ISSN 1095-4120 (print)
ISSN 2473-3717 (online)

Vol 20 | No. 7 | July 2017

EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

EDITORIAL

2 Part way

IN DEPTH

3 Sensitivity of colon cancer screening modalities

DIVING FOR PURLs

4 CV risk reduction with liraglutide

Treating acute respiratory tract infection in children

ADVANCES IN GERIATRICS

5 Psychotherapy for depression among the elderly

HELPDESK ANSWERS

6 Best management of ovarian failure in women with Turner syndrome

Imaging for patients with suspected scaphoid fractures

7 Monofilament testing for diagnosing diabetic peripheral neuropathy

8 Risks of oral contraceptives in females with migraines

9 Duration of effectiveness of IUDs

Use of atypical antipsychotic agents in children with disruptive behaviors

10 Beta-agonists for CHF

11 Antiplatelet therapy during dental procedures

12 Lumbar puncture for suspected sepsis in infants

SPOTLIGHT ON PHARMACY

14 Treatment for asymptomatic bacteriuria in pregnancy

ONLINE CONTENT

E1 First trimester screening for Down syndrome

E2 Low FODMAPs diet for irritable bowel syndrome

E3 High-dose influenza vaccine for elderly patients

E4 Initiating fetal surveillance in postdates gestation

E5 Risk of esophageal adenocarcinoma in patients with Barrett's esophagus

E6 Liver function test monitoring in statin-treated patients

E7 Edinburgh Postnatal Depression Scale for postpartum depression

E8 Probiotics for preventing antibiotic-associated diarrhea

E9 Vitamin D and stress fractures

E10 Best treatment for adult somatization disorder

E11 Secondary stroke prevention in patients with patent foramen ovale

E13 Escitalopram and depression in heart failure

Vitamin K and stable INRs

View this issue and access the online content at: **www.fpin.org/ebparchives**

FPIN
Family Physicians Inquiries Network

FPIN envisions a primary care workforce that thinks critically, communicates expertly, and utilizes the best current evidence to improve the health of patients.

Part way

This summer, I tried day hiking into the Goat Rocks Wilderness in southwestern Washington state. The experience reminded me of all the other times I have tried day hiking in wilderness areas—most recently the Bob Marshall, Norse Peak, Wind River, and William O. Douglas Wilderness Areas. In all instances, I walked for 7 or 8 miles, often at a considerable incline, until I was utterly exhausted. Repeatedly, just when my legs and my watch demanded I turn around, I would look up and see, on the far horizon, the hazy peaks I thought I was going to visit standing yet another 10 miles away.

The trailheads I used were all deep in the woods and down in the canyons. Miles went by when all I could see were old growth trees and maybe a river. Then, somewhere near the end of my endurance, the trail cut up a side canyon, the trees thinned out, and an obscure ridgeline was attained. There, I could finally make out the topology. While the view always revealed summits beyond reach, it also revealed the undulating landscape falling away, the mood of the sky, the immensity of the Earth, and the considerable work of the day.

So, I started celebrating getting part way.

Today I want to invite you to celebrate getting part way in the management of diabetes. Several researchers have posted a progress report in the *New England Journal of Medicine*.[1] You might have missed it because it had a terrible title: "Excess mortality among persons with type 2 diabetes." That sounds like a downer, but the details were remarkable. Looking at a nationwide registry of 435,369 Swedish patients followed for more than 4 years, a diagnosis of diabetes was associated with mortality rates only 15% over baseline. That sounds bad until you reflect that the historical rate was double the baseline. Amazingly, for patients 65 to 74 years old with good glycemic control and normal kidneys, the mortality rate was *lower* than controls!

So diabetes has not been conquered, but we have made considerable progress. Pull out the water bottle and have some trail mix. It is time to celebrate getting part way.

Jon O. Neher, MD

REFERENCE

1. Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, Gudbjörnsdottir S, et al. Excess mortality among persons with type 2 diabetes. *N Engl J Med*. 2015; 373(18):1720–1732.

STATEMENT OF PURPOSE

Evidence-Based Practice (EBP) addresses important patient care questions asked by practicing family physicians, using the best sources of evidence in a brief, clinically useful format. Our goal is to instruct our authors on how to write peer-reviewed scholarly research for the medical and scientific community.

EDITORIAL POLICY

Statements and opinions expressed in articles and communications in this journal are those of the author(s) and not necessarily those of the editor, publisher, or any organizations endorsing this journal. The Publisher and editors of EBP do not endorse any methods, products, or ideas mentioned in the journal, and disclaim any liability which may arise from any material herein. Unless noted, authors have reported no competing interests and have nothing to disclose.

DISCLOSURE

The PURLs Surveillance System is supported in part by Grant Number UL1RR024999 from the National Center for Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

2017 SUBSCRIPTION RATES

PERSONAL SUBSCRIPTIONS:	
FPIN Member	$59
Non-member	$119
International (outside of the US or Canada)	$179
INSTITUTIONAL SUBSCRIPTIONS:	
US and Canadian Institutions	$209
International Institutions	$259
EBP Electronic Archives	$500

Third Class postage paid at Columbia, MO 65202.
The GST number for Canadian subscribers is 124002536.
Postmaster: Send address changes to FPIN, Inc., 401 West Boulevard North, Suite D, Columbia, MO 65203; Attn: Adelina Colbert. Adelina@fpin.org. 573-256-2066.

What percentage of advanced colonic neoplasms can be found by colonoscopy, flexible sigmoidoscopy, and stool guaiac?

EVIDENCE-BASED ANSWER

Colonoscopy detects about 98% of large (≥10 mm) adenomas (SOR: **A**, meta-analysis of cohort studies). When colonoscopy is used as the reference standard, simulated flexible sigmoidoscopy has a sensitivity for detecting any advanced colonic neoplasm throughout the colon of 70% to 86% (SOR: **A**, systematic review of cohort studies) and a single stool guaiac test is 50% to 65% sensitive for detecting colorectal cancer (SOR: **B**, small prospective cohort study with a case-control arm).

Evidence summary

A 2006 meta-analysis examined pooled data from 6 cohort studies evaluating the large adenoma (≥10 mm diameter) detection rate in tandem, same-day colonoscopies performed on 465 adult patients aged 37 to 92 years.[1] The training level of the endoscopists differed among the studies and overall risk of colorectal cancer varied from high to low, but all studies compared the detection of large adenomas between both same-day examinations. Indications for colonoscopy also varied, most commonly follow-up of previously detected polyps and screening.

In total, 96 large adenomas were found, with only 2 additional adenomas discovered in the second examination. Thus, the large adenoma detection rate was approximately 98% (95% CI, 92.7–99.7). Although colonoscopy is the gold standard for adenoma detection, the use of tandem colonoscopy for control cannot be assumed to be 100% accurate as there is a risk of missing lesions in awkward positions, variability based on bowel prep, and inaccuracy in size measurement with the tools available.[1]

A 2008 systematic review examined pooled data from 6 cohort studies evaluating the advanced neoplasia detection rate of simulated flexible sigmoidoscopy compared with screening colonoscopy in 14,938 adults 40 to 79 years old with average colorectal cancer risk—ie, no personal or family history of colon cancer, inflammatory bowel disease, or familial polyposis.[2] The term "advanced neoplasia" was used to include adenocarcinoma, adenomas with high-grade dysplasia or villous histology, and adenomas ≥10 mm in diameter. Simulated flexible sigmoidoscopy included the actual findings and hypothetical follow-up action on all lesions distal to the splenic flexure observed during screening colonoscopy.

