MAYO CLINIC

Clinical Pearls in General Internal Medicine 2012

John B. Bundrick, MD, and Scott C. Litin, MD

See end of article for correct answers to questions.

From the Division of General Internal Medicine, Mayo Clinic, Rochester, MN.

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. The following "Clinical Pearls in General Internal Medicine 2012" is one of them.

CASE 1

A 32-year-old woman presents to your office with 2 days' duration of rhinorrhea, nasal congestion, and a slight dry cough. She denies any fever, headache, or sore throat and has otherwise been well. She is not taking any medications. She works as a nurse in an outpatient internal medicine clinic, and her symptoms have been a considerable nuisance as she interacts with her patients. On examination, she appears generally well and is afebrile. She has moderate nasal edema and pale yellow mucus in both nasal passages. The pharynx appears normal, and there is no tenderness over the maxillary sinuses. There is no lymphadenopathy. Her lungs are clear.

Question

Which *one* of the following intranasal topical therapy combinations would provide the *most effective* relief of her symptoms in the next 7 days?

a. Zinc and oxymetazoline
b. Ipratropium and oxymetazoline
c. Ipratropium and zinc
d. Fluticasone and oxymetazoline
e. Fluticasone and ipratropium

Discussion

The common cold is a viral upper respiratory tract infection (URTI) for which there is no known cure, although the nasal symptoms may be substantially alleviated by topical therapies. The use of nasal ipratropium was assessed in a recent Cochrane Review that involved 7 randomized controlled trials of 2144 patients with acute viral URTI.[1] In a representative study of 943 patients, rhinorrhea scores decreased from a baseline of 6.5 (on a 1-10 scale) to 3.4 with treatment. In another trial of 410 patients, global improvement on day 5 was rated 81% with nasal ipratropium treatment compared with 65% in the placebo group and only 18% in a group that received no treatment. Adverse effects included primarily mild epistaxis and nasal dryness, both of which were judged tolerable by the study participants. The dose of ipratropium used in most studies was 2 sprays of the 0.06% solution in each nostril 4 times daily. The Cochrane reviewers concluded: "For people with the common cold, the existing evidence, which has some limitations, suggests that ipratropium bromide is likely to be effective in ameliorating rhinorrhoea."[1]

Nasal congestion was not affected by ipratropium treatment and can also be quite annoying for patients with URTI. A review of trials of intranasal xylometazoline (which is equivalent to oxymetazoline) for the common cold demonstrated a 34% reduction in symptom scores for nasal congestion (alone and combined

Mayo Clin Proc. ■ January 2013;88(1):106-112 ■ http://dx.doi.org/10.1016/j.mayocp.2012.11.003
www.mayoclinicproceedings.org ■

with nasal ipratropium) compared with placebo.[2] Mild epistaxis was the only adverse effect. Treatment was used for up to 10 days, and there was no evidence of rhinitis medicamentosa in these trials (although it would be wise to avoid nasal decongestant use in patients with a history of rhinitis medicamentosa).

Trials of intranasal fluticasone in the common cold show a lack of benefit. Whereas oral zinc use has been found to modestly decrease the duration and severity of common cold symptoms,[3] intranasal zinc use has no efficacy (and may lead to permanent anosmia).

Clinical Pearl

Intranasal ipratropium and oxymetazoline treatment reduces the symptoms of rhinorrhea and nasal congestion (respectively) in the common cold.

CASE 2

A 72-year-old woman presents with 4 months' duration of right upper quadrant anterior abdominal pain. The pain is described as a "deep burning ache" that is continuous for most of the day and is worse as the day progresses. It is better with lying down and bothers her only at night if she lies on either side. It is unaffected by meals. She has no history of trauma and has not had a rash. She has no back pain. Her medical history is remarkable for a remote cholecystectomy and a diagnosis of osteoporosis. Her medications include alendronate, 70 mg by mouth once weekly; vitamin D, 1000 U daily; and a calcium supplement, 600 mg twice daily. Her examination reveals moderate kyphosis and tenderness in the right lateral abdomen. There is no mass or organomegaly and no rash.

