ANSWERS TO NEPHROLOGY: CHALLENGING CASES

UPDATE IN INTERNAL MEDICINE – 2016

Robert S. Brown, M.D.

1. A. The sodium-glucose transporter-2 (SGLT-2) inhibitors, empagliflozin (Jardiance®), dapagliflozin (Farxiga®), and canagliflozin (Invokana®) inhibit proximal tubular glucose reabsorption resulting in renal glucosuria. These drugs can cause weight loss, natriuresis with volume depletion, hypotension, bacterial or fungal UTI, and ketoacidosis even in Type 2 diabetics. Ketoacidosis is more likely with fasting (or alcohol intake) as occurred in this patient. The increased anion gap metabolic acidosis would not be present in RTA, hyperventilation or UTI (without a septic picture).

2. C. While mild magnesium depletion may increase PTH levels, more severe hypomagnesemia may cause hypocalcemia resistant to calcium replacement due to decreased secretion of PTH and also resistance to the peripheral effect of PTH. Renal potassium wasting with hypokalemia also occurs in hypomagnesemia, as does paraesthesias, muscle cramps, tetany and a wide QRS on ECG, all important signs to consider. One of the more common causes of hypomagnesemia has become the concomitant use of proton pump inhibitors, e.g., omeprazole, and diuretics as in this case. Zika virus can cause Guillain Barre syndrome and anxiety about microcephaly in pregnancy but not hypokalemia or hypocalcemia.

3. C. This young man has proteinuria and hematuria with acanthocytic RBCs which suggest glomerular hematuria similar to the finding of RBC casts in the urinary sediment (rather than the non-glomerular hematuria as might occur with nephrolithiasis). Therefore, we would suspect a glomerulonephritis that has occurred shortly after the onset of an upper respiratory infection. The timing of the hematuria is not consistent with post-streptococcal glomerulonephritis which usually occurs 10-14 days after a Group A beta-hemolytic streptococcal sore throat (but may occur up to 3 weeks later and even longer after a streptococcal skin infection). This patient has no evidence for granulomatosis with polyangiitis (formerly Wegener's granulomatosis) which would be expected to cause a rise in serum creatinine from a necrotizing glomerulonephritis, and lupus nephritis is less likely than IgA nephropathy. In fact, the history is classic for IgA nephropathy. Some patients will have a history of recurrent episodes of gross hematuria or Coca-Cola colored urine (from heme pigments) concomitant with, or 1-3 days after, an upper respiratory infection. These episodes are self-limited, but a percentage of patients with IgA nephropathy will progress to end stage renal disease. This subgroup may respond to aggressive immune suppressive treatment.

4. B. The objective of this question is to know how to evaluate young persons with proteinuria by dipstick. It would be inappropriate to wait a year to follow up this patient since proteinuria may represent a serious underlying renal disorder. One plus (1+) proteinuria, since the dipstick is relatively insensitive to low grade albuminuria, suggests that this is already more than microalbuminuria. Without hematuria or renal insufficiency, complement levels and ASO are not indicated and a urine protein electrophoresis is unnecessary now since myeloma would be
highly unlikely at his age. A renal ultrasound is an anatomic test which is unlikely to yield useful information in a patient with isolated proteinuria, except for reflux nephropathy in which case the BUN and creatinine would usually be elevated. “Functional” proteinuria may be seen with some acute illnesses, fever, or congestive heart failure, but those conditions aren’t apparent here now (though functional proteinuria may have been the case with the 3+ urine protein when febrile 3 weeks before). The important question is to determine whether the proteinuria is benign or whether further investigation is needed. A cause of benign proteinuria in young patients (under the age of 30) may be seen with so-called orthostatic or postural proteinuria. In these patients a 24-hour urine should be collected in split samples – supine and ambulatory. If the supine urinary protein excretion is normal, i.e., less than 5 mg of protein excreted per hour, then no further work-up is necessary. Orthostatic proteinuria progresses only uncommonly and usually resolves with age. If this really was a case of transient or intermittent proteinuria (also benign), presumably both the upright and supine collections would now be normal.

