

Clinical Pearls in General Internal Medicine

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At the 2001 annual conference of the American College of Physicians, a new teaching format to aid physician learning, Clinical Pearls, was introduced. Clinical Pearls is designed with the 3 qualities of physician-learners in mind. First, we physicians enjoy learning from cases. Second, we like concise, practical points that we can use in our practice. Finally, we take pleasure in problem solving.

In the Clinical Pearls format, speakers present a number of short cases in their specialty to a general internal medicine audience. Each case is followed by a multiple-choice question answered live by attendees using an audience response system. The answer distribution is shown to attendees. The correct answer is then displayed and the speaker discusses teaching points, clarifying why one answer is most appropriate. Each case presentation ends with a Clinical Pearl, defined as a practical teaching point that is supported by the literature but generally not well known to most internists.

Clinical Pearls is currently one of the most popular sessions at the American College of Physicians meeting. As a service to its readers, *Mayo Clinic Proceedings* has invited a selected number of these Clinical Pearl presentations to be published in our Concise Reviews for Clinicians section. "Clinical Pearls in General Internal Medicine" is one of them.

CASE 1

A 69-year-old man with hyperlipidemia and hypertension has had 2 episodes of classic podagra per year for the past 3 years. In the past, he developed a rash and nausea after taking allopurinol. He has no history of nephrolithiasis and does not use alcohol. He has a mild peripheral neuropathy (idiopathic) and diarrhea-predominant irritable bowel syndrome. Through diet and exercise, he lost 13.6 kg (30 lbs) a couple of years ago, but his weight has since stabilized.

MEDICATIONS

Gemfibrozil, 600 mg twice daily
Atenolol, 50 mg once daily
Lisinopril, 10 mg once daily

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EXAMINATION FINDINGS

Body mass index, 26 kg/m²
Blood pressure, 130/70 mm Hg
Pulse, 60 beats/min and regular
A small tophus on the distal interphalangeal joint of his right index finger
Otherwise unremarkable

LABORATORY RESULTS

Complete blood cell count (CBC), normal
Aspartate aminotransferase (AST), normal
Alanine aminotransferase (ALT), normal
Creatinine, 1.0 mg/dL (to convert to μmol/L, multiply by 88.4)
Serum uric acid, 7.2 mg/dL (to convert to μmol/L, multiply by 59.485)
Total cholesterol, 198 mg/dL
Low-density lipoprotein cholesterol, 129 mg/dL
High-density lipoprotein cholesterol, 39 mg/dL
(To convert cholesterol values to mmol/L, multiply by 0.0259)
Triglycerides, 149 mg/dL (to convert to mmol/L, multiply by .0113)

QUESTION

Which *one* of the following would be *most effective* in reducing the patient's risk of recurrent gout at this point?

- Switch the gemfibrozil to fenofibrate
- Switch the gemfibrozil to niacin
- Add 0.6 mg/d of colchicine
- Switch lisinopril to irbesartan
- Switch lisinopril to candesartan

DISCUSSION

Hyperuricemia and gout often occur in the context of hypertension and hyperlipidemia. Not infrequently, patients may be intolerant of allopurinol, have hyperuricemia that is suboptimally controlled by it, or simply may not wish to add another medication to their regimen. Conveniently, a couple of the medications used for hyperlipidemia and hypertension also lower levels of serum uric acid (by enhancing uric acid excretion).

Losartan has been shown to decrease serum levels of uric acid by approximately 10% to 15%, even in patients who are already taking fenofibrate. The 100 mg/d dose does not seem to be more effective than the 50 mg/d dose.

This effect is not seen with other angiotensin II receptor blockers.¹ In patients with hypertension, overall benefits may be further multiplied by replacing a thiazide diuretic with losartan.

Fenofibrate has a more potent effect and decreases serum uric acid by 20% to 30%, even in patients with tophaceous gout who are already taking allopurinol.² This effect is not seen with gemfibrozil, and niacin is actually contraindicated in patients with gout.

Colchicine would not be a good long-term option in this patient because it could potentially worsen his neuropathy or his bowel symptoms (and would not address the underlying problem of hyperuricemia and urate deposition).

Because losartan and fenofibrate lower serum urate by means of uricosuria, these agents should be avoided in patients with a history of uric acid nephrolithiasis.

CLINICAL PEARL

Fenofibrate and losartan have uric acid–lowering effects and may be agents of choice in patients with primary indications for either drug who have coexisting hyperuricemia.

CASE 2

A 32-year-old woman, previously healthy, presents with 2 days of right flank pain radiating to the right groin. She denies any dysuria, urgency, frequency, or fever and has no history of nephrolithiasis. Her pain is fairly well controlled on a regimen of 220 mg of naproxen twice daily, and she is taking no other medications. Computed tomography by the kidney stone protocol shows a 5-mm calculus at the right ureterovesical junction.

