- Renal artery stenosis: **Bruit is** auscultated at the flank. The bruit is continuous throughout systole and diastole.
- Glomerulonephritis
- Coarctation of the aorta: **upper extremity > lower extremity** blood pressure
- Acromegaly
- Pheochromocytoma: **episodic** hypertension with flushing
- Hyperaldosteronism: weakness from **hypokalemia**

Hypertension is rarely symptomatic at first presentation.

Diagnostic Tests

Repeated in-office measurement or home ambulatory measurements carry equal significance.

Those with hypertension are also tested with:

- EKG
- Urinalysis
- Glucose measurements to exclude concomitant diabetes
- Cholesterol screening

Treatment

The best initial therapy is with lifestyle management such as:

> Lifestyle modifications are tried for 3 to 6 months before medications are started.

- **Weight loss** (most effective)
- Sodium restriction
- Dietary modification (less fat and red meat, more fish and vegetables)
- Exercise
- Tobacco cessation does not stop hypertension, but becomes especially important to prevent cardiovascular disease.

Summary of JNC 8 Management of Hypertension

- Blood pressure goal in diabetes is 140/90.
- Initial management is with either thiazides or calcium blockers or ACE inhibitor or angiotensin receptor blocker. Diuretics are not considered specifically better as the initial therapy.
- The main point is to control the blood pressure. The specific agent is not as important.
- With age above 60, the goal of BP is 150/90.

Drug Therapy

The best initial therapy is a thiazide diuretic, calcium blocker, ACE inhibitor, or angiotensin receptor blocker.

Sixty to 70 percent of patients are controlled by a single medication. If blood pressure is very high on presentation (above 160/100), 2 medications should be used at the outset.

> Ninety percent of hypertension patients will be controlled by 2 medications.

If diuretics do not control blood pressure, the most appropriate next step in management is:

- ACE inhibitor

> Pregnancy safe hypertension drugs:
>
> - BB—use first
> - CCB
> - Hydralazine
> - Alpha methyldopa

- Angiotensin receptor blocker (ARB)
- Beta blocker (BB)
- Calcium channel blocker (CCB)

Medications that are not considered first-line or second-line therapy are:

- Central-acting alpha agonists (alpha methyldopa, clonidine)
- Peripheral-acting alpha antagonists (prazosin, terazosin, doxazosin)
- Direct-acting vasodilators (hydralazine, minoxidil)

Compelling Indications for Specific Drugs

If there is another significant disease in the history, you should add a specific drug to lifestyle modifications. In these circumstances you should not start with a thiazide.

Compelling Indications	
If this is in the history…	**This is the best initial therapy…**
Coronary artery disease	BB, ACE, ARB
Diabetes mellitus	ACE, ARB (goal <140/90)
Benign prostatic hypertrophy	Alpha blockers
Depression and asthma	Avoid BBs
Hyperthyroidism	BB first
Osteoporosis	Thiazides

Hypertensive Crisis

Hypertensive crisis is defined as high blood pressure in association with:

> Hypertensive crisis is not defined as a specific level of blood pressure. It is defined as **hypertension associated with end-organ damage**.

- Confusion
- Blurry vision
- Dyspnea
- Chest pain

The best initial therapy for hypertensive crisis is **labatolol or nitroprusside**. Because nitroprusside needs monitoring with an arterial line, this is not usually the first choice.

Equally acceptable forms of therapy for acute hypertensive crises are:

- Enalapril
- CCBs: diltiazem, verapamil
- Esmolol
- Hydralazine
- Peripheral dopamine receptor antagonist: fenoldopam

Any intravenous medication is acceptable. The specific drug available is not as important as giving enough of it to control the blood pressure.

> Do not lower blood pressure in hypertensive crisis to normal, or you may provoke a stroke.

10 Nephrology

Acute Renal Failure

The first step is to **evaluate whether the renal failure is prerenal (perfusion), renal (parenchymal), or postrenal (drainage).**

- Clues to the renal failure being of **short duration** are the following:
  - Normal kidney size
  - Normal hematocrit
  - Normal calcium level

- **Chronic renal failure** will have the following effects:
  - It makes the kidneys smaller.
  - With renal failure of more than 2 weeks, the hematocrit will drop from loss of erythropoietin production.
  - Calcium levels drop from the loss of vitamin D hydroxylation (i.e., activation).

PRERENAL AZOTEMIA

Any cause of **hypoperfusion** will lead to renal failure:

- **Hypotension,** generally with a systolic pressure < 90 mm Hg
- **Hypovolemia** from dehydration or blood loss
- **Low oncotic pressure** (low albumin)
- **Congestive heart failure:** You can't perfuse the kidney if the pump doesn't work.
- **Constrictive pericarditis:** You can't perfuse the kidney if the heart cannot fill.

- **Renal artery stenosis:** Although the systemic pressure may be high, the kidney thinks the body is hypotensive because of the blockage.

Diagnostic Testing

Prerenal azotemia will have the following characteristics:

- **BUN to creatinine ratio of > 15:1 and often > 20:1**
- **Urinary sodium is low** (< 20)
- **Fractional excretion of sodium < 1 percent:** This is largely the same thing as a low urine sodium. Do not spend your time learning to do the calculation.
- **Urine osmolality > 500**
- May have hyaline casts on urinalysis.

BASIC SCIENCE CORRELATE

MECHANISM OF ELEVATION OF BUN IN PRERENAL AZOTEMIA

Low volume status increases ADH. ADH increases urea absorption at the collecting duct. There is a urea transporter that brings urea in. ADH increases the activity of the urea transporter.

Treatment

Treatment of prerenal azotemia is *entirely* based on the underlying cause.

CCS Tip: On CCS, all renal cases should have the following tests performed:

- Urinalysis
- Chemistries
- Renal ultrasound

POSTRENAL AZOTEMIA (OBSTRUCTIVE UROPATHY)

Any cause of obstruction of the kidney will lead to renal failure:

- **Stone in the bladder or ureters**
- **Strictures**
- **Cancer of the bladder, prostate, or cervix**
- **Neurogenic bladder** (atonic or noncontracting, such as from multiple sclerosis or diabetes)

> Remember: The obstruction *must* be bilateral to cause renal failure. Unilateral obstruction cannot cause renal failure.

Obstructive uropathy will give an **elevated BUN-to-creatinine ratio of > 15:1**, similar to that seen in prerenal azotemia.

Clues to obstructive uropathy are the following:

- **Distended bladder** on exam
- **Large volume diuresis** after passing a urinary catheter
- **Bilateral hydronephrosis on ultrasound**

INTRARENAL CAUSES OF RENAL FAILURE

Intrarenal causes of renal failure result in the following:

- **BUN-to-creatinine ratio closer to 10:1**
- **Urinary sodium > 40**
- **Urine osmolality < 350**

Acute tubular necrosis (ATN) can be caused by either **hypoperfusion** to the point of death of the tubular cells or by various **toxic injuries to the kidney.** It is often caused by a combination of both.

Toxin-Induced Renal Insufficiency

In these cases, there is *no* single test to prove that a particular toxin caused the renal failure. Common causes are these:

- **Aminoglycosides,** such as gentamicin, tobramycin, or amikacin: Hypomagnesemia is suggestive of aminoglycoside-induced renal failure, but it is *not* conclusive. It usually takes 4–5 days of use to effect damage.
- **Amphotericin**
- **Contrast agents:** Urine sodium low (< 20); can happen 12 hours later
- **Chemotherapy**, such as cisplatin

Contrast is extremely rapid in onset.

BASIC SCIENCE CORRELATE

MECHANISM OF RAPID ONSET OF RENAL FAILURE WITH CONTRAST AGENT

Contrast agents are directly toxic to kidney tubules, as are aminoglycosides. Contrast also causes an intense vasoconstriction of the afferent arteriole. This combination of direct toxicity and decreased perfusion is why there is such a rapid rise in creatinine during contrast-induced renal failure. It is also why contrast-induced renal failure causes a low urine sodium, as in prerenal azotemia.

The urinalysis may show **"muddy brown" or granular casts.** There is *no* specific therapy to reverse toxin-induced renal failure.

A man is admitted for pneumonia from a nursing home. He is placed on piperacillin-tazobactam, and he becomes afebrile. Two days later, his BUN and creatinine start to rise. He develops a new fever and a rash. What is the most likely diagnosis, and what is the most accurate diagnostic test?

Answer: Allergic interstitial nephritis is a hypersensitivity reaction to medications such as penicillin or sulfa drugs. Other common culprits are phenytoin, allopurinol, cyclosporine, quinidine, quinolones, or rifampin. The clue to the diagnosis is the **fever and rash.** The best initial test is a **urinalysis (UA) that shows white cells.** However, the UA is not capable of distinguishing between neutrophils and eosinophils. The most accurate test is a **Wright stain** or **Hansel's stain of the urine** that will show eosinophils. This is more sensitive than either the blood eosinophil level or an

elevated IgE level. There is no specific therapy generally given for allergic interstitial nephritis; it resolves on its own.

Cyclophosphamide causes hemorrhagic cystitis, *not* renal failure.

Rhabdomyolysis

In cases of rhabdomyolysis, large-volume **muscular necrosis** is associated with renal failure from the direct **toxic effect of myoglobin on the kidney tubule.** Look for the following in presentation:

- Crush injury
- Seizure or cocaine toxicity
- Prolonged immobility in an intoxicated patient
- Hypokalemia resulting in muscle necrosis
- A patient recently started on a "statin" medication for hyperlipidemia

Diagnostic Testing

- Best initial test: **Urinalysis** showing dipstick positive for large amounts of blood with no cells seen on the microscopic examination
- **CPK level:** Will be elevated.
- Most accurate test: **Urine myoglobin** is probably the single most accurate test.
- On a CCS, also order the following:
  - **Potassium level (hyperkalemia):** Potassium goes up from any cellular destruction, such as from a tumor lysis, hemolysis, or rhabdomyolysis.
  - **Calcium level (hypocalcemia):** Damaged muscle binds increased amounts of calcium. Hyperphosphatemia may lead to binding of calcium with the phosphate.
  - **Chemistries especially for detecting a decreased serum bicarbonate**

BASIC SCIENCE CORRELATE

MECHANISM OF LOW CALCIUM IN RHABDOMYOLYSIS

Damaged muscle binds calcium. Each skeletal muscle cell contains sarcoplasmic endoplasmic reticulum for calcium (SERCA). SERCA is the normal mechanism for ending contraction, which it achieves by pulling all the cell calcium out of the cytosol. When the outside covering, or sarcolemma, is damaged, the SERCA can suck up calcium and lower the blood level.

Treatment

- **Bolus of normal saline**
- **Mannitol and diuresis** to decrease the contact time of myoglobin with the tubule
- **Alkalinization of the urine** may decrease precipitation of myoglobin at the tubule

A patient is brought to the emergency department after a seizure leading to prolonged immobility on a sidewalk. He has dark urine and myalgias. What is the most urgent step in the management of this patient?

(A) Urinalysis.
(B) Urine myoglobin level.
(C) EKG.
(D) CPK level.
(E) Phosphate level.
(F) Creatinine.

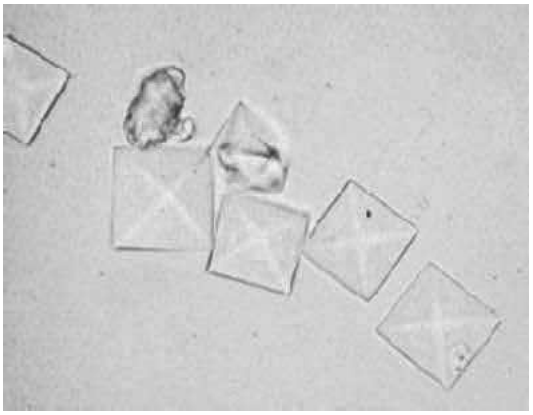
Answer: C. EKG is the most urgent step in an acute case of rhabdomyolysis. This case tests your knowledge of how people die with rhabdomyolysis. Severe muscle necrosis leads to **hyperkalemia,** which leads to **arrhythmia.** If this is a CCS case, then all of the tests should be done simultaneously. A specific diagnosis with urinalysis or urine myoglobin is not as important as detecting and treating potentially life-threatening conditions, such as hyperkalemia with peaked T waves. This condition would be treated with immediate intravenous calcium gluconate, insulin, and glucose.

Crystal-Induced Renal Failure

This condition can result from oxalate crystals or uric acid crystals.

- Oxalate crystals: Look for **suicide by antifreeze ingestion** (ethylene glycol). The patient will be intoxicated with metabolic acidosis with an elevated anion gap.

- Best initial test: **Urinalysis** showing **envelope-shaped oxalate crystals**
- Best initial treatment: **Ethanol** or **fomepizole** with **immediate dialysis**



Oxalate crystals

- **Uric acid crystals:** Look for **tumor lysis syndrome,** most often after chemotherapy for lymphoma.
  - Treat with hydration, allopurinol, and rasburicase.

Rasburicase breaks down uric acid.

Prevention of Contrast-Induced Renal Failure

To test your knowledge of this situation, the case will describe a patient who *must* have a radiologic procedure with contrast *and* common reasons for renal insufficiency, such as an elderly patient with hypertension and diabetes. There will be no attempt to hide the etiology. Mild renal insufficiency with a creatinine just above the normal range at 1.5 to 2.5 will be shown.

What is the best method to prevent contrast induced renal failure?

Answer: Give hydration with **normal saline** and possibly **bicarbonate, N-acetyl cysteine,** or **both.**

Step 3 wants you to know that even a very slight elevation in creatinine means the *loss of 60–70 percent of renal function* at a minimum. Preserve what is left!

Kidney Damage Caused by NSAIDs

NSAIDS can cause the following:

- **Direct toxicity and papillary necrosis**
- **Allergic interstitial nephritis** with eosinophils in the urine
- **Nephrotic syndrome**
- **Afferent arteriolar vasoconstriction and decreased perfusion of the glomerulus,** worsening renal function

Glomerulonephritis

All forms of glomerulonephritis (GN) can have the following characteristics:

- **Red blood cells** in the urine
- **Red cell casts** in the urine
- Mild degrees of **proteinuria** (< 2 g per 24 hours)
- **Edema**
- May lead to **nephrotic syndrome**
- Are most accurately diagnosed with **kidney biopsy,** although this is not always necessary

> Think: What are the few extra words to remember about each disease in order to answer the diagnostic and treatment questions? Step 3 does *not* generally emphasize the "most likely diagnosis" question.

GOODPASTURE'S SYNDROME

Cough, hemoptysis, shortness of breath, and lung findings will be present in the case.

Diagnostic Testing

- Best initial test: **Anti–basement membrane antibodies**
- Most accurate test: **Renal biopsy showing "linear deposits"**

Treatment

Treatment is with **plasmapheresis** and **steroids**.