5. D. This patient has severe acute renal failure with a relatively high creatinine for the BUN elevation, together with hyperkalemia, hyperphosphatemia and very high uric acid level, all findings that are consistent with cell lysis. The potassium would likely be higher were it not for vomiting and prior HCTZ use. Hypertensive nephrosclerosis without malignant hypertension (for which he has no papilledema) would not cause this acute picture, and there are few urinary WBC's to point to an interstitial nephritis or RBC's to suggest a vasculitis with rapidly progressive glomerulonephritis. Focal glomerular sclerosis, whether associated with HIV or other etiologies, would be expected to have heavy proteinuria. Urate nephropathy which can be seen with uric acids in this range would usually have many uric acid crystals in the urinary sediment and be seen as part of the “tumor lysis” syndrome not present here. Acute tubular necrosis due to myoglobinuria would best explain the 4+ heme in the urine with only 3-5 RBC/hpf; muscle necrosis with release of intracellular phosphate, uric acid, and creatine (which gets converted to creatinine in the plasma, increasing the creatinine to BUN ratio) would account for the other metabolic findings. Likely the rhabdomyolysis, which should be documented by a very high CPK level, was precipitated by cocaine and/or heroin in the setting of alcohol use, and possibly, prior hypokalemia due to hydrochlorothiazide.

6. E. This patient fulfills the clinical criteria for thrombotic thrombocytopenic purpura (TTP). She has fever, mental status changes, a microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure. This syndrome may follow a diarrheal illness and is part of the clinical/pathological spectrum of TTP/HUS (hemolytic uremic syndrome). Though just supportive care is often advised for E. coli associated HUS, there is significant morbidity and mortality in adults (although support may be all that is necessary in many children). The best initial treatment for adults presenting with TTP/HUS is plasma exchange therapy using fresh frozen plasma (FFP) as replacement. This is often done in conjunction with steroid treatment. If plasma exchange is unavailable, then infusion with FFP may have efficacy. It should be noted that treatment with antibiotics of Shiga-toxin producing E. coli (STEC) O157:H7 diarrhea with antibiotics in children appears to be associated with an increased incidence of HUS/TTP when compared with those that did not receive antibiotic therapy. Also, a study in adults showed that antibiotic treatment had neither benefit nor detriment. In addition to E. coli O157:H7, two other STEC organisms, O104:H4 and 0111:H8, have been found to cause outbreaks of HUS/TTP in Germany and in Oklahoma, respectively. It is important to test for Shiga-toxin producing E. coli to diagnose STEC-HUS and for ADAMTS-13 where a low level (<10% of normal) suggests “typical” TTP/HUS and a level of >10% suggests “atypical” TTP/HUS. “Typical” TTP/HUS is
often idiopathic with an auto-antibody to ADAMTS-13, but may be associated with genetically low ADAMTS-13 levels. It is usually treated with plasma exchange (TPE) + FFP, and usually, steroids or rituximab. “Atypical” TTP/HUS may be complement mediated, thus now eculizumab is being utilized. While TPE + FFP is commonly used for STEC-HUS, its benefit is being questioned. Either way, initiating treatment with TPE + FFP is best in adults to see the clinical response (usually assessed by correction of the thrombocytopenia) while tests are done, particularly since diarrhea, even when bloody, isn’t an absolutely diagnostic symptom for STEC-HUS.

