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INSIDE

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To ED or Not to ED

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

Professor, Department of Introduction to Clinical Medicine, Ross University School of Medicine, Commonwealth of Dominica

Dr. Wilke reports no financial relationships relevant to this field of study.

Synopsis: *Elderly nursing home patients who were sent to an emergency department for evaluation were 2-4 times more likely than patients who remained at the nursing home to develop an acute respiratory or gastrointestinal infection within the next week.*

Source: Quach C, et al. Risk of infection following a visit to the emergency department: A cohort study. *CMAJ* 2012;184:E232-E239.

In this cohort, retrospective chart review study, Quach and her colleagues from Montreal investigated the relationship of a visit by an elderly nursing home (NH) patient to an emergency department (ED) with the development of a respiratory or gastrointestinal (GI) illness. The investigators selected 22 long-term care facilities in Quebec and Ontario that had previously participated in infection control research. They enrolled 424 patients ≥ 65 years who were sent to an ED for something other than a respiratory or GI illness and who were not admitted to hospital (exposed patients). They matched each of these patients with two others from the same area of the NH who were within 5 years of age and the same gender as the index patient and who had not gone to an ED in the previous 2 weeks (unexposed patients). This totaled 845 unexposed patients. They excluded immunocompromised patients and those with chronic fever. The primary outcome of interest was the development of symptoms of an acute respiratory or GI infection within 2-7 days after return from the ED. To avoid including patients who might have contracted these infections at the nursing home about the time of the ED visit, infection control NH staff kept records of outbreaks. They compared the exposed and unexposed patients and performed multivariable analysis to adjust for confounding variables, including smoking sta-

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tus, other infectious contacts, Charlson Comorbidity Index (CCI) score, independence in activities of daily living (ADLs), influenza vaccine status, patients' visitors, asthma, and heart disease.

The participants' mean age was 85 years (range, 65-105), and they were predominantly female. The two groups were dissimilar in that exposed patients were more likely to eat their meals in their rooms, had visitors more often, had higher CCIs, and were less independent in ADLs.

Twenty-one (5.0%) residents who made an ED visit and 17 (2.0%) who did not developed new infections. In univariable unmatched analysis, exposed residents had an incidence of infection of 8.3/1000 resident-days, compared to 3.4/1000 resident-days for unexposed residents (relative risk 2.5, 95% confidence interval [CI] 1.3-4.6). In multivariable conditional logistic regression, the adjusted odds ratio for infection was 3.86 (95% CI 1.38-10.77). Stratifying exposed patients by reason for ED visit did not identify a subgroup that was more likely to become infected. If an ED visit coincided with an outbreak at the NH, there was no increased risk of infection. Having a roommate (even an ill one), influenza vaccine status, smoking status, asthma, and heart disease did not affect risk.

■ COMMENTARY

The study confirms my anecdotal observation: emergency rooms are cesspools of infection! They are almost as bad as the typical pediatric or family medicine waiting room during cough and cold season! Certain of its associations have face value. It makes sense that patients with more morbidly and less independence in ADLs would be more likely to have to make a visit to the ED, and, conversely, infections can cause functional impairment. It does raise some curious questions, though. Why would an ongoing NH outbreak "immunize" a resident from an infection? Why would a patient who made a trip to the ED be more likely to eat in their room? Is it related to the increased morbidity or decreased independence? It shouldn't, if these are truly independent variables. And eating in one's room would seem to isolate the patient from outbreaks in the NH. On the other hand, having visitors more frequently would increase exposure to whatever was floating around in the community.

Are the results of this study generalizable? I think so. The patient population, NHs, and ED physicians in Canada are not fundamentally different than their counterparts in the United States, even if the health care system is. It is reasonable to assume that NHs that had previous experience with infection control research might be different than ones that had not. The staff of such facilities might be more assiduous in identifying residents to include in this study, but do they respond differently or are they more susceptible to infection? This is the problem with cohort studies: associations, not causations.