LABORATORY RESULTS

Urinalysis, 4 to 10 red blood cells per high-power field
Urine Gram stain and culture, negative
Serum creatinine, 1.0 mg/dL

QUESTION

Beyond the usual advice to increase fluids and strain the urine, which *one* of the following would be the *most appropriate* next step?

- Urology consultation
- Verapamil
- Oxybutynin
- Tamsulosin
- Bethanechol

DISCUSSION

A 5-mm calculus in the distal ureter has about a 50% to 60% chance of spontaneous passage and, in the absence of infection, renal failure, or unmanageable pain, may be

managed conservatively for up to 4 weeks. However, the average time to passage in some studies is as long as 22 days, and thus it is reasonable to use “medical expulsive therapy” to expedite resolution. Both α -blockers and calcium channel blockers have been shown to inhibit the contraction of the smooth muscle responsible for ureteral spasms (while still allowing antegrade stone propagation). The agent that has been most studied in this setting is tamsulosin, generally in a dosage of 0.4 mg/d given for as long as 1 month.³ In a recent meta-analysis of 9 randomized trials of this agent vs placebo in patients referred to urology clinics for moderate-sized ureteral stones (5-7 mm in diameter), stones passed an average of 2 to 6 days earlier in the treatment group. In these trials, the mean time to stone expulsion was less than 14 days (including the upper bound of the 95% confidence interval). Nifedipine, the only calcium channel blocker that has been systematically evaluated, appears to be slightly less effective than tamsulosin.⁴

CLINICAL PEARL

Both tamsulosin and nifedipine have been shown to expedite the expulsion of moderate-sized distal ureteral calculi.

CASE 3

A 26-year-old woman presents with right upper quadrant abdominal pain of 18 months' duration that began after an episode of self-limited viral gastroenteritis. She describes it as a “sharp,” “burning” discomfort that is well localized and continuous. It may be slightly worse after eating and definitely seems to worsen after having a bowel movement. Her bowels are moving normally, and she has experienced no weight loss or fever. Her review of systems is otherwise unremarkable, and she was previously healthy apart from mild depression that is being effectively treated with fluoxetine. The patient is taking no other medications. She does not smoke or drink alcohol.

Evaluation thus far has included abdominal ultrasonography that showed sludge in the gallbladder with a normal liver and unremarkable findings on esophagogastroduodenoscopy.

EXAMINATION FINDINGS

Body mass index, 30 kg/m²
Moderate focal tenderness in the right upper quadrant of the abdomen

LABORATORY RESULTS

ALT, 50 U/L
AST, 30 U/L
Chemistry group and CBC otherwise unremarkable

QUESTION

Which *one* of the following approaches would be *most likely* to yield a diagnosis?

- Performing a hepatobiliary iminodiacetic acid scan
- Initiating an empiric trial of omeprazole
- Checking for Murphy sign
- Performing the Carnett maneuver
- Performing a mesenteric arterial Doppler study

DISCUSSION

This case is classic for chronic abdominal wall pain, an entity first described by the British surgeon J. B. Carnett in 1926. He described the maneuver whereby the tender spot is located and then patients are asked to raise either their legs or torso (thus tensing the abdominal muscles). If the pain does not decrease (and especially if it increases) during the maneuver, then it is very unlikely to be from a visceral source and may reliably be localized to the abdominal wall muscles. False-positive Carnett maneuvers occur infrequently (<5% or so), almost always in the setting of acute appendicitis (due to irritation of the adjacent parietal peritoneum). Chronic abdominal wall pain is typically described by the patient as being constant in nature and may worsen slightly after eating (abdominal distention) or more commonly after a bowel movement (from straining of the abdominal muscles). Obesity and depression are common comorbid conditions, as are fibromyalgia and other painful conditions.⁵

The Carnett maneuver is not only useful in diagnosis but is also helpful in educating and reassuring patients as to the true source of their pain. Local heat or ice treatments, sometimes accompanied by gentle stretching of the abdominal muscles, have been tried with variable success. With a conservative approach, about 50% of patients will improve over several months of follow-up. Trigger point injections provide relief in about two-thirds of patients. In all cases, the diagnosis helps to provide reassurance, while avoiding unnecessary expense, testing, and confusion.⁶

In this case, the pain is too constant and prolonged to represent biliary colic, and the elevated ALT is compatible with fatty liver. The features are not compatible with gastroesophageal reflux, and upper endoscopy did not show any gastritis or ulceration, making it unlikely that a trial of a proton pump inhibitor would be of benefit. The patient does not have atrial fibrillation and is far too young to have (and does not have the pattern to suggest) symptomatic atherosclerosis (the most common conditions associated with mesenteric ischemia).

