Letters

COMMENTS AND RESPONSES

Will Recommendations against Spirometry Make Chronic Obstructive Pulmonary Disease Harder to Treat?

TO THE EDITOR: We are concerned about the recent series of guideline papers and recommendation statements published in Annals (1–3), which seem to advise primary care physicians not to perform spirometry. This could be a big blow (no pun intended) to a nationwide effort to diagnose and treat chronic obstructive pulmonary disease (COPD) early (4, 5). Chronic obstructive pulmonary disease is the only disease among the top 5 fatal diseases in the United States that is increasing in morbidity and mortality (6). What separates the diseases that are decreasing (heart disease, stroke, cancer, and accidents) from COPD are effective early detection and prevention strategies. The recommendation in the U.S. Preventive Services Task Force (USPSTF) clinical summary figure, in large bold letters, states: “Do not screen for chronic obstructive pulmonary disease using spirometry” (2). In the text below the figure, however, there are caveats: this recommendation applies to healthy adults who do not recognize or report symptoms to a clinician and does not apply to individuals with a family history of α₁-antitrypsin deficiency. Thus, the flip side of the argument against screening is that unhealthy people (particularly those with a diagnosed respiratory disease), people with respiratory symptoms, and people with a family history of α₁-antitrypsin deficiency should have spirometry done. We would add to this list people who are at increased risk for COPD (adults older than 40 years with current or former tobacco use or exposure to occupational or environmental pollutants). This, of course, is not screening but appropriate clinical care.

How are we doing in this regard as clinicians? Not very well. National data from the United States and other countries demonstrate that a high proportion of adults with documented impaired lung function have not had any respiratory disease diagnosed (7–9). Furthermore, among people with a clinical diagnosis of COPD, in whom spirometry is mandatory, few patients have had testing done (10, 11). If spirometry use in a group with a clear-cut indication is so low, one can imagine that use in patients with chronic respiratory symptoms but no diagnosis is even lower.

Can information obtained from spirometry provide information beyond detecting severe COPD (the end point used in the USPSTF guideline’s background paper [3])? Yes. Even small decrements in lung function, which can be related to such processes as heart disease and diabetes (12), are associated with an increase in all-cause mortality, which has been known since the Framingham Study (13, 14). Furthermore, in the early stages of COPD, patients frequently have no symptoms but avoid dyspnea by progressively restricting activity. The resulting deconditioning is a major clinical problem that further compromises performance. Failure to diagnose COPD at this stage removes the opportunity to intervene early to interrupt a vicious cycle that often leads to a severely restricted functional status that is very difficult to treat when diagnosis is finally made. Finally, without readily obtainable spirometry, the clinician will be tempted to diagnose COPD by using clinical judgment, which is strikingly inaccurate. Specifically, not only are most patients with COPD without diagnosis, but a large proportion of individuals with the diagnosis do not have COPD.

The USPSTF argued that spirometry does not influence smoking cessation. Several new studies refute this conclusion (15–18). The most recent, by Parkes and colleagues (17), in which all patients (smokers age ≥35 years) had spirometry and equal exposure to cessation resources but patients in the intervention group were told their lung age, found that cessation rates more than doubled in the intervention group (6.4% vs. 13.6%).

Performance of spirometry is both easy and inexpensive. Industry has responded to the need for spirometry by providing devices that cost $1000 to $2000, and reimbursement is established at a very reasonable rate, averaging about $30 (Current Procedural Terminology code 94040) or $57 with bronchodilator evaluation (Current Procedural Terminology code 94060). Most important, this test not only provides strong evidence for a diagnosis of COPD but also can indicate the presence of other diseases, such as restrictive lung disease.

So what’s the bottom line? Should we continue the national drive to find and treat COPD and related disorders early, or should we abandon facts and reason and retreat to where we were a half-century ago, when COPD was essentially ignored by the medical profession? At a minimum, good clinical practice mandates that adults with COPD or other chronic respiratory disease (asthma, sarcoidosis, pulmonary fibrosis) should have spirometry. In addition, patients with respiratory symptoms or a family history of α₁-antitrypsin deficiency should have spirometry. This is case finding and appropriate treatment of our patients. Finally, we hope that the Task Force will expeditiously reevaluate the evidence for spirometry as an adjunct in encouraging smoking cessation.

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References
IN RESPONSE: We appreciate the letter from Drs. Petty and Mannino regarding the USPSTF’s recent recommendation against screening for COPD by using spirometry (1). Their comments provide us the opportunity to emphasize some important issues that the USPSTF considered in making this recommendation.