ALLERGIC ANGIITIS (CHURG-STRAUSS SYNDROME)

Asthma, cough, and eosinophilia are present in addition to the **renal abnormalities.**

Diagnostic Testing

- Best initial test: **CBC for eosinophil count**
- Most accurate test: **Biopsy**

Treatment

- Best initial therapy: **Glucocorticoids** (e.g., prednisone)
- If there is no response to prednisone, add **cyclophosphamide.**

GRANULOMATOSIS WITH POLYANGIITIS (WEGENER'S)

Upper respiratory problems such as **sinusitis and otitis** are the key to diagnosis. **Lung problems** (cough, hemoptysis, abnormal chest x-ray) are present as well.

Wegener's is a **systemic vasculitis,** so joint, skin, eye, brain, and GI problems are also present, but the key is both upper and lower respiratory involvement *in addition* to renal involvement. Often the case will be misdiagnosed as pneumonia.

Diagnostic Testing

- Best initial test: **c-ANCA** (antineutrophil cytoplasmic antibodies)
- Most accurate test: **Biopsy of kidney**

Treatment

The best initial therapy is **cyclophosphamide and steroids.**

POLYARTERITIS NODOSA (PAN)

Polyarteritis nodosa is a **systemic vasculitis** with involvement of every organ *except* the lung.

Presentations include the following:

- Renal
- Myalgias
- GI bleeding and abdominal pain
- Purpuric skin lesion
- Stroke
- Uveitis
- Neuropathy

The very nonspecific findings of fever, weight loss, and fatigue will also be present. **Multiple motor and sensory neuropathy with pain** are key to diagnosis.

Diagnostic Testing

- Best initial test: **ESR and markers of inflammation**
- Most accurate test: **Biopsy of sural nerve or the kidney**
- Test for **hepatitis B and C,** which can be associated with 30 percent of PAN.
- **Angiography showing "beading"** can spare the need for biopsy.

Treatment

The best initial therapy is **cyclophosphamide and steroids.**

IGA NEPHROPATHY (BERGER'S DISEASE)

This condition presents with **painless recurrent hematuria,** particularly in an **Asian patient** after a very **recent viral respiratory tract infection.** Proteinuria and red cells and red cell casts can be present in all forms of glomerular disease. There is *no* specific physical finding that clearly defines the disease.

Diagnostic Testing

- Best initial test: There is *no* specific blood test. IgA levels are sometimes elevated.
- Most accurate test: **Renal biopsy is essential,** because there is no blood test or specific physical findings to use in diagnosis. Complement levels are normal.

Treatment

There is *no* proven effective therapy to reverse IgA nephropathy.

- **Steroids** are used in boluses when there is a sudden worsening of proteinuria.
- **ACE inhibitors** are used as they are for all patients with proteinuria.
- **Fish oil** *may* have some effect in delaying progression.

HENOCH-SCHÖNLEIN PURPURA

This presents in an **adolescent or child** with the following symptoms:

- **Raised, nontender, purpuric skin lesions,** particularly on the buttocks
- **Abdominal pain**
- Possible **bleeding**
- **Joint pain**
- **Renal involvement**

Diagnostic Testing

- Best initial test: The presentation of GI, joint, skin, and renal involvement is the best indicator of Henoch-Schönlein purpura.
- Most accurate test: Although a biopsy is the most accurate test, showing deposition of IgA, it is *not* necessary.

Treatment

No specific therapy is necessary because Henoch-Schönlein purpura **resolves spontaneously** over time.

POST-STREPTOCOCCAL GLOMERULONEPHRITIS (PSGN)

PSGN results in dark urine, described as “tea colored” or “cola colored.” **Periorbital edema** and **hypertension** also occur. Many other infections can lead to glomerulonephritis; both throat and skin infections can lead to PSGN.

Diagnostic Testing

- **Best initial test:** Antistreptolysin O (ASLO), anti-DNase, antihyaluronidase in blood. Complement levels are low.
- **Most accurate test:** Although **biopsy** is the most accurate test, it should *not* be done routinely,

because the blood tests are most often sufficient. Biopsy shows subepithelial deposits of IgG and C3.

Treatment

- **Penicillin and other antibiotics** for the infection should be given, although they do *not* clearly reverse the disease.
- Control the hypertension and fluid overload with **diuretics.**

CRYOGLOBULINEMIA

This presents in a patient with a history of **hepatitis C with renal involvement.** The patient may have **joint pain and purpuric skin lesions.**

New oral drugs for hepatitis C:

- boceprevir
- telaprevir
- simeprevir
- sofosbuvir

Diagnostic Testing

- Best initial test: **Serum cryoglobulin component levels** (immunoglobulins and light chains, IgM). Complement levels (especially C4) are low.
- Most accurate test: **Biopsy**

Treatment

Treat the hepatitis C as previously described. Rituximab helps with severe disease.

LUPUS (SLE) NEPHRITIS

The patient presents with a history of SLE. Note that drug-induced lupus spares the kidney and brain.

Diagnostic Testing

- Best initial test: **ANA and anti-double-stranded DNA**
- Most accurate test: **Renal biopsy.** The biopsy in the case of lupus nephritis is very important. It is not to diagnose the presence of renal involvement but to **determine the extent of disease to guide therapy.**

Treatment

- **Sclerosis only:** *No* treatment. This is a "scar" of the kidney.
- **Mild disease, early stage, nonproliferative: Steroids**
- **Severe disease, advanced, proliferative: Mycophenolate mofetil and steroids.** Mycophenolate is superior to cyclophosphamide.

ALPORT SYNDROME

Alport's syndrome is a congenital problem with **eye and ear problems,** such as **deafness**. Renal failure occurs in the second or third decade of life.

There is *no* specific therapy.

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) AND HEMOLYTIC UREMIC SYNDROME (HUS)

Look for a history of ***E. coli* 0157:H7 for HUS.** There is no specific diagnostic test for these conditions.

HUS is a triad:

- **Intravascular hemolysis** (fragmented cells on smear)
- **Elevated creatinine**
- **Thrombocytopenia**

TTP has the same 3 findings *plus* the following:

- **Fever**

- **Neurological abnormalities**

Treatment is with plasmapheresis in severe cases.

> Do *not* give platelets for TPP or HUS. They can make both conditions worse. Also, do *not* give antibiotics for the infection; doing so may also worsen the disease.

Nephrotic Syndrome

Any of the glomerular diseases just described can lead to nephrotic syndrome if they are severe. Nephrotic syndrome is often a term of **severity of renal disease.** Hypertension is common.

- When the damage becomes severe enough, the condition leads to the **loss of more than 3.5 g per day of protein in the urine.** When this happens, **albumin levels in the blood fall,** and there is also **edema.**
- **Hyperlipidemia** is a part of nephrotic syndrome.

BASIC SCIENCE CORRELATE

LDL and VLDL are removed from serum by lipoprotein signals. If the lipoprotein is lost in the urine with nephrotic syndrome, then the lipid levels in the blood rise.

- **Thrombosis** can occur because of the loss of antithrombin III, protein C, and protein S in the urine.

Nephrotic syndrome is defined as follows:

- **Hyperproteinuria**
- **Hypoproteinemia**
- **Hyperlipidemia**
- **Edema**

Diagnostic Testing

- Best initial test: **Urinalysis showing a markedly elevated protein level**
- The next best test is one of these:
  - **Spot urine for a protein-to-creatinine ratio > 3.5:1.** The spot urine protein creatinine level is equal in accuracy to a 24-hour urine collection.
  - **24-hour urine protein collection showing > 3.5 g of protein**

- Most accurate test: **Renal biopsy**

Urine protein:creatinine ratio is same as 24-hour urine.

Other Primary Renal Disorders

In addition to the glomerular diseases previously described with systemic manifestations and specific blood tests, there are several primary renal disorders with *no* specific physical findings to make a precise diagnosis. There are features in the history that are suggestive. The following table summarizes specific types of nephrotic syndromes and their associations.

Children	Adults, Cancer Such as Lymphoma	Hepatitis C	HIV, Heroin Use	Unclear
Minimal change disease	Membranous	Membranoproliferative	Focal segmental	Mesangial

Diagnostic Testing

In all of these cases, testing is as follows:

- Best initial tests: **Urinalysis,** followed by **spot protein-to-creatinine ratio** or **24-hour urine**
- Most accurate test: Renal biopsy

Treatment

Treatment for all of these cases is as follows:

- Best initial therapy: **Steroids**
- If there is no response, such as a decrease in urine protein excretion after 12 weeks, **cyclophosphamide** is used.

The biopsy findings drive the choice of treatment with steroid or cyclophosphamide.

Proteinuria

At any given time, 2–10 percent of the population has mild proteinuria. The first step when this presents is always to **repeat the urinalysis.** Very often, the proteinuria disappears on repeat testing. These patients need no further follow-up.

If proteinuria persists, you should see if the patient has a reason for transient mild proteinuria, such as the following:

- **CHF**
- **Fever**
- **Exercise**
- **Infection**

If these reasons are not present, the next possibility is **orthostatic proteinuria.** Look for a history of **a job in which people must stand all day,** such as waiters, teachers, security, and so on.

Diagnostic Testing

The first step to confirm orthostatic proteinuria is to **split the urine.** Do a morning urine for protein and then one in the afternoon. If protein is present in the afternoon and not in the morning, then the patient likely has orthostatic proteinuria. Orthostatic proteinuria does *not* need to be treated.

If proteinuria is persistent and not orthostatic, a **24-hour urine** or **spot protein/creatinine ratio** is necessary. If this is elevated, a renal biopsy should be performed.

Steps for proteinuria evaluation:

1. Repeat the UA.
2. Evaluate for orthostatic proteinuria.
3. Get a protein/creatinine ratio.
4. Perform a renal biopsy.

End-Stage Renal Disease

When is dialysis indicated?

Answer: Dialysis is essential with renal failure in the following circumstances:

- Hyperkalemia
- Metabolic acidosis
- Uremia with encephalopathy
- Fluid overload
- Uremia with pericarditis
- No renal failure, but patient has toxicity with dialyzable drug, such as lithium, ethylene glycol, or aspirin.
- Uremia-induced malnutrition

Phosphate binders:

- Sevelamer
- Lanthanum
- Calcium acetate
- Calcium carbonate

The following table summarizes other manifestations of uremia and their treatment.

Hyperphosphatemia	Calcium acetate, calcium carbonate phosphate binders
Hypermagnesemia	Dietary magnesium restriction
Anemia	Erythropoietin replacement
Hypocalcemia	Vitamin D replacement

Hypernatremia

Elevated serum sodium always implies a free water deficit. Dehydration is treated with **normal saline replacement** at first. Step 3 does *not* require knowledge of specific dosing. However, fluids should be first ordered as a bolus, then given continuously.

Besides **simple dehydration,** which can occur from poor oral intake, fever, pneumonia, or other types of increased insensible losses, the other main cause is **diabetes insipidus (DI).** Diabetes insipidus can be caused by either:

- **failure to produce antidiuretic hormone (ADH) in the brain (central);** or
- **insensitivity of the kidney (nephrogenic).** Nephrogenic DI can result from hypokalemia, hypercalcemia, or lithium toxicity.

Hypernatremia leads to **neurological abnormalities,** such as confusion, disorientation, or seizures. The worst manifestation is a **coma.** Sodium disorders do not cause cardiac rhythm disturbance.

Both central and nephrogenic DI give the following results:

- **Low urine osmolality**
- **Low urine sodium**
- **Increased urine volume**
- *No* change in urine osmolality with water deprivation

The following table summarizes specific diagnostic tests and treatment for central DI and nephrogenic DI.

	Central DI	Nephrogenic DI
Urine volume	Prompt **decrease** in urine volume with administration of vasopressin (DDAVP)	**No change** in urine volume with DDAVP
Urine osmolality	Prompt **increase** in urine osmolality with DDAVP	**No change** in urine osmolality with DDAVP

Treatment	Treat with **DDAVP** or **vasopressin**	**Correct underlying cause,** such as hypokalemia or hypercalcemia.**Thiazide diuretics** are used in other cases.

Hyponatremia

Hyponatremia presents with **neurological abnormalities, such as confusion, disorientation, seizures, or coma.** There will be *neither* edema *nor* signs of dehydration.

The first step in the management of hyponatremia is to **assess volume status** to determine the cause and, therefore, the treatment.

HYPERVOLEMIC HYPONATREMIA

Hypervolemic causes of hyponatremia are the following:

- **Congestive heart failure (CHF)**
- **Nephrotic syndrome**
- **Cirrhosis**

These are managed by correcting/managing the underlying cause.

HYPOVOLEMIC HYPONATREMIA

Hypovolemic causes of hyponatremia are the following:

- **Diuretics** (urine sodium elevated)
- **GI loss of fluids (vomiting, diarrhea)** (urine sodium low)
- **Skin loss of fluids (burns, sweating)** (urine sodium low)

The diuretic, sweating, or other cause makes the patient lose water and a little salt, but the patient replaces free water only. Over time the sodium level drops. **Correct the underlying cause and replace with normal (isotonic) saline.** Remember to check serum sodium frequently.

EUVOLEMIC (NORMAL) VOLUME STATUS

This can be caused by the following:

- **Syndrome of inappropriate ADH release (SIADH)**
- **Hypothyroidism**
- **Psychogenic polydipsia**
- **Hyperglycemia:** Glucose above normal drops sodium by 1.6 points for each 100 mg above normal glucose

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> Hyperglycemia causes an artificial drop in sodium by 1.6 points of sodium for each 100 points of glucose.

Addison's Disease

Addison's disease also causes hyponatremia from **insufficient aldosterone production.** The key to this diagnosis is the presence of hyponatremia with **hyperkalemia and mild metabolic acidosis.** Treat with **aldosterone replacement, such as fludrocortisone.**

SIADH

SIADH can be caused by the following:

- Any **CNS abnormalities**
- Any **lung disease**
- Medications such as **sulfonylureas, SSRIs, carbamazepine**
- **Cancer**

SIADH is associated with the following:

- Inappropriately **high urine sodium** (> 20 mEq/L)
- Inappropriately **high urine osmolality** (> 100 mOsm/kg)
- **Low serum osmolality** (< 290 mOsm/kg)

- **Low serum uric acid**
- Normal BUN, creatinine, and bicarbonate

> Hyperglycemia causes an artificial drop in sodium by 1.6 points of sodium for each 100 points of glucose.

Treatment

Mild Hyponatremia (no symptoms)

Treat by restricting fluids.

Moderate to Severe Hyponatremia (confused, seizures)

Treat as follows:

- **Saline infusion** with loop diuretics
- **Hypertonic (3 percent) saline**
- **Check serum sodium frequently**
- **ADH blockers (conivaptan, tolvaptan)**

Do not correct serum sodium more than 10–12 mEq/L in the first 24 hours or more than 18 mEq/L in the first 48 hours. Otherwise, you run the risk of **central pontine myelinosis.**

> Conivaptan raises sodium as an ADH blocker.

Chronic SIADH (as from malignancy)

Demeclocycline blocks the effect of ADH at the kidney. Conivaptan and tolvaptan are inhibitors of ADH at the V2 receptor of the collecting duct.