How should this information influence your practice? One thing to keep in mind is these much older patients were ultimately discharged back to the NH. Knowing how cautious ED physicians are, these patients were not all that sick; otherwise they would have been admitted. Step one then is to think twice about sending your elderly NH patient to the ED. Long-term care residents make frequent visits, often for low-acuity reasons. Can your patient be evaluated on site? Does your NH have access to laboratory and imaging? Aside from avoiding exposing your patient to a toxic environment, the very act of transport can be profoundly disruptive and uncomfortable, not to mention expensive. The second step would be to watch your patient for signs and symptoms of infection in the 2- to 7-day window after he or she returns from the ED. ■

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Effect of Elevated Blood Pressure on Lifetime Risk for Cardiovascular Disease

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman serves on the speakers bureau for Forest Laboratories.

Synopsis: *Individuals who experienced increases in blood pressure in middle age have an associated higher remaining lifetime risk for cardiovascular disease (CVD), especially if untreated. Decreases in an elevated blood pressure in middle age will result in a significant lowering of the remaining lifetime risk for CVD.*

Source: Allen N, et al. Impact of blood pressure and blood pressure change during middle age on the remaining lifetime risk for cardiovascular disease. The Cardiovascular Lifetime Risk Pooling Project. *Circulation* 2012;125:37-44.

CARDIOVASCULAR DISEASE (CVD) MORTALITY RATES HAVE decreased over the past four decades, yet CVD remains the leading cause of death and functional disability and is responsible for more than one-third of all deaths in the United States.[1] The lifetime risk (LTR) for CVD among Caucasians has been estimated to be one in two for men and one in three for women[2] and it appears to be at least as high among African Americans.[3] The LTR for CVD, particularly stroke, increases dramatically with increasing blood pressure (BP). The risk of developing CVD is twice as high among middle-aged individuals with stage II hypertension than it is in those individuals with optimal BP levels.[4]

Allen and colleagues investigated how changes in BP during middle age affect LTR for CVD and the frequency of occurence of CAD and stroke by pooling and evaluating data from seven diverse U.S. cohort studies.[5] They recognized that the systolic BP generally increases linearly with age and that individuals with higher systolic BPs experience the largest increases in the LTR for CAD. However, very little information had previously been published about how changes in BP during middle age may affect the LTR for CVD. Rather than simply evaluating the effects of high BP on LTR for CVD by taking a single measurement of BP during middle age, they evaluated the effects that changes in BP had over an average of 14 years on the LTR for CVD starting at age 55 by following 61,585 men and women for 700,000 person years. Individuals who maintained or decreased their BP to normal levels had the lowest LTR for CVD (22%-41%), compared with individuals who either had or developed hypertension by 55 years of age (42%-69%), suggesting a dose-response effect for the length of time at high BP levels.

■ COMMENTARY

The results obtained from this study are particularly meaningful because they were obtained from large diverse samples of population-based cohorts, which included almost 700,000 person-years of follow-up. In addition, because the studies were relatively recent, they provide more current estimates of LTR for CVD than were obtained from earlier studies. Equally important, the longitudinal BP measurements were measured over an average span of 14 years during middle age. It should be recognized that most of the follow-up information was obtained before the widespread use of antihypertensive and lipid-lowering therapies and, therefore, current results may be even more beneficial because of improved effects of more contemporary treatment regimens. Individuals who were able to either maintain controlled BPs or decrease their elevated BP to normal BP levels during middle age had the lowest LTR for CVD whereas individuals who experienced an increase in BP had higher LTRs for CVD. Therefore, taking BP measurements into account in all patients — but especially those who are middle aged — can provide more accurate estimates for LTR for CVD. This information represents a step forward in helping the medical profession develop individualized risk-prediction strategies.

In summary, the data presented in this article[5] clearly support the widespread clinical impression that avoiding hypertension at any age or lowering an existing and elevated BP into a properly controlled range will significantly improve the LTR for CVD. ■

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Where's the Beef?

ABSTRACT & COMMENTARY

By Ralph R. Hall, MD, FACP, FACSM

Professor of Medicine Emeritus, University of Missouri, Kansas City School of Medicine

Dr. Hall reports no financial relationships relevant to this field of study.

