Announcing the FPIN Community Challenge!

THE CHALLENGE: Each residency program or an individual from each program purchase a print subscription of Evidence-Based Practice.

WHY: We need your help! While Evidence-Based Practice continues to receive high marks for quality, due to rising costs in the publishing world we are at risk of losing our ability to print issues. FPIN’s finance committee reviewed EBP’s budget last year and will consider recommending a stop to the print issue if we are not successful.

ACTION NEEDED: Go to www.fpin.org/subscribe or call Denise at 573-256-2066. Cost is $59.
Which oral antifungal works best for toenail onychomycosis?

Evidence-based answer

Terbinafine, 250 mg daily for 12 to 16 weeks, produces higher clinical cure rates than either pulsed-dose itraconazole or weekly fluconazole (strength of recommendation [SOR]: A, multiple randomized controlled trials [RCTs]).

- Daily oral dosing is more effective than pulsed-dose terbinafine (SOR: A, multiple RCTs).
- No long-term or large studies have evaluated terbinafine’s safety. However, patients who have diabetes or are older than 65 years who take terbinafine along with antihypertensives, lipid-lowering agents, or “diabetic medications,” don’t manifest abnormal serum liver enzymes, creatinine, or glucose levels in the short term (SOR: C, 2 small cohort studies with disease-oriented outcomes).

Evidence summary

Multiple head-to-head RCTs of oral treatments for toenail onychomycosis demonstrate that terbinafine taken 250 mg per day for at least 12 weeks is superior to pulse itraconazole, weekly fluconazole, or pulse terbinafine (TABLE). In these studies the number needed to treat (NNT) favoring daily terbinafine ranged from 2 to 12.

Recurrence is less common in patients who take terbinafine daily. In a prospective cohort study of 73 patients (21–81 years of age) followed for 5 years after clinical and mycological cure, onychomycosis recurred in 7 of 59 (12%) patients treated with daily terbinafine and 5 of 14 (36%) treated with pulse itraconazole ($P=.046$; NNT=4.2).

Terbinafine doesn’t cause drug interactions in patients with diabetes, the elderly

A prospective open study of 89 diabetic patients with longstanding toenail onychomycosis, treated with terbinafine 250 mg/day for 12 weeks (mean age 56 years, 42% with insulin-dependent diabetes mellitus), showed a clinical cure rate of 57% at 48 weeks. No hypoglycemic episodes were reported during the
Oral treatments for onychomycosis: RCTs reveal how they compare

<table>
<thead>
<tr>
<th>Total subjects</th>
<th>Mean age, y (range); sex</th>
<th>Follow-up (wk)</th>
<th>Drug</th>
<th>Duration (wk)</th>
<th>Dose (mg)</th>
<th>Frequency</th>
<th>Clinical cure* %</th>
<th>NNT (95% CI)</th>
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<tbody>
<tr>
<td>151†</td>
<td>48 (18–75); 66% male</td>
<td>Median 234 (range 35–251)</td>
<td>Terbinafine</td>
<td>12–16</td>
<td>250</td>
<td>Daily</td>
<td>42</td>
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<td>496‡</td>
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<td>306‡</td>
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<td>2,005††</td>
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<td>Trial 1</td>
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<td>350</td>
<td>Pulsed: 14 of 30 days</td>
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</table>

CI, confidence interval; NA, not available; NNT, number needed to treat to effect 1 cure when compared with alternate therapy (see below); NS, not statistically significant; RCT, randomized controlled trial.
*Defined as 100% normal-appearing toenails.
†NNT when compared with itraconazole 400 mg pulsed dosing 7 of 28 days.
‡NNT when compared with fluconazole 150 mg weekly for 12 weeks.
§NNT when compared with terbinafine 350 mg pulsed dosing 14 of 30 days.
††Two studies in reference 5 were run as identical parallel group RCTs; 979 patients completed trial 1, and 1,026 patients completed trial 2 (90% completion rate).

Treatment phase, and no changes in liver enzymes or creatinine levels occurred. An open-label trial of 75 patients older than 65 years compared terbinafine alone (34 patients) with terbinafine and nail debridement (41 patients). Subjects took 250 mg terbinafine per day for 12 weeks; 73 (97.3%) took concomitant medications, including antihypertensives (64%), diabetic medications (25%), and lipid-lowering agents (47%). No clinically significant drug interactions or elevations in liver function tests occurred. Three patients (4%) withdrew from the study because of drug-related adverse effects (nausea, headache, or flank pain).

**Recommendations**

No major American medical organization has published guidelines addressing treatment of onychomycosis. The British Association of Dermatologists guidelines (2003) recommend terbinafine as first-line treatment for fungal toenail infections, with itraconazole as the next best alternative.

**REFERENCES**

Dear EBP Readers,

Ever wonder what the world would be like without evidence-based medicine? We need only go back in our own history about 100 years to find the tragicomic answer. Around the time of WWI, a fractured medical system, social upheaval, and the rise of radio spawned huge quack industries that thrived on testimonials. The whole era is described delightfully in Pope Brock’s book, *Charlatan.*¹

Brock’s list of medical frauds is remarkable. Elisha Perkins treated the gullible with his “galvanic tractors.” Ellie Metchnikoff (a Nobel Prize winner) touted yogurt as an anti-aging food. Walter Camp, a Yale football coach, claimed the same thing for his daily exercise program. John Paul Fernel developed a “sleeping brassiere” that supposedly shrank oversized busts. Dr. Eugene Steinach even did vasectomies to promote youthful vigor.