The sensitivity of simulated flexible sigmoidoscopy for detecting advanced neoplasia throughout the colon, compared with screening colonoscopy, ranged from 70% to 86%. The use of simulated flexible sigmoidoscopy likely overestimated sensitivity due to improved bowel prep with colonoscopy, as well as reliably reaching the splenic flexure.[2]

A 2015 multicenter prospective cohort study with a case-control arm evaluated the sensitivity of stool guaiac testing for detecting colorectal cancer in both a screening population (n=257) and a known colorectal cancer (n=20) control population.[3] The screening population used in the study consisted of adults aged 50 to 74 years old who were hospitalized for nongastrointestinal-related complaints. This screening group first underwent testing with stool guaiac and then shortly after underwent a confirmatory colonoscopy in which 4 colorectal cancers were found (1.6% prevalence).

The sensitivity of stool guaiac testing for detecting cancer in the screening population was 50% (95% CI, 6.8–93). The control group with known cancer was recruited independently and underwent stool guaiac testing alone, demonstrating a sensitivity of 65% (95% CI, 41–85). There was a very slight trend showing increased sensitivity as the cancer stage increased, but this finding was not significant. This trial was limited by its small sample size, particularly with its small rate of colorectal cancer and the methodology of administering the stool guaiac test only once.[3] EBP

Rae Adams, MD
Tessa Reinke, MD
Texas A&M FMR
Bryan, TX

REFERENCES

1. van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss determined by tandem colonoscopy: a systematic review. *Am J Gastroenterol*. 2006; 101(2):343–350. **[STEP 1]**
2. Whitlock EP, Lin J, Liles E, Beil TL, Fu R. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2008; 149(9):638–638. **[STEP 1]**
3. Elsafi SH, Alqahtani NI, Zakary NY, Al Zahrani EM. The sensitivity, specificity, predictive values, and likelihood ratios of fecal occult blood test for the detection of colorectal cancer in hospital settings. *Clin Exp Gastroenterol*. 2015; 8:279–279. **[STEP 3]**

Liraglutide has less adverse cardiovascular outcomes than placebo

Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016; 375(4):311–322.

This double-blind RCT compared liraglutide with placebo in 9,340 patients with type 2 diabetes in 32 different countries. All patients had an HbA1C of >7% and were either older than 50 years with cardiovascular (CV) disease or older than 60 years with an additional CV risk factor.

Liraglutide was given by subcutaneous injection in doses up to 1.8 mg. Target HbA1C was <7% and investigators could add other diabetes medication (not glucagon-like peptide 1 [GLP-1] agonists or dipeptidyl peptidase 4 inhibitors) as needed. The primary outcome was time to event of death from CV causes, nonfatal myocardial infarction (MI), or stroke.

The primary outcomes occurred less often in the liraglutide group than in the placebo group (13% vs 15%; hazard ratio 0.87; 95% CI, 0. 78–0.97; number needed to harm=53). Adverse events that led to discontinuation were higher in the liraglutide group than in the placebo group (9.5% vs 7.3%; $P \leq .001$).

Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	No	Clinically meaningful	Yes

Bottom line: Liraglutide appears to lead to less death from CV causes, nonfatal MI, and stroke compared with placebo in patients with type 2 diabetes, but also has higher discontinuation rates. This trial did not achieve the criteria for a PURL because many practitioners are using GLP-1 agonists already.

Review and Summary Author: Anne Mounsey, MD, University of North Carolina at Chapel Hill, Chapel Hill, NC

Additional information regarding the PURLs and Diving for PURLs series can be found at: **http://www.fpin.org/purls-faqs/**

Clinical rule to decrease antibiotics?

Hay AD, Redmond NM, Turnbull S, Christensen H, Thornton H, Little P, et al. Development and interval validation of a clinical rule to improve antibiotic use in children presenting to primary care with acute respiratory tract infection and cough: a prognostic cohort study. *Lancet Respir Med*. 2016; 4(11):902–910.

This prospective prognostic study of 8,394 children (3 months to 16 years old) with cough evaluated the predictive value of several patient characteristics on risk of hospital admission for any respiratory tract infection in the 30 days after recruitment.

Clinicians recorded sociodemographic data, past medical history, parent-reported symptoms, physical examination findings, and whether or not antibiotics were prescribed. Odds ratios were calculated for 33 associated symptoms and examination findings.

Hospital admission for respiratory tract infection in the 30 days after presentation could be accurately predicted with a clinical rule using 7 predictors, with a mnemonic of STARWAVe (Short illness up to 3 days prior to presentation to the clinician, Temperature of ≥37.8°C, Age <2 years, costal Retractions, Wheeze, history of Asthma, and Vomiting). This rule determined the risk of hospitalization in the 30 days after presentation (area under ROC curve of 0.81; 95% CI, 0.76–0.85).

One point was given to each of the STARWAVe criteria listed above. Patients with 0–1 points were placed in the very-low-risk category, 2–3 in the normal-risk category, and ≥4 in the high-risk category.

Hospital admission rates for each risk strata were as follows: very low, 0.3%; normal, 1.5%; and high, 11.8%.

Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	No	Clinically meaningful	No

Bottom line: Predictors of hospital admission for children presenting to a primary care clinic with cough can be useful for parent education and follow-up purposes. However, the data presented in the study do not support whether or not antibiotics should be prescribed for any of the risk strata. The "leap of faith" to not prescribe antibiotics to patients in the very-low-risk group seems reasonable, but the primary data analyzed do not answer this question. EBP

Review and Summary Authors: Carlton Covey, MD, FAAFP, and David Moss, MD, Nellis Air Force Base FMR, Las Vegas, NV

In older adults with depression, is psychotherapy effective?

CASE

A 72-year-old woman with congestive heart failure, hypertension, and atrial fibrillation, and a complex medication regimen, is diagnosed with moderate depression. She and her family are concerned about adding more medications and want to know if counselling might be effective.

Bottom line

Psychotherapy is an effective treatment for geriatric depression, and is a reasonable first-line treatment for mild to moderate depression. Problem-solving therapy seems to be especially effective, and telemedicine is not inferior to in-person psychotherapy.

Evidence summary

A meta-analysis of 9 RCTs, with a total of 569 participants (>60 years old), examined problem-solving therapy for depression.[1] After deleting a duplicate study and 2 heterogeneous studies from the meta-analysis, the authors found that problem-solving therapy significantly reduced depression based on the Hamilton Rating Scale for Depression (scored 0–50, with >7 indicative of mild depression, and >23 indicative of very severe depression), with a pooled mean difference of 6.9 (95% CI, 3.0–11).