CLINICAL PEARL

The Carnett maneuver can be very useful in both diagnosing chronic abdominal wall pain and reassuring patients who receive that diagnosis.

CASE 4

A 79-year-old man was diagnosed as having prostate cancer 3 years ago after an area of induration was found on rectal examination. At that time, biopsy revealed Gleason 3+4 adenocarcinoma. He was treated with a course of external-beam radiation therapy that was well tolerated, and his prostate-specific antigen (PSA) level decreased from a baseline level of 2.8 ng/mL (to convert to µg/L, multiply by 1) to a nadir of 0.3 ng/mL. He continued to feel well but had a biochemical recurrence of his cancer, and his PSA increased 9 months ago to 2.3 ng/mL. This prompted the initiation of androgen deprivation therapy with leuprolide and bicalutamide.

At presentation, the patient has mild hot flashes but otherwise feels well. He specifically denies any pain, dyspnea, neurologic symptoms, abdominal discomfort, melena, or hematochezia. Findings on examination are unremarkable. Findings on a screening colonoscopy performed 2 years previously were normal.

MEDICATIONS

- Omeprazole, 20 mg once daily
- Lisinopril, 10 mg once daily
- Hydrochlorothiazide, 25 mg once daily
- Leuprolide, 22.5 mg intramuscularly every 3 months
- Bicalutamide, 50 mg once daily
- Alendronate, 70 mg once weekly
- Vitamin D, 1000 IU once daily
- Calcium, 600 mg twice daily

LABORATORY RESULTS

- Hemoglobin, 12.3 g/dL (vs 14.2 g/dL 1 year ago) (to convert to g/L, multiply by 10)
- Mean corpuscular volume, 90 fL
- White blood cell count and platelets, normal
- Serum creatinine, 1.2 mg/dL
- PSA, <0.10 ng/mL

QUESTION

Which *one* of the following would be the *most appropriate* next step in the evaluation of this patient's anemia?

- Discontinue omeprazole
- Perform bone scan
- Repeat colonoscopy
- Conduct serum ferritin assay
- Recheck hemoglobin concentration in 3 to 6 months

DISCUSSION

The lower limit of the reference range for hemoglobin concentration in men is about 2 g/dL higher than in women, almost exclusively as a result of the influence of testosterone.

Biochemically castrated men thus would be expected to have concentrations of serum hemoglobin within the normal female range. This has been documented in studies of men with localized prostate cancer who begin androgen deprivation therapy. The mean decrease in hemoglobin over 6 months was 1.5 g/dL in one study⁷ and as high as 2.6 g/dL in another.⁸ The mean corpuscular volume remains normocytic. In those who discontinue androgen deprivation therapy, the recovery is slow and parallels the recovery of testosterone. Only about 14% of patients develop a hemoglobin concentration of 10 g/dL or lower, with symptoms referable to anemia.

In this patient, iron deficiency is not suggested by the data, and the reasons for the decrease in hemoglobin concentration are well understood, making a ferritin assay or a second colonoscopy unnecessary. Although omeprazole may interfere with iron absorption in those who are receiving iron replacement therapy, it should not produce a de novo normocytic anemia. The patient's prostate cancer is biochemically in remission, and he has no bone symptoms.

CLINICAL PEARL

Androgen deprivation therapy produces a predictable decrease in hemoglobin; in the absence of bleeding or other causes of anemia, this decrease does not require additional diagnostic testing and may simply be periodically monitored for stability.

CASE 5

A 78-year-old man whose type 2 diabetes mellitus has been well controlled with metformin for the past 5 years presents with mild paresthesia and decreased sensation in his toes during the past year. He has hypertension and hyperlipidemia, both of which are well controlled with lisinopril and simvastatin. Otherwise, he is healthy.

MEDICATIONS

Metformin, 1 g twice daily
Lisinopril, 10 mg/d
Simvastatin, 20 mg/d
Aspirin, 81 mg/d

EXAMINATION FINDINGS

Mildly reduced vibratory sensation in the toes
Otherwise unremarkable

LABORATORY RESULTS

CBC, normal
AST, normal
ALT, normal
Electrolytes, normal
Creatinine, 1.2 g/dL

Glucose, 116 mg/dL (to convert to mmol/L, multiply by 0.0555)
Glycated hemoglobin, 6.3%
Microalbumin, negative

QUESTION

Which one of the following additional tests would be most useful to conduct at this visit?