But the biggest fraud of all was John R. Brinkley, who, in another youthful vigor scam, made more than a million dollars a year implanting goat glands into his patients. He owned a “border-blaster” radio station in Mexico that pumped his infomercials all across the plains states. His market was a country depopulated by war and disease, where many older adults were trying to build (or rebuild) families. And he had just enough surgical training to be dangerous.

But he got away with it for years because there were some people who claimed the operations helped and were willing to give glowing testimonials. Brinkley also sent goon squads to silence those who complained publically. It was testimonial-based medicine in its most degenerate form.

For me, though, there was one brief section early in the book that really highlighted the tragedy of medicine without evidence. Apparently John R. Brinkley, early in his otherwise nefarious career, was forced to serve the general public during the flu pandemic of 1918. It was reported that the survival rate under his care (someone later claimed that he lost only 1 patient) was dramatically better than for folks receiving usual care (who had a 10%–20% mortality rate).

But unfortunately, con men don’t keep meticulous notes. We will never know if he had some trick up his sleeve that could have saved millions of lives, or if it was just one more flimflam.

Regards,

Jon O. Neher, MD


From the Editor
Diving for PURLs

Value of laxative-free colon cancer screening


This cohort study evaluated the diagnostic accuracy of laxative-free computed tomographic (CT) colonography using information-processing algorithms for “electronic cleansing” compared with (traditional) optical colonoscopy for detection of adenomatous polyps ≥6 mm in 605 asymptomatic patients 50–85 years old. Optical colonoscopies were performed second, with initial blinding of CT colonography results as well as second-pass unblinded optical colonoscopy and histological evaluation of target lesions. More patients were unable to complete CT colonography prep than optical colonoscopy prep due to adverse effects.

In detecting polyps ≥10 mm, CT colonography had a sensitivity of 91% and a specificity of 85%, compared with first-pass optical colonoscopy sensitivity of 95% and specificity of 89%. In detecting polyps 6–10 mm, CT colonography had sensitivity of 59% and specificity of 88%, compared with first-pass optical colonoscopy sensitivity of 76% and specificity of 94%. For lesions ≥10 mm, both CT colonography (+LR 6.16; 95% CI, 4.87–7.8) and optical colonoscopy (+LR 8.43; 95% CI, 6.6–10.77) had negative predictive values of 100%.

Seventeen percent of patients who underwent CT colonography would have needed follow-up optical colonoscopy to remove suspected lesions. Participants reported improved comfort with and preference for CT colonography over optical colonoscopy.

Bottom line: While laxative-free CT colonography performed as well as optical colonoscopy at detecting polyps ≥10 mm, it performed less well in detecting polyps 6–10 mm. Because 90% of clinically important lesions are ≥10 mm, laxative-free CT colonography may be an acceptable screening modality for low-risk patients. Concerns with cost, availability of the technology, and the authors’ financial ties to the technology keep it from being a practice change.

Review Author and Summary Author: Jen Bello, MD, The University of Chicago, Department of Family Medicine, Chicago, IL

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Imiquimod: an alternative treatment for high-grade cervical intraepithelial neoplasia


This double-blind RCT compared topical imiquimod with placebo for high-grade cervical dysplasia. It included women who were at least 18 years old, not pregnant, recently diagnosed with CIN 2 or 3, and not previously treated. Fifty-nine women were randomized to either a placebo vaginal suppository or an imiquimod (6.25 mg) vaginal suppository (1x/week for 2 weeks, then 2x/week for 2 weeks, then 3x/week for 12 weeks).

After 4 weeks of treatment, 73% in the imiquimod group and 39% in the placebo group had histologic regression to CIN 1 or less (95% CI for difference, 8%–57%; NNT= 3). At week 20, 60% of women in the imiquimod group and 14% in the placebo group had human papillomavirus (HPV) clearance (95% CI for difference, 22%–67%).

The most common adverse effects of the imiquimod were mild pruritus and vulvar pain. For women who experienced these adverse effects (n=9), the dose was decreased to 3.125 mg. No participants discontinued the study due to these adverse effects.

Bottom line: For women with CIN 2 or 3, topical imiquimod promotes regression of dysplasia or HPV clearance. However, imiquimod is not widely available as a vaginal suppository.

Review Author and Summary Author: Dionna Brown, MD, The University of Chicago, Department of Family Medicine, Chicago, IL

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PURLs Criteria

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<td>Clinically meaningful</td>
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Bottom line: For women with CIN 2 or 3, topical imiquimod promotes regression of dysplasia or HPV clearance. However, imiquimod is not widely available as a vaginal suppository.
Rivaroxaban is an option for acute PE


Rivaroxaban is an oral factor Xa inhibitor that is FDA approved for anticoagulation in nonvalvular atrial fibrillation and postoperative venous thromboembolism (VTE) prophylaxis. In this unblinded noninferiority study, investigators hypothesized it would be as effective for treatment of symptomatic pulmonary embolism (PE) as vitamin K antagonists.