Identifying a disease earlier in its natural course does not automatically improve health outcomes. Clinicians should screen patients only if effective interventions are more beneficial during the asymptomatic disease stage than at clinical diagnosis and if the harms of screening or treatment do not outweigh the benefits. The USPSTF’s review of the evidence (2) found that for more than 90% of individuals without respiratory symptoms who would have airflow obstruction on spirometry, the sole effective therapy was tobacco cessation interventions, which the USPSTF already recommends for all adult smokers (3). Even accounting for the few individuals who might gain symptomatic relief from medications, several hundred patients would need to be screened with spirometry to defer a single COPD exacerbation. The USPSTF judged that the harms of such screening—false-positive test results leading to adverse effects from treatment (for example, tachycardia or urinary retention), coupled with the substantial time and effort required by patients and the health care system—were at least equal to this small potential benefit.

Although Drs. Petty and Mannino argue that providing smokers with spirometry results may motivate them to quit smoking, no studies they cite were designed to appropriately test this hypothesis. For example, because all of the participants in the randomized trial by Parkes and colleagues (4) had spirometry, the only definite conclusion that can be drawn is that communicating spirometry results to smokers in understandable terms (lung age) was more effective than providing the underlying clinical data.

The USPSTF does not discourage clinicians from using spirometry to diagnose unexplained respiratory symptoms or to monitor patients with an established pulmonary diagnosis. We are puzzled by the assertion that recommending against inappropriate overuse of spirometry (screening) will lead to underuse of the test in appropriate (diagnostic or monitoring) clinical situations.

Although the American College of Physicians’ COPD practice guideline (5) came to the same conclusion about screening as did the USPSTF, the USPSTF includes a broad representation of primary care clinicians and generalists and has an independent guideline development process. The difference in the composition and processes used by these 2 groups support the idea that evidence-based guidelines are highly reliable.

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Potential Financial Conflicts of Interest: None disclosed.

References
**Letters**

**Did Prescription Bias Affect Outcomes in a Study of the Relative Effectiveness of Osteoporosis Drugs?**

**TO THE EDITOR:** We read with interest the article by Cadarette and colleagues (1). Osteoporosis and fracture risk in the elderly, especially postmenopausal women, is a growing problem. A few things came to mind while reading this article. First, the authors do not mention or control patients’ dietary calcium intake and physical activity, 2 factors that are the first recommendations for prevention of osteoporosis. Second, the authors do not provide an estimate of prescription and over-the-counter calcium and vitamin D supplementation in the patients (2, 3). This may be lower in poorer patients, who might have been preferentially included. Third, the subset that was prescribed calcitonin was less healthy, as evidenced by their age, higher comorbid condition score, and use of more prescription drugs. We would point out that a history of falls, vertebral fractures, Parkinson disease, and dementia was almost 50% more common in this group than in the other drug groups. A basic requirement for prescription of bisphosphonates is the ability to sit upright or stand for 30 minutes after swallowing these drugs (4). Patients with the previously mentioned comorbid conditions are less likely to have this ability. Therefore, we feel that a bias during prescription may have been present and that the less healthy patients were prescribed calcitonin. And because we do not know the T-scores for these patients, we cannot estimate their true degree of osteoporosis.

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**Potential Financial Conflicts of Interest:** None disclosed.

**References**

**IN RESPONSE:** We agree with and appreciate the comments by Drs. Beri and Khattri. They highlight our finding that calcitonin recipients were sicker than alendronate recipients in terms of measured variables. They also point out that bisphosphonate dosing instructions are complex, and thus frail patients may have been preferentially treated with calcitonin, administered by daily nasal spray. We agree that residual confounding could explain part of our findings, and we discussed limitations of administrative claims data in our article. Results from our theoretical sensitivity analysis showed that the higher fracture risk among calcitonin recipients compared with alendronate recipients is probably not due to unmeasured confounding. However, because our analysis was based on the assumption of a single unmeasured confounder (1), multiple unmeasured confounding factors may have collectively introduced bias into the results. Nonetheless, we did adjust for many factors associated with frailty, such as age, history of falls, vertebral fractures, Parkinson disease, dementia, comorbidity score, and medication use. We also completed 7 different subgroup analyses, all with results similar to our main findings: no large difference in nonvertebral fracture rates between risedronate or raloxifene and alendronate recipients, and higher nonvertebral fracture risk among calcitonin recipients than among alendronate recipients. However, we did document more fractures among raloxifene recipients than among alendronate recipients in the subgroup with previous fracture. We therefore emphasize caution in interpreting findings comparing calcitonin and alendronate, as well as results comparing raloxifene and alendronate, because raloxifene recipients were apparently healthier in terms of measured variables. Our results comparing bisphosphonates are more compelling because risedronate and alendronate recipients were similar in terms of measured risk factors for fracture; however, we cannot rule out potential differences in unmeasured factors.