Synopsis: *These studies support inclusion of beef in heart-healthy diets.*

Source: de Souza RJ, et al. Effects of 4 weight-loss diets differing in fat, protein, and carbohydrate on fat mass, lean mass, visceral adipose tissue, and hepatic fat: Results from the POUNDS LOST trial. *Am J Clin Nutr* 2012;95:614-625.

THE AUTHORS STUDIED THE EFFECT ON LDL CHOLESTEROL OF four cholesterol-lowering diets with varying amounts of lean beef: Dietary Approach to Stop Hypertension (DASH), 28 g beef/day; Beef in an Optimal Lean Diet (BOLD), 113 g beef/day; Beef in an Optimal Lean Diet plus additional protein (BOLD+), 153 g beef/day, compared to that of a healthy American diet (HAD).

Thirty-six hypercholesterolemic participants (with LDL cholesterol concentrations > 2.8 mmol/L) were randomly assigned to consume each of four diets, HAD (33% total fat, 12% saturated fatty acid [SFA], 17% protein, and 20 g beef/day), DASH (27% total fat, 6% SFA, 18% protein, and 28 g beef/day), BOLD (28% total fat, 6% SFA, 19% protein, and 113 g beef/day), and BOLD+ (28% total fat, 6% SFA: 27% protein, and 153 g beef/day) for 5 weeks.

There was a decrease in total cholesterol (TC) and LDL cholesterol concentrations ($P > 0.05$) after consumption of the DASH (-0.49 and 0.37, respectively), BOLD (-0.48, and -0.35 mmol/L, respectively), and BOLD+ (-0.50 and -0.345 mmol/L, respectively) diets compared to consumption of HAD (-0.22 and -0.14 mmol/L, respectively).

Apolipoprotein A1, C-111, and C-111 bound to apolipoprotein A1 particles decreased after BOLD and BOLD+ diets compared with after consumption of the HAD, and there was a greater decrease in apolipoprotein B after the consumption of the BOLD+ diet than after consumption of HAD.

LDL cholesterol and TC decreased after consumption of the DASH, BOLD, and BOLD+ diets when the baseline C-reactive protein (CRP) concentration was < 1 mg/L. With the BOLD and BOLD+ diets, LDL cholesterol and TC decreased when the baseline CRP concentration was > 1 mg/L.

Low-SFA heart-healthy dietary patterns that contain lean beef elicit favorable effects on cardiovascular disease (CVD) lipid and lipoprotein risk factors that are comparable to those elicited by a DASH dietary pattern.

These results, in conjunction with the beneficial effects on apolipoprotein CVD risk factors after consumption of the BOLD and BOLD+ diets, which were greater with the BOLD+ diet, provide support for including beef in a heart-healthy dietary pattern.

■ COMMENTARY

The abstract did not include the subjects' adherence to the diet (calculated to be 93%) or that weights were measured daily to make certain there were no significant weight changes.

As the authors note, beef is a popular food. Patients often find that doing without beef is a major problem, making it difficult to follow dietary recommendations.

Red meat is limited in the DASH diet as a strategy to decrease SFA. The DASH diet is included in the study because it is "the gold standard of contemporary dietary recommendations."

There was a significant contrast between this study and previous studies in that despite the increase in CRP in some subjects, the LDL and TC were significantly decreased in the BOLD and BOLD+ diets.[1]

The authors discuss the difficulty in selecting cuts of lean beef. However, the new standards recently introduced for meat labels should help consumers in selecting cuts of beef that are lean.[2] Still, another potential for selecting appropriate beef cuts is the use of grass-fed beef. Grass-fed beef results in more favorable effects on lipid metabolism than the usual corn-fed beef.[3]

Red meat has a poor reputation as a food due to the fact that the majority of the studies have included processed meats. Processed meats contain nitrosamines that have been shown to be toxic in beta cells, which is associated with an increase in the incidence of diabetes, and high amounts of advanced glycation end products that unfavorably affect inflammation and oxidative stress.[4]

Previous studies on the effects of red meat may not have accounted for the fat content of the meat. It appears that we can cautiously increase the amount of lean beef in our patients' diets. The most perplexing problem, however, is the ability of patients to follow whatever diet is prescribed. ■

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Patients Placed in Contact Isolation Are at Increased Risk for Delirium