Patients with confirmed PE (with or without concurrent deep vein thrombosis; N=4,800) were randomized to either rivaroxaban (15 mg orally twice a day for 3 weeks then 20 mg once daily) or usual care with a vitamin K antagonist after initial enoxaparin. Treatment duration was 3, 6, or 12 months based on physician discretion, with an additional month of surveillance. Investigators defined the noninferiority threshold as a hazard ratio (HR) up to 2.0 for recurrent symptomatic VTE in the rivaroxaban group.

There was a 2.1% recurrence rate in the rivaroxaban group and a 1.8% recurrence rate in the standard therapy group and (HR 1.12; 95% CI, 0.75–1.68; *P* =.003 for noninferiority, *P* =.57 for superiority). Major bleeds (overt and either at a critical site or needing transfusion) were less frequent in the rivaroxaban group than the standard therapy group (1.1% vs 2.2%; *P* =.003; NNT=91).

**Bottom line:** Although patients were not blinded to treatment assignment, the committee adjudicating events was blinded to treatment group assignment, minimizing potential bias. More patients in the rivaroxaban group presented with suspected recurrent VTE than the standard therapy group (although frequency of confirmed VTE was similar in the groups), making detection bias unlikely.

Based on this single RCT, rivaroxaban is an option for treatment of acute PE. It has a lower bleeding risk than warfarin with comparable value in preventing recurrent VTE.

**Review Author and Summary Author:** Umang Sharma, MD, The University of Chicago, Department of Family Medicine, Chicago, IL

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Bariatric surgery induces remission of type 2 diabetes


This single-centered, nonblinded RCT compared conventional medical therapy with bariatric surgery in 60 patients with type 2 diabetes and a body mass index (BMI) of ≥35 kg/m². The 2 bariatric surgeries were gastric bypass or biliopancreatic diversion. The primary outcome was the rate of remission of type 2 diabetes at 2 years. Remission was defined as a fasting blood glucose level of <100 mg/dL and a glycated hemoglobin (HbA1c) level of <6.5% for at least 1 year without active medication therapy. Secondary outcomes included changes in fasting blood glucose, HbA1c level, body weight, waist circumference, blood pressure, and lipid profiles at 2 years.

Diabetes remission occurred in 75% in the gastric bypass group with a relative risk of remission of 7.5 and NNT of 2 (*P*<.001 vs medical therapy). In the biliopancreatic diversion group, remission occurred in 95% with a relative risk of remission of 9.5 and NNT of 1 (*P*<.01 vs medical therapy). No remissions occurred in the medical therapy arm; relative risks were calculated assuming that the 2 dropouts in the medical therapy arm both had remission of their diabetes.

Patients in the bariatric surgery group also had significantly greater reductions in average body weight, BMI, and waist circumferences compared with the medical therapy arm. There were few adverse events and no operative deaths.

**Bottom line:** Remission of type 2 diabetes should be considered an important benefit of gastric bypass or biliopancreatic diversion for morbidly obese patients with type 2 diabetes.

**Review Author and Summary Author:** Mari Egan, MD, The University of Chicago, Department of Family Medicine, Chicago, IL

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Additional information can be found at: [www.fpin.org/purlsoverview](http://www.fpin.org/purlsoverview)
What sleeping arrangements are safe for infants and at what age are these precautions no longer needed?

**Bottom line**
Evidence supports supine sleep position, room sharing, a smoke-free environment, and breastfeeding as protective against sudden infant death syndrome (SIDS) during the first year of life. Bed sharing (as opposed to room sharing) is not recommended by the American Academy of Pediatrics.

**Evidence summary**
A 2003 population-based case-controlled study evaluated 260 SIDS cases from Chicago, Illinois. Multivariate analysis identified several independent risk factors for SIDS, including prone sleeping position (OR 2.3; 95% CI, 1.5–3.5), maternal smoking during pregnancy (OR 4.3; 95% CI, 2.1–8.9), soft sleep surfaces (OR 5.2; 95% CI, 2.6–10.2), and pillow use (OR 2.8; 95% CI, 1.3–6.2). Bed sharing by infants with mothers or mother and father did not significantly increase SIDS risk (OR 1.4; 95% CI, 0.7–2.8), but bed sharing with any other combination of factors increased SIDS risk significantly (OR 3.6; 95% CI, 1.4–9.4).

Data from a 2004 case-control study of 745 SIDS deaths from 20 centers in Europe with standardized reporting yielded similar results. In the multivariate analysis, prone sleeping position increased risk of SIDS (OR 13; 95% CI, 8.5–13). There appeared to be a dose–response increase in SIDS risk with increased smoking by others in the household, from smoking >10 cigarettes by others in the household (OR 1.5; 95% CI, 1.1–2.1) to smoking >30 cigarettes by others in the household (OR 3.3; 95% CI, 1.8–6). Maternal smoking independent of bed sharing slightly increased the risk of SIDS (OR 1.5; 95% CI, 1.1–2.1), but this risk was significant only for infants younger than 8 weeks of age. Any maternal smoking with bed sharing dramatically increased the risk of SIDS (OR 17; 95% CI, 10–30). Finally, SIDS risk was reduced for infants who room shared without bed sharing as the usual arrangement (OR 0.48; 95% CI 0.34–0.69) or at last sleep (OR 0.32; 95% CI, 0.19–0.55).