Hyperkalemia

Hyperkalemia is predominantly caused by **increased potassium release from tissues, such as muscles, or red blood cells, such as in rhabdomyolysis or hemolysis.** Increased dietary potassium can *only* cause hyperkalemia if it is associated with renal insufficiency. If kidney function is normal, it is almost impossible to ingest potassium faster than the kidney can excrete it. Also, the GI tract is not able to absorb potassium faster than the kidney can excrete it. Aldosterone normally functions to excrete potassium from the body. If there is a **deficiency or blockade of aldosterone,** potassium levels will rise.

Other causes of hyperkalemia are the following:

- **Metabolic acidosis** from transcellular shift out of the cells
- **Adrenal aldosterone deficiency,** such as from Addison's disease
- **Beta blockers**
- **Digoxin toxicity**
- **Insulin deficiency,** such as from diabetic ketoacidosis (DKA)
- **Diuretics,** such as spironolactone
- **ACE inhibitors and angiotensin receptor blockers,** which inhibit aldosterone
- **Prolonged immobility, seizures, rhabdomyolysis, or crush injury**
- **Type IV renal tubular acidosis,** resulting from decreased aldosterone effect
- **Renal failure,** preventing potassium excretion

BASIC SCIENCE CORRELATE

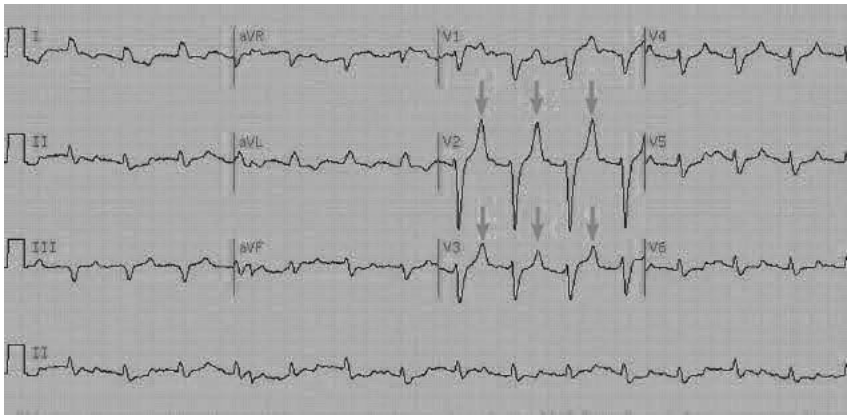
MECHANISM OF HYPERKALEMIA WITH BETA BLOCKER USE

Normal Na/K ATPase activity lowers blood potassium. Beta blockers decrease the activity of the sodium/potassium ATPase. When you inhibit Na/K ATPase with a beta blocker, potassium levels can go up.

Pseudohyperkalemia is an artifact caused by the hemolysis of red cells in the laboratory or prolonged tourniquet placement during phlebotomy. Pseudohyperkalemia does not need therapy; you need only repeat the test.

Hyperkalemia can lead to **cardiac arrhythmia.** Potassium disorders are not associated with seizures or neurological disorders.

Remember: First peaked T-waves occur, then loss of the P-wave, and then the widened QRS complex occurs.



Hyperkalemia Peaked T-Waves

Treatment

Severe Hyperkalemia (EKG abnormalities, such as peaked T-waves)

- Administer **calcium gluconate intravenously** to protect the heart.
- Follow with **insulin and glucose intravenously.**
- Conclude with **kayexalate**.

Moderate Hyperkalemia (no EKG abnormalities)

- Administer **insulin and glucose intravenously.**
- Use **bicarbonate** to shift potassium into the cell when acidosis is the cause of the hyperkalemia or there is rhabdomyolysis, hemolysis, or another reason to alkalinize the urine.
- **Kayexalate** (potassium-binding resin) is administered **orally** to remove potassium from the body. This

takes several hours.

BASIC SCIENCE CORRELATE

MECHANISM OF HOW BICARBONATE LOWERS POTASSIUM

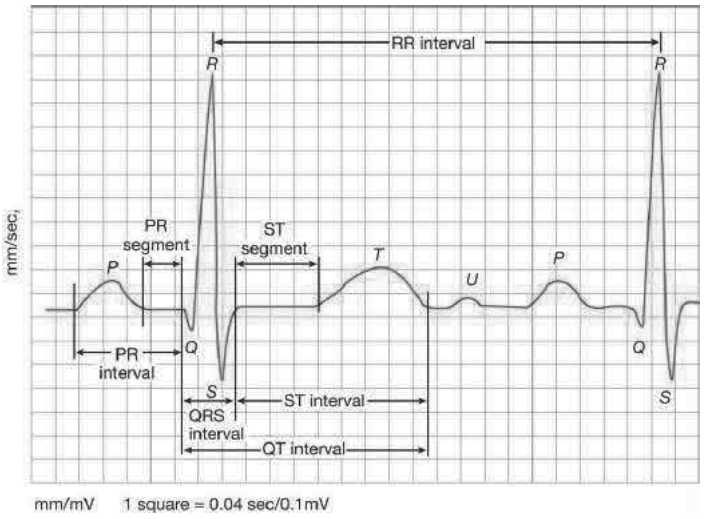
When alkalosis pulls hydrogen cations out of cells, another cation must go in to maintain electrical neutrality. As hydrogen ions come out of cells, potassium goes in.

Hypokalemia

Dietary insufficiency can lead to hypokalemia. Other causes are:

- Increased urinary loss caused by **diuretics**
- **High-aldosterone states, such as Conn syndrome**
- **Vomiting** leads to metabolic alkalosis, which shifts potassium intracellularly, and volume depletion, which leads to increased aldosterone.
- **Proximal and distal renal tubular acidosis (RTA)**
- **Amphotericin** from the RTA it causes
- **Bartter syndrome** is the inability of the loop of Henle to absorb sodium and chloride. It causes secondary hyperaldosteronism and renal potassium wasting.

Hypokalemia leads to **cardiac rhythm disturbance.** The EKG will show **"U- waves,"** which have an extra wave after the T-wave indicative of Purkinje fiber repolarization. Hypokalemia can also cause muscular weakness from its **ability to inhibit contraction;** this effect can be so severe that rhabdomyolysis occurs.



EKG-Normal Intervals

Treatment

Therapy is to **replace potassium.** There is no maximum rate on oral potassium replacement; the bowel will regulate the rate of absorption.

Avoid glucose-containing fluids in cases of hypokalemia. They will increase insulin release and worsen the hypokalemia.

In hypokalemia cases, IV potassium replacement must be *slow* so as not to cause an arrhythmia with overly rapid administration.

Magnesium Disorders

HYPERMAGNESEMIA

Hypermagnesemia is caused by the **overuse of magnesium-containing laxatives** or from **iatrogenic administration,** such as during premature labor when it is administered as a tocolytic. It is rare to have hypermagnesemia without renal insufficiency. Hypermagnesemia leads to **muscular weakness and loss of deep tendon reflexes.**

Treat hypermagnesemia as follows:

- **Restricting intake**
- **Saline administration** to provoke diuresis
- Occasionally **dialysis**

HYPOMAGNESEMIA

Hypomagnesemia is caused by the following:

- **Loop diuretics**
- **Alcohol withdrawal, starvation**
- **Gentamicin, amphotericin, diuretics**
- **Cisplatin**
- **Parathyroid surgery**
- **Pancreatitis**

Hypomagnesemia presents with **hypocalcemia and cardiac arrhythmias.**

Magnesium is required for parathyroid hormone release. This is particularly important in the management of torsade de pointes.

Metabolic Acidosis

METABOLIC ACIDOSIS WITH AN INCREASED ANION GAP

This condition is caused by the following:

Lactic Acidosis

This is caused by any form of **hypoperfusion,** such as hypotension, resulting in **anaerobic metabolism.** Anaerobic metabolism leads to glycolysis, which results in the accumulation of lactic acid.

Treat the underlying cause of hypoperfusion.

Aspirin Overdose

Aspirin overdose originally gives **respiratory alkalosis from hyperventilation.** Over a short period, **metabolic acidosis** develops from poisoning of mitochondria and the loss of aerobic metabolism. This gives lactic acidosis.

Treat with **bicarbonate,** which corrects the acidosis and increases urinary excretion of aspirin.

Methanol Intoxication

This toxic alcohol leads to **formic acid and formaldehyde production.** Look for an **intoxicated patient with visual disturbance.**

After **getting a methanol level,** order **fomepizole** or **ethanol** administration. These substances block the production of formic acid and allow time for **dialysis** to remove the methanol.

Uremia

Renal failure prevents the excretion of the 1 mEq/kg of organic acid that is formed each day.

This is an indication for dialysis.

Diabetic Ketoacidosis

Acetone, acetoacetate, and beta hydroxybutyric acid lead to an increased anion gap.

A **low serum bicarbonate** is the fastest single test to tell if a patient's hyperglycemia is life threatening. Treat with normal **saline hydration and insulin.** Place the patient in the **ICU.**

Isoniazid Toxicity

Just **stop the medication** and move the clock forward on CCS.

Ethylene Glycol

Look for an **intoxicated patient with a renal abnormality,** such as oxalate crystals in the urine. There is also renal failure and hypocalcemia, because the oxalate binds with calcium to form crystals. **Suicide attempt with ethylene glycol is key.**

Treat the same as methanol intoxication with **fomepizole** or **ethanol,** which blocks the production of oxalic acid and allows time for dialysis to remove the ethylene glycol.

METABOLIC ACIDOSIS WITH A NORMAL ANION GAP

This results from either **diarrhea** or **renal tubular acidosis (RTA).**

Diarrhea

Diarrhea causes metabolic acidosis via **increased bicarbonate loss from the colon.** The colon secretes both bicarbonate and potassium, so the potassium level will be low **(hypokalemia)** as well. Because there is increased chloride reabsorption, there is **hyperchloremia,** and that is why there is a normal anion gap.

Renal Tubular Acidosis (RTA)

- **Distal RTA (Type I):** There is an **inability to excrete acid of hydrogen ions in the distal tubule**. This results in the accumulation of acid in the body. The urine pH rises because the body cannot excrete acid. In an alkaline environment, stones will form. **Serum potassium is low** (body excretes + ions in the form of K^+ since it can't excrete H^+) and **serum bicarbonate is low**.
  - Test by **intravenously administering acid** (ammonium chloride—which should lower urine pH secondary to increased H^+ formation). In distal RTA the person cannot excrete the acid, and the urine pH stays abnormally basic.
  - Treat by administering **bicarbonate**. The proximal tubule is still working; therefore the patient will still absorb the bicarbonate.
- **Proximal RTA (Type II):** There is an **inability to reabsorb bicarbonate in the proximal renal tubule**. Initially there is an elevated urine pH, but when the body loses substantial amounts of bicarbonate, the **urine pH drops**. Because urine pH is often low, kidney stones do *not* develop. A low serum bicarbonate leaches calcium out of the bones, and there is also **osteomalacia**.
  - Test by giving **bicarbonate**. A normal person with metabolic acidosis will absorb all of the bicarbonate, and there should still be a low urine pH in a normal patient. In proximal RTA, the patient cannot absorb the bicarbonate and the urine pH rises from the bicarbonate malabsorption.
  - Treat by giving a **thiazide diuretic**, which results in a volume contraction. The contracted blood volume raises the concentration of serum bicarbonate. Large quantities of serum bicarbonate are also given (bicarbonate is generally ineffective and that is why they must be used in such high amounts).
- **Hyporeninemic hypoaldosteronism (Type IV):** There is **decreased aldosterone production or effect.** Look for a **diabetic patient with a normal anion gap metabolic acidosis.** This is the *only* RTA with an **elevated potassium level.**
  - Treat with **aldosterone** administration in the form of **fludrocortisone,** which is the steroid with the highest mineralocorticoid content.

The following table compares Types I, II, and IV RTA.

	Distal RTA (Type I)	Proximal RTA (Type II)	Type IV (Diabetes)
Urine pH	High	Low	Low
Serum Potassium	Low	Low	High
Stones	Yes	No	No
Test	Give acid	Give bicarbonate	Urine sodium loss
Treatment	Bicarbonate	Thiazide diuretic **high dose** bicarbonate	Fludrocortisone

Urine Anion Gap (UAG)

The UAG is the way to **distinguish between diarrhea and RTA** as the cause of the normal anion gap metabolic acidosis:

- **UAG = Urine Na^+ – Urine Cl^-**

When acid is excreted from the kidney, it goes out as NH_4Cl. Acid excretion from the kidney goes out with chloride.

If you *can* excrete acid from the kidney, the urine chloride goes up. If the urine chloride is up, then the number (UAG) is negative. **Diarrhea causes a negative UAG**, because the kidney can excrete acid and the net UAG is negative. In metabolic acidosis, a **negative UAG means the kidney works.**

If you *cannot* excrete acid from the kidney, the urine chloride goes down. This gives a positive number (UAG). **In RTA, you cannot excrete acid from the kidney.** The urine chloride will be low, and the **UAG will be positive.**

Metabolic Alkalosis

VOLUME CONTRACTION

Volume contraction leads to metabolic alkalosis because there is a **secondary hyperaldosteronism,** which causes increased urinary loss of acid.

Treat the underlying cause.

CONN SYNDROME OR CUSHING SYNDROME

Hyperaldosteronism resulting from primary hyperaldosteronism (Conn syndrome) or Cushing syndrome causes urinary acid loss.

Surgically remove the adenoma. Also look for **hypokalemia,** which often accompanies the increased urinary acid loss.

HYPOKALEMIA

Hypokalemia causes metabolic alkalosis, because **potassium ions shift out of the cell** to correct the hypokalemia. This shifts hydrogen ions into the cell in exchange for the potassium ions leaving.

MILK-ALKALI SYNDROME

Metabolic alkalosis occurs from the administration of **too much liquid antacid.**

VOMITING

Vomiting causes a **loss of acid from the stomach.** In addition, the loss of fluids leads to **volume contraction** and secondary hyperaldosteronism.

Cystic Disease

Cystic disease presents with **recurrent hematuria, stones, and infections.** There are **cysts throughout the body,** such as in the liver, ovaries, and circle of Willis; **mitral valve prolapse; and diverticulosis.** The most common site of extrarenal cysts is the **liver.** The most common cause of death is **end-stage renal disease.**

> Subarachnoid hemorrhage is *not* the most common cause of death in cystic disease.

There is *no* specific therapy.

Incontinence

The following table summarizes the presentation, diagnosis, and treatment of incontinence.

> Mirabegron relaxes the bladder by beta-3 stimulation.

	Urge Incontinence	Stress Incontinence
Presentation	Pain followed by urge to urinate	*No* pain
	No relationship to coughing, laughing, or straining	Brought on by coughing and laughing
Testing	Urodynamic pressure monitoring	Observe leakage with coughing
Treatment	• Behavior modification • Anticholinergic medications — Tolterodine — Trospium — Darifenacin — Solifenacin — Oxybutynin — Mirabegron	• Kegel exercises • Estrogen cream

Hypertension

> A man comes to the office for a routine visit. He is found to have a blood pressure of 145/95. What is the next best step in management?
>
> **Answer:** Repeat the blood pressure measurement in 1–2 weeks.

Diagnostic Testing

The first step when a case of hypertension presents is to **repeat the blood pressure measurement.** It may take 3–6 measurements to get an accurate assessment of blood pressure.