Problem-solving therapy was demonstrated to benefit older adults with both depression and significant disability, and this effect was demonstrated across various care models, including in-home services, telemedicine, primary care, and collaborative care.[1]

The largest meta-analysis included 44 RCTs of 4,409 participants at least 50 years old in which psychological treatments were compared with a control group, with another psychological treatment, and with pharmacotherapy.[2] The overall standardized mean difference (SMD) between psychotherapy and control groups was 0.64 (95% CI, 0.47–0.80), corresponding to a number needed to treat (NNT) of 3, with benefits persisting at 6-month follow-up. When separated, trials with wait-list controls (nontreatment control) showed greater effect size than those with care-as-usual or other control groups.

A 2015 systematic review and meta-analysis identified 27 RCTs with 37 therapy-control pairs and 2,245 participants at least 55 years old.[3] This review focused on comparing therapies with a variety of different types of controls (waitlist, usual-care, placebo, attention, or supportive therapy).

All treatment was shown to be more effective than control (SMD 0.73; 95% CI, 0.51–0.95). The SMDs of improvement within the control subgroups ranged from 0.05 to 1.36.[3]

In 74 patients with dementia, psychotherapy in the form of problem adaptation therapy (an in-home psychosocial intervention designed to treat mild to moderately cognitively impaired older adults with major depression), versus supportive therapy, provided greater depression remission (38% vs 14%; *P*=.017; NNT=4) and partial remission (62% vs 30%; *P*=.005; NNT=3).[4] These findings are limited by the short duration of the trial (12 weeks).

One proposed solution to the problem of inadequate access to psychotherapy for the elderly is telemedicine, which allows therapists to access more remote locations via videoconferencing or other methods. An RCT among elderly veterans showed that teletherapy was noninferior to in-person therapy.[5] Treatment response rates did not differ significantly between groups: telemedicine at 45% (22 patients; 90% CI, 16–29 patients) and in-person at 39% (20 patients; 90% CI, 14–27).

CASE WRAP-UP

You refer your patient to see a psychotherapist who provides standard cognitive behavioral therapy twice a month. Your patient returns to you after 3 months of treatment, and her depression is in remission. EBP

Irene Hamrick, MD
Rebecca Radue, MD
University of Wisconsin
Madison, WI

REFERENCES

1. Kirkham JG, Choi N, Seitz DP. Meta-analysis of problem solving therapy for the treatment of major depressive disorder in older adults. *Int J Geriatr Psychiatry*. 2016; 31(5):526–535. **[STEP 1]**
2. Cuijpers P, Karyotaki E, Pot AM, Park M, Reynolds CF 3rd. Managing depression in older age: psychological interventions. *Maturitas*. 2014; 79(2):160–169. **[STEP 1]**
3. Huang AX, Delucchi K, Dunn LB, Nelson JC. A systematic review and meta-analysis of psychotherapy for late-life depression. *Am J Geriatr Psychiatry*. 2015; 23(3):261–273. **[STEP 1]**
4. Kiosses DN, Ravdin LD, Gross JJ, Raue P, Kotbi N, Alexopoulos GS. Problem adaptation therapy for older adults with major depression and cognitive impairment: a randomized clinical trial. *JAMA Psychiatry*. 2015; 72(1):22–30. **[STEP 2]**
5. Egede LE, Acierno R, Knapp RG, Lejuez C, Hernandez-Tejada M, Payne EH, et al. Psychotherapy for depression in older veterans via telemedicine: a randomised, open-label, non-inferiority trial. *Lancet Psychiatry*. 2015; 2(8):693–701. **[STEP 2]**

What is the best management of ovarian failure in women with Turner syndrome?

EVIDENCE-BASED ANSWER

Parenteral estrogen starting at age 12 is associated with about 6 cm more growth than oral estrogen (SOR: **B**, cohort study). It is unclear if starting parenteral estrogen at age 12 or 14 makes a difference (SOR: **B**, underpowered RCT). Transdermal estrogen therapy is associated with achieving at least Tanner stage 4 and more growth than expected by historical standards. All patients with Turner syndrome should receive estrogen at age 12 and cyclic progesterone 2 years later to induce sexual maturity (SOR: **C**, expert opinion).

A 2005 RCT compared early and late administration of parenteral estrogen in 2 groups of girls (N=14) with Turner syndrome.[1] Both groups received growth hormone (GH, 0.05 mg/kg per day) starting around age 10; one group received parenteral estrogen (0.2 mg/month intramuscular, increased by 0.2 mg every 6 months) beginning at age 12 and the other group beginning at age 14; both groups were followed for 1 to 4 years until reaching adult height. In a cohort study format, they were also compared with age-matched registry patients who started GH around age 10 and oral estrogen beginning at age 12 or 14.

Both parenteral estrogen groups showed age-appropriate feminization (Tanner breast staging 2–5, mean 3–4). The early parenteral estrogen group grew 17.3 cm compared with 14.9 cm in the late parenteral estrogen group ($P<.07$) and 11.4 cm in early oral estrogen registry patients ($P<.05$).[1] It is unclear if the study had enough power to detect a difference between the parenteral estrogen groups.

A 2004 case series of 23 females with Turner syndrome (age >12 years) evaluated growth and feminization with percutaneous estrogen gel, 0.1 to 1.5 mg daily, increased step-wise over 5 years.[2] Mean height and weight for the treatment group were above Ranke growth standards for girls with Turner syndrome by 1.51 and 0.58 standard deviation scores, respectively (no statistical analysis was provided). All patients reached a Turner stage of at least 4 for breast and pubic hair (B4P4); 79% reached B5 and 58% reached P5.

The 2007 Turner Syndrome Study Group guidelines recommend puberty and menarche be induced with estrogen supplementation and progesterone.[3] Low-dose estrogen therapy, increased over 2 years, should be initiated at age 12 if secondary sexual development is absent. After 2 years of therapy or after breakthrough bleeding occurs (whichever occurs first), cyclic progesterone therapy should be added. Oral contraceptive pills are not recommended. Estrogen supplementation should be continued until the normal time of menopause.

Vincent Tichenor, MD
Matthew Snyder, DO, FAAFP
Saint Louis University FMR
Belleville, IL

The opinions and assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of Saint Louis University, the US Air Force Medical Service, or the US Air Force at large.

1. Rosenfield RL, Devine N, Hunold JJ, Mauras N, Moshang T Jr, Root AW. Salutary effects of combining early very low-dose systemic estradiol with growth hormone therapy in girls with Turner syndrome. *J Clin Endocrinol Metab*. 2005; 90(12):6424–6430. **[STEP 2]**
2. Piippo S, Lenko H, Kainulainen P, Sipilä I. Use of percutaneous estrogen gel for induction of puberty in girls with Turner syndrome. *J Clin Endocrinol Metab*. 2004; 89(7):3241–3247. **[STEP 3]**
3. Bondy C. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. *J Clin Endocrinol Metab*. 2007; 92(1):10–25. **[STEP 5]**

What is the best imaging test for patients with suspected scaphoid fractures and normal plain radiographs?