A 2011 meta-analysis of 18 case-control studies (N=2,810) of the effects of breastfeeding on SIDS concluded that any breastfeeding of any duration appears to have a protective effect on SIDS (summary multivariate OR 0.55; 95% CI, 0.44–0.69), with a greater reduction of risk with exclusive breastfeeding of any duration (summary univariate OR 0.27; 95% CI, 0.24–0.31). The American Academy of Pediatrics (AAP) recommends a supine sleep position on a firm sleep surface (not a chair or sofa) without soft pillows or blankets until 12 months of age. Room sharing, a smoke-free environment, and breastfeeding are also recommended. Caregivers should avoid overheating infants. The AAP does not recognize any particular bed sharing situation as safe.

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**REFERENCES**

**GLOSSARY**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<td>ARR</td>
<td>absolute risk reduction</td>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<td>CI</td>
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<td>CT</td>
<td>computed tomography</td>
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<td>number needed to treat</td>
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<td>NSAID</td>
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<td>selective serotonin reuptake inhibitor</td>
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Are lesbian, gay, bisexual, and transgender patients at higher risk for mental health disorders?

Summary
Yes. Lesbian, gay, bisexual, and transgender (LGBT) patients have higher rates of mental health disorders and higher rates of suicidality and self-harm than their heterosexual counterparts.

The evidence
Since the early 2000s, research has increased on the prevalence of mental disorders in the LGBT population. The rates are higher than the general population, and the social stigma, prejudice, and discrimination associated with minority sexual orientation are thought to be at least partially responsible.

The 1995 MacArthur Foundation National Survey of Midlife Development in the United States (MIDUS) assessed >3,000 American adults, 25–74 years of age, collecting data on sexual orientation and 1-year prevalence of major depression, generalized anxiety disorder, panic disorder, and alcohol and drug dependency. The use of mental health services by individuals of minority sexual orientations was also examined.

Gay and bisexual men were 3 times more likely to meet criteria for major depression and 4.7 times more likely to meet criteria for a panic disorder than their heterosexual counterparts (P<.05 for both). Nearly 20% of gay and bisexual men had ≥2 comorbid mental health disorders, higher rates than among heterosexual men. Among lesbian women, there was a higher rate of generalized anxiety disorder (14.7% vs 3.8% for all women; P<.05) but not depression or panic. More lesbian and bisexual women had ≥2 comorbid mental health disorders than heterosexual women.

A 2008 meta-analysis of mental disorders, suicide, and deliberate self-harm in LGBT patients included 25 trials that met inclusion criteria (had valid definitions of sexual orientation; a concurrent heterosexual comparison group within either a cohort, case-control, or cross-sectional study; outcomes identified as a DSM or ICD psychiatric disorder; and scores for psychiatric morbidity on standardized scales). Data were extracted on 214,344 heterosexual and 11,971 nonheterosexual patients.

The risk for depression and anxiety disorders was 1.5 times higher in LGB patients over 12 months than in heterosexuals. Substance dependence was also significantly higher in lesbian and bisexual women (alcohol dependence RR 4; 95% CI, 2.9–5.6; and drug dependence RR 3.5; 95% CI, 1.9–6.5). The lifetime prevalence of suicide attempt was especially high in gay and bisexual men (RR 4.3; 95% CI, 2.3–7.9).

A large New Zealand birth cohort study published findings specific to LGB youth. Data were gathered during the course of the Christchurch Health and Development Study, a 21-year longitudinal study of 1,265 children. At the age of 21, 1,007 members were questioned regarding their sexual orientation and relationships with same-sex partners since the age of 16. Also, from the ages of 14 to 21, data were gathered on a range of psychiatric disorders that included major depression, generalized anxiety disorder, conduct disorder, substance use disorders, suicidal ideation, and suicide attempts.

LGB status was a high risk of major depression (OR 4.0; 95% CI, 1.8–9.3), conduct disorder (OR 3.8; 95% CI, 1.7–8.7), suicidal ideation (OR 5.4; 95% CI 2.4–12), suicide attempts (OR 6.2; 95% CI, 2.7–14.3), and generalized anxiety disorder (OR 2.8; 95% CI, 1.2–6.5). LGBT youth also had a higher prevalence of 2 or more comorbid psychiatric disorders compared with their heterosexual counterparts (OR 5.9; 95% CI, 2.4–15).

The most comprehensive transgender survey to date, the National Transgender Discrimination Study, queried 6,450 transgender and gender-nonconforming adults. The study was conducted via mail and online questionnaires, and results were tallied from all 50 states. Authors reported that 41% of transgender respondents had attempted suicide (vs rates in the general population often cited at 1.5%–2%), with rates rising when additional stressors were reported—loss of job, harassment and bullying, low household incomes, or experiencing physical and/or sexual assault.