CCS Tip: Routine tests for hypertension cases on CCS are:

- **Urinalysis**
- **EKG**
- **Eye exam** for retinopathy
- **Cardiac exam** for murmur and S4 gallop

Treatment

If the blood pressure is repeatedly abnormal, initiate lifestyle modifications such as these:

- **Sodium restriction**
- **Weight loss**
- **Dietary modification**
- **Exercise**
- **Relaxation techniques**

> What is the most effective lifestyle modification for hypertension?
>
> **Answer:** Weight loss.

If lifestyle modifications have no effect over 3–6 months, initiate medical therapy:

- Use a **thiazide diuretic,** such as **hydrochlorothiazide** or **chlorthalidone, and a calcium blocker or ACE inhibitor.**
- In **diabetics,** however, use **ACEI/ARB** as the first-line therapy.

About 60–70 percent of patients will be controlled with one drug. If pressure control is not achieved with the first drug, add a second and possibly a third drug:

- **Beta blocker** (metoprolol, carvelodil)
- **ACE inhibitor**
- **Angiotensin receptor blocker (ARB)**
- **Calcium channel blocker (CCB)**

About 90–95 percent of patients should achieve control with the use of 3 medications. If 2 drugs do not work, **add a third drug. Investigate for causes of secondary hypertension if 3 drugs do not work.**

Compelling Indications for Specific Medications

If any of the conditions in the following table are present, do not start with a diuretic. Go straight to the specific medication.

> Thiazides are not better than CCBs, ACEIs, or ARBs as a first drug.

Condition	Medication
Coronary artery disease	Beta blocker
Congestive heart failure	Beta blocker, ACEI, or ARB
Migraine	Beta blocker, CCB
Hyperthyroidism	Beta blocker
Osteoporosis	Thiazide
Depression	*No* beta blockers

Asthma	*No* beta blockers
Pregnancy	Alpha methyldopa
BPH	Alpha blockers
Diabetes	ACEI/ARB

Thiazides are not better as a first choice than ACE inhibitors, ARBs, or calcium channel blockers. Diabetes alone can be controlled to 140/90. Start with 2 medications if baseline blood pressure is > 160/100. In those over age 60, blood pressure need only be controlled to < 150/90.

BP target for those age > 60 is 150/90.

Secondary Hypertension

Investigate for secondary hypertension if you see the following:

- Young (< 30) or old (> 60) patient
- Failure to control pressure with 3 medications
- Specific findings in the history or physical (see table below)

Condition	Finding
Closure of renal artery (stenosis)	Bruit
Pheochromocytoma	Episodic hypertension
Conn syndrome	Hypokalemia
Cushing syndrome	Buffalo hump, truncal obesity, striae
Coarctation of the aorta	Upper extremity > lower extremity pressure
Congenital adrenal hyperplasia	Hirsutism

Specific Findings in the History or Physical

RENAL ARTERY STENOSIS

Look for an **abnormal sound (bruit)** auscultated in the flanks or abdomen. **Hypokalemia** may be present.

Diagnostic Testing

- Best initial test: **Renal ultrasound with Doppler**
- If a **small kidney** is seen, any of the following tests can be done next:
  - **Magnetic resonance angiography (MRA)**
  - **Duplex ultrasonogram**
  - **Nuclear renogram**
- Most accurate test: **Renal angiogram**

Treatment

Best initial therapy: **Renal artery angioplasty and stenting**

BASIC SCIENCE CORRELATE

DIAMETER AND FLOW

Flow markedly increases as radius of a tube increases. The flow increases to the fourth power of the radius. For example, if the radius or diameter doubles in size, flow will go up 16 times, or 2 × 2 × 2 × 2.

10

Nephrology

Case 1

Chief Complaint

Nausea and malaise

History and Physical Examination

A 72-year-old woman comes to the emergency department complaining of nausea and generalized malaise for the past day. There is no associated fever, chills, chest or abdominal pain, or other constitutional symptoms. Her past medical history is significant for severe osteoarthritis, which is controlled with ibuprofen. She had a recent flare-up of back pain and had taken "a number of extra pills."

She appears to be in no acute distress. Vital signs are temperature 37° C (98.6° F), blood pressure 100/60 mm Hg, pulse 100/min, and respirations 26/min. Physical examination shows mild jugular venous distension, a heart that is mildly tachycardic but otherwise normal, and left basilar crackles in her lungs. Her abdomen is soft, nontender, and without hepatosplenomegaly. There is 1+ bilateral lower extremity edema.

Differential Diagnosis

1. Acute kidney injury (AKI)
2. Congestive heart failure
3. Viral gastroenteritis
4. Nephrotic syndrome

Initial Management

Setting: emergency department

Diagnostic/Therapeutic Plan

- CBC, serum electrolytes, BUN, creatinine
- Urinalysis
- ABGs
- Chest x-ray
- Calcium and uric acid levels

Test Results

- Normal CBC; sodium 138 mEq/L, potassium 5.8 mEq/L, chloride 106 mEq/L, bicarbonate 12 mEq/L; BUN 78 mg/dL; creatinine 6.3 mg/dL
- Urinalysis: trace proteinuria
- ABGs: pH 7.29, PCO2 20 mm Hg, PO2 80 mm Hg
- Chest x-ray: small left pleural effusion
- Calcium and uric acid levels: normal

Assessment

The clinical presentation of this patient is nonspecific. The history of an elderly person who has taken an excess dose of a nonsteroidal anti-inflammatory drug (NSAID), however, should

alert the clinician to the possibility of acute kidney injury. This diagnosis becomes quite obvious with measurements of serum electrolytes and BUN.

CCS NOTE

You may not be able to determine a specific diagnosis from the history of present illness. Order the routine admitting labs (CBC, chemistry panel [basic metabolic panel], urinalysis, and chest x-ray) if you don't know what to do.

Acute kidney injury impairs excretion of salt and water with alteration of acid-base mechanisms; therefore, it is frequently complicated by fluid overload, hyperkalemia, and metabolic acidosis. The patient should be hospitalized and monitored closely, given the severity of the abnormalities.

AKI is often classified into 2 groups: oliguric (<400 mL/24 hrs) and nonoliguric (>400 mL/24 hrs). The lower the urine output, the worse the prognosis. In cases where hypovolemia contributes to the development of AKI, fluid challenges are often given in an effort to convert a patient from the oliguric to the nonoliguric state. In this patient, however, there are already significant signs of volume overload (jugular venous distension, left basilar crackles, peripheral edema), and adding fluid would not be wise.

It is important to differentiate between prerenal, intrarenal, and postrenal causes. **Prerenal** azotemia gives a BUN/creatinine ratio of 20:1. This patient's ratio is closer to 10:1, indicating a problem in the kidney itself. There are no crystals in her urine consistent with hyperuricemia or oxalate causing renal failure, and no history of gout. There are no RBCs in the urine. RBCs generally indicate a glomerular disorder. If no urine is produced, an obstructive uropathy must be ruled out by bladder catheterization and renal U/S.

Further Management Plan	Results
U/S of kidneys	Normal
Urine stain for eosinophils	Negative
Urine sodium	>40 mmol/L

Treatment Plan

- Discontinue all nonsteroidal anti-inflammatory drugs, as well as all other possible nephrotoxic agents
- Admit to hospital
- Hemodynamic monitoring
- Close monitoring of electrolytes
- Possible dialysis

Discussion

NSAIDs can cause renal toxicity (interstitial nephritis, nephrotic syndrome, and prerenal azotemia), although the risk is low. Patients age >60 or with history of renal disease, CHF, ascites, or diuretic use are at higher risk. NSAIDs inhibit prostaglandins, which are vasodilatory in the kidney. Therefore, NSAIDs lead to vasoconstriction.

One of the most important decisions in assessing a patient with acute kidney injury is to determine when and if hemodialysis is appropriate. Indications for **emergency dialysis** are:

- Refractory hyperkalemia
- Profound metabolic acidosis
- Alteration in mental status
- Refractory fluid overload
- Uremic pericarditis

When BUN remains consistently >100 mg/dL, dialysis is often begun.

Dialysis is used to treat life-threatening complications of renal failure that are not correctable by other means. For example, anemia can be life-threatening, but it is correctable with transfusions or erythropoietin use, and hence does not require dialysis. Pericarditis, however, is not correctable by other means.

CCS NOTE

If you want to know how the patient is doing and you don't get nurses' notes informing you, click the INTERVAL HISTORY button on the physical exam page.

Hemodialysis is not without risks, however. The associated volume shifts may predispose patients with underlying cardiac disease to ischemic events. Additionally, the risk of infection is significant.

PATIENT SAFETY NOTE

Aspiration precautions should be ordered in uremic patients who complain of nausea and vomiting, and especially in patients with altered mental status, as they are at high risk for aspiration.

There are a few associations that should prompt you to think about specific diagnoses; however, these have to be assessed on a case-by-case basis.

- **Minimal proteinuria with muddy brown casts:** acute tubular necrosis (ATN)
  - Check the fractional excretion of sodium (FENa). Excess sodium is usually lost because of damage in the tubules or glomeruli. Consequently, the calculated FENa would be high (>2%) in ATN, while FENa that is low (<1%) would indicate prerenal causes.

- **Erythrocyte or dysmorphic erythrocyte casts:** glomerulonephritis
  - Investigate the cause by checking dsDNA, ANA, antistreptolysin O antibodies, complement level (C3, C4, CH50), HIV and hepatitis serologies, cryoglobins, p-ANCA/c-ANCA, and antiglomerular basement membrane antibodies.

- **Eosinophilia, eosinophiluria with or without a rash:** acute interstitial nephritis (AIN)
  - Patient's medication list should be reviewed, as well as history for recent vascular procedure. Another clue for cholesterol emboli is a rash that is described as a "violaceous reticular rash" or "livedo reticularis."

- **Pyuria:** pyelonephritis or AIN, as above
  - Patient's medication list should be reviewed and urine culture checked

- **Nephrotic range proteinuria (urine protein >300 mg/dL):** diabetes and renal vein thrombosis
  - Check patient's blood glucose or HbA1c, and perform renal Doppler study

- **Obstructive uropathy**
  - Check for prostate pathology, kidney stones, retroperitoneal fibrosis, or other malignant obstructing masses; investigations include checking residual bladder volume, and taking noncontrast CT or MRI

- **Enlarged kidneys on U/S**
  - Check for obstructive uropathy (as above) or early diabetes, amyloidosis, and HIV nephropathy. Investigations include serum electrophoresis, HIV testing and blood glucose

or HbA1c

CCS NOTE

You will not get confirmation of your final diagnosis on the CCS.

Final Diagnosis

Acute kidney injury, NSAID-induced

Case 2

Chief Complaint

"I feel really weak and confused."

History and Physical Examination

A 52-year-old woman, who has insulin-dependent diabetes, comes to the clinic because of several months of generalized, progressive weakness. She has not seen you in nearly a year because she has been "scared of what you might tell" her. She comes in now because she is finding it difficult to think clearly. She gets her prescriptions when she needs them from local walk-in clinics. When she was last in the clinic a year ago, she was asymptomatic; lab studies at that time showed hematocrit 34% (normal 38–44%), BUN 42 mg/dL (normal 7–18 mg/dL), creatinine 3.2 mg/dL (normal 0.5–1.3 mg/dL), and potassium 4.9 mEq/L (normal 3.5–5.2 mEq/L).

Her vital signs today are temperature 36.4° C (97.5° F), blood pressure 110/70, pulse 95/min, and respirations 18/min. She has no neck stiffness. Examination of the chest shows mild, bibasilar rales, and cardiovascular examination shows no murmurs or rubs. She has 1–2+ edema of lower extremities bilaterally. Neurologic examination shows no focal defects, but she is somewhat confused. She does not know the exact date or day of the week and cannot do calculations, serial sevens, or remember 3 objects at 5 minutes.

Initial Management

Setting: outpatient workup and treatment

Differential Diagnosis

1. Hypoglycemia (usually episodic)
2. Hyperglycemia/diabetic ketoacidosis
3. Renal failure
4. Anemia
5. Cerebrovascular accident (unlikely since exam nonfocal)

Diagnostic/Therapeutic Plan

- Glucose
- BUN, creatinine
- Hematocrit
- Serum bicarbonate
- Potassium
- ABGs

Test Results

- Glucose: 142 mg/dL (normal 80–120 mg/dL)
- BUN, creatinine: 92 mg/dL, 8.4 mg/dL
- Hematocrit: 29%
- Serum bicarbonate: 15 mEq/L (normal 22–26 mEq/L)
- Potassium: 5.8 mEq/L (normal 3.5–5.2 mEq/L)
- ABGs: metabolic acidosis

Assessment

This patient has had insulin-dependent diabetes, and she could potentially have any of the end-organ manifestations of the disease. These are all related to damage to the microvasculature.

Manifestations of long-term diabetes are the following:

- Nephropathy
- Stroke
- Myocardial infarction
- Retinopathy (strongly suggests coexisting diabetic nephropathy)
- Neuropathy
- Peripheral vascular disease

This patient had evidence of renal insufficiency in the past but it was not severe enough to cause symptoms. The renal insufficiency has now progressed and is causing acidosis (decreased bicarbonate), hyperkalemia, mild encephalopathy, and anemia.

The patient's complaints are unlikely to be due to stroke because there is no headache or focal neurologic finding. Meningitis is unlikely in the absence of fever, headache, and neck stiffness. Ketoacidosis is unlikely with a low glucose, but is still possible. Ketoacidosis could also account for the acidosis and the hyperkalemia.

The most immediate concern is should always be to address the most life-threatening problem: in this case, the hyperkalemia. The most dangerous effect of hyperkalemia is arrhythmia, and the earliest electrocardiogram finding of hyperkalemia is peaked T waves.

Further Management Plan	**Results**
1. Electrocardiogram	1. Normal rate and rhythm; normal T waves; normal QRS
2. Serum acetone	2. Negative
3. Urinalysis	3. 3^+ protein; 1^+ glucose

4. Renal U/S	4. Bilaterally large kidneys

Treatment Plan

- Correct hyperkalemia
- Continue insulin at present dose
- Refer to nephrologist for institution of dialysis

CCS NOTE

On the CCS if you order EKG, chest x-ray, urinalysis, and U/S at the same time, they will all be done simultaneously and immediately.

Treatment of chronic kidney disease is as follows:

- **Hypertension**: an ACEI or ARB in the early stages to prevent further worsening; in late stages when hyperkalemia is evident, caution should be used with ACEI and ARBs. Use calcium blockers and vasodilators.
  - Choose loop diuretic rather than thiazide if GFR< 30 mL/min/1.73 m^2

- **Proteinuria (serum protein-creatinine ≥200 mg/mg)**: ACEI or ARB even if patient is normotensive
- **Hemoglobin A1c >7%**: intensive control of DM
- **Anemia:** check iron storage and replete if inadequate; erythropoietin to maintain Hb 10–11 g/dL. **Always check iron studies** before starting erythropoietin.