EVIDENCE-BASED ANSWER

For a patient with a suspected scaphoid fracture but normal plain radiographs, computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy are all reasonable next-step imaging modalities (SOR: **A**, meta-analysis of cohort studies). From a healthcare spending perspective, CT or MRI may be more cost effective than a strategy of immobilization with follow-up after 2 weeks for repeat plain radiographs and orthopedic consultation (SOR: **B**, cost-effectiveness analysis).

A 2015 systematic review and meta-analysis examined 11 cohort studies including 717 patients with suspected scaphoid fracture but normal plain radiographs.[1] The objective was to identify the best subsequent imaging modality (hence referred to as index study) for diagnosing scaphoid fractures.

TABLE

Sensitivity, specificity, and likelihood ratios of imaging tests for diagnosing scaphoid fractures in patients with suspicious signs and symptoms but normal plain radiographs[1]

Imaging study	No. of trials	No. of fractures suspected	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio	Negative likelihood ratio
Bone scan	6	543	0.99 (0.69–1.0)	0.86 (0.73–0.94)	7.4	0.01
Computed tomography	4	277	0.72 (0.36–0.92)	0.99 (0.71–1.0)	120	0.3
Magnetic resonance imaging	5	221	0.88 (0.64–0.97)	1.0 (0.38–1.0)	827	0.1

CI=confidence interval.

Four studies examined CT, 5 examined MRI, and 6 examined bone scintigraphy. The reference standard was typically results of plain radiography at 6 weeks follow-up; however, some studies also used 2 positive index studies, 2 negative index studies, or clinical follow-up along with an index study. The studies were all of moderate to good quality.

Based on the pooled results, all imaging tests were reasonable modalities, with bone scintigraphy being the most sensitive, but CT and MRI were more specific (see **TABLE**). The review noted additional advantages and disadvantages of each imaging modality aside from accuracy. CT is generally more readily available but has a radiation dose of 0.03 mSv per imaging study. MRI has less availability but no radiation. Bone scintigraphy has a radiation dose of 4 mSv per imaging study, must be done at least 72 hours after the injury to detect the fracture, and requires a radioisotope intravenous injection.[1]

A cost-effectiveness analysis compared empiric cast immobilization with 2-week orthopedic follow-up and repeat plain radiographs against either immediate CT or MRI.[2] The researchers estimated the costs of imaging, follow-up, lost worker productivity, surgical costs of nonunion, and development of arthritis based on literature reports. Repeat plain radiographs at 2 weeks after immobilization were assumed to be 100% accurate for diagnosing scaphoid fractures.

The societal cost per case of empiric cast immobilization was $1,227, while the cost of immediate CT was $411 and immediate MRI was $526. The study was limited by controversy about the value of missed work and poor-quality cost data.[2]

Eric Li, MD
Christopher Sanford, MD
University of Washington FMR
Seattle, WA

1. Mallee WH, Wang J, Poolman RW, Kloen P, Maas M, de Vet HC, et al. Computed tomography versus magnetic resonance imaging versus bone scintigraphy for clinically suspected scaphoid fractures in patients with negative plain radiographs. *Cochrane Database Syst Rev.* 2015; (6):CD010023. **[STEP 1]**
2. Karl JW, Swart E, Strauch RJ. Diagnosis of occult scaphoid fractures: a cost-effectiveness analysis. *J Bone Joint Surg Am.* 2015; 97(22):1860–1868. **[STEP 4]**

How accurate is monofilament testing for the diagnosis of diabetic peripheral neuropathy?

EVIDENCE-BASED ANSWER

Abnormal monofilament testing has positive likelihood ratios >7 and negative likelihood ratios ranging from 0.07 to 0.61 for diagnosing neuropathy in patients with diabetes. (SOR: **B**, systematic review of heterogeneous cohort studies and single cohort study). Absent monofilament sensation is sufficient to diagnose diabetic peripheral neuropathy (SOR: **C**, expert opinion).

A 2009 systematic review of cohort studies compared the accuracy of 10-g Semmes-Weinstein monofilament (SWMF) testing with nerve conduction testing to diagnose diabetic peripheral neuropathy.[1] The lack of standardized test procedures markedly limited study inclusion. Three of 54 studies (N=641) qualified for review; all participants had been previously diagnosed with diabetes mellitus (DM). The SWMF

methods varied from single testing of the hallux to testing on 10 locations on the foot, including ventral and dorsal base of some digits, medial and lateral midfoot, and the heel. The threshold for determining a positive SWMF test also varied.

SWMF testing was very good for diagnosing peripheral neuropathy, with positive likelihood ratios (LR+) from 10.6 (95% CI, 4.0–28) to 16.5 (95% CI, 1.1–245), but not consistently helpful for ruling out diabetic peripheral neuropathy, with negative likelihood ratios (LR–) from 0.07 (95% CI, 0.02–0.26) to 0.61 (95% CI, 0.56–0.67).[1]

A 2011 diagnostic cohort study (N=314) compared SWMF testing on the dorsal and plantar aspects of the halluces to determine the accuracy of each method in patients with type 2 diabetes with a mean duration of illness of more than 12 years.[2] SWMF was applied 4 times to the dorsal and plantar aspects of each hallux, with patients reporting normal (1 point), decreased (0.5 points), or absent sensation (0 points) for each application of the filament. Investigators assigned a total score of ≥7 points as a negative test and ≤3 points as a positive test. Nerve conduction studies served as the reference standard.

In patients reporting neuropathy signs or symptoms, the LR+ were 7.8 and 7.1, and LR– were 0.16 and 0.092 for dorsal and ventral testing, respectively. In patients denying neuropathy signs or symptoms, the LR+ for dorsal and ventral tests were 8.2 and 7.3, and the LR– were 0.20 and 0.15, respectively. Due to the chosen cutoff values, SWMF testing in many subjects was indeterminate.[2]

In 2016, the Diabetes Care Guidelines by the American Diabetic Association recommended that all patients be screened with "10-g monofilament testing and at least one of the following tests: pinprick, temperature, or vibration sensation" (level of evidence B, well-conducted cohort studies).[3] The guidelines stated, "absent monofilament sensation suggests loss of protective sensation" and that diagnosis and treatment of diabetic peripheral neuropathy rarely required nerve conduction testing or neurology referral.

Mattie White, MD
Morgan Schiller, MD
Saint Louis University
St. Louis, MO

1. Dros J, Wewerinke A, Bindels PJ, van Weert HC. Accuracy of monofilament testing to diagnose peripheral neuropathy: a systematic review. *Ann Fam Med*. 2009; 7(6):555–558. **[STEP 1]**
2. Orszag A, Shin TM, Bril V, Perkins BA. Dorsal versus ventral monofilament testing of the great toe for the identification of diabetic sensorimotor polyneuropathy. *Diabetes Res Clin Pract*. 2011; 93(2):e71–e73. **[STEP 2]**
3. American Diabetes Association. 9. Microvascular complications and foot care. *Diabetes Care*. 2016; 39(suppl 1):S72–S80. **[STEP 5]**

What are the risks of oral contraceptives in females with migraines?