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REFERENCES
Which patients undergoing colonoscopy should have spontaneous bacterial endocarditis (SBE) prophylaxis?

Evidence-Based Answer
Routine administration of prophylactic antibiotics to prevent infective endocarditis (IE) from colonoscopy is not recommended. It is reasonable to give prophylactic treatment to patients with a known gastrointestinal (GI) tract infection as well as a prosthetic heart valve, valve repair with prosthetic material, or previous IE, cardiac transplant patients with subsequent valvulopathy, and some patients with congenital heart disease (SOR: C, consensus guidelines).

In 2007, the American Heart Association (AHA) appointed a group of experts to update and simplify the 1997 guidelines for the prevention of IE. The group analyzed literature from 1950 through 2006, and no RCTs were available. AHA incorporated the following information into the revision:

- Transient viridans group streptococci bacteremia occurs more frequently during daily events like tooth brushing (20%–68%) than during invasive procedures like colonoscopy (0%–25%, mean 4.4%).
- Antibiotic prophylaxis in general has not been proven to prevent IE.
- There is some risk of adverse events from prophylactic antibiotics.
- Widespread antibiotic use promotes resistant strains of enterococci and viridans group streptococci likely to cause IE.

Therefore, routine administration of prophylactic antibiotics, prior to colonoscopy was not recommended (Recommendation Class III: “evidence or general agreement that treatment is not useful”).

Nevertheless, the 2007 guideline authors also stated that they could not exclude the possibility that a few IE cases could be prevented using prophylactic antibiotics, and viridans group streptococcal IE carries a much higher mortality risk in patients with a prosthetic valve than in those with a native valve (~20% vs <5%). Therefore, this guideline recommended prophylaxis for the highest risk patients if a GI tract infection thought to be due to enterococci was present (Class IIb: “usefulness is less well established by evidence or opinion”). Patients with the following conditions were considered highest risk:

- Prosthetic cardiac valve or valve repair with prosthetic material
- Previous episode of IE
- Congenital heart disease (CHD)
  - Unrepaired cyanotic CHD
  - CHD repair with prosthetic material within 6 months of procedure
  - Repaired CHD with residual defects
- Cardiac transplant with subsequent valvulopathy

In 2008, the American Society for Gastrointestinal Endoscopy (ASGE) and the National Institute for Health and Clinical Excellence (NICE) conducted independent reviews, examining the available evidence and the 2007 AHA document. ASGE issued a document agreeing with the 2007 AHA guidelines. NICE also agreed with the AHA guidelines, adding patients with hypertrophic cardiomyopathy and acquired valvular heart disease (with stenosis or regurgitation) to their list of those at highest risk.

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What is the underlying rate of serious colonic disease in low-risk patients under age 50 with mild hematochezia?

Evidence-Based Answer
Serious colonic disease—defined as colon cancer, adenomatous polyps, or inflammatory bowel disease—is found in 15% to 31% of hemodynamically stable patients aged less than 50 years with hematochezia (SOR: B, observational studies).

Five studies published in the last 10 years report data on the rate of serious colonic disease in young patients with hematochezia. These studies excluded patients with a personal history of inflammatory bowel disease, colon cancer or polyps, unexplained weight loss, iron deficiency anemia, or recent colonoscopy. Patients with a family history of colon cancer were also excluded. Patients did not require hospitalization or transfusion.
Evidence-Based Answer

Megestrol acetate is associated with improved appetite and weight gain in cancer-related anorexia-cachexia syndrome (CACS), but has not been shown to improve survival (SOR: A, meta-analysis). Thalidomide treatment results in less weight loss, but again any impact on survival is unknown (SOR: B, RCT). Eicosapentaenoic acid is not effective (SOR: B, meta-analysis of small RCTs).

Anorexia, weight loss, and muscle and adipose tissue wasting is the main cause of death in >20% of patients with advanced cancer.1

A 2011 Cochrane meta-analysis compared megestrol acetate (MA) 100 to 1,600 mg/d versus placebo over an average of 8 weeks for the treatment of CACS.2 The meta-analysis included 8 RCTs with 565 patients studying appetite, and 7 RCTs of 895 patients studying weight gain.
When assessed as a dichotomous variable, MA was more likely to increase appetite (RR 3.0; 95% CI, 1.8–5.0) and result in weight gain (RR 2.1; 95% CI, 1.4–3.2) than placebo. The mean difference in weight gain between MA and placebo was 3.6 kg (95% CI, 1.3–5.9). A 2008 meta-analysis of 9 trials totaling 994 patients with CACS treated with MA in the same dosage range as the Cochrane review also demonstrated a higher likelihood of weight gain (33% of the MA group vs 19% of the placebo group; RR 1.7; 95% CI, 1.2–2.4; NNT=8). In 5 trials with 563 patients, appetite was also more likely to increase (57% of the MA group vs 18% of the placebo group; RR 3.0; 95% CI, 1.9–4.8; NNT=3–4). Despite these benefits, there was no demonstrable impact on 1-year survival (RR 1.0; 95% CI, 0.73–1.4).