- **Hyperphosphatemia and hypocalcemia**: phosphate binders (calcium acetate, calcium carbonate, sevelamer) to maintain phosphate levels at 3.5–5.5 mg/dL
- **Hyperlipidemia**: statins with target LDL <100 mg/dL
- **Vitamin D deficiency**: vitamin D analogs

CCS NOTE

The consultant will not make specific recommendations. However, asking for a consultation at the appropriate time shows good judgment.

Discussion

The most important initial management here is to lower the potassium, because that is the most immediate life-threatening problem. Sodium polystyrene sulfonate is a sodium/potassium exchange resin, given orally, which will remove potassium from the body. If the potassium were higher, bicarbonate alone or glucose combined with insulin could be given to lower the potassium more rapidly. With extremely high potassium level and electrocardiogram abnormalities, calcium chloride or calcium gluconate is injected intravenously (and given along with the insulin) to protect the heart from arrhythmia.

There are a large number of manifestations of renal failure. These are all due to loss of the excretory, productive, or reabsorptive functions of the kidney. The kidney excretes water, potassium, acid, magnesium, phosphate, uric acid, and nitrogenous waste products. Therefore, kidney failure can result in fluid overload, hyperkalemia, acidosis, hypermagnesemia, hyperphosphatemia, and hyperuricemia. Accumulation of nitrogenous waste products gives the encephalopathy, pericarditis, pruritus, and increased infections and bleeding. These last 2 occur because platelets and WBCs don’t work well in a uremic environment.

The kidney produces erythropoietin and vitamin D2. Therefore, kidney failure results in anemia and osteodystrophy. Hypocalcemia can occur from insufficient calcium absorption from both the intestine and the kidney.

Although there are many manifestations of chronic renal failure, only a few need emergent dialysis. All are life-threatening and none can be treated well by other means.

- Intractable hyperkalemia (i.e., doesn't respond to sodium polystyrene sulfonate)
- Pericarditis
- Intractable fluid overload
- Acidosis
- Encephalopathy

PATIENT SAFETY NOTE

- All patients with ESRD are considered candidates for kidney transplant unless not warranted (chronic infection, neuropsychiatric disease, malignancy, severe cardiovascular disease). Kidney transplant is associated with better quality of life and is less expensive to the health care system than long-term dialysis.
- Advise patients to not use aluminum-containing antacids (aluminum toxicity) or magnesium-containing antacids.

Final Diagnosis

Chronic renal failure from diabetes

Case 3

Chief Complaint

"I don't want to have diarrhea on my vacation to Thailand."

History and Physical Examination

A 47-year-old man comes to the office for advice about how to prevent diarrhea on the vacation he is planning to Thailand. He sees you about once a year for minor problems and routine evaluation and is generally quite healthy. His last evaluation the prior year was completely normal. He uses no medications, except occasional vitamins, and smokes 1 pack of cigarettes every 2 days.

Vital signs are temperature 37° C (98.6° F), blood pressure 155/95 mm Hg, and respirations 12/min. He appears not to be in distress. Physical examination shows eye grounds with no hemorrhages or exudates. The remainder of the physical examination is unremarkable.

Differential Diagnosis

1. Essential hypertension
2. Renal artery stenosis
3. Pheochromocytoma
4. Hyperaldosteronism

Initial Management

Setting: outpatient

Diagnostic/Therapeutic Plan

- BUN, creatinine
- Urinalysis
- CBC
- Potassium
- Electrocardiogram

Test Results

- BUN: 14 mg/dL; creatinine: 0.8 mEq/L (normal)
- Urinalysis: normal
- CBC: normal
- Potassium: normal
- Electrocardiogram: normal

CCS NOTE

Office management of non-urgent cases such as this may go on for "months" of simulated time. Do not worry if the case doesn't seem to end. Just keep moving the clock forward and manage the patient.

Assessment

This patient is in his usual state of good health, except for elevated systolic and diastolic BP. Over 95% of high blood pressure cases are of unknown etiology and are referred to as

"essential" hypertension. The most common presentation of essential hypertension is an incidental finding (with no symptoms). When BP is high enough to cause symptoms on presentation, this is often called hypertensive "emergency."

These are poorly defined terms that do not refer to any specific numbers in terms of the pressure. They refer instead to the presence of symptoms—including headache, visual disturbance, dyspnea, chest pain, and mental status changes. Patients with high BP and these symptoms should be treated immediately. A person can have a very high BP and still have no symptoms; this is referred to as hypertensive "urgency."

A single elevation on a single visit is not sufficient to warrant initiation of drug treatment. Up to 1/3 of hypertension is so-called "white-coat" hypertension. This means that the general anxiety of being in the doctor's office can artificially raise BP. When the same patients are given a BP cuff to measure at home, their BP is normal. True hypertension should be defined as an elevation found on several visits over time.

Further Management Plan/Results

- Diet modification (salt restriction, weight loss), exercise, relaxation methods, and reduction in alcohol intake
- If no response to lifestyle modifications is seen after 6 months, use diuretics first (see Discussion section for choices)

CCS NOTE

Do not skip steps such as lifestyle modification just because you don't think they could be effective. Always "advise," "counsel," or "educate" about exercise, weight loss, and diet.

Discussion

Start with a diuretic. If a diuretic alone does not control the pressure, then add a calcium channel blocker (CCB), ACE inhibitor, or angiotensin-receptor blocker. There are now dozens of medications approved for first-line management of hypertension, but diuretics are still recommended as the first choice—particularly the thiazides, CCBs, and ACE inhibitors.

The goal with BP is <140/90 mm Hg. If BP >160/100, start with 2 medications. If patient has BP >140/90 mm Hg and has diabetes, add 2 medications.

- Diuretics: hydrochlorothiazide
  - Diuretics clearly lower mortality through prevention of stroke and heart disease. They can rarely cause hyperlipidemia, hyperuricemia, hypokalemia, and hyperglycemia. They are not antianginal.

- Beta-blockers: atenolol, metoprolol, propranolol, nadolol, labetalol or carvedilol (a combined nonspecific beta-blocker and central-acting alpha agent)
  - Besides lowering BP, beta-blockers have antianginal effect by decreasing myocardial work. Certain forms are also antiarrhythmic and, for example, can control rate in atrial fibrillation.
  - Disadvantages are occasional depression, memory loss, impotence, and fatigue. In addition, they must be used with caution in diabetics because they mask the symptoms of hypoglycemia and may precipitate bronchospasm in asthmatics. They can cause Raynaud phenomenon and worsen peripheral vascular disease by contributing to constriction of peripheral vasculature (beta-2 stimulation dilates small arteries).

- CCBs: nifedipine, diltiazem, verapamil, amlodipine, felodipine, isradipine, nicardipine
  - Some CCBs are antianginal as well. Verapamil and diltiazem are also useful for tachyarrhythmias. They are used to treat Raynaud syndrome and relieve esophageal spasm.
  - They have relatively few major side effects and there are no lipid effects. They can cause

constipation, pedal edema, and reflex tachycardia.

- ACE-inhibitors: captopril, enalapril, lisinopril, fosinopril, ramipril, benazepril, quinapril
  - ACE inhibitors are neither antianginal nor antiarrhythmic. They have few side effects, such as cough, hyperkalemia, angioedema, and rash. They have no significant lipid, CNS, or sexual side effects.
  - ACE inhibitors are all first-choice therapy for those with diabetes, CHF, previous myocardial infarction, and chronic renal failure with proteinuria.
  - Efficacy is an effect of the whole class of medications; it is not based on a specific drug.

- ARBs: losartan, valsartan, irbesartan, candesartan
  - Angiotensin II blockers have the same indications as ACE inhibitors, such as congestive heart failure and diabetes. They are best used if ACE inhibitors cannot be tolerated. Cough is the most common reason why a patient can't tolerate an ACE inhibitor.

Do **not** select beta-blockers as initial monotherapy unless there is a compelling indication present, such as CHF or CAD.

Drugs	**Indications**	**Contraindications**
Diuretics	Systolic hypertension, heart failure	Gout
Beta-blockers	CHF, angina, MI, tachyarrhythmias	Heart block, severe asthma/COPD, pregnancy
ACE-Is	CHF, diabetic nephropathy, proteinuria, post-MI	Hyperkalemia, pregnancy, bilateral renal artery stenosis
ARBs	ACE-I induced cough, diabetic nephropathy, CHF	Same as ACE-I
CCBs	Angina, CAD, cyclosporine induced	Heart block (diltiazem, verapamil)

	HTN	
Alpha-blockers	BPH	Orthostatic hypotension

Hypertensive urgency is defined as **systolic BP >180 mm Hg** and/or **diastolic BP >120 mm Hg**, **with no ongoing end-organ damage**. Management depends on whether or not the patient is on treatment.

- If patient is being treated and is compliant, then adjust medication by either increasing the medication dose or adding a new agent. If patient is noncompliant, restart his home medication and provide counseling.
- If patient is not on treatment and presents with hypertensive urgency, observe for several hours; treatment should include small doses of clonidine or captopril to gradually reduce BP 20–30 mm Hg. Once that is achieved, start a long-acting antihypertensive agent and discharge the patient, with a follow-up appointment in a few days.

Hypertensive emergency is defined as **systolic BP >180 mm Hg** and/or **diastolic BP >120 mm Hg, with end-organ damage**. Symptoms may include shortness of breath, chest pain, encephalopathy or stroke, retinopathy, or acute kidney injury.

- Admit the patient and gradually reduce the BP no more than 25% in the first hour; IV medications such beta-blockers (metoprolol), CCB (nicardipine), hydralazine, nitroprusside, and nitroglycerin, are preferred.

Second- and third-line agents are direct vasodilators (hydralazine, minoxidil), central-acting alpha agents (alpha methyldopa, clonidine), and ganglionic blockers (reserpine, guanethidine). These agents are rarely used because of their side effects. The direct vasodilators are typically used in patients with resistant HTN associated with chronic kidney disease.

- Peripheral-acting alpha-blockers: prazosin, terazosin, doxazosin

— Note these are **not** used routinely for the treatment of hypertension.

CCS NOTE

One of the most anxiety-provoking challenges of the CCS is determining how often to bring a patient back to the office for routine management for a disorder like hypertension. Choose intervals of 2–4 weeks until BP is stable.

An important factor is to rule out the relatively small population that has an underlying cause for their elevation in pressure. Patients presenting at age <25 or >60, or those who have an unusual physical examination finding, such as an abdominal bruit (renal artery stenosis), moonlike facies or striae (Cushing syndrome), hypokalemia (hyperaldosteronism), or signs of acromegaly, should have further investigation for these conditions.

Other indications for which further evaluation may be necessary are:

- Protein in the urine
- Elevation of BUN and creatinine
- Rapidly progressing eye ground abnormalities (hemorrhages, exudates, papilledema)

The electrocardiogram abnormalities associated with longstanding hypertension (which are absent in this patient) are most often signs of left ventricular hypertrophy. These are an S-wave in V1 and an R-wave in V5 >35 mm. This is not so much an indication of secondary hypertension as an indication of longstanding disease.

Final Diagnosis

Essential hypertension

Case 4

Chief Complaint

Headache and high blood pressure

History and Physical Examination

A 27-year-old woman comes to your office because of a continuous frontal headache for the last several months. You noted her to be hypertensive on examination several months ago, and she has been on nifedipine for the last 8 weeks. Prior to that, she had been healthy her entire life and is on no other medications. The nifedipine dose was raised on her last visit.

Vital signs are temperature 37° C (98.6° F), blood pressure 170/100 mm Hg, and pulse 70/min. Examination of the head, eyes, ears, nose, and throat shows normal eye grounds and no papilledema. The chest is clear bilaterally. She has a regular heart rate and rhythm, with no murmurs or gallops. The abdomen is soft and nontender, with a rhythmic, high-pitched sound in the epigastric area. The extremities are nonedematous.

Differential Diagnosis

1. Renovascular hypertension (renal artery stenosis)
2. Pheochromocytoma
3. Primary hyperaldosteronism
4. Essential hypertension
5. Coarctation of the aorta

Initial Management

Setting: outpatient

Diagnostic/Therapeutic Plan

- BUN, creatinine
- Renal U/S
- Potassium

Test Results

- BUN: 36 mg/dL; creatinine: 1.2 mg/dL
- Renal U/S: bilaterally small kidneys; left smaller than right
- Potassium: 3.4 mEq/L (normal 3.5–5.2 mEq/L)

Assessment

Over 95% of patients with hypertension have "essential" (or idiopathic) hypertension. Because it is expensive and inefficient to evaluate all patients with new onset hypertension for causes of secondary hypertension, it is important to develop criteria for determining who to screen.

In general, indications for further evaluation include any of the following:

- Onset of hypertension at age <30 or >55
- Hypertension that remains high despite medication
- Progression from normal to severe hypertension over the course of several months

The list of secondary causes includes those listed in the Differential Diagnosis section above, as well as oral contraceptives, acromegaly, Cushing syndrome, and congenital adrenal enzyme

deficiencies. Renal artery stenosis is the most common; in addition, it gives abdominal bruits such as the one in this patient, and is common in young women.

Further Management Plan	**Results**
Magnetic resonance angiography, *or*	Decreased uptake in left kidney
Duplex U/S of the renal artery	Renal artery stenosis on left
Renal artery arteriography (gold standard)	Stenotic lesion in the distal renal artery on the left

Treatment Plan

- Balloon angioplasty of stenotic lesion
- Repeat the angioplasty if initial one fails
- Operative repair only if angioplasty is not possible or not effective
- Medical treatment (ACE inhibitors) only if angioplasty and surgery are not possible

CCS NOTE

There are often multiple pathways to the correct management of individual cases on the CCS. There is more flexibility on the CCS than you might think.

Discussion

The causes of renal artery stenosis can be divided into 2 types:

- Fibromuscular dysplasia of the arterial wall occurs in younger woman, particularly age <30

- Atherosclerotic disease occurs in older men

Although it seldom gives useful specific information, renal sonogram is usually done initially because it is an inexpensive and noninvasive examination. The main finding is of **kidneys different in size**. MRI angiography approaches 95% sensitivity and specificity for stenotic lesions of >50% diameter. The ultimate, and best, test for renal artery stenosis is the arteriogram. This test, however, is not performed, because of its invasiveness, until after the others described above are done.

This patient's hypokalemia is because the high renin-angiotensin state leads to a large amount of aldosterone. The high aldosterone state can cause hypokalemia and alkalosis because aldosterone causes an increased urinary loss of potassium and hydrogen ions in exchange for the reabsorption of sodium.

Treatment is based on reversing the stenotic lesion.

- Balloon angioplasty cures 50% of cases and provides improvement in 30%. If the initial angioplasty fails, it may be repeated.
- If angioplasty repeatedly fails or is not possible, then surgical resection is performed.
- Chronic medical management with ACE inhibitors is used only when these 2 modalities are not effective or possible.
- ACE inhibitors will control the blood pressure, but the kidney will fail in bilateral renal artery stenosis.

CLINICAL PEARL

Consider secondary hypertension in patients with atypical clinical features such as presenting age <30 or new onset age >55, no family history, hypokalemia, metabolic

alkalosis, kidney disease, or persistent hypertension despite the use of multiple medications.