EVIDENCE-BASED ANSWER

Oral contraceptive use in women with migraines is associated with a 7- to 8-fold greater risk of ischemic stroke compared with women without migraines not using oral contraceptives (SOR: **B**, meta-analysis of observational studies).

A 2009 meta-analysis of 25 case-control, cohort, and cross-sectional studies that investigated the association of cardiovascular disease and migraines included data regarding use of oral contraceptives in reproductive age females as part of their risk factor stratification.[1] The meta-analysis included more than 300,000 male and female individuals between 15 and 80 years old, all with a diagnosis of migraine.

Three case-control studies (number of patients not reported) assessed cardiovascular risk in females with migraines with and without aura currently using oral contraceptives and identified an increased risk of ischemic stroke, with a relative risk of 7.0 (95% CI, 1.5–33) compared with women without migraines. The specific oral contraceptives used and length of use were not reported. Limitations included pooling of patients with different migraine subtypes and the possibility of publication bias.[1]

A 2005 meta-analysis of 14 case-control and cohort studies evaluating the risk of ischemic stroke in patients with migraines also included data regarding oral contraceptive use.[2] The studies included more than 40,000 participants between 15 and 84 years old, with a diagnosis of migraine. A subset of 3 case-control studies (number of patients not reported) assessed risk of ischemic stroke in women with any migraine diagnosis and current oral contraceptive use (specific contraceptives used and length of use not reported). The exact studies included in this analysis were not specified but it appears to include at least 1 different study from the meta-analysis above.

Compared with women without migraines not using oral contraceptives, the risk of ischemic stroke in oral contraceptive users with migraines was higher (risk ratio 8.7; 95% CI,

5.0–15). The meta-analysis was limited by the inclusion of case-control studies, which increased the possibility of recall bias.[2]

Chris Fortson, MD
Lisa Mattam, MD
George Zabakolas, MD
AHEC West FPR
Fort Smith, AR

1. Schürks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systemic review and meta-analysis. *BMJ*. 2009; 339:b3914. **[STEP 2]**
2. Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischaemic stroke in people with migraine: systemic review and meta-analysis of observational studies. *BMJ*. 2005; 330(7482):63. **[STEP 2]**

Is the levonorgestrel intrauterine device effective for 7 years, 2 years beyond the FDA-approved duration?

EVIDENCE-BASED ANSWER

Probably. The unintended pregnancy rate cumulative or between years 5 and 7 in women with a levonorgestrel intrauterine device (LNG-IUD) is very low (SOR: **B**, RCTs and observational studies).

A 2016 multinational, prospective open-label RCT compared the rates of unintended pregnancy in 3,755 women who had 52 mg LNG-IUDs placed in comparison with women with 380 mm^2 copper IUD.[1] The observation period was extended through 7 years, 2 years after the US Food and Drug Administration (FDA)-approved duration of use for the LNG-IUD. The women were parous, age 16 to 40 years old, with a mean age of 30 years. Of the total population, 717 women initially randomized to the LNG-IUD started the 7th year and 398 completed the seventh year.

The cumulative pregnancy rate in year 7 was lower in the LNG-IUD group than the TCu380A group (0.53 vs 2.5 per 100 patients; rate difference 1.9; 95% CI, 0.97–2.9). Of note, the cumulative lost to follow-up rate over 7 years was 26 per 100 patients.[1]

A 2015 prospective observational study of 263 women, age 18 to 45 years old (mean 32 years), with LNG-IUD use within 3 months of the current FDA-approved duration, were observed for up to 36 additional months.[2] Women using LNG-IUD contributed 197 women-years, with a mean duration of an additional 11.7 months of use.

Only 1 pregnancy was observed during the study, less than a month after the FDA-approved duration ended and with a partially expelled IUD. Thus, the failure rate was 0.51 per 100 women-years (95% CI, 0.01–2.82).[2]

A 2014 systematic review of 4 studies (3 RCTs, 1 observational) evaluated the rate of unintended pregnancy in parous women (N=289) 25 years and older with LNG-IUD between 5 and 7 years after insertion.[3] Among these patients, no pregnancies were reported between years 5 to 7 in all studies.

Hayley Marcus, MD
Corey Lyon, DO
University of Colorado FMR
Denver, CO

1. Rowe P, Farley T, Peregoudov A, Piaggio G, Boccard S, Landoulsi S, et al. Safety and efficacy in parous women of a 52-mg levonorgestrel-medicated intrauterine device: a 7-year randomized comparative study with the TCu380A. *Contraception*. 2016; 93(6):498–506. **[STEP 3]**
2. McNicholas C, Msci D, Maddipati R, Zhao Q, Swor E, Peipert JF. Use of the etonogestrel implant and levonorgestrel intrauterine device beyond the U.S. Food and Drug Administration–approved duration. *Obstet Gynecol*. 2015; 125(3):599–604. **[STEP 3]**
3. Wu JP, Pickle S. Extended use of the intrauterine device: a literature review and recommendations for clinical practice. *Contraception*. 2014; 89(6):495–503. **[STEP 1]**

What are the benefits and risks of using atypical antipsychotic agents in children with disruptive behaviors?

EVIDENCE-BASED ANSWER

Risperidone is moderately effective in decreasing aggression and conduct problems in children with disruptive behaviors, but may be associated with increased appetite, weight gain, hyperprolactinemia, and gastrointestinal symptoms (SOR: **A**, a meta-analysis of effects and systematic review of harms). Quetiapine, aripiprazole, and ziprasidone may also be effective, but quetiapine can cause weight gain (SOR: **C**, low-quality RCT and cohort study).

A 2015 systematic review and meta-analysis included 11 RCTs of antipsychotic medications and 7 RCTs of lithium and anticonvulsants used for treatment of aggression and conduct problems in children and adolescents.[1] Eight trials (n=827) evaluated risperidone in doses ranging from 0.75 to 2.9 mg/d, and 1 trial (n=19) studied quetiapine (dose range 216–372 mg/d). Among the risperidone RCTs, 4 (n=279) included children with subaverage intelligence quotient (IQ)

test scores, and 59% to 76% of these patients had a diagnosis of attention-deficit hyperactivity disorder (ADHD). Three studies (n=213) included children with average IQ scores, most of whom also had ADHD. The largest trial (n=335) included children with both average and subaverage IQ scores. A variety of standardized scales were used in these trials to evaluate outcomes.