Question

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

a. Check for the Murphy sign
b. Perform the Carnett maneuver
c. Measure the rib-pelvis distance
d. Thoracic spine films
e. Computed tomography of the abdomen

Discussion

In patients with osteoporosis, the cumulative effects of vertebral compression fractures (which are frequently occult) often lead to a narrowing of the distance between the lowest anterior rib (the 10th rib, at its most inferior point, which is generally the midaxillary line) and the top of the iliac crest. This narrowing can be easily measured by fingerbreadths on examination with the patient in the seated or standing position. Even in asymptomatic patients, this measurement may be a helpful diagnostic clue to the presence of subclinical compression fractures. A distance of 2 fingerbreadths or less progressively increases the odds of such fractures, and at 4 fingerbreadths they would be virtually excluded (negative likelihood ratio of 0.1).[4,5]

In this case, measurement of the rib-pelvis distance would provide a further clue to the mechanism of her abdominal pain. If the distance were 1 fingerbreadth or less, and the tenderness could be localized to the tip of the 10th rib (which is the lowest anterior rib), then a clinical diagnosis of iliocostal syndrome (aka "ribs on pelvis syndrome") may be confidently established.[6] Treatment is aimed at postural training (to avoid contact of the rib with the pelvis) and other physical therapy modalities. If these are not effective, then a local injection of anesthetic and corticosteroid may sometimes be of benefit. In all cases, reassurance as to the benign nature of the diagnosis and avoidance of further testing is helpful. A similar syndrome of back and flank pain may develop in these patients in which the tip of the 12th rib contacts the top of the pelvis posteriorly.[7]

The Carnett maneuver is a test for abdominal wall pain that involves tensing the abdominal muscles while palpating a tender spot to see whether the pain increases (which localizes the pain to the abdominal wall and helps exclude intra-abdominal causes). Although generally a useful maneuver, in this case the pain is farther lateral than in most cases of abdominal wall pain and the context is weighted more toward a rib-tip mechanism of pain. Thoracic spine films would simply confirm her kyphosis but would be unlikely to provide further insight into the cause of her abdominal pain. Findings on computed tomography of the abdomen would be expected to be normal in iliocostal syndrome and would be unnecessary in this case.

Clinical Pearl

Patients with osteoporosis may develop chronic pain over the tip of the 10th rib where it contacts the pelvis, and this may be strongly suspected based on features of the clinical examination.

CASE 3

A 69-year-old man reports a history of nocturia that has become progressively more bothersome to him during the past couple of years. He now gets up 3 times at night to void and has trouble getting back to sleep each time. His daytime voiding pattern is normal (about 4 times during the day), and he has no hesitancy, decreased force of stream, urgency, or sensation of incomplete voiding. His wife has mentioned that he has snored loudly for many years, but she has not noticed any apnea. He has gained approximately 10 lb during the past year, but his fasting glucose level was recently only 92 mg/dL (to convert to mmol/L, multiply by 0.0555). His only medication is lisinopril, 10 mg/d, for hypertension. His body mass index is 34 (calculated as weight in kilograms divided by height in meters squared), and his blood pressure is 136/76 mm Hg. Heart and lungs are normal. There is trace pitting edema at the ankles. His prostate is mildly enlarged (1+). Laboratory tests revealed normal serum sodium, potassium, creatinine, and calcium levels.

Question

Which *one* of the following diagnoses *best* explains his nocturia?

a. Obstructive sleep apnea (OSA)
b. Remobilization of peripheral edema
c. Benign prostatic hypertrophy (BPH)
d. Detrusor instability
e. Superficial bladder cancer

Discussion

Nocturia is a common symptom in older individuals (especially men) and may be associated with sleep disruption, poor quality of life, and falls at night. It generally arises in relation to reduced bladder capacity, increased nocturnal urine volume, or some combination of the two. Bladder causes include BPH, detrusor instability, and (less often) infection or tumor. Nocturnal urine volume in healthy individuals is much less than daytime output owing to decreased meal-related solute at night and a natural increase in vasopressin (antidiuretic hormone). This circadian increase in nocturnal antidiuretic hormone is blunted in elderly individuals and is one of many factors predisposing them to nocturia. Specific diseases may also increase nocturnal urine volume, including diabetes mellitus, congestive heart failure, renal disease, and hypercalcemia.[8]

More recently, OSA has been strongly linked to nocturia, which may occur in as many as 50% of patients with OSA.[9] Levels of atrial natriuretic factor (ANF) have been documented to be significantly elevated in patients with OSA, and this is thought to be the mechanism of the nocturia. The elevated ANF level is most likely from right atrial stretch related to either the negative intrathoracic pressure directly, hypoxia-induced pulmonary vasoconstriction, or some combination of the two. Continuous positive airway pressure (CPAP) therapy has been shown to improve nocturia in concert with reducing the levels of ANF. One representative trial of CPAP treatment resulted in nocturia decreasing from a mean of 2.5 times per night to 0.7 times per night. More than 70% of the patients reported good to excellent relief of their nocturia with CPAP treatment in that study.[10]

Remobilization of edema on assuming the recumbent position at night is certainly a common cause of nocturia as well, but the present patient (even when examined toward the end of the day) does not have sufficient edema for that to be the cause. He has no daytime symptoms to suggest BPH, detrusor instability, or bladder neoplasm.