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**Reference**

**The Effects of Race, Ethnicity, and Underlying Medical Diseases on Osteoporosis Are Still Unguided Territory for Internists**

**TO THE EDITOR:** We were pleased to read the recently published American College of Physicians (ACP) clinical guidelines (1) and systematic review (2) on screening for osteoporosis in men. These articles represent closure of a substantial gap in previous guidelines issued to general internists, and we commend the authors and ACP for undertaking this project. Currently, Medicare coverage for bone mass measurements is limited to at-risk women with estrogen deficiency, individuals with vertebral radiographs suggestive of underlying osteoporosis, individuals receiving prolonged glucocorticoid therapy, patients with primary hyperparathyroidism, and those already taking osteoporosis medication (3). Hopefully, the new ACP guidelines will help extend Medicare coverage to include at-risk male patients, because out-of-pocket expenses for dual x-ray absorptiometry screening are approximately $180 at our institution.

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**The Effects of Race, Ethnicity, and Underlying Medical Diseases on Osteoporosis Are Still Unguided Territory for Internists**

**TO THE EDITOR:** We were pleased to read the recently published American College of Physicians (ACP) clinical guidelines (1) and systematic review (2) on screening for osteoporosis in men. These articles represent closure of a substantial gap in previous guidelines issued to general internists, and we commend the authors and ACP for undertaking this project. Currently, Medicare coverage for bone mass measurements is limited to at-risk women with estrogen deficiency, individuals with vertebral radiographs suggestive of underlying osteoporosis, individuals receiving prolonged glucocorticoid therapy, patients with primary hyperparathyroidism, and those already taking osteoporosis medication (3). Hopefully, the new ACP guidelines will help extend Medicare coverage to include at-risk male patients, because out-of-pocket expenses for dual x-ray absorptiometry screening are approximately $180 at our institution.
Although the new ACP guidelines fulfill an unmet need, several questions remain unanswered. For example, the article quoted a prevalence of osteoporosis estimated at 7% in white men, 5% in black men, and 3% in Hispanic men, with few data on Asian-American men and other ethnic groups (1, 4). However, the article does not mention issues of race and ethnicity again. Given that prevalence of osteoporosis in women has been clearly associated with racial and ethnic background (5), further evaluation of such cultural and genetic factors in men should be considered.

Secondary osteoporosis, a topic that may have received even less attention in the literature than osteoporosis in men, has thus far not been included in the screening guidelines for this population. Among men, 30% to 60% of osteoporosis cases are associated with secondary causes (most commonly hypogonadism, glucocorticoid use, and alcoholism). Secondary causes also affect perimenopausal women, with more than 50% of this population affected (6).

The systematic review by Liu and colleagues (2) is one of the first to evaluate the often confusing and contradictory literature addressing which secondary causes are most likely to affect bone health and eventually fracture risk. For example, studies suggest that hyperthyroidism, whether treated or untreated, is a secondary risk factor for osteoporosis. Yet, a 2004 study (7) found that the risk for osteoporosis in women with hyperthyroidism increased in the 3 years after induction of therapy, with treated women having a Z-score no different from that of age-matched control participants after 3 years of therapy. No official recommendations have been made based on these data.

Long-term oral glucocorticoid therapy also accounts for 1 of 6 cases of male osteoporosis (8). The extent of bone damage is related to the duration of therapy and the steroid dosage, leading to a recommendation from the American College of Rheumatology to treat patients taking 5 mg of steroids or more daily for more than 6 months (9). Yet, no statement from other societies endorses this recommendation or forms screening guidelines of their own. Is it reasonable to classify steroid “exposure-years” in the same way as we classify tobacco “pack-years”?