- Vitamin B₁₂ assay
- 25-Hydroxyvitamin D assay
- Serum folate assay
- Serum homocysteine assay
- Serum ubiquinone (coenzyme Q10) assay

DISCUSSION

Metformin has been associated with vitamin B₁₂ deficiency, and this is more likely to occur after more than 3 years of use. It is a dose-related phenomenon and more prevalent at dosages of more than 1.5 g/d.⁹ In a recent randomized trial using 2.5 g/d of metformin for 4 years, the treatment group had a 7.2% greater absolute risk of developing vitamin B₁₂ deficiency (<200 pg/mL; to convert to pmol/L, multiply by 0.7378) vs the group receiving placebo.¹⁰ Homocysteine is often modestly elevated as well; however, in this case, checking for elevated homocysteine levels would not be indicated. The clinical severity is mild to moderate in most cases, with mild peripheral neuropathy and anemia (hemoglobin values in the 11 g/dL range) being the most common findings in symptomatic patients.

The mechanism is thought to be malabsorption of food cobalamin in the distal ileum. The ileal cell surface receptor depends on intraluminal calcium to function effectively, and metformin interferes with this interaction. In fact, one report of patients taking metformin indicated significant improvement in vitamin B₁₂ absorption with increased intake of calcium.

It would be reasonable to check a vitamin B₁₂ level periodically in patients who have been taking metformin for several years.

CLINICAL PEARL

Significant deficiency of vitamin B₁₂ may develop in patients who have been taking metformin for several years.

CASE 6

A 72-year-old woman presents with proximal myalgia and morning stiffness, with an elevated erythrocyte sedimentation rate and clinical picture compatible with polymyalgia rheumatica. Prednisone therapy (15 mg/d) is initiated, to which she has a dramatic and complete response within a few hours of the first dose. One double-strength tablet of trimethoprim-sulfamethoxazole daily is prescribed for *Pneumocystis* prophylaxis. She is taking no other medications.

Two weeks later, the patient returns for a follow-up visit. She feels well and has no new symptoms. Her laboratory results are as follows:

LABORATORY RESULTS

Hemoglobin	
Initial, 10.8 g/dL	
2-week follow-up, 11.5 g/dL	
Erythrocyte sedimentation rate	
Initial, 75 mm/h	
2-week follow-up, 21 mm/h	
White blood cell count	
Initial, 8000	
2-week follow-up, 11,000 (normal differential)	
Serum creatinine	
Initial, 1.1 mg/dL	
2-week follow-up, 1.4 mg/dL	
Blood urea nitrogen	
Initial, 19 mg/dL (to convert to mmol/L, multiply by 0.357)	
2-week follow-up, 32 mg/dL	
Glucose	
Initial, 88 mg/dL	
2-week follow-up, 115 mg/dL	
Sodium	
Initial, 137 mEq/L (to convert to mmol/L, multiply by 1)	
2-week follow-up, 136 mEq/L	
Potassium	
Initial, 4.6 mEq/L (to convert to mmol/L, multiply by 1)	
2-week follow-up, 5.4 mEq/L	
Urinalysis, normal	

QUESTION

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

- Discontinue trimethoprim-sulfamethoxazole
- Check eosinophil levels in urine
- Discontinue prednisone
- Check antineutrophil cytoplasmic antibody level
- Check urine microalbumin level

DISCUSSION

Some medications, such as trimethoprim, cause an elevation in serum creatinine levels that does not reflect an actual decrease in glomerular filtration rate.¹¹ A small portion of overall creatinine excretion occurs through tubular secretion; however, the proportion eliminated through that route may vary a bit between individuals and is relatively greater in those with some degree of chronic renal insufficiency. Trimethoprim is an inhibitor of tubular

creatinine secretion and may also interfere with excretion of potassium.

Several studies have documented an increase of 15% to 30% in serum creatinine levels with the use of trimethoprim, which would be compatible with the effect seen in this patient. The elevation begins within a few hours of the first dose and is rapidly reversed on discontinuation. This medication also causes reversible hyperkalemia, with an average increase of 0.3 mEq/L in serum potassium levels.¹² Although this hyperkalemia is generally not clinically relevant, caution and vigilance are advised in those with other risk factors for hyperkalemia (eg, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, spironolactone, chronic kidney disease).

This patient has no other clinical evidence of acute interstitial nephritis or vasculitis. Although prednisone likely accounts for the elevated blood urea nitrogen levels (through increased production of urea from catabolic effects), there is no reason to discontinue it. The hyperglycemia is transient and related to corticosteroid use. She has no history of diabetes, and her microalbumin level does not need to be checked.

CLINICAL PEARL

Trimethoprim causes reversible elevation of serum potassium and creatinine levels.

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Correct answers: Case 1: a, Case 2: d, Case 3: d, Case 4: e, Case 5: a, Case 6: a