Clinical Pearl

Nocturia is a common symptom in OSA and is substantially improved after initiation of CPAP therapy.

CASE 4

A 62-year-old woman is bothered by a sensation of dry eyes. This is more noticeable toward the end of the day and interferes at times with her ability to work on her computer. She has no dry mouth and is otherwise healthy. On examination, she has perhaps a slight decrease in tear production, but the eyes otherwise appear normal.

Mayo Clin Proc. ■ January 2013;88(1):106-112 ■ http://dx.doi.org/10.1016/j.mayocp.2012.11.003
www.mayoclinicproceedings.org

Question

In addition to the use of artificial tears, which *one* of the following is *most* likely to help her symptoms?

a. Evening primrose oil
b. Vitamin E
c. Vitamin D
d. Horse chestnut extract
e. Fish oil

Discussion

Dry eyes are a common symptom and occur in up to 30% of those older than 50 years.[11] Mechanisms include decreased tear production and increased evaporative loss (often related to changes in the complex lipid composition of the outer layer of the tear film). Several medications have been implicated, including estrogens, antihistamines, anticholinergics, and selective serotonin reuptake inhibitors. The symptoms can be quite distracting in some cases and can have a major effect on visual acuity, social functioning, and workplace productivity. Most cases will not be related to Sjögren syndrome or other systemic diseases and may be treated symptomatically.

The first line of treatment in all cases is the use of artificial tears. In addition, fish oil may be beneficial. Several studies have established an association between decreased dietary intake of omega-3 fatty acids and dry eye syndrome.[12-14] The mechanism is not entirely clear but is thought to relate to effects on meibomian gland oils. A recent small, randomized, double-blind trial of patients with mild to moderate dry eye syndrome used a daily dose of fish oil that contained 450 mg of eicosapentaenoic acid, 300 mg of docosahexaenoic acid, and 1000 mg of flaxseed oil. After 90 days, those in the treatment group had a notable increase in tear volume compared with the placebo group. Furthermore, 70% of the treated group had become asymptomatic compared with only 37% of those who took placebo.[15]

Clinical Pearl

Fish oil seems to be beneficial in treating the symptoms of dry eye syndrome.

CASE 5

Three months ago, a 64-year-old male accountant experienced an episode of left arm weakness lasting 15 minutes that was diagnosed as a transient ischemic attack (TIA). He was found to be in atrial fibrillation at that time. Findings on carotid ultrasonography were normal, and his echocardiogram showed normal left ventricular function and no valvular disease. He has no cardiac symptoms and no additional remarkable medical history apart from hypertension. He takes lisinopril, 10 mg/d, and warfarin, 5 mg/d. His international normalized ratio has been consistently in the 2 to 3 range on his current dose of warfarin. His examination findings are normal except for an irregular heart rhythm at a rate of 84 beats/min. His blood pressure is 130/82 mm Hg. His father died of intracranial bleeding while taking warfarin, and the patient worries that he may be at risk for the same outcome. He has also been troubled by epistaxis and easy bruising and wonders just how important it is for him to continue taking anticoagulants.

Question

If the patient were to stop taking warfarin, what would be his risk of a stroke within the next year?

a. 4%
b. 6%
c. 7.5%
d. 12%
e. 18%

Discussion

The $CHADS_2$ score is a well-validated method of estimating the risk of stroke in patients with atrial fibrillation[16,17] and is enormously helpful in making decisions as to who should be undergoing long-term anticoagulation. It is also easy to use and remember, as patients are assigned 1 point each for congestive heart failure, hypertension, age 75 years and older, and diabetes mellitus and 2 points for stroke or TIA. However, there are currently 2 commonly used versions of the $CHADS_2$ score, each derived from different populations with considerable interstudy variation in risk of stroke. This is illustrated in Table 1, which shows rates of stroke in patients with atrial fibrillation not undergoing anticoagulation from the 2 studies.