All 5 trials including children with subaverage IQ demonstrated a decrease in conduct problems and aggression with risperidone versus placebo. A meta-analysis of 3 of these trials (n=266) showed a moderate effect of risperidone on aggression and conduct (standard mean difference [SMD] –0.72; 95% CI, –0.47 to –0.97). A meta-analysis of 2 of these trials in children with average IQ (n=188) demonstrated a moderate treatment effect on disruptive or aggressive behavior (SMD –0.60; 95% CI, –0.89 to –0.31).[1]

One small (n=19) RCT in the systematic review evaluated the effects of quetiapine compared with placebo in adolescents with moderate to severe aggressive behavior. A diagnosis of ADHD was present in 79% of patients; however, the use of ADHD medication was not allowed. Compared with placebo, quetiapine demonstrated a decline of 1.8 units in the Clinical Global Impression-Severity score (a 7-point scale with 1=normal and 7=extremely ill), resulting in a large treatment effect (SMD 1.6; 95% CI, 0.9–3.0).[1]

A 2011 systematic review of 32 double-blind RCTs evaluated the safety and tolerability of atypical antipsychotic agents in children and adolescents diagnosed with bipolar disorder, autism, disruptive behavior disorders, or Tourette's syndrome; no trials included patients with schizophrenia.[2] Six of the RCTs (n=634) comparing risperidone with placebo and the single quetiapine study were included in the systematic review above.

Fourteen of the trials (n=1,171) reported adverse events related to use of risperidone as number needed to harm (NNH). In these studies, the ranges of NNH for somnolence/fatigue/sedation was 1 to 200 (13 trials), for extrapyramidal symptoms (EPS) 5 to 167 (8 trials), for increased appetite 3 to 43 (9 trials), for increased weight 3 to 167 (13 trials), for hyperprolactinemia 9 to 10 (7 trials), for gastrointestinal symptoms 3 to 59 (11 trials), and for cardiovascular symptoms 8 to 10 (2 trials). In all cases the largest NNH was associated with the largest trial (n=335). Although formal statistical analyses were not provided for any of the trials, 3 trials that reported EPS symptoms and 6 that reported cardiovascular symptoms noted nonsignificant differences between groups. Increased appetite (NNH=4) was reported with quetiapine along with a 2.3 kg weight gain compared with a 1.1 kg weight gain with placebo (no statistical analysis reported).[2]

An open-label, nonrandomized trial compared aripiprazole with ziprasidone in 46 children and adolescents (age range 6–17 years) with clinically significant aggressive behavior.[3] Thirty-six of these patients had a diagnosis of ADHD.

Compared with baseline, both groups had similar significant decreases in aggression (aripiprazole –4.5; *P*=.0005 and ziprasidone –4.3; *P*=.0018) as measured by the Overt Aggression Scale (scale range 0–16).[3]

Abigail Moore, PharmD candidate
Connie Kraus, PharmD
U of WI School of Pharmacy
UW-Madison Department of Family Medicine and Community Health
Madison, WI

1. Pringsheim T, Hirsch L, Gardner D, Gorman DA. The pharmacological management of oppositional behaviour, conduct problems, and aggression in children and adolescents with attention-deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder: a systematic review and meta-analysis. Part 2: antipsychotics and traditional mood stabilizers. *Can J Psychiatry*. 2015; 60(2):52–61. **[STEP 1]**
2. Zuddas A, Zanni R, Usala T. Second generation antipsychotics (SGAs) for non-psychotic disorders in children and adolescents: a review of the randomized controlled studies. *Eur Neuropsychopharmacol*. 2011; 21(8):600–620. **[STEP 1]**
3. Bastiaens L. A non-randomized, open study with aripiprazole and ziprasidone for the treatment of aggressive behavior in youth in a community clinic. *Community Ment Health J*. 2009; 45(1):73–77. **[STEP 3]**

Is it safe to use beta-agonists in patients who have congestive heart failure (CHF)?

EVIDENCE-BASED ANSWER

There is concern. Beta-agonist use is associated with a dose-dependent increase in all-cause mortality and heart failure (HF) hospitalization in patients with known HF. Beta-agonist use is also associated with increased vasodilator use and mechanical ventilation in patients admitted for acute decompensated HF (SOR: **B**, 2 cohort study and 1 case-control study).

A 2002 observational cohort evaluated HF outcomes based on number of beta-agonist canisters filled per month for 1,529 VA patients over 6 years.[1] Patients averaged 68 years old and had a left ventricular ejection fraction <45% on echocardiography.

Patients who filled a prescription for beta-agonists had increased all-cause mortality in a dose-dependent pattern compared with no prescription. Adjusted hazard ratios were 1.3 (95% CI, 0.9–2.1) for 2 canisters per month and 2.0 (95% CI, 1.3–3.1) for 3 canisters per month. Use of 1 canister per month did not significantly increase risk over no use. Patients who filled at least 1 prescription for nebulized beta-agonists had a relative risk of hospital admission for CHF of 1.9 (95% CI, 1.0–3.5), while the estimated relative risk of all-cause mortality was 3.2 (95% CI, 1.7–6.0) compared with patients who had not filled a prescription for a beta-agonist.[1]

The study corrected for comorbidities, including obstructive lung disease, and did not differentiate between beta-agonists. The authors noted that the results might have been confounded by disease severity and improperly treating dyspnea with beta-agonists. The study was limited by its measurement of prescriptions filled and not actual use.[1]

A 2008 multicenter, prospective cohort study compared acute use of bronchodilators in the emergency room (ER) and adverse hospital outcomes.[2] The 10,987 patients averaged 73 years old and had undifferentiated shortness of breath. The study focused on the subset of patients without a diagnosis of chronic obstructive pulmonary disease (COPD) (n=7,299).

In cases for whom the patient care team determined acute decompensated HF was the cause of shortness of breath, the patients given bronchodilators in the ER had increased morbidity compared with patients not treated with a bronchodilator. Patients given bronchodilators were more likely to receive IV vasodilators (28% vs 17%; propensity-adjusted odds ratio [OR] 1.4; 95% CI, 1.2–1.7) and inpatient mechanical ventilation (6.0% vs 2.4%; propensity-adjusted OR 1.7; 95% CI, 1.2–2.4). This study did not differentiate beta-agonists from anticholinergics, but the agents were often used together. The study did not account for confounding of disease severity.[2]

A 2004 case-control study evaluated beta-agonist use and rehospitalizations in patients discharged from a VA hospital with a primary diagnosis of CHF who were observed for 1 year.[3] The study identified 1,121 CHF patients (diagnostic criteria not reported) with a mean age of 72 years.

The odds of rehospitalization increased in a dose-dependent pattern with increased prescriptions of beta-agonists (1–2 canisters per month, adjusted OR 1.8; 95% CI, 1.1–3.0; 3 canisters per month, adjusted OR 2.1; 95% CI, 1.2–3.8). ORs were adjusted for age, myocardial ischemia, COPD, diabetes, hypertension, cardiology clinic visits, and angiotensin-converting enzyme inhibitor and beta-blocker use but not lung disease severity. This study measured number of prescriptions filled and not actual use.[3]

Joel Geurin, DO
Matthew Acker, MD
In His Image Family Medicine
Tulsa, OK

1. Au DH, Udris EM, Fan VS, Curtis JR, McDonell MB, Fihn SD. Risk of mortality and heart failure exacerbations associated with inhaled beta-adrenoceptor agonists among patients with known left ventricular systolic dysfunction. *Chest*. 2003; 123(6):1964–1969. **[STEP 3]**
2. Singer AJ, Emerman C, Char DM, Heywood JT, Kirk JD, Hollander JE, et al. Bronchodilator therapy in acute decompensated heart failure patients without a history of chronic obstructive pulmonary disease. *Ann Emerg Med*. 2008; 51(1):25–34. **[STEP 3]**
3. Au DH, Udris EM, Curtis JR, McDonell MB, Fihn SD; ACQUIP Investigators. Association between chronic heart failure and inhaled beta-2-adrenoceptor agonists. *Am Heart J*. 2004; 148(5): 915–920. **[STEP 4]**

How should chronic antiplatelet therapy be managed in patients requiring common dental procedures?