CLINICAL PEARL

A specific differential diagnosis to keep in mind is primary hyperaldosteronism, which also presents with hypertension and hypokalemia. However, physical examination is usually normal, and patients may present with muscle cramping and muscle pain. Further investigation reveals elevated aldosterone to plasma renin activity ratio.

Final Diagnosis

Renal artery stenosis

Case 5

Chief Complaint

"I'm feeling confused. What day is it?"

History and Physical Examination

A 57-year-old man who is a long-term smoker is brought to the emergency department by his family because of mild confusion that has been developing slowly over the last several days. He was diagnosed with lung cancer by bronchoscopy 2 months ago and is about to undergo chemotherapy. He still has the hemoptysis that led to his original presentation, and his chest x-ray has a left perihilar infiltrate. Besides confusion, he has also been somewhat weaker. There are no other specific complaints. His past medical history is significant for depression and diabetes. He is on an SSRI antidepressant and glyburide.

Vital signs are temperature 37.4° C (99.3° F), blood pressure 120/70 mm Hg, pulse 78/min, and respirations 16/min. There is no neck stiffness. He has a regular heart rate and rhythm, with no murmurs, and his chest is clear to auscultation. Neurologic examination shows that he is awake and alert but disoriented to the exact day. He knows he's in the doctor's office and what the year is. There are no focal deficits, but his muscles are somewhat weak.

Differential Diagnosis

1. Paraneoplastic syndrome
2. Metastatic cancer to the brain

3. Hyponatremia
4. Hypoxia
5. Meningitis

Initial Management

Setting: emergency department

Diagnostic/Therapeutic Plan

- Head CT scan with contrast
- Serum electrolytes
- Urine sodium
- Pulse oximetry on room air

Test Results

- Head CT scan with contrast: normal
- Serum electrolytes: sodium 122 mEq/L (normal 135–145 mEq/L), potassium 4.2 mEq/L (normal 3.5–5.2 mEq/L), chloride 102 mEq/L (normal 98–106 mEq/L), BUN 18 mg/dL (normal 7–20 mg/dL), glucose 90 mg/dL
- Urine sodium: 42 mmol/L
- Pulse oximetry on room air: 96% saturation

Assessment

Generalized confusion in a patient with a known malignancy should always suggest metastatic disease to the brain. Lung cancer, breast cancer, and melanoma are frequently metastatic to the brain. The absence of focal neurologic findings generally points away from this. However, CT scan or MRI of the head with contrast effectively excludes this as a cause of the symptoms.

There is no neck stiffness indicative of meningitis, and lung cancer is not a specific risk factor for meningitis. Metabolic abnormalities, such as hyponatremia and hypernatremia, can cause confusion, as can hypoglycemia, hypoxia, and drug intoxications. This patient has a focal lung lesion that is unlikely to be large enough to cause lung damage sufficient to lead to hypoxia. Oxygen saturation is normal. Pulse oximetry is acceptable instead of an ABG test when the CO_2 does not have to be evaluated. Labs reveal sodium 122 mEq/L (normal 135–145 mEq/L), which is sufficiently low to cause these symptoms.

Further Management Plan	**Results**
Serum osmolality	254 mOsm/kg H_2O
Urine osmolality	540 mOsm/kg H_2O

Treatment Plan

- Fluid restriction to 1–2 liters per day
- Loop diuretic (furosemide, bumetanide, ethacrynic acid) if there is no improvement with fluid restriction alone and give with normal saline
- Stop the SSRI and sulfonylurea
- Demeclocycline chronically if the underlying cause cannot be corrected

Discussion

The most common cause of hyponatremia in a patient with a malignancy or any pulmonary abnormality is the syndrome of inappropriate antidiuretic hormone (SIADH). This is a normovolemic form of hyponatremia. A diagnosis of SIADH is confirmed with high urine sodium (>20 mmol/L) and a urine osmolality greater than serum osmolality in the presence of hyponatremia.

In fact, the diagnosis of SIADH is virtually assured if urine osmolarity is >100. In that case anything—except a maximally dilute urine in the presence of hyponatremia—is consistent with SIADH.

The causes of hyponatremia can be divided into 3 categories:

- **Hypervolemic**: occurs in congestive heart failure, nephrotic syndrome, and cirrhosis
- **Hypovolemic**: occurs with Addison disease, GI losses, burns, and diuretic use combined with drinking free water
- **Normovolemic**: SIADH, psychogenic polydipsia, or pseudohyponatremia from hyperglycemia, hypothyroidism

The causes of SIADH can be divided into 4 categories:

- **Pulmonary**: virtually anything—pneumonia, atelectasis, emphysema, embolism, etc.
- **CNS**: virtually anything—tumor, stroke, hematoma, dementia, encephalitis, meningitis, etc.
- **Neoplasm**: only a few are commonly associated with ectopic production, e.g., small-cell (oat-cell) cancer of the lung, thymus, duodenal cancer (although any cancer could be associated)
- **Medications**: any oral hypoglycemic agent can do it, but chlorpropamide is most often associated; cyclophosphamide, clofibrate, and SSRIs (sertraline) are also common causes

Thus, in this patient, oat-cell carcinoma or the involvement of the lung alone can be causing the SIADH. As stated above, the diagnosis of SIADH is confirmed by the finding of a urine osmolarity greater than serum osmolality in the presence of hyponatremia. This is because a normal person's urine would become maximally dilute (osmolality <100) if they became hyponatremic, in the body's attempt to rid itself of the free water. SIADH is a problem with free water, not a problem with sodium metabolism.

CLINICAL PEARL

Don’t forget that severe hyperglycemia causes pseudohyponatremia.

Treatment, therefore, is based on controlling the free water.

- For mild SIADH (sodium level ≥120–125 mEq/L) with few or no symptoms, treatment is fluid restriction.
- For more severe hyponatremia (sodium about 110–120 mEq/L), treatment is normal saline and a diuretic. Saline gives salt, and the diuretic promotes a free water diuresis.
- For profoundly low sodium levels (<110 mEq/L) or severe symptoms, the fastest way to raise sodium is with hypertonic saline.

These numbers are approximations only. The development of symptoms is also highly dependent upon the rate at which sodium declines. In general, whenever there is an altered mental status, you should use hypertonic saline.

Although this patient is symptomatic with disorientation, the symptoms have been present for some time, and the hyponatremia may have developed over several weeks to months. There is no urgency to raise his sodium level over just a few hours. Raising or lowering a patient’s sodium too rapidly for therapeutic purposes can also precipitate symptoms.

When you raise the sodium too rapidly, you are at risk for causing central pontine myelinolysis. When you lower it too rapidly, you risk cerebral edema. Mild abnormalities should be corrected at 0.5 mEq/L/hr. With severe symptoms, you can correct it as fast as 1–2 mEq/L/hr.

Because fluid restriction to 1–2 liters can be quite difficult to tolerate on a long-term basis, this patient may need to be maintained on demeclocycline. Demeclocycline is a tetracycline

antibiotic which causes a nephrogenic diabetes insipidus and hence makes the kidney insensitive to antidiuretic hormone.

PATIENT SAFETY NOTE

Do not correct the serum sodium faster than 0.5 mEq/L/hr (12 mEq over 24 hrs).

Final Diagnosis

Hyponatremia due to SIADH

CLINICAL PEARL

The approach to hyponatremia starts with determining the patient's clinical volume status.

Hypovolemia (hypotension, dehydration)

- Spot urine sodium <10 mEq/L
- BUN/creatinine >20:1
- Urine osmolarity >450 mOsm/L
- Renal or GI losses, dehydration, adrenal insufficiency

Hypervolemia (ascites, edema)

- Spot urine sodium <10 mEq/L
- BUN/Creat >20:1
- Urine osmolarity >450 mOsm/L
- Liver cirrhosis, ascites, kidney failure

Euvolemia: normal volume

- Spot urine sodium >10 mEq/L
- BUN/creatinine <20:1
- Urine osmolarity; as below
- Urine osmolarity >300 mOsm/L: SIADH, hypothyroidism
- Urine osmolarity: 50–100 mOsm/L: psychogenic polydipsia

CLINICAL PEARL

Cerebral salt-wasting syndrome causes hypo-osmolar hyponatremia showing similar labs to SIADH. However, this syndrome is associated with hypovolemia and develops within days of a neurological procedure or a subarachnoid hemorrhage.

Case 6

Chief Complaint

Severe flank pain and blood in the urine

History and Physical Examination

A 27-year-old woman comes to the emergency department because of severe pain in her left side and dark urine. She denies fever but states that a local internist had seen her several days ago for urinary frequency and burning. She had been treated with 2 double-strength tablets of trimethoprim-sulfamethoxazole at that time, and the dysuria had resolved. The pain she now feels came on very suddenly and is so severe that she cannot walk. There is some nausea, and she vomited twice in the back of her father's car on the drive to the hospital. There is pain in her vaginal area.

Vital signs are temperature 37.2° C (98.9° F), blood pressure 110/70 mm Hg, pulse 95/min, and respirations 14/min. Physical examination of the chest and heart are normal. Her abdomen is soft and nontender with no guarding. Her back is also nontender.

Differential Diagnosis

1. Nephrolithiasis
2. Pyelonephritis
3. Cystitis

Initial Management

Setting: outpatient or emergency department

Diagnostic/Therapeutic Plan

- Urinalysis
- Abdominal x-ray
- BUN, creatinine

CCS NOTE

Renal colic is a perfect example of when an analgesic such as ketorolac should be ordered with the first screen. It does not matter what order you write in the tests and treatments, as long as they are on the screen at the same time.

Test Results

- Urinalysis: no WBCs, large amount of blood, nitrates negative
- Abdominal x-ray: normal
- BUN, creatinine: normal

Assessment

A history of very severe flank pain is consistent with an origin in the kidney. Pyelonephritis gives pain in the flank, but there should be clear tenderness, particularly in the costovertebral angle. Pyelonephritis should also give fever and WBCs in the urine, though it can also give RBCs.

Pain as severe as this is profoundly unlikely with a cystitis alone, which at most should give some suprapubic tenderness. Pain in the flank without tenderness associated with hematuria is most consistent with stones in the kidney or ureter. It is not possible to tell the difference between these two by history and physical alone.

The major clue to the diagnosis of nephrolithiasis is a characteristic type of profoundly severe pain. Renal colic is said to be the most severe pain a human can experience, even greater in intensity than childbirth. This pain characteristically radiates to the groin, and pain in the vulva or scrotum is classic.

Further Management Plan	**Results**
1. CT scan without contrast	1. 1.4-cm stone visualized in the left renal pelvis
2. Serum calcium and uric acid	2. Normal
3. 24-hour urine calcium	3. Normal
4. Urine culture	4. Normal

Treatment Plan

- Hydration to keep urine output 2–3 liters per day
- Analgesia
- Straining the urine
- Shock wave lithotripsy (if available) or percutaneous removal if hydration does not result in passage of the stone. Small stones will pass spontaneously, but they must be small enough to enter the ureter.

CCS NOTE

Order all the tests you think are appropriate. The software will tell you which ones need consultations. You won't lose points if the software asks you to order a consult.

Discussion

Kidney stones are composed of calcium oxalate (70%), calcium phosphate (10%), struvite (10–15%), uric acid (5–10%), and cysteine (1%). Nephrolithiasis affects about 1–5% of the population, with recurrences in 50–80% of those patients.

Alkaline urine predisposes to the formation of calcium-containing stones, whereas acidic urine predisposes to the formation of uric-acid stones. Magnesium-ammonium-phosphate (or struvite) stones are formed in the presence of repeated UTI, particularly with urea-splitting organisms such as *Proteus*.

A patient's history must be explored for causes of increased calcium or oxalate levels, such as abundant milk-product ingestion, vitamin D ingestion, large doses of vitamin C, or a family history of stones. Gout predisposes a person to uric-acid stone formation, but clinical gout is not necessary for the production of these stones. Ten to 30% of patients with hyperparathyroidism present with nephrolithiasis. Serum and urine should be checked for calcium levels in a patient with stones.

The most common initial treatment is **hydration and analgesia**, which allows spontaneous passage of the stones in the majority of patients. The stones must be smaller than 5 mm to have a chance of passing into the ureter. For those patients whose stones do not pass, extracorporeal shock-wave lithotripsy can break up calcium-containing stones that are not excessively large

(generally <2 cm). Problems with this technique are its lack of availability, expense, and the entrapment of smaller stone fragments in the ureters later.

Percutaneous removal of stones from the renal pelvis is used when lithotripsy is not an option and the stone does not pass spontaneously. Open procedures are rarely necessary any longer. Ureteral stones can be removed percutaneously or by passing a basket up the ureter via a cystoscope.

Because about 80% of kidney stones contain calcium, about the same amount are visible on an abdominal x-ray. Straining the urine for the stone is also a time-honored method of confirmation. In an emergency room, however, the diagnostic accuracy of the x-ray may be diminished if someone who is not an expert reads the films. Renal sonogram is almost 100% sensitive for stones in the kidney. This sensitivity decreases for stones that are in the ureter: Because the ureters pass posteriorly, they are not well visualized by the anteriorly placed sonogram transducer.

IVP is essentially a historical test and is **a wrong answer choice**. A CT scan is the study of greater sensitivity and specificity. CT scanners are able to perform thin-slice sections through the ureter and can detect even very small stones. When the question asks what the **most accurate diagnostic test** is, answer **CT scan**.

CLINICAL PEARL

The best test for nephrolithiasis is CT without contrast.

In addition to diagnosing the stone, U/S and CT scan are used to diagnose other anatomic abnormalities such as strictures and obstruction.

Final Diagnosis

Nephrolithiasis

CLINICAL PEARL

- To determine the type of stone, straining and checking the urine for stone collection are appropriate.
- Stones <5 mm in size tend to pass spontaneously; those >10 mm often require invasive intervention.
  - Uric acid stones and hyperuricosuria: allopurinol and decreased animal protein intake
  - Large struvite stones: long-term prophylactic antibiotics and invasive removal
  - If patient is pregnant, choose U/S for the diagnosis of nephrolithiasis (no CT)

Case 7

Chief Complaint

"Why am I swelling up?"

History and Physical Examination

A 52-year-old woman comes to your office because of generalized edema for the last several weeks. She was recently diagnosed with breast cancer and has had a lumpectomy and axillary lymph node dissection. Her lymph nodes were free of cancer, and she has not had any chemotherapy. Besides the swelling, she has generally been well and offers no other complaints.

Vital signs are temperature 37.2° C (98.9° F), blood pressure 110/70 mm Hg, pulse 95/min, and respirations 14/min. Results of examination of head, eyes, ears, nose, and throat are normal, except for periorbital edema. Her chest is clear to auscultation, and her abdomen is soft, nontender, and without hepatosplenomegaly. Her heart has no murmurs or gallops. Her lower extremities have edema up to the hips, and they are nontender and nonerythematous.