In a 2005 RCT of 50 patients with pancreatic cancer and cachexia, patients randomized to receive thalidomide 200 mg daily lost on average 3.6 kg less than those treated with placebo over an 8-week period (95% CI, –6.8 to –0.3 kg). The treatment group also experienced 7.9 cm less wasting of bone-free arm muscle area (95% CI, –14.0 to –1.8), suggesting preservation of lean body mass. Mortality was not used as an outcome.

In a 2007 Cochrane meta-analysis, 2 RCTs (N=77) compared eicosapentaenoic acid (EPA) with placebo and showed no significant improvement in total caloric intake (standard mean difference 0.20; 95% CI, –0.25 to 0.65). There was also no significant difference in weight gain (1 trial, N=30; mean difference [MD] 0.92 kg; 95% CI, –0.77 to 2.6) or appetite improvement (1 trial, N=30; MD –0.80; 95% CI, –13 to 11) with EPA compared with placebo.

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The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Medical Department of the US Navy or the US Navy Service at large.

There was more of a reduction of lymphedema at 4 weeks compared with 6 months. Study quality was poor, with a lack of control group and low power. No information was given on symptoms. The Steering Committee for Clinical Practice Guidelines for the Care and Treatment of Breast Cancer consensus opinion states that practitioners “may want to encourage long-term and consistent use of compression garments by women with lymphedema.” The Oncology Nursing Society consensus opinion guideline states that the effectiveness of compression garments used alone in lymphedema has not been established.

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In adults hospitalized with pneumonia, does the use of a \( \beta_2 \)-agonist alter clinical outcomes?

Evidence-Based Answer

We do not know. But \( \beta_2 \)-agonists do not appear to improve symptoms in patients with acute bronchitis or cough (SOR: B, systematic review of low-quality RCTs) and current practice guidelines do not include use of \( \beta_2 \)-agonists in the treatment of pneumonia (SOR: C, consensus guideline).

A systematic review of RCTs evaluating adjuvant therapies in the treatment of community-acquired pneumonia (CAP) stated there were no clinical trials evaluating the routine use of \( \beta_2 \)-agonists for the treatment of CAP.

A Cochrane systematic review of 4 RCTs (N=2,54) comparing \( \beta_2 \)-agonists with placebo for the treatment of acute bronchitis or acute cough in adults did not find sufficient evidence to support the routine use of \( \beta_2 \)-agonists in these patients.

The combined data in the Cochrane review did not demonstrate a statistically significant improvement in daily cough score at 7 days (RR 0.77; 95% CI, 0.54–1.1) in the \( \beta_2 \)-agonist group compared with placebo. Subjects exposed to \( \beta_2 \)-agonists were more likely to report adverse effects such as tremors or nervousness (RR 8.0; 95% CI, 1.2–53). This review was limited by the small number of studies and participants as well as the short duration of the trials (3–7 days).

The most current Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of CAP in adults do not include use of \( \beta_2 \)-agonists for treatment.

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The opinions stated above are those of the authors and do not represent the opinions of the US Air Force.


Does colon cancer screening with surveillance colonoscopy reduce colorectal cancer mortality in adults with long-standing inflammatory bowel disease (>8 years)?

Evidence-Based Answer

Surveillance colonoscopy in patients with long-standing inflammatory bowel disease (IBD) leads to earlier diagnosis of colon cancer and may reduce colorectal cancer mortality (SOR: B, systematic review of cohort studies and evidence-based guideline).

Patients with IBD are at higher risk for developing colorectal cancer than the general population. The duration of IBD is an important risk factor for developing colorectal cancer.

In 2008, a Cochrane systematic review (including 1 case-control study with 142 patients, 1 prospective surveillance program with 41 patients, and 1 retrospective cohort analysis with 186 patients) assessed the effectiveness of colon cancer surveillance in patients with IBD. There was no evidence that surveillance colonoscopy prolonged survival in extensive colitis compared with the nonsurveillance group (RR 0.81; 95% CI, 0.17–3.8).

In one 8-year prospective study analyzed in this Cochrane review, carcinoma developed in 41 of 2,050
patients with ulcerative colitis; of these 41 patients, 19 were undergoing surveillance and 22 were not. Carcinoma was detected significantly earlier (Dukes’ stage A or B carcinoma) in the surveillance group (15 of 19 patients) compared with the nonsurveillance group (9 of 22 patients) \((P=0.039)\). The 5-year survival rate was 77\% for cancers occurring in the surveillance group and 36\% for the nonsurveillance group \((P=0.026)\). The authors concluded the evidence is unclear whether surveillance colonoscopies improved longevity, but that cancers do tend to be diagnosed earlier. They recommended screening every 3 years, increasing to 2 years after the first decade and annually after the second decade.\(^1\)

In 2006 a prospective surveillance analysis, published after the Cochrane search, evaluated a 30-year colonoscopy surveillance program in 600 patients with ulcerative colitis.\(^2\) The primary endpoints included death, colectomy, or withdrawal from the surveillance program. Thirty patients were identified with colorectal cancer during surveillance and 8 after leaving surveillance. Seventy-six patients died, 13 as a result of colorectal cancer. In patients with pancolitis, the colorectal cancer rate was 2.5\% (95\% CI, 1.2\%–4.8\%) at 20 years and 7.6\% (4\%–13\%) at 30 years, which is lower than in most other studies (possibly secondary to selection bias). Overall, 1 in 21 patients benefited from asymptomatic surveillance. Of the patients found to have cancer during surveillance, 76\% (13 of 17) were found to have Dukes’ stage A or B.