7. A. A renal biopsy is most likely to document a crescentic glomerulonephritis as part of a pulmonary-renal syndrome, but may at times show an acute proliferative glomerulonephritis with congestive heart failure explaining the pulmonary findings. Bronchoscopy would not be helpful and lung biopsy would be useful only in Goodpasture’s syndrome. The renal arteriogram is useful in only a small minority of cases of polyarteritis nodosa. The anti-GBM antibodies and ANCA tests would be very important, but actually are somewhat less likely than the renal biopsy to offer definitive findings to guide therapy. This is due to overlap syndromes with both positive anti-GBM antibodies and ANCA, or to cases of crescentic glomerulonephritis or polyarteritis nodosa with both antibodies negative, or to occasional “false positive” ANCA tests that may occur with inflammatory conditions, including pulmonary infections. The biopsy also documents the degree of fibrosis, helping with the decision about reversibility and the length and intensity of immunosuppressive treatment needed, especially with complications associated with immune suppression.

8. C. This patient’s presentation is likely that of a pulmonary-renal syndrome. Although Goodpasture’s syndrome is a pulmonary-renal syndrome, it is not associated with a vasculitic rash, as is suggested by the description of lower extremity palpable purpura in this patient. Cryoglobulinemia could account for this presentation but it is typically associated with hypocomplementemia, as is lupus nephritis, and this patient has normal complement levels. Henoch-Schönlein purpura is associated with a rash and renal failure but does not explain the pulmonary findings. The most likely diagnosis in this patient is a systemic vasculitis associated with an anti-neutrophil cytoplasmic antibody (ANCA). The vasculitic skin rash, together with renal findings consistent with a rapidly progressive glomerulonephritis and the pulmonary infiltrates, would suggest a systemic vasculitis. This can be seen in association with either the P-ANCA (perinuclear pattern), usually with anti-myeloperoxidase antibodies as is seen in most cases of microscopic polyarteritis, drug-induced vasculitis or the Churg-Strauss syndrome, or the C-ANCA (cytoplasmic pattern), usually with anti-proteinase 3 antibodies, seen commonly in granulomatosis with polyangiitis (formerly Wegener’s granulomatosis). With polyarteritis nodosa, ANCA may often be negative (though PAN is much less common, involves the lungs less frequently, and often has fewer RBCs and RBC casts in the urinalysis, more in keeping with vascular disease and ischemic necrosis than a glomerulonephritis).

9. C. This question addresses the issue of treating an infection in patients with polycystic kidneys. Antibiotic penetration into the cyst fluid is desirable, and sulfathrimethoprim, ciprofloxacin, chloramphenicol and clindamycin have been shown to have better penetration into cyst fluid than other antibiotics, such as gentamicin. In this case, intravenous antibiotics are not necessary at this time unless there was bacteremia. So I would choose to treat either with ciprofloxacin or sulfathrimethoprim alone, recognizing that there is an increasing
percentage of bacterial resistance to sulfa-trimethoprim (about 25%, and parenthetically, this increase in resistance is occurring for ciprofloxacin as well). Therefore, modification of the antibiotic choice may be necessary once antibiotic sensitivities from the patient’s urine culture become known. If a cyst infection were to be suspected (such as with relapse of fever and back pain after treatment), CT scan, MRI and ultrasound have not been particularly effective at diagnosis of an infected cyst. In such cases, a PET scan appears to be the imaging modality of choice to diagnose cyst infection in adults with PKD. But initially, no imaging or invasive procedures are indicated at all, so choices D or E would not be advisable.

10. D. This recurrent calcium oxalate stone-former has hypercalciuria (over 300 mg/ day in a male, 250 mg/day in a female, or over 4mg/Kg body weight/day in either sex), hyperuricosuria (over 750-800 mg/day), hypocitraturia (under 320 mg/day), mild hyperoxaluria (over 40-45mg/day), and a high salt intake (which will enhance urinary calcium excretion). Hydrochlorothiazide and a low sodium diet both decrease urinary calcium, thereby decreasing supersaturation of the urine. Potassium citrate will increase urinary citrate to help diminish crystallization of calcium oxalate and also alkalinize the urine to avoid uric acid crystallization as a nidus for calcium oxalate stones. Allopurinol has been shown to be an effective therapy for hyperuricosuric calcium oxalate stone formers even though recent data casts doubt upon the mechanism of calcium oxalate stone formation with hyperuricosuria. A low calcium diet does not appear to have a role in reducing the incidence of calcium oxalate stones. Since bone density is generally reduced in patients with hypercalciuria, a low calcium diet may further promote osteopenia, in addition to increasing urinary oxalate by decreased gastrointestinal binding of oxalate by dietary calcium. Medicinal, rather than dietary, calcium (such as calcium carbonate tablets) should be avoided, however.