EVIDENCE-BASED ANSWER

Patients requiring long-term use of single or dual antiplatelet therapy should continue rather than discontinue these medications prior to most common dental procedures (SOR: **B**, systematic review and individual prospective RCT).

A 2013 systematic review of 15 trials (3 RCTs, 9 prospective cohort trials, 3 retrospective cohort trials) evaluated the risk of bleeding complications for patients on antiplatelet therapy after dental procedures (N=2,428).[1] Studies had to have at least 1 study arm of patients on at least 1 antiplatelet medication and track at least 1 bleeding outcome after a dental procedure. Antiplatelet medication use included aspirin, clopidogrel, ticlopidine, and triflusal. Dental procedures were single or multiple tooth extraction, alveoloplasty, apicoectomy, implant replacement, torus removal, excisional biopsies, flap surgeries, periodontal surgery, deep scaling, and root planning or periodontal probing. Six trials evaluated dual antiplatelet use.

No significant intraoperative increased bleeding risk was noted for single or dual antiplatelet therapy compared with

controls. The definition of bleeding was not standardized and patient grouping varied significantly, so data could not be combined.

A 2015 single-blinded RCT evaluated the risk of bleeding in patients on oral single and dual antiplatelet therapy undergoing a single molar tooth extraction (N=190).[2] Patients were randomized to discontinue antiplatelet therapy 5 days prior to the procedure or to continue antiplatelet therapy uninterrupted through surgery. Bleeding was assessed as no bleeding (wound is clean, dry), actively bleeding (blood filled mouth), and/or oozing (pressure pack with gauze is completely red). Bleeding was assessed by a single surgeon and monitored at 1 and 24 hours after surgery.

In 24 hours after the procedure, no difference was noted in oozing or active bleeding between the continued therapy group and the discontinued group (6 patients [6.3%] vs 2 patients [2.1%]; *P*=.28). At 48 hours, no patients in either group had oozing or active bleeding.[2]

The 2012 *Chest* Guidelines on Perioperative Management of Antithrombotic Therapy recommended patients not discontinue aspirin use for secondary cardiovascular risk reduction when undergoing minor dental procedures (grade of recommendation 2C, based on low- or very-low-quality evidence of at least one critical outcome from observational studies, case series, or randomized controlled trials with serious flaws or indirect evidence).[3]

Peter Miller, MD
Janice Frueh, PharmD
IL SIU Springfield FMRP
Springfield, IL

1. Napeñas JJ, Oost FC, DeGroot A, Loven B, Hong CH, Brennan MT, et al. Review of postoperative bleeding risk in dental patients on antiplatelet therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2013; 115(4):491–499. **[STEP 1]**
2. Varghese KG, Manoharan S, Sadhanandan M. Evaluation of bleeding following dental extraction in patients on long-term antiplatelet therapy: a clinical trial. *Indian J Dent Res*. 2015; 26(3):252–255. **[STEP 2]**
3. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012; 141(2 suppl):e326S–e350S. **[STEP 5]**

Which infants need lumbar puncture (LP) for suspected serious bacterial infection?

EVIDENCE-BASED ANSWER

The evidence is unclear. Comparison of the Boston, Philadelphia, Milwaukee, and Rochester protocols for serious bacterial infection (SBI) in infants showed no protocol was superior to another (SOR: **A**, meta-analysis of prospective and retrospective studies). C-reactive protein (CRP) is the most accurate individual laboratory value for ruling out SBI in an infant younger than 90 days (SOR: **A**, meta-analysis of prospective and retrospective studies). Clinical guidelines support LP in febrile infants <28 days old, but may not be indicated for age >29 days if they meet low-risk criteria (SOR: **C**, opinion, clinical guideline).

A 2012 meta-analysis of 84 prospective and retrospective cohort studies (N=53,873) conducted by the Agency for Healthcare Research and Quality addressed effectiveness of the Boston, Philadelphia, Milwaukee, and Rochester criteria (see **TABLE 1**) in detecting SBI (meningitis, bacteremia, urinary tract infection [UTI], and pneumonia) in febrile infants.[1] Infants younger than 90 days were included with numerous exclusion criteria, such as recent antibiotic use and recent immunization.

All 4 clinical decision support tools from the 2012 meta-analysis were found to be comparable in detecting SBI (sensitivity: 89%–96%; negative likelihood ratio [LR–] 0.12–0.2, positive likelihood ratio [LR+] 1.3–2.0) (see **TABLE 2**). The main difference among the criteria is that the Rochester criteria do not require an LP. Effectiveness of clinical criteria, laboratory results, and combined results were also compared for detecting SBI. The CRP had a higher accuracy versus other individual laboratory finding for SBI, though there was no consistent cutoff for laboratory values reported. The most sensitive combination of findings found for ruling out SBI was a previously healthy infant with good appearance and nonfocal physical examination, combined with laboratory values of white blood cell (WBC) count between 5,000 and 15,000/mm^3, erythrocyte sedimentation rate (ESR) <30, and urine without leukocyte esterase or nitrites (combined sensitivity 99%; specificity 59%; LR+ 2.43, LR– 0.02).

TABLE 1

Simplified comparison of recommended laboratory tests among protocols for evaluating febrile, well-appearing infants[1,2]

	Protocol					
	Boston	Milwaukee	Philadelphia	Rochester	Cincinnati	
Age, days	28–89	28–56	29–60	<60	<28	28–60
Laboratory/ radiology tests	CSF CBC UA ± CXR	CSF CBC UA ± CXR	CSF CBC UA CXR ± STOOL	— CBC UA — ± STOOL	CSF CBC UA ± CXR ± STOOL	± CSF CBC UA ± CXR ± STOOL

Note: This Table is not a complete description of each protocol, but is meant for comparison of recommended laboratory tests. Please see individual protocols for laboratory cutoffs and recommended algorithms.

CBC=complete blood count; CSF=cerebrospinal fluid; CXR=chest x-ray; STOOL=stool cultures; UA=urinalysis.