The American Gastroenterology Association (AGA) published an evidence-based guideline in 2010 on the diagnosis and management of colorectal cancer in patients with IBD.\(^3\) This review included the Cochrane review previously discussed; no RCTs were found. Based on case series and case-control studies, the AGA stated that surveillance colonoscopy is warranted in patients with IBD (Recommendation Grade B: “certainty of evidence is moderate that the magnitude of net benefit is either moderate or substantial”) and that the risk of developing colorectal cancer is significant after 8 years of disease. It also noted that colorectal cancer is detected at an earlier stage with a better prognosis with colonoscopy surveillance (Recommendation Grade B). The guidelines authors recommended performing colonoscopies every 1 to 3 years increasing to every 1 to 2 years after 20 years.

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A cost analysis compared bone densitometry testing followed by 5 years of treatment with alendronate for those with a femoral neck T-score of –2.5 or lower with no densitometry or no drug therapy. Authors assumed that if the cost per quality-adjusted life year (QALY) was less than $50,000, then the intervention was cost effective and represented a good utilization of resources. The model showed that the cost per QALY for universal bone densitometry combined with alendronate therapy for those diagnosed with osteoporosis was cost effective for women aged ≥65 and ≥75 years ($43,000 and $5,600, respectively) and the screening and treatment was actually cost saving for patients aged >85 (no value provided).

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<table>
<thead>
<tr>
<th>Screening outcomes</th>
<th>Number per 10,000 women, by age (years)</th>
<th>55–59</th>
<th>65–69</th>
<th>75–79</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identified with osteoporosis</td>
<td>445</td>
<td>1,200</td>
<td>2,850</td>
<td></td>
</tr>
<tr>
<td>Hip fracture prevented with medication</td>
<td>2</td>
<td>14</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>NNS to prevent 1 hip fracture</td>
<td>4,338</td>
<td>731</td>
<td>143</td>
<td></td>
</tr>
<tr>
<td>NNT to prevent 1 hip fracture</td>
<td>193</td>
<td>88</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Vertebral fractures prevented</td>
<td>7</td>
<td>40</td>
<td>134</td>
<td></td>
</tr>
<tr>
<td>NNS to prevent 1 vertebral fracture</td>
<td>1,338</td>
<td>248</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>NNT to prevent 1 vertebral fracture</td>
<td>60</td>
<td>30</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

NNS=number needed to screen; NNT=number needed to treat; USPSTF=US Preventive Services Task Force.

A 2006 Cochrane systematic review identified only 1 useful study of valerian for the treatment of generalized anxiety disorder (GAD). This was a 4-week double-blind RCT of 36 adults (mean age 41 years, 66% female) with GAD divided into 3 groups. The treatment group received 50–150 mg valerian extract per day, while the 2 comparison groups received either a placebo or 2.5–7.5 mg diazepam per day. Anxiety symptoms were measured using a clinician-rated Hamilton Anxiety Scale (HAM-A, a 0–56 point scale) as well as a self-reported State-trait Anxiety Inventory (STAI-T, a 20–80 point scale).

At the 4-week follow-up, HAM-A scores were similar in the valerian and placebo groups (weighted mean difference [WMD] −1.4; 95% CI, −7.9 to 5.1) as well as the valerian and diazepam groups (WMD 0.40; 95% CI, −6.2 to 7.0). Likewise, with the STAI-T scores, no significant difference was observed for valerian versus placebo (WMD 0.70; 95% CI, −0.93 to 11). However, the diazepam group had significantly lower STAI-T scores than the valerian group (WMD 11; 95% CI, 1.9 to 20). No adverse effects were reported.

The Natural Medicines Comprehensive Database editorial staff reported that valerian is likely safe when used in medicinal amounts up to 28 days, based on clinical studies involving more than 12,000 patients. Adverse effects listed include headache, excitability, uneasiness, and insomnia. These editors also recommend reducing doses slowly over a week or two prior to discontinuing valerian in order to prevent potential withdrawal symptoms.

We invite your questions and feedback.
Email us at EBP@fpin.org.
Is long-term use of zolpidem for the treatment of insomnia habit forming?

**Bottom line**

Use of zolpidem for 6 to 12 months does not result in tolerance, escalation of dosing, or rebound insomnia (SOR: A, multiple RCTs). Zolpidem dependence or abuse is rare but has been reported, primarily in patients who have psychiatric or substance use disorders (SOR: C, case reports).

**Evidence summary**

A double-blind RCT was conducted in 1,016 patients with chronic primary insomnia (ages 18–64) to assess the efficacy and tolerance of zolpidem ER 12.5 mg for 6 months.¹ Patients self-administered either zolpidem or placebo a minimum of 3 and a maximum of 7 days per week for 24 weeks followed by a “run out” week with no medication.