Differential Diagnosis

1. Nephrotic syndrome
2. Cirrhosis
3. Heart failure
4. Myxedema

5. Other causes of hypoalbuminemia (malabsorption)

Initial Management

Setting: outpatient

Diagnostic/Therapeutic Plan

- Albumin
- BUN, creatinine
- Urinalysis
- 24-hour urine protein; or protein:creatinine ratio on random sample
- Serum LDL and cholesterol
- Liver function tests

Test Results

- Albumin: 2.1 g/dL (normal 3.5–5.5 g/dL)
- BUN, creatinine: normal
- Urinalysis: 4+ protein; oval fat bodies seen; few RBC; no casts
- 24-hour urine protein: 5.5 g/24 hours; protein:creatinine ratio on random sample: 5
- Serum LDL and cholesterol: elevated
- Liver function tests: normal

Assessment

Although the patient has breast cancer, the central problem is generalized edema, or anasarca. Edema forms for 2 basic reasons: Either plasma protein level is too low to provide enough oncotic pressure to hold fluid in the vessels; or the heart is not pumping well enough, and the hydrostatic forces are increased enough to push the fluid out.

CLINICAL PEARL

Protein:creatinine ratio on random sample is as sensitive and specific as the 24-hour urine protein.

This patient gives no cardiac history; there are no murmurs or gallops, and the lungs are clear (arguing against cardiac failure). The low serum albumin with hyperlipidemia and evidence of protein and lipids in the urine are suggestive of nephrotic syndrome. Neither malnutrition, myxedema, nor malabsorption gives proteinuria. Hyperlipidemia is explored when there is already possible evidence for the nephrotic syndrome.

Further Management Plan	**Results**
Renal biopsy	Light microscopy: thickened glomerular basement membrane with spikes for basement membrane material
Electron microscopy	Subepithelial deposits seen

CCS NOTE

One of the idiosyncrasies of the CCS is that it allows a patient to simultaneously undergo multiple tests on different parts of the body.

Treatment Plan

1. Monitoring of BUN, creatinine, proteinuria, and ACE inhibitors
2. Trial of steroids
3. Cytotoxics (e.g., cyclophosphamide) and steroids

Discussion

Nephrotic syndrome is a constellation of edema, proteinuria, hypoalbuminemia, hyperlipidemia, and lipiduria. By definition, nephrotic-range proteinuria is >3.5 grams per 24 hour period.

CCS NOTE

You do not have to change location to order complex tests. The patient stays in the same location, and the test is done from there.

About one-third of adults have nephrotic syndrome on the basis of systemic disease, most commonly diabetes, systemic lupus erythematosus, HIV, or amyloidosis. In this patient, the lack of evidence of any systemic disease besides breast cancer suggests a primary renal cause, such as minimal change disease, mesangial, membranous, focal segmental, or membranoproliferative glomerulonephritis. It is impossible to tell the difference between these on clinical grounds alone. Diagnosis is entirely based on biopsy.

On initial presentation, there is nothing obvious to signal a diagnosis of membranous glomerulonephropathy. However, membranous glomerulonephropathy is a common cause of idiopathic nephrotic syndrome in adults, and this type has an association with malignancies such as breast, lung, and colon cancers. Besides systemic disease, such as lupus erythematosus, diabetes, amyloid, and HIV, virtually any type of glomerulonephritis can develop into nephrotic syndrome. A certain percentage of patients with postinfectious glomerulonephritis, Wegener,

Goodpasture, immunoglobulin A nephropathy, polyarteritis nodosa, etc., will eventually develop enough glomerular damage and proteinuria to be diagnosed with nephrotic syndrome.

Membranous nephropathy is more common in whites, and focal segmental glomerulosclerosis is more common in African Americans.

The prognosis of membranous glomerulonephritis is quite variable. One-third will resolve spontaneously; one-third have persistent nephrotic range proteinuria even as BUN and creatinine stay normal; and one-third develop slowly worsening renal function over time. Response to steroids is generally undramatic and disappointing, so this medication is withheld until there is evidence of significant deterioration. Minimal change disease is the most steroid-sensitive glomerular disease.

Current treatment strategies are as follows:

1. *Patients at low risk for progression.* ACE inhibitors or angiotensin receptor blockers (ARBs) to reduce proteinuria, or
2. *Patients at high risk for progression.* Immunosuppressives with or without steroids for those at high risk for progression. Steroids alone are not recommended.

Immunosuppressive therapy is indicated in patients with the highest likelihood of developing progressive renal failure. These include patients with severe symptoms, those with progressive disease, men age > 50 years with persistent nephrotic syndrome, and patients with thromboembolic complications. Hemodialysis, peritoneal dialysis, and kidney transplantation are indicated in advanced kidney disease from nephrotic syndrome.

CLINICAL PEARL

- The most common cause of nephrotic syndrome in adults is FSGS.

- The most common cause of nephrotic range proteinuria (without the ‘syndrome’) is diabetes.

Final Diagnosis

Nephrotic syndrome

PATIENT SAFETY NOTE

Renal vein thrombosis, DVT, and PE may complicate the disease in patients with nephrotic syndrome, especially those with membranous glomerulonephritis. Special attention should be paid to possible thromboembolism, if renal failure worsens unexpectedly or the patient develops flank/abdominal pain.

Case 8

Chief Complaint

Hematuria

History and Physical Examination

A 32-year-old man comes for evaluation of painless gross hematuria 2 days after he developed an upper respiratory tract infection. He had a similar episode 3 years ago, but the hematuria resolved after a course of antibiotics. He otherwise feels very well and has no complaints of diarrhea, arthritis, or weight loss. He has not had recent abdominal or pelvic trauma. He has had no previous episodes of pharyngitis. The patient does not drink alcohol, smoke tobacco, or use illicit drugs. His family history is only significant for hypertension and hyperlipidemia. He works as an architect and has had no occupational exposures. He eats a healthy diet but exercises rarely; he has not exercised for the past few weeks.

Vital signs are BP 155/92 mm Hg, pulse 82/min, and respirations 12/min. The patient is afebrile. The head and neck exam are unremarkable except nasal erythema. There are no tonsillar exudates. He has no lymphadenopathy. The heart and lung exam are unremarkable. The abdominal exam is normal with no hepatosplenomegaly. The extremities are normal and without edema. There is no evidence of penile trauma.

Differential Diagnosis

1. Exercise-induced hematuria

2. Nephritic syndrome: postinfectious glomerulonephritis, rapidly progressive glomerulonephritis, IgA nephropathy
3. Bladder cancer
4. Renal cell cancer
5. Nephrolithiasis
6. UTI with certain bacteria (e.g., Staph)
7. AV malformations
8. Polycystic kidney disease

Initial Management

Setting: outpatient

Diagnostic/Therapeutic Plan

- Urinalysis
- Creatinine
- Serum albumin
- Urine protein:creatinine (a spot specimen which is as specific as a 24-hr protein collection)
- Serologies:
  - C3 and C4
  - ANA
  - ANCA
  - anti-GBM antibodies

- HIV
- ESR
- Cholesterol
- Renal U/S and/or CT scan
- Cystoscopy

Test Results

- Urinalysis: +3 protein and >10 RBCs per high power field, no casts
- Creatinine: 1.2 mg/dL
- Serum albumin: 3.6 mg/dL
- Urine protein:creatinine 1.8 g/dL creatinine
  - CS and C4: normal
  - ANA: negative
  - ANCA: negative
  - anti-GBM: negative

- HIV: negative
- ESR: normal
- Cholesterol: normal
- Renal U/S and/or CT scan: normal size kidneys with no evidence of mass or stone
- Cytoscopy: negative for bladder lesions

Assessment

First confirm hematuria with dipstick or urinalysis. Next, some experts recommend renal U/S (or CT scan) and cystoscopy to exclude focal process such as bladder and renal cancer. If both of those are negative, then check creatinine, serum albumin, urine protein, and serologies (ANA, ANCA, C3 and C4, ESR, etc.) to exclude or diagnose glomerular disease.

Another approach to hematuria undertakes a twofold urinalysis, simultaneously confirming hematuria and inspecting for protein in the urine. Positive proteinuria indicates the presence of intrinsic renal disease, and it would make sense to check serologies, albumin, etc., before doing a urologic workup with an U/S, cystoscopy, etc. If there is hematuria *without proteinuria*, then proceed to a urologic evaluation.

Several conditions can cause hematuria, most of them not serious.

- Exercise may cause hematuria that goes away in 24 hours, but the negative history in this patient makes this unlikely.
- Nephrolithiasis is a common cause of hematuria but is accompanied by flank pain, absent here.
- UTI (especially Staph) may cause hematuria, but it is accompanied by bladder or flank pain as well as urgency, fever, and pyuria.

When hematuria is the result of a tumor, such as bladder or renal cancer, it is usually painless and gross (unless the tumor causes obstruction). This is why painless hematuria, especially absent evidence of proteinuria, requires urologic evaluation with renal imaging (U/S or CT scan) and cystoscopy (needs referral to urologist).

Glomerular diseases cause hematuria and are associated with proteinuria as well as serologic abnormalities. IgA nephropathy, postinfectious glomerulonephritis and rapidly progressive glomerulonephritis are some of the more common diseases in this group, but hematuria can also be part of systemic diseases like Goodpasture syndrome, Wegener granulomatosis, or SLE. Confirm glomerular diseases via renal biopsy.

Often, despite extensive workup, no specific cause can be found for hematuria. The following findings are consistent with IgA nephropathy.

Further Diagnostic Testing	**Results**
Renal biopsy	
Light microscopy	• A few glomeruli show complete sclerosis; other glomeruli are mildly enlarged and display mesangial hypercellularity • Tubules and interstitium show regenerative changes including nuclear enlargement • Arterial vessels show medial sclerosis and intimal fibrosis • There is evidence of hyalinosis in arterioles

Electron microscopy	Glomerular capillary lumina show widespread attenuation with ischemic-type wrinkling of basement membranes and segmental duplication of basement membranes with cellular interposition and subendothelial immune-type electron dense deposits
Immunofluorescence	Diffuse mesangial and segmental glomerular capillary wall staining for IgA (3^{+})

Treatment Plan

- Use ACE-Is or ARBs to optimize BP control and reduce proteinuria; both agents reduce proteinuria and are renoprotective.
- Refer to nephrologist for consideration of corticosteroid treatment with or without immunosuppressive agents (e.g., cyclophosphamide).

Discussion

IgA nephropathy is the most common glomerulonephritis throughout the world. It occurs when IgA deposits in the kidneys and causes inflammation and scarring of the glomeruli. Initially IgA nephropathy has no symptoms and can be silent for many years, even decades. IgA nephropathy is more common among Caucasians and Asians. About 25% of adults with IgA nephropathy develop end-stage kidney failure.

The classic presentation of IgA nephropathy is frank hematuria. Hematuria in IgA nephropathy appears during a cold or other infection (pharyngitis here). This presentation is referred to as synpharyngitic hematuria, i.e., the hematuria and infection coincide. (The alternative is postpharyngitic hematuria, typically seen after 2 weeks of poststreptococcal glomerulonephritis.) The gross hematuria resolves after a few days but microscopic hematuria persists. There may also be evidence of proteinuria but it is usually not in the nephritic range. Hypertension and elevated creatinine are also common on presentation, or they may occur later

in the disease. If creatinine is high at the time of diagnosis, the patient is more likely to develop kidney failure.

Renal biopsy confirms IgA deposits in the glomeruli. The biopsy can also assess how much kidney damage has already occurred. Remember, other diseases are associated with IgA deposition in the glomeruli (e.g., Henoch-Schonlein purpura), so IgA deposition in the glomeruli is not pathognomonic for IgA nephropathy.

IgA nephropathy cannot be cured. Hence, treatment focuses on slowing the disease and preventing complications. ACE inhibitors and ARBs protect kidney function by controlling BP and reducing proteinuria. Because of this effect, they are the drugs of choice in IgA nephropathy. Drugs such as corticosteroids (prednisone) and immunosuppressive agents (cyclophosphamide, mycophenolate mofetil) may also be helpful.

Patients with IgA nephropathy may develop high cholesterol. Lowering elevated cholesterol may help to slow kidney damage. In research studies, vitamin E and fish oil supplements containing omega 3 fatty acids also slowed kidney damage in some patients.

CLINICAL PEARL

Distinguish IgA nephropathy from postinfectious glomerulonephritis as follows:

IgA nephropathy:

- Painless hematuria
- Hematuria occurs during the infection
- Proteinuria and hypertension may accompany
- No systemic manifestations
- Normal complement levels

- Diagnose by biopsy

Postinfectious glomerulonephritis:

- Painless hematuria
- Hematuria occurs 2 weeks after the pharyngitis
- Proteinuria and hypertension may accompany
- Edema (periorbital)
- Decreased complement levels

Final Diagnosis

IgA nephropathy

Case 9

Chief Complaint

"I feel very tired and my back hurts."

History and Physical

A 56-year-old woman with a past medical history significant for hypertension comes to your office with complaints of feeling tired and having back pain for the last 3 months. The patient also noticed that her urine appears "frothy" lately, but otherwise denies symptoms of dysuria or signs of blood in her urine. Her medications include metoprolol and a daily multivitamin only.

Vitals signs are: temperature 37° C (98.6° F), blood pressure 127/78 mm Hg, and respirations 22/min. The patient is in no acute distress. Physical examination reveals pallor of the conjunctiva and mucosal membranes. The patient's lower back is tender to palpation, but she does not display any limitations in range of motion. There is no lower extremity edema noted, and no clubbing or cyanosis in the extremities.

Differential Diagnosis

1. Multiple myeloma
2. Anemia
3. Osteoporosis
4. Renal tubular acidosis

Initial Management

Setting: outpatient

Diagnostic/Therapeutic Plan

- CBC
- Serum electrolytes
- BUN, creatinine
- Urinalysis
- Plain x-ray film of the lumbosacral region

Test Results

- CBC: WBC count 7,400/mm^3, hemoglobin 9.6 mg/dL, platelets 221,000/mm^3
- Serum electrolytes: sodium 135 mEq/L, potassium 3.1 mEq/L, chloride 109 mEq/L, bicarbonate 16 mEq/L, glucose 98 mg/dL
- BUN: 28 mg/dL; creatinine: 2.1 mg/dL
- Urinalysis: 2+ protein, 1+ glucose, pH 5.6, protein:creatinine ratio 4.2
- Lumbosacral x-ray: lytic lesions present

Assessment

The patient presents with fatigue, back pain, and frothy urine. She was found to have anemia, elevated BUN and creatinine, hypokalemia, low bicarbonate, and significant proteinuria along with a normal anion gap, metabolic acidosis, and alkalotic urine pH. She also has glucosuria with normal blood glucose.

Although the clinical picture clearly points to a diagnosis of multiple myeloma, the underlying findings (low bicarbonate, alkalotic urine pH, and hypokalemia) point to a renal tubular

acidosis (likely, type 2) secondary to multiple myeloma in view of her clinical presentation and lab results.

Further Management Plan	Results
ABGs	pH 7.31, PCO2 30 mm Hg, bicarbonate 18
Serum protein electrophoresis (SPEP)	IgG monoclonal spike
Urine protein electrophoresis (UPEP)	Positive for Bence-Jones proteins

Treatment Plan

This patient should be worked up further for multiple myeloma. The next step would be peripheral smear, bone morrow biopsy, and skeletal survey for further evaluation of her bone pain.