Given the effects of race, ethnicity, and underlying medical disease on bone mineral density, are sex-based guidelines for osteoporosis the most appropriate tack to take? In addition, patients younger than the “usual” screening ages for osteoporosis may be at considerable risk for fractures depending on their underlying medical condition or treatments for the same. Perhaps an expanded fracture-risk algorithm, similar to but more comprehensive than the World Health Organization risk calculator, can be developed. The undertaking for such an endeavor may be arduous, but such groups as ACP and the American Association of Clinical Endocrinologists can perhaps work together to ensure better and more cost-effective screening guidelines for a disease with such substantial morbidity, mortality, and financial burden.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: We thank Drs. Bohinc and Snyder for their insightful comments regarding our recent systematic review and guideline on screening for osteoporosis in men. We concur that a deeper evaluation of race and ethnicity in male osteoporosis, as has been performed in women, is much needed. Our ability to make conclusive remarks regarding the effects of race and ethnicity on screening in men is limited by the lack of research in this area. We attempted to better understand the effects of secondary causes of male osteoporosis. Our review evaluates the existing literature on key secondary causes of male osteoporosis, including alcoholism, androgen deprivation therapy or hypogonadism, and rheumatologic disease. Once again, the limited data in men makes it difficult to draw strong conclusions regarding many of these risk factors.

Ultimately, our review and guideline serve not only to synthesize the current literature on screening in male osteoporosis but also to highlight the major gaps in our understanding of this topic.

As Drs. Bohinc and Snyder point out, these gaps in the existing literature are many. As such, our papers serve not only as a review and guideline to be used by clinicians but as a call for increased research and awareness of this important yet often underdiagnosed and undertreated condition.

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Hepaticitis Associated with the Use of Herbal Red Yeast Rice

**Background:** Red yeast rice is a dietary supplement that contains 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and is used for over-the-counter self-treatment of hyperlipidemia.

**Objective:** To report a case of severe hepatitis associated with use of red yeast rice.

**Case Report:** A 62-year-old woman was brought to the emergency department of our institution with a 10-week history of flu-like symptoms followed by 1 week of nausea, vomiting, diarrhea, chills, and daily fever (temperature, 102 °F). She did not report history of liver disease, blood transfusion, contact with ill persons, or recent travel. She had a history of asthma, allergic rhinitis, and depression. Her medications included montelukast sodium and fluoxetine, and she took two 600-mg red yeast rice capsules twice a day for her underlying hyperlipidemia.

Her vital signs were normal except for a temperature of 100.8 °F. Results of thyroid, chest, heart, vascular, musculoskeletal, and neurologic examinations were normal. Laboratory results revealed elevated liver enzyme levels (aspartate aminotransferase, 211 U/L [normal range, 15 to 46 U/L]; alanine aminotransferase, 1034 U/L [normal range, 9 to 72 U/L]) and elevated erythrocyte sedimentation rate (60 mm/h [normal range, 10 to 20 mm/h]). Abdominal sonography revealed possible fatty liver with no stones or ductal dilatation. Daily temperature spikes to 102 °F continued. Blood cultures and viral hepatitis panel were negative, as were antinuclear, anti–smooth muscle, anti–neutrophil cytoproteinase-3, antimielyoperoxidase, and HIV antibody screenings. Angiotensin-converting enzyme and ceruloplasmin levels were normal. Cytomegalovirus and Epstein–Barr virus antibody titers were consistent with old infection.

A liver biopsy (Figure 1) showed moderate acute and chronic lobular inflammation with areas of patchy parenchymal necrosis, lymphoplasmacytosis, occasional eosinophils, and mild sinusoidal fibrosis. These findings are compatible with drug-induced hepatitis.

The patient improved clinically with cessation of red yeast rice ingestion, becoming afebrile with reduction in liver enzymes and erythrocyte sedimentation rate. Several months after discharge, all laboratory studies were normal. She was treated with diet, exercise, and weight reduction for her underlying hyperlipidemia.

**Discussion:** Red yeast rice is prepared by growing red yeast (Monascus purpureus) on rice to produce a red-colored product. In China, it has a long history, dating back to the Tang dynasty (around 800 AD), of use as a food colorant and preservative (1). Ingestion of the product reduces lipid levels substantially (2). The antihyperlipidemic effects of red yeast rice are attributable to the presence of HMG-CoA reductase inhibitors, including lovastatin.

Hepatotoxicity is a well-known side effect of various statin drugs, yet a PubMed search using the terms red yeast rice and hepatitis reveals no reports in the medical literature of hepatitis associated with consumption of red yeast rice (3). Several reports describe rhabdomyolysis and myopathy associated with the use of this supplement (4–7). Under the terms of Dietary Supplement Health and Education Act of 1994, nutritional “supplements” are exempt from U.S. Food and Drug Administration inspection and approval and may not have accurate labeling of their composition (Figure 2) (8, 9).