Efficacy (as measured by a patient global impression scale) was significantly higher with zolpidem (85% zolpidem vs 38% placebo at week 4; \(P < .001\); and 92% vs 60% at week 24; \(P < .001\)). Comparing month 1 to month 6, there was no statistical difference in number of zolpidem pills taken per month (19 vs 20 pills per month). There was no worsening of insomnia from baseline on the first 3 nights after discontinuation of zolpidem as measured by patient-recorded total sleep time and wake time after sleep onset.¹

A randomized, double-blind, placebo-controlled trial of 33 patients with chronic insomnia evaluated the likelihood of dose escalation of zolpidem over a 12-month period.² Patients in the zolpidem and placebo groups were allowed to self-administer up to 3 tablets a night (total dose 15 mg zolpidem). Dose escalation was not seen in the zolpidem group from month 1 to month 12 (1.8 tablets at month 1, 1.9 tablets at month 4 and 12; \(P > .05\)) but was seen in the placebo group (1.5 tablets at month 1, 1.9 tablets at month 4 and 12; \(P < .02\)).

A 6-month prospective cohort trial of 10 or 20 mg zolpidem nightly was conducted in 96 patients older than 40 years with chronic insomnia.³ Fifty percent of the patients completed an additional 6 months of therapy. Efficacy was assessed by patient self-report and physician interviews.

Total sleep time of more than 6 hours was noted in 21% of patients at baseline, 84% at 180 days, and 81% at 360 days. Time to sleep of less than 30 minutes was noted for 14% at baseline, 80% at 180 days, and 81% at 360 days. Escalation of dosages was not seen.³

A literature review of case reports of zolpidem dependence and abuse found 53 reports from 1993 to 2005.⁴ Sixty-three percent of the patients had a history of a psychiatric disorder and 43% had other substance abuse disorders. Unlike the general populations described above, 51% of the patients in the case reports developed tolerance to zolpidem and 81% had a withdrawal syndrome after stopping the medication.⁴

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REFERENCES


1. According to the best evidence available at this time:
   a. Infants are at no higher risk sleeping in the same room with a smoker as with a nonsmoker, as long as they are not on the same sleep surface as the smoker.
   b. Sharing a room with an infant can reduce the risk of sudden infant death syndrome (SIDS).
   c. For nonsmoking mothers, bed sharing poses a risk for SIDS up until age 1 year.
   d. Infants should be swaddled tightly when sleeping to prevent rolling into the prone position when asleep.

2. The 1995 MacArthur Foundation National Survey of Midlife Development in the United States (MIDUS) found that gay and bisexual men are statistically more likely to suffer from _______ & _______ than their heterosexual counterparts, and lesbian and bisexual women are statistically more likely to suffer from _______ & _______ than their heterosexual counterparts.
   a. Suicidal ideation & suicide attempts; panic disorder.
   b. Major depression & panic disorder; generalized anxiety disorder.
   c. Drug & alcohol dependency; major depression.
   d. Generalized anxiety disorder & alcohol dependence; major depression.

3. Which patient should undergo spontaneous bacterial endocarditis prophylaxis while undergoing colonoscopy?
   a. A patient with mitral valve prolapse and known gastrointestinal (GI) infection.
   b. A patient with a prosthetic cardiac valve and no GI infection.
   c. A patient with unrepaired cyanotic congenital heart disease and no GI infection.
   d. A patient with history of infective endocarditis and known GI infection.

4. In which patient population is universal screening for osteoporosis indicated?
   a. All postmenopausal women.
   b. Women <65 years of age, without additional risk factors.
   c. All women ≥65 years of age.
   d. Only those women who are ≥65 years of age and have additional risk factors.

5. When treating community-acquired pneumonia in adults, which statement best describes the role of β₂-agonists?
   a. Every patient with community-acquired pneumonia should receive β₂-agonists to improve oxygenation.
   b. The most current Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults strongly support the use of β₂-agonists.
   c. There is insufficient evidence to recommend β₂-agonists routinely for community-acquired pneumonia, more studies in this area are needed.
   d. Patients treated with β₂-agonists for community-acquired pneumonia are unlikely to experience adverse effects.

6. What range best corresponds to the underlying rate of adenomas, cancer, and inflammatory bowel disease found in low-risk patients under age 50 with hematochezia?
   a. 5%–10%.
   b. 15%–30%.
   c. 40%–50%.
   d. 60%–70%.

7. Which of the following statements is true regarding cancer-associated anorexia/cachexia?
   a. Thalidomide has no evidence of any benefit compared with placebo.
   b. Eicosapentaenoic acid is associated with improved appetite and weight gain.
   c. Megestrol acetate has been shown to improve survival.
   d. Megestrol acetate is associated with improved appetite and weight gain.

8. Which of the following statements is true regarding zolpidem for insomnia?
   a. Patients frequently need a higher dose of zolpidem after a few months of use.
   b. Patients with psychiatric or substance use disorders are at higher risk for abuse of zolpidem.
   c. Rebound insomnia is common after 6 months of zolpidem use.
   d. Zolpidem is not effective for long-term treatment of chronic insomnia.
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