RTA (type 2 in this case) is usually treated with bicarbonate and thiazide diuretics because thiazide diuretics will cause volume depletion, thus enhancing bicarbonate reabsorption.

Discussion

Renal tubular acidosis type 2 (proximal RTA) is caused by an inability to reabsorb bicarbonate at the level of the proximal tubules. The body excretes bicarbonate in the urine until the supply is so depleted that the distal tubule can absorb the rest.

Initially the urine pH is basic, and then it becomes acidic (pH <5.4). Patients with type 2 RTA usually present with hypokalemia and serum bicarbonate 18–20. The major cause of proximal RTA in adults is proximal tubular damage due to increased excretion of light chain immunoglobulins; this is seen in patients with multiple myeloma. This final defect impairs all sodium-coupled transport processes and can produce Fanconi syndrome, as in this case. Such

patients can present with hypophosphatemia, renal glucosuria with normal glucose level, and hypouricemia.

Renal tubular acidosis type 1 (distal RTA) is caused by the body's inability to excrete acid or hydrogen ions at the distal tubule. The results are alkaline urine and inability to lower the urine pH (kidney stones will develop in alkaline urine), hypokalemia, and hyperchloremic metabolic acidosis. The failure of the H+/K+-ATPase leads to urinary potassium loss, which explains the hypokalemic hyperchloremic metabolic acidosis.

Renal tubular acidosis type 4 is a normal anion gap metabolic acidosis with hyperkalemia, resulting from a hypoaldosterone-like state that highlights the major role of aldosterone in urinary potassium excretion.

Normal anion gap metabolic acidosis:

RTA and diarrhea (loss of bicarbonate) are the most common causes of RTAs. Other causes include ileostomy fluid loss and carbonic anhydrase inhibitors (acetazolamide). The challenge is to differentiate between diarrhea and RTAs. Urine pH alone is not enough to distinguish between them: urine pH in GI loss is low, but it is also low in proximal RTA.

In the case of diarrhea, the kidney still has the ability to excrete acid. In distal RTA the problem is inability to excrete acid. In proximal RTA, the problem is inability to reabsorb bicarbonate.

To differentiate between diarrhea and RTA, calculate the urinary anion gap.

$$\text{UAG} = \textbf{urine sodium} + \textbf{urinary potassium} - \textbf{urinary chloride}$$

UAG is positive in RTA, suggesting the inability to excrete acid in the urine. If UAG is negative, ability to excrete acid is intact, suggesting diarrhea as a cause of the acidosis.

Different Types of RTA

Type	Findings	Treatment
Type 1: Distal RTA	Normal anion gap metabolic acidosis, **hypokalemia**, urine pH >5.5, low serum bicarbonate, positive urine anion gap, nephrolithiasis, associated with autoimmune disorders (SLE, Sjögren)	Bicarbonate
Type 2: Proximal RTA	Normal anion gap metabolic acidosis, with positive urine anion gap, **hypokalemia**, urine pH <5.5, low bicarbonate with a higher range than in type 1 (16–18), Fanconi syndrome with loss of glucose, amino acids, phosphate, uric acid, and tubular proteinuria	High dose of bicarbonate, thiazide diuretics
Type 4: Hyperkalemic RTA	Normal anion gap metabolic acidosis, **hyperkalemia**, positive UAG and urine pH <5.5. Seen in DM, UTI.	Fludrocortisone

CLINICAL PEARL

In cases with a normal anion gap metabolic acidosis, UAG can help distinguish the cause for the acidosis.

- RTA has positive UAG
- Diarrhea has negative UAG
- **RTA + ↑ potassium = type 4 RTA** (most common type)

Case 10

Chief Complaint

Altered mental status

History and Physical Examination

A 66-year-old man with history of alcohol abuse is brought to the emergency department because of confusion and unresponsiveness. Family members state that he was in his usual state of health the day before. On physical examination the patient is confused.

Vital signs are temperature 37° C (98.6° F), blood pressure 110/68 mm Hg, heart rate 117/min, respirations 26/min, and O_2 saturation at 98% on room air. Physical examination of the heart reveals tachycardic, normal S1/S2, no S3, no murmurs or rubs. Chest examination is clear bilaterally, with no wheezing or rales. Neurologic exam is nonfocal.

Differential Diagnosis

1. Remember the differential diagnosis of altered mental status (confusion) in a patient with nonfocal neurologic exam: (mnemonic "DIM")
   - **D**rugs (drugs of abuse as well as side effects of prescription drugs especially in geriatric patients)
   - **I**nfections
   - **M**etabolic (hypernatremia, hyponatremia, hyperglycemia, hypoglycemia, renal failure, etc.)

2. In this patient, specifically consider ethanol toxicity; methanol toxicity; ethylene glycol toxicity; other drug ingestion; infectious process (aspiration pneumonia, lung abscess)

CLINICAL PEARL

In a patient with alcohol abuse, remember to consider "other" toxic alcohols that are of medical and toxicological importance as they cause various syndromes; the principal ones are ethylene glycol and methanol.

Initial Management

Setting: emergency department

Diagnostic/Therapeutic Plan

- Initial antidote
- ABG
- CBC
- Basic metabolic panel
- Chest x-ray
- Electrocardiogram
- Urinalysis
- Blood alcohol
- Plasma osmolarity

Test Results

- Initial antidote: dextrose, thiamine, naloxone

- ABG: pH 7.3, PCO_2 20 mm Hg, PO_2 99 mm Hg
- CBC: normal
- Glucose 105 mg/dL, sodium 142 mEq/L (normal 135–145 mEq/L), potassium 3.6 mEq/L (normal 3.5–5.2 mEq/L), chloride 105 mEq/L (normal 99–106 mEq/L), bicarbonate 7 mEq/L (normal 18–22 mEq/L), BUN 10 mg/dL, creatinine 2.2 mg/dL
- Chest x-ray: normal
- Electrocardiogram: tachycardia
- Urinalysis: >50 RBCs per high-power field, trace bacteria, unidentifiable crystals; urine toxicology screen: negative
- Blood alcohol: <10 mg/dL
- Plasma osmolarity: 316 mOsm/kg H_2O

Assessment

This patient presents with an anion gap metabolic acidosis—note the bicarbonate of 7. The next step is to **calculate the anion gap** as follows:

$$\text{Anion gap} = \textbf{serum sodium} - \textbf{(serum chloride} + \textbf{serum bicarbonates)}$$

$$142 - (105 + 7) = 30$$

The patient has a high anion gap metabolic acidosis (anion gap = 30). The next step is to look at the expected respiratory compensation using Winter's formula:

$$\text{Expected } PCO_2 = \textbf{1.5} \times \textbf{[bicarbonate]} + \textbf{8} \pm \textbf{2 mm Hg}$$

This patient's predicted PCO_2 is 18 ±2 mm Hg, while the measured PCO_2 is 20 mm Hg. Therefore, only the high anion gap acidosis accounts for the acid base abnormality.

CCS NOTE

You may not be able to determine a specific diagnosis from the history and physical. Initial management of any altered mental status includes administration of dextrose, thiamine, naloxone. Order routine admitting labs (CBC, chemistries, urinalysis) and chest x-ray simultaneously.

Further Management Plan

When considering alcohol toxicity, serum osmolar gap must be calculated. The serum osmolar gap is the difference between measured and calculated plasma osmolarity. The ***calculated*** *plasma osmolarity* is as follows:

$$2 \times [\text{serum sodium}] + [\text{blood urea nitrogen}] \div 2.8 + [\text{plasma glucose}] \div 18$$

Normal osmolar gap is <10 mOsm/kg H_2O. If the gap is >10, consider alcohol poisoning as the source of the unmeasured osmoles. Ethanol is the most common cause of alcohol poisoning, but in this case ethanol levels were low. The osmolar gap is roughly 23.

CLINICAL PEARL

Activated charcoal and nasogastric lavage have no role in toxic alcohol poisoning. Typically the alcohols will be absorbed too quickly for either of these modalities to have any efficacy.

Treatment and Management Plan

Many patients with ethylene glycol ingestion are extremely obtunded and are at high risk of aspiration; endotracheal intubation may need to be considered. Immediately obtain intravenous access and laboratory specimens.

- Obtain ethylene glycol level
- Administer aggressive IV fluids to enhance renal clearance and to limit deposition of oxalates in renal tubules
- Always place symptomatic patients in monitored setting (ICU or step-down units)
- ECG may be useful for detecting arrhythmias resulting from hypocalcemia
- The low serum calcium may also induce a prolonged QT interval
- Foley catheterization is usually indicated for patients with altered mental status to monitor urinary output and allow serial examination of urine for crystals or fluorescence

If the serum osmolal gap is elevated, begin **antidotal** therapy empirically while awaiting confirmation. This is performed with either fomepizole or ethyl alcohol. The latter is usually administered intravenously but may be administered orally (in remote settings where emergency hospital care is not immediately available). Contemporary treatment of this poisoning is most commonly done with fomepizole alone and not alcohol.

Fomepizole (Antizol) is a convenient therapy for treatment of ethylene glycol or methanol intoxication. Many emergency departments have adopted routine use of this agent for cases of suspected toxic alcohol poisoning. The advantages of fomepizole are that it does not depress the patient's mental status or airway, and it needs to be administered only every 12 hrs. Its main drawback is the cost, which can total thousands of dollars. Fomepizole is equally efficacious for the treatment of methanol intoxication and causes no alteration in mental status, hypoglycemia, or respiratory depression. Less commonly oral or parenteral ethanol can be used as a temporizing measure while awaiting test results.

Hemodialysis is used to treat severe metabolic acidosis or to prevent renal insufficiency. Early in the intoxication, the toxin is present as the parent compound, ethylene glycol. As time passes, toxic metabolites accumulate and the patient develops metabolic acidosis. Eventually, oxalate is deposited in the kidney and elsewhere, potentially resulting in renal insufficiency. Once any of these manifestations occurs, antidotal therapy alone (used to block alcohol dehydrogenase with ethanol or fomepizole) is insufficient to treat the poisoning. Consequently, alcohol dehydrogenase–blocking therapy must be accompanied by dialysis in these cases to remove the metabolites. Traditional dialysis indications include acute renal failure and ethylene glycol level >50.

Further Results	**Treatment**
Serum ethylene glycol	Level of 112 mg/dL (15.6 mmol/L) reported from outside laboratory approximately 7 hours after the blood sample taken
Nephrology consult initiated	Acute hemodialysis

Discussion

Alcohol poisoning causes high anion gap metabolic acidosis, typically with anion gap above 25. Ethylene glycol is an automotive radiator fluid added to prevent overheating or freezing, depending on the season. Ethylene glycol is extremely toxic and ingestion can be fatal if untreated. Fluorescein dye is often added to radiator fluid to help mechanics identify the source of a radiator leak. The fluorescein in the fluid fluoresces when viewed under ultraviolet light.

Basic Science Correlate

The toxic alcohols (ethanol, ethylene glycol, and methanol) are parent compounds that exert most of their toxicity by conversion to metabolites. Although the parent compound, ethylene glycol, may cause some alteration of mental status, it is relatively nontoxic. It is the metabolites that cause the distinctive toxicity associated with this compound. Ethanol is metabolized by the enzyme alcohol dehydrogenase (ADH) pathway, which is located in the liver and gastric mucosa, and by the cytochrome P-450 mixed function oxidase (MFO) system in the liver.

As with ethyl alcohol and methanol, ethylene glycol is metabolized by the enzyme alcohol dehydrogenase. In this step it forms glycoaldehyde.

- Through interaction with aldehyde dehydrogenase, ethylene glycol is metabolized to glycolic acid (GA).
- A profound acidosis often ensues with this intoxication, attributable to the glycolic acid in circulation.
- This glycolate is then transformed into glyoxylic acid. At this point, the molecule may be transformed into the highly toxic oxalate.
- With the formation of oxalate crystals in the urine, calcium oxalate crystals form and accumulate in blood and other tissues.
- The precipitation of calcium oxalate in the renal cortex results in decreased glomerular filtration and renal insufficiency.
- Calcium is consumed in circulation, and hypocalcemia may occur.
- The rate-limiting step of ethylene glycol metabolism is the alcohol dehydrogenase–catalyzed step.

Common ethyl alcohol (ethanol) binds much more easily to alcohol dehydrogenase than either ethylene glycol or methanol. Because ethanol is the preferred substrate for alcohol dehydrogenase, the presence of ethanol may essentially block metabolism of ethylene glycol. In addition, this enzyme is blocked by the administration of fomepizole (4-methylpyrazole [4-MP]).

When the diagnosis of alcohol poisoning is suspected, obtain the following:

- Serum ethylene glycol level
- Osmolar gap and anion gap
- Baseline creatinine and BUN level
- Urine examination for evidence of fluorescence
  - Because fluorescein is excreted in the urine faster than ethylene glycol, however, fluorescence can be eliminated before the patient even arrives in the emergency department. Hence, the presence of fluorescence of urine under a Wood's lamp is not a sensitive test, but it is highly specific.

- Both a serum calcium level and electrocardiogram, since hypocalcemia may occur as calcium combines with oxalate in the form of calcium oxalate crystals

Ethylene glycol produces CNS depression similar to that of ethanol. Symptoms of ethylene glycol toxicity include confusion, ataxia, hallucinations, slurred speech, and coma. Symptoms are most severe 6–12 hrs after ingestion, when the acidic metabolites of ethylene glycol are at their maximal concentration. If the patient presents early or has consumed small amounts of ethylene glycol, presentation may be similar to ethanol intoxication. However, an ethanol odor will be absent, and serum or respiratory ethanol levels will be too low to account for the degree of CNS depression. **Absence of a strong odor of alcohol** in a patient who appears intoxicated should raise the suspicion of ethylene glycol ingestion.

PATIENT SAFETY NOTE

Begin aspiration precautions in every comatose patient.

Following a period of CNS depression, metabolic acidosis and cardiopulmonary symptoms become prominent. Renal involvement becomes apparent within 24 to 72 hours after ingestion. (Ethylene glycol needs time to be metabolized into oxalate before urinary crystals can form.) Calcium oxalate formation depletes serum calcium levels and deposits in intestinal mucosa, liver, brain, heart, lung, and kidney. Calcium oxalate crystals are usually present in the urine, but not always.

Summary of the different types of alcohol poisoning:

Isopropyl Alcohol	**Methanol**	**Ethylene Glycol**	**Ethanol**
Somnolence or coma with normal acid-base status	Pancreatitis and retinal toxicity Severe anion gap metabolic acidosis with acute visual changes or severe abdominal pain	Acute kidney failure and calcium oxalate nephrolithiasis Severe anion gap metabolic acidosis and acute kidney failure	Anion gap metabolic acidosis with osmolar gap >10 mOsm/kg H_2O
Treat with IV fluid and gastric lavage, if severe, hemodialysis	Treat with fomepizole and hemodialysis	Treat with fomepizole and hemodialysis	Treat with IV normal saline and dextrose

Final Diagnosis

Ethylene glycol toxicity