The product our patient used was not included in an August 2007 U.S. Food and Drug Administration online news release, which warned consumers that 3 red yeast rice products—Red Yeast Rice and Red Yeast Rice/Policosanol Complex (Swanson Healthcare Products, Fargo, North Dakota) and Cholestrix (Sunburst Biorganics, Baldwin, New York)—contain lovastatin and should not be used (10).

An article (11) recommending the use of over-the-counter red yeast rice capsules for lowering cholesterol was recently published in *AARP The Magazine* (11). This publication reaches a mass audience of senior citizens. Because patients may not recognize these supplements as “drugs,” physicians must remain alert to the possibility of chemical poisoning or of hypersensitivity reactions in perplexing cases (12, 13).

**Conclusion:** Red yeast rice, like any HMG-CoA inhibitor, can cause hepatitis. Physicians and patients should be aware of these effects.
potential side effects (13, 14) and should obtain a detailed history of supplement use by patients.

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References

Table. Laboratory Test Results at Admission

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ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; LDH = lactate dehydrogenase.
oportunism, Q fever, Bartonella, Chlamydia, tularemia, and brucellosis. A bone marrow smear was normal, and bone marrow cultures were negative. Computed tomography of the chest, abdomen, and pelvis revealed no masses or deep lymphadenopathy.

During the hospital stay, an evanescent rash appeared over the patient’s chest at the same time as bilateral knee arthritis. Joint fluid showed inflammatory properties, with $4200 \times 10^9$ cells/L and no detectable microorganisms. At this point, the patient met all criteria for AOSD (2). However, transthoracic echocardiography showed a mass consistent with a tricuspid valve vegetation (Figure). Because the most common cause of right-sided endocarditis in a young adult is infection related to intravenous substance use, in which blood cultures are often negative (3), vancomycin and aminoglycoside treatments were started. However, 7 days later, the patient had persistent fever and acute-phase reaction with unchanged transthoracic echocardiography findings. We suspected an atypical cardiac manifestation of AOSD. We stopped the antibiotics and started prednisone (0.5 mg per kg of body weight per day). The fever disappeared. The tricuspid valve was normal by transthoracic echocardiography 1 month later. We tapered the prednisone dosage over the next 18 months, during which the symptoms and laboratory test abnormalities continued to improve.

Discussion: The diagnosis of AOSD is invariably challenging, given its protean clinical manifestations and nonspecific laboratory test abnormalities. Endocarditis caused by connective tissue diseases is exceedingly rare, and cases involving the right side of the heart have been reported only in patients with systemic lupus erythematosus. This case report constitutes the first evidence that AOSD can cause right-sided endocarditis. There is now consensus that patients with systemic inflammation and valve vegetations by echocardiography should receive treatment for infective endocarditis (3), given that arthralgia, aseptic arthritis, low back pain, or myalgia occurs in about 50% of patients with infective endocarditis and constitutes the inaugural symptom in about one third of cases (5). We considered infective endocarditis, but the patient did not respond to appropriate antibiotics. Furthermore, prednisone treatment was dramatically effective, leading to prompt disappearance of the tricuspid valve vegetation and gradual resolution of symptoms.

Conclusion: Adult-onset Still disease can cause fever and right-sided noninfective endocarditis, which in our patient responded to prednisone.

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Potential Financial Conflicts of Interest: None disclosed.

References
1. Cunha BA. Fever of unknown origin: focused diagnostic approach based on clinical clues from the history, physical examination, and laboratory tests. Infect Dis Clin
Corrections

Correction: Using Standardized Serum Creatinine Values in the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate

A 2006 article on using study equations for estimating glomerular filtration rate contained an error in a figure (1). The article’s Figure 2 shows the performance of glomerular filtration rate estimating equations in detecting rates less than 60 mL/min per 1.73 m². The plot in the published article was incorrect, although the reported sensitivity, specificity, and predictive values are correct. The corrected plot is reprinted here (Figure). The lines for C–G (original and adjusted for bias) are not completely identical but are indistinguishable in the figure.

Reference

Corrections: Is There Enough Evidence to Support Use of N-Acetylcysteine in Contrast-Induced Nephropathy?

In a recent letter on prevention of contrast-induced nephropathy (1), there is a misprint in the last sentence. Instead of “P of 397%,” it should say “P of 39.7%.”

Reference

Correction: Trial by Fire: In Memoriam

The events described by Muller in his essay (1) took place 15 years ago, during his residency training. The rotation was disbanded 2 years later, and these experiences became the impetus for a sea change in medical training at Mount Sinai that culminated with the appointment of Muller as Dean for Medical Education and with a major reform of their medical school curriculum.

Reference