ABSTRACT & COMMENTARY

By David J. Pierson, MD

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This article originally appeared in the February issue of Critical Care Alert. *At that time it was peer reviewed by William Thompson, MD, Associate Professor of Medicine, University of Washington, Seattle, WA. Dr. Pierson and Dr. Thompson report no financial relationships relevant to this field of study.*

Synopsis: *This retrospective study of all non-psychiatric patients admitted to an academic medical center found that although those placed in contact isolation from the time of admission had no increased risk for delirium, patients moved into isolation after admission were twice as likely to develop delirium during the hospital stay.*

Source: Day HR, et al. Association between contact precautions and delirium at a tertiary care center. *Infect Control Hosp Epidemiol* 2012;33:34-39.

To examine the association between being placed in contact isolation and delirium, Day and colleagues at the University of Maryland Medical Center reviewed administrative data on all patients admitted during a 2-year period ending in 2009. They excluded patients with underlying schizophrenia or bipolar disorder, those admitted to the psychiatry service, and alcohol-related admissions, as well as patients under age 18. Patients placed into contact isolation during hospitalization were stratified into those assigned this status on admission (because of pre-existing risk or documented infection) and those subsequently moved into isolation (because of positive surveillance or clinical cultures, acquired risk, or other factors). Because delirium is underdiagnosed and incompletely identified by its direct ICD-9 code, the authors also used as proxy measures the otherwise-unexplained use of haloperidol or other antipsychotic drugs and the use of physical restraints during the admission. They performed selected chart reviews to assure that the variables under study were recorded in the administrative database with acceptable accuracy.

Of 70,275 admissions during the study period, 60,151 (in 45,266 unique patients; 9869 ICU admissions) were evaluated after a priori exclusions. Contact precautions were used in 9684 admissions (15%), 58% of them from the time of admission and 42% commencing at some point following admission. The authors' criteria for delirium were met in 7721 admissions (13.5%). Overall, patients placed in contact isolation at any time during hospitalization were twice as likely to have delirium compared to non-isolated patients (16.1% vs 7.6%, respectively; odds ratio [OR], 2.4; 95% confidence interval [CI], 2.2-2.5%). There was no relationship between contact precautions and delirium among patients who were placed in isolation immediately on admission. However, being moved into isolation sometime after admission because of identification of a multiple-drug-resistant bacterium was associated with increased risk for delirium (OR, 1.75; 95% CI, 1.60-1.92; $P < 0.01$). Although ICU patients had significantly more delirium than non-ICU patients, being placed in contact isolation had no independent effect.

■ COMMENTARY

Delirium, which occurs in about 15% of all hospitalized patients and is considerably more common in the ICU, is associated with numerous bad outcomes, including increased mortality, morbidity, and length of stay. Under current recommendations by the Centers for Disease Control and Prevention, contact precautions — including the use of gloves and gowns and isolation in a private room — are now used in a substantial number of hospitalized patients. Several studies have documented that physicians, nurses, and other clinicians interact with patients in isolation less often than non-isolated patients, and that those in isolation have more symptoms of depression and anxiety. Because decreased environmental stimuli predispose to delirium, it is hardly surprising that patients placed in isolation are more likely to develop this important disorder.

This study does not show that isolation causes delirium. Patients placed in isolation had increased mortality and lengths of stay, were more likely to be admitted to the ICU, and had more positive cultures suggesting clinical infections with resistant organisms than patients who were never placed in contact precautions. Thus, delirium was likely influenced by some or all of

these and other factors that could not be controlled for in a retrospective study. The fact that patients placed in isolation from the time of admission — because of a past history of colonization with resistant organisms or the presence of specific risk factors — did not have a higher risk for delirium suggests that those who required the institution of contact precautions subsequent to admission were sicker and perhaps more predisposed to delirium in the first place. These points are acknowledged by the authors.