TABLE 1. Rates of Stroke in Patients With Atrial Fibrillation Not Undergoing Anticoagulation

$CHADS_2$ or CHA_2DS_2-VASc score	Annual stroke risk		Annual thromboembolism risk in the CHA_2DS_2-VASc cohort
	Lower-risk cohort	Higher-risk cohort	
0	0.49	1.9	0.8
1	1.52	2.8	2.0
2	2.50	4.0	3.7
3	5.27	5.9	5.9
4	6.02	8.5	9.3
5	6.88 (5 or 6 combined)	12.5	15.3
6	6.88 (5 or 6 combined)	18.2	19.7
7	NA	NA	21.5
8	NA	NA	22.4
9	NA	NA	23.6

NA = not applicable.

The lower-risk cohort involved ambulatory patients with a mean age of 71 years,[17] and the original study (the higher-risk cohort) validating the index involved Medicare patients with a mean age of 81 years who had been hospitalized in the past year.[18] Although either index may be used in the appropriate setting, the higher-risk cohort is likely better matched to a substantial proportion of the frail elderly patients seen by many physicians.

The CHA_2DS_2-VASc score adds another layer of precision by giving 1 point for age 65 to 74 years (and an additional point for age $\geq$75 years) and adding 1 point for vascular disease and female sex. This prediction rule has particular utility in identifying patients who are truly at low risk for stroke and for whom warfarin therapy may be safely withheld.[18,19]

For patients with a history of stroke or TIA, all of these models may underestimate the risk of recurrent stroke. The patient in this case has a $CHADS_2$ and a CHA_2DS_2-VASc score of 3 (2 points for TIA and 1 point for hypertension) and would thus be estimated to have an annual stroke risk of approximately 5% to 6%. However, data from the placebo arm of the European Atrial Fibrillation Trial (a randomized trial of warfarin for secondary prevention after TIA or minor stroke) indicate that his actual stroke risk is closer to 12% per year.[20] In that study, the patients were randomized within 3 months after a TIA or stroke, but the curves for this increased risk in the placebo arm did not significantly flatten through up to 3 years of follow-up.

Clinical Pearl

The $CHADS_2$ and CHA_2DS_2-VASc scores provide an accurate estimation of stroke risk in patients with atrial fibrillation but considerably underestimate the risk in those who have experienced a TIA or stroke.

TABLE 2. Time Required for 10% of Women to Transition to a BMD of Osteoporosis

Baseline osteopenia level	T score	Interval to reach a BMD of osteoporosis (y)
Normal	−1.00 or better	17.4
Mild	−1.01 to −1.49	16.5
Moderate	−1.50 to −1.99	4.6
Advanced	−2.00 to −2.49	1.0

BMD = bone mineral density.

CASE 6

A 67-year-old woman undergoes osteoporosis screening using dual-energy x-ray absorptiometry (DXA) and is found to have osteopenia. Her T scores at the femur neck and total hip are both −1.6. She receives appropriate vitamin D and calcium therapy and has no other osteoporosis risk factors. She took estrogen for 4 years after menopause at age 50 years.

Mayo Clin Proc. ■ January 2013;88(1):106-112 ■ http://dx.doi.org/10.1016/j.mayocp.2012.11.003
www.mayoclinicproceedings.org

Question

What is the *most appropriate* interval to wait before retesting her bone density?

a. 1 year
b. 2 years
c. 3 years
d. 5 years
e. 10 years

Discussion

Current osteoporosis screening guidelines advise bone mineral density (BMD) screening for osteoporosis in women 65 years and older. However, evidence-based guidance has been lacking as to the optimal screening interval for repeating this testing based on the initial BMD result. This question has now been addressed by data from a cohort of women from the Study of Osteoporotic Fractures. Five thousand women 67 years and older without osteoporosis on their initial DXA screening were followed prospectively for up to 15 years. The DXA screening was repeated in years 2, 6, 8, 10, and 16. The outcome of interest was the time required for 10% of women to transition to a BMD of osteoporosis (T score ≤ -2.5) before incident hip/clinical vertebral fracture or before receiving treatment for osteoporosis. Patients were classified according to their baseline BMD, and the time required to reach this primary outcome was found to vary considerably (Table 2).

Age was a factor in determining the testing intervals. For example, although the overall testing interval was approximately 5 years for those with moderate osteopenia, for women 85 years and older it was closer to 3 years.[21] Although these data provide useful information to physicians regarding when to retest with DXA, it is important to remember that BMD is only one factor in determining risk of fracture. Treatment and testing decisions should ultimately be based on overall risk assessment (eg, Fracture Risk Assessment score). Women at higher risk (eg, corticosteroid users) need more frequent testing.