11. E. The larger the stone is, the less likely it is to pass spontaneously. For stones <2mm, about 90% or more will pass without an intervention, for those 2-4mm, about 80%, for those 4-6mm, 50-60%, for those 7-9mm, 48%, and for those >9mm, only 25%. So this 5mm stone is likely to pass spontaneously, particularly in the distal, rather than proximal, ureter. Both tamsulosin, an alpha blocker, and calcium channel blockers, such as nifedipine, have been shown to increase ureteral stone passage (by about 65%), but with distal ureteral stones <6mm in men, sexual intercourse 3-4 times per week compared with tamsulosin increased the percent of stones passed by two weeks (84% vs 48%, p=0.001) and shortened the mean expulsion time (10 ± 5.8 days vs 16.6 ± 8.5 days, p=0.0001). Perhaps nitric oxide ureteral muscle relaxation explains this effect.

12. C. ACE inhibitors, by decreasing angiotensin II effect on the adrenal zona glomerulosa to release aldosterone, and heparin, by a direct toxic effect on zona glomerulosa cells, can both cause decreased secretion of aldosterone and hyperkalemia. Trimethoprim (and also pentamidine) can cause hyperkalemia by a mechanism similar to amiloride, a blockade of principal cell sodium channels in the distal renal tubule which limits electronegativity in the renal tubular lumen, and thereby, resultant potassium and hydrogen secretion in exchange for sodium in the urine. Succinyl choline, a depolarizing muscle relaxant working by increasing acetyl choline receptors, causes muscle release of potassium, and for that reason, should not be used in hyperkalemic patients with renal insufficiency. Amphotericin B causes increased renal tubular cell membrane permeability with increased urinary potassium excretion and hypokalemia. It can also cause Type 1 renal tubular acidosis and renal failure.
13. C. All of these choices may be considered in poisoned patients. Methanol, ethylene glycol, and isopropyl alcohol all elevate the serum osmolal gap. However, isopropyl alcohol is metabolized to acetone, the alcohol and acetone are both neutral chemicals so it does not cause an acidosis or an increased anion gap as can the other four choices. Methanol has formic acid as a major metabolite and ethylene glycol, oxalic acid. Ethanol may cause ketoacidosis, of note, which can be seen on withdrawal without remaining ethanol present. Acetaminophen, even at therapeutic levels with chronic use, may cause a high anion gap acidosis from pyroglutamic acid (also called 5-oxoproline), an organic acid intermediate in the gamma-glutamyl cycle. Metformin overdose toxicity can cause lactic acid by interfering with oxidative metabolism. Of note, inhibition of alcohol dehydrogenase to slow isopropyl alcohol metabolism is not helpful since acetone is less toxic than the parent alcohol.