I think the important contribution of this study is the spotlight it shines on contact isolation as a marker for the development of delirium. Regardless of the contribution of isolation per se to this development, knowing that isolated patients are at increased risk can help — at the level of the individual clinician as well as for hospital policy — with respect to efforts at early detection, appropriate treatment, and prevention of this important complication of acute illness. ■

Pharmacology Update

Ivermectin Lotion 0.5% (Sklice™)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

A NEW TOPICAL PREPARATION FOR THE TREATMENT OF HEAD lice has been approved by the FDA. Ivermectin is a macrocyclic lactone antibiotic that has been used orally both on and off label for head lice since 2001. This new formulation is a topical lotion (oral invermectin is not approved in the United States). It is manufactured by DPT Laboratories and is distributed by Sanofi Pasteur, Inc., as Sklice.

Indications

Ivermectin lotion is indicated for the topical treatment of head lice infestation in patients 6 years of age and older.[1]

Dosage

Ivermectin is applied as a single 10-minute application to the hair and scalp. It is available as a 0.5% lotion.

Potential Advantages

Ivermectin solution is well tolerated and provides another option for the treatment of head lice.

Potential Disadvantages

Approximately 25% of those treated with topical ivermectin were not lice free. It may be less effective than other products (e.g., spinosad or oral invermetin).

Comments

Ivermectin is believed to cause paralysis and death of mites by selective binding to glutamate-gated chloride channels.[1] Its efficacy was shown in two randomized, vehicle controlled studies in subjects with head lice.[1] The youngest subject from each household was the primary subject for assessment of efficacy. Other members were evaluated for safety. All infected subjects were randomized to ivermectin or vehicle only as a single application. The primary endpoint was percent free of lice 14 days after application. The results from the two studies were 76.1% (54/71) and 71.4% (50/70) for ivermectin compared to 16.2% (12/74) and 18.9% (14/74) for the vehicle. Ivermectin appears to be well tolerated as adverse reactions (conjunctivitis, ocular hyperemia, eye irritation, dandruff, dry skin, and skin burning sensation) occurred in fewer than 1% of subjects.[1] There are no published comparative studies with other topical agents such as permethrin, benzyl alcohol, malathion, spinosad, or oral ivermectin. For rough comparisons, the cure rate (lice free in 2 weeks) of approximately 74% compared to 44%-68% for permethrin, 76% for benzyl alcohol, 85% for spinosad, 85%-98% for malathion, and 95% for oral ivermectin.[2-5]

Clinical Implications

Head lice is a common infestation in children ages 3-12.[6] Permethrin is commonly used but generally requires two applications. Benzyl alcohol and spinosad need one application with success rates at least as good as topical ivermectin. ■

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CME Objectives

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

CME Questions

1. **Your 85-year-old nursing home patient has been sent to the emergency department to have a finger laceration repaired. Which one of the following statements about her risk of developing an acute respiratory or gastrointestinal infection in the next week is true?**
   a. If her roommate is ill, it decreases her risk.
   b. Having had an influenza vaccination decreases her risk.
   c. If she has a history of asthma, she is at greater risk.
   d. If she has a history of heart disease, she is at lower risk.
   e. She is at greater risk than her 85-year-old friend across the hall who did not make an ED visit.

2. **Individuals who have an elevated blood pressure in middle age:**
   a. will always have an elevated lifetime risk for cardiovascular disease.
   b. will have a decreased lifetime risk for cardiovascular disease if blood pressure is brought under control.
   c. need not be concerned about elevated blood pressure if they are on statin therapy.
   d. should be simply followed and treated only with lifestyle changes.

3. **Which of the following is *not* correct regarding the effects of weight loss diets and beef?**
   a. There was a decrease in TC and LDL after following the DASH, BOLD, and BOLD+ diets.
   b. Apolipoprotein B did not decrease with the BOLD+ diet.
   c. New food labeling standards for beef were recently introduced.
   d. Processed meats contain chemicals that adversely affect beta cells in the pancreas.

4. **The development of delirium during acute hospitalization increases the risk for which of the following?**
   a. Mortality
   b. Morbidity
   c. Increased length of stay
   d. All of the above

CME Instructions

To earn credit for this activity, follow these instructions:

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5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter!

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is an advisor for Endo, Kowa, Pricara, and Takeda.

Our Patients May Not be Getting the Message About Colon Cancer Screening

Source: Barton MK. *CA Cancer J Clin* 2012;62:1-2.