Clinical Pearl

In most women who are at average risk for osteoporosis, the decision of when to retest the BMD may be based on the initial BMD result. Longer intervals may be appropriate for many of these women.

Abbreviations and Acronyms: **ANF** = atrial natriuretic factor; **BMD** = bone mineral density; **BPH** = benign prostatic hypertrophy; **CPAP** = continuous positive airway pressure; **DXA** = dual-energy x-ray absorptiometry; **OSA** = obstructive sleep apnea; **TIA** = transient ischemic attack; **URTI** = upper respiratory tract infection

Correspondence: Address to John B. Bundrick, MD, Division of General Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (bundrick.john@mayo.edu).

REFERENCES

1. Albalawi ZH, Othman SS, Alfaleh K. Intranasal ipratropium bromide for the common cold. *Cochrane Database Syst Rev*. 2011;(7):CD008231.
2. Eccles R, Martensson K, Chen SC. Effects of intranasal xylometazoline, alone or in combination with ipratropium, in patients with common cold. *Curr Med Res Opin*. 2010;26(4):889-899.
3. Singh M, Das RR. Zinc for the common cold. *Cochrane Database Syst Rev*. 2011;(2):CD001364.
4. Siminoski K, Warshawski RS, Jen H, Lee KC. Accuracy of physical examination using the rib-pelvis distance for detection of lumbar vertebral fractures. *Am J Med*. 2003;115(3):233-236.
5. Green AD, Colon-Emeric CS, Bastian L, Drake MT, Lyles KW. Does this woman have osteoporosis? *JAMA*. 2004;292(23):2890-2900.
6. Simpson C, Greenough WB III. Abdominal pain in an elderly osteoporotic patient: ribs on pelvis syndrome. *J Am Geriatr Soc*. 2004;52(6):1039.
7. Wynne AT, Nelson MA, Nordin BE. Costo-iliac impingement syndrome. *J Bone Joint Surg Br*. 1985;67(1):124-125.
8. Weiss JP, Blaivas JG. Nocturia. *Curr Urol Rep*. 2003;4(5):362-366.
9. Krieger J, Petiau C, Sforza E, Delanoe C, Hecht MT, Chamouard V. Nocturnal pollakiuria is a symptom of obstructive sleep apnea. *Urol Int*. 1993;50:93-97.
10. Margel D, Shochat T, Getzler O, Livne PM, Pillar G. Continuous positive airway pressure reduces nocturia in patients with obstructive sleep apnea. *Urology*. 2006;67(5):974-977.
11. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf*. 2007;5(2):93-107.
12. Miljanovic B, Trivedi KA, Dana MR, Gilbard JP, Buring JE, Schaumberg DA. Relation between dietary n-3 and n-6 fatty acids and clinically diagnosed dry eye syndrome in women. *Am J Clin Nutr*. 2005;82(4):887-893.
13. Oxholm P, Asmussen K, Wiik A, Horrobin DF. Essential fatty acid status in cell membranes and plasma of patients with primary Sjogren's syndrome: correlations to clinical and immunologic variables using a new model for classification and assessment of disease manifestations. *Prostaglandins Leukot Essent Fatty Acids*. 1998;59(4):239-245.
14. Sullivan BD, Cermak JM, Sullivan RM, et al. Correlations between nutrient intake and the polar lipid profiles of meibomian gland secretions in women with Sjogren's syndrome. *Adv Exp Med Biol*. 2002;506(pt A):441-447.
15. Wojtowicz JC, Butovich I, Uchiyama E, Aronowicz J, Agee S, McCulley JP. Pilot, prospective, randomized, double-masked, placebo-controlled clinical trial of an omega-3 supplement for dry eye. *Cornea*. 2011;30(3):308-314.
16. Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA*. 2003;290(20):2685-2692.
17. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for

predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285(22):2864-2870.

18. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest*. 2010;137(2):263-272.
19. Olesen JB, Lip GY, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2011;342:d124.
20. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet*. 1993; 342(8882):1255-1262.
21. Gourlay ML, Fine JP, Preisser JS, et al. Bone-density testing interval and transition to osteoporosis in older women. *N Engl J Med*. 2012;366(3):225-233.

CORRECT ANSWERS: Case 1: b. Case 2: c. Case 3: a. Case 4: e. Case 5: d. Case 6: d.

Mayo Clin Proc. ■ January 2013;88(1):106-112 ■ http://dx.doi.org/10.1016/j.mayocp.2012.11.003
www.mayoclinicproceedings.org