14. E. This patient has renal tubular acidosis (RTA) with a low serum bicarbonate and an acidic blood pH, but without proper urinary acidification. The alkaline urine pH of 7.0 suggests that bicarbonaturia is present due to a proximal tubular defect in bicarbonate reabsorption. This tubular defect is also manifested by hypophosphatemia due to phosphaturia and renal glucosuria with a normal blood glucose. So the RTA found in this patient appears to be proximal, or Type 2, RTA in the setting of the Fanconi syndrome, which might be expected to also include hypouricemia due to uricosuria and aminoaciduria (which were not measured in this case). Type 2 RTA usually does not have nephrocalcinosis or nephrolithiasis, as does Type 1 distal RTA. Clinical clues to the correct diagnosis in this patient are the finding of anemia, mild hypercalcemia, a low anion gap (only 5mEq/L), and the marked disparity of the relatively low dipstick protein of 1+ on urinalysis with the high urinary protein to creatinine ratio of 2.7 (suggesting excretion of 2.7 grams of total protein per 1.0 gram of creatinine). The dipstick detects mainly albumin whereas the laboratory chemical determination for a urine protein to creatinine ratio measures all proteins, including immunoglobulins and light chains. The disparity would suggest that a urinary Bence-Jones light chain protein associated with multiple myeloma is present. In this case, light chain nephropathy would be most likely. Light chain nephropathy is the most common cause of acquired Type 2 proximal renal tubular acidosis in older adults who have not received a tubular toxic drug. With either membranous or HIV nephropathy, the predominant urinary protein would be albumin. Sjogren’s syndrome nephropathy may present with Type I distal RTA and nephrogenic diabetes insipidus, with rare cases of concomitant membranous or membranoproliferative glomerulonephritis, but would not demonstrate the other findings seen in this patient.

Extra Credit Questions

15. E. With a normal blood pH of 7.43 and a reduced pCO2 of 26, there is clearly a respiratory alkalosis. For a pCO2 of 26 (↓ 14 mmHg from a normal pCO2 of 40), the serum HCO3 should be decreased by 3 (acute) or 8 (chronic) mEq/L or as low as (24 – 8) = 16. Therefore, this could be a simple chronic respiratory alkalosis with compensatory low serum bicarbonate level were it not for the increased anion gap of 22, documenting a mixed acid base disorder – thus, both high anion gap metabolic acidosis and respiratory alkalosis resulting in a normal pH.

16. E. In ill patients presenting with a mixed metabolic acidosis and respiratory alkalosis as noted in the question above, two important diagnostic considerations should be sepsis and
salicylate toxicity. In septic patients, endotoxin stimulates respiratory drive and septic shock will cause an increased anion gap metabolic acidosis. High levels of salicylate also stimulate hyperventilation with a respiratory alkalosis, and particularly in children or highly poisoned adults, salicylate interferes with the tricarboxylic acid cycle causing a concomitant increased anion gap metabolic acidosis. Hyperventilation causes a pure respiratory alkalosis and RTA a metabolic acidosis, both with a low serum bicarbonate, but both have normal, not elevated, anion gaps.

17. C. This patient has ARF following cardiac catheterization, an arteriographic procedure. The main differential diagnosis includes radiocontrast-induced ARF and atheroembolic renal failure. Radiocontrast nephropathy occurs more frequently following intraarterial exposure to volumes over 100 ml whether hyperosmolar, “low osmolar” (which is actually still hyperosmolar, though less so) or iso-osmolar radiocontrast. Radiocontrast nephropathy, which may be accompanied by polyuria for up to 24 hours, would, nevertheless, usually cause a significant creatinine rise by 48 hours. There is no pain associated with radiocontrast nephropathy. In this case, the patient has the classic skin findings of atheroembolic disease (bluish discoloration of the toes) and abdominal pain. He will probably have an elevated amylase to suggest pancreatitis as the cause of either abdominal or back pain, another common complication of atheroemboli. The unchanged pulses make dissection less likely and unilateral renal artery embolism would cause unilateral flank pain (and not explain the blue toes). Other findings which may be present in atheroembolic disease include eosinophilia and Hollenhorst plaques (retinal cholesterol emboli) on funduscopic exam. Although a renal biopsy will yield the diagnosis, a much less invasive procedure, but probably not necessary here, would be a skin biopsy of a lesion on the foot which would likely reveal cholesterol cleft deposits. Many such patients experience a slow, progressive deterioration in renal function, but recovery may also occur.