In its most recent guidance regarding colon cancer screening (CCS), the American Cancer Society iterated a new position on choice of tests, basically stating that "the best test is the test you can get done." This new orientation reflects both the philosophical and logistical realities that of the preventable cancers, CCS is the area in which we see the most missed opportunity. Currently, only about 60% of individuals are receiving any of the age-appropriate CCS available.

Barton reports on an observational study performed in 26 clinics in Michigan in which physicians volunteered to have patient visits audio-recorded, understanding that investigators were evaluating communication in general, but the study physicians were not told about any particular disease-state focus. Prior to the office visit, patients (n = 415) wrote down what information they felt they needed to understand to decide whether to participate in CCS.

Of the patients who indicated that information about test accuracy was very important, such information was imparted by the physician only 7% of the time. Even though most patients (77%-89%) rated information about pros/cons of testing and alternative testing methods as very important, communication about these components was similarly lacking (4% and 29%, respectively).

About half of patients did have questions about CCS, but clinicians invited questions in only about 5% of interviews. These well-demonstrated communication gaps provide an important opportunity for meeting patient needs, which will hopefully translate into better adherence with CCS recommendations. ■

BMD Testing: What's the Appropriate Interval?

Source: Gourlay ML, et al. *N Engl J Med* 2012;366:225-233.

Several national and international guidelines provide advice about when to consider bone mineral density (BMD) screening to identify osteoporosis (OSPS) based upon age, ethnicity, gender, and other risk factors. However, conspicuously lacking from these guidelines is an evidence-based path for when to recheck BMD, once a baseline is established.

The Study of Osteoporotic Fractures enrolled mid-life American women without OSPS at baseline (n = 4957; age ≥ 67) in an observational study. After baseline DEXA, scans were performed again at year 2, year 6, year 8, year 10, and year 16. The primary outcome of the trial was the interval after a baseline DEXA at which point 10% of participants would progress from normal BMD or osteopenia to OSPS.

As might be completely intuitive, the interval for progression to lower BMD levels was proportional to the degree of bone loss at baseline. That is, the interval before progression to OSPS for women with normal BMD or mild osteopenia at baseline was about 17 years; for those with moderate osteopenia, the interval was 4.7 years, and 1.1 years for women with advanced osteopenia (T-score = -2 to -2.49).

Based on these data, the authors suggest that for women with baseline T scores > -1.5, there is little likelihood of progression to osteoporosis (< 10%) over 15 years, and — in the absence of additional new risk factors to dictate otherwise — re-testing BMD might be reasonably put off for that same interval. For women with lower levels of BMD at baseline, however, a shorter interval for re-testing would be appropriate: 5 years for those with moderate osteopenia, and only 1 year for those with advanced osteopenia. ■

How Common is Vitamin B12 Deficiency in Patients on Metformin?

Source: Reinstatler L, et al. *Diabetes Care* 2012;35:327-333.

It has been recognized since the first published metformin clinical trials that B_{12} levels were impacted. For instance, a recent clinical trial found a 19% reduction in B_{12} levels (compared with placebo) after 4 years. Perhaps because common clinical signs of B_{12} deficiency (e.g., anemia, neuropathy, cognitive impairment) related to metformin treatment are rarely seen, clinicians have had low levels of apprehension about the effects of metformin on vitamin B_{12} levels.

How common is B_{12} deficiency in patients on metformin? An answer can be found in the NHANES data. Comparing adults with (n = 1621) and without (n = 6867) type 2 diabetes, Reinstatler et al report that biochemical deficiency of B_{12} (defined as level B_{12} < 148 pmol/L) was seen in 5.8% of diabetics on metformin; this was more than twice as frequent as the prevalence among diabetics not on metformin (2.4%), and about more than 1.5 times as frequent as in non-diabetics (3.3%).

One curious finding from this study was that consumption of B_{12} supplements by diabetics did *not* reduce the frequency of deficiency. It might be that the amount typically found in over-the-counter multivitamin supplements (6 mcg) is insufficient, even though the amount recommended by the Institute of Medicine is only 2.4 mcg/day. ■