TABLE 2

Percent pooled sensitivity and specificity of major sepsis criteria in newborns from 0 to 3 months old[1]

Protocol	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio
Rochester	94%	49%	1.8	0.12
Philadelphia	93%	46%	1.7	0.15
Boston	89%	56%	2.0	0.2
Milwaukee	96%	28%	1.3	0.14

A clinical impression of sepsis/toxic appearance with WBC ≥15,000/mm^3, ANC ≥5,000/µL, ESR ≥30 mm/h, and positive CRP (which was defined differently in the included studies) had a sensitivity of 100% and specificity 17% to 75% for sepsis, meningitis, or bacteremia.[1]

A 2010 opinion-based guideline built off a systematic review published by Cincinnati Children's Hospital recommended that every febrile child younger than 28 days should receive an LP, but children 29 to 60 days old could have the LP delayed or omitted if they met low-risk criteria (grade of strength/evidence not assessed) (see **TABLE 1**).[2] Low-risk criteria included well-appearing infants, previously healthy, with no focal source identified on physical examination, urinalysis with <10 WBC/hpf and no bacteria on gram stain, WBC 5,000–15,000/mm^3, <1,500 band cells/hpf, chest x-ray showing no infiltrate, stool smear negative for blood, and <5 WBC/hpf on urinalysis (LR– 0.08).[2]

A 1993 practice guideline published by the American Academy of Pediatrics recommended febrile infants younger than 28 days receive a full sepsis workup, including LP followed by empiric antibiotics and admission for 48 hours, but also identified a low-risk category of children aged 29–90 days who did not require an LP if available for close observation.[3] The published low-risk criteria included being previously healthy, with a nontoxic appearance, no focal infection on examination, WBC 5,000–15,000/mm^3, <1,500 bands/mm^3, normal urinalysis (<5 WBC/hpf) and negative urine gram stain, and <5 WBC/hpf for stool. EBP

Laurel Neff, DO
Jonathan Pickett, MD
Madigan AMC FMR
Tacoma, WA

The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.

1. Hui C, Neto G, Tsertsvadze A, et al. Diagnosis and management of febrile infants (0–3 months). Rockville, MD: Agency for Healthcare Research and Quality; 2012. Evidence Report/ Technology Assessment 205. http://www.effectivehealthcare.ahrq.gov/ehc/products/279/1015/EvidenceReport205_Febrile-Infants_20120322.pdf. Accessed May 16, 2017. **[STEP 2]**
2. Cincinnati Children's Hospital Medical Center. Evidence-based clinical care guideline for fever of uncertain source in infants 60 days of age or less. Guideline 02, pages 1–14. Cincinnati, OH: Cincinnati Children's Hospital Medical Center; October 2010. **[STEP 5]**
3. Baraff LJ, Bass JW, Fleisher GR, Klein JO, McCracken GH Jr, Powell KR, et al. Practice guideline for the management of infants and children 0 to 36 months of age with fever without source. Agency for Health Care Policy and Research. *Ann Emerg Med*. 1993; 22(7):1198–1210. **[STEP 5]**

What is the most appropriate treatment for asymptomatic bacteriuria in pregnancy?

Bottom line

The answer is unclear. Seven days of nitrofurantoin was better than a single day of nitrofurantoin, but no difference was found between fosfomycin and cefuroxime and no difference between 1 day and 4 to 7 days of co-trimoxazole, trimethoprim, amoxicillin, ampicillin, sulfamethoxazole, or cephalexin (SOR: **B**, meta-analyses of heterogeneous RCTs). The Infectious Diseases Society of America recommends treatment for 3 to 7 days but does not favor a specific antibiotic (SOR: **B**, evidence-based guideline).

Evidence summary

A 2011 meta-analysis of 13 RCTs and quasirandomized trials (N=1,622) compared single-day versus multiple-day antibiotic treatment on "no cure" rates for asymptomatic bacteriuria in pregnancy.[1] "No cure" rate was defined as persistence of asymptomatic bacteriuria despite antibiotic treatment. Asymptomatic bacteriuria was defined by 9 of the trials as 2 consecutive cultures with >100,000 CFU/mL of identical organisms with no symptoms; 4 of the trials used a single culture of >100,000 CFU/mL with no symptoms.

Nine of the trials compared a 1-day course with a 4- to 7-day course of a single antibiotic agent, but only 7 trials compared antibiotics available in the United States: amoxicillin (4 trials), trimethoprim-sulfamethoxazole, trimethoprim, and nitrofurantoin. One trial compared single-day versus 1- to 2-week durations of amoxicillin, ampicillin, trimethoprim, sulfamethoxazole, or cephalexin and 3 trials compared single-dose fosfomycin with longer durations of different antibiotic agents: cefuroxime for 5 days, amoxicillin-clavulanate for 7 days, or nitrofurantoin for 7 days.[1]

For 1-day versus 7-day treatment with a single antibiotic agent, no difference was noted in no-cure rates (10 trials, n=1,378; RR 1.4; 95% CI, 0.87–2.3). Significant study heterogeneity was noted for this outcome. One study contributed approximately half of the data (n=778) and found the 1-day versus 7-day treatment with nitrofurantoin increased the no-cure rates (RR 1.8; 95% CI, 1.3–2.4). The 3 trials comparing single-dose fosfomycin with longer durations of different antimicrobial agents demonstrated no statistically significant difference in the no-cure rate.[1]

A 2010 systemic review of 5 RCTs (N=1,140) compared different antibiotic regimens for treating asymptomatic bacteriuria in pregnancy.[2] Asymptomatic bacteriuria was defined as 2 consecutive cultures with >100,000 CFU/mL of identical organisms with no symptoms in 1 trial, and as >100,000 CFU/mL in a single sample in 4 trials. Results were not pooled. This review had only 1 study in common with the meta-analysis above—the study comparing 1-day versus 7-day treatment with nitrofurantoin which is summarized above.

Of the 4 studies that compared different antibiotics, none demonstrated statistically significant advantages of any specific antibiotic for treating asymptomatic bacteriuria, as defined by either persistent or recurrent infections

TABLE

Comparison of different antibiotic regimens for treatment of asymptomatic bacteriuria in pregnancy[2]

Antibiotics studied	No. of patients	Outcome	Relative risk (95% CI)[a]
Fosfomycin 3 g × 1 dose vs cefuroxime 250 mg 2 times daily × 5 days	84	Persistent infection	1.4 (0.24–7.8)
Pivmecillinam 400 mg 4 times daily × 7 days vs ampicillin 500 mg 4 times daily × 7 days	65	Persistent infection after 2 weeks	1.0 (0.28–3.8)
		Recurrent infection	0.69 (0.12–3.9)
Pivmecillinam 200 mg and pivampicillin 250 mg 2 times daily × 3 days vs cephalexin 1 g 2 times daily × 3 days	47	Persistent infection	5.8 (0.75–44)
		Recurrent infection	0.77 (0.23–2.5)
Cycloserine 250 mg 2 times daily × 14 days vs sulfadimidine 500 mg 4 times daily × 14 days	160	Persistent infection	0.70 (0.41–1.2)
		Recurrent infection	0.89 (0.47–1.7)

[a]None of the results are statistically significant.

(see **TABLE**). Only 1 of these comparisons was between antibiotics available in the United States.[2]

The Infectious Diseases Society of America released an evidence-based guideline in 2005 recommending that pregnant women with asymptomatic bacteriuria be treated for 3 to 7 days (A-II, good evidence to support from 1 or more well-designed nonrandomized studies).[3] The guideline did not provide recommendations for selecting an antibiotic. EBP

Jesse Clark, DO, FAAFP
SIU Family Medicine
Carbondale, IL

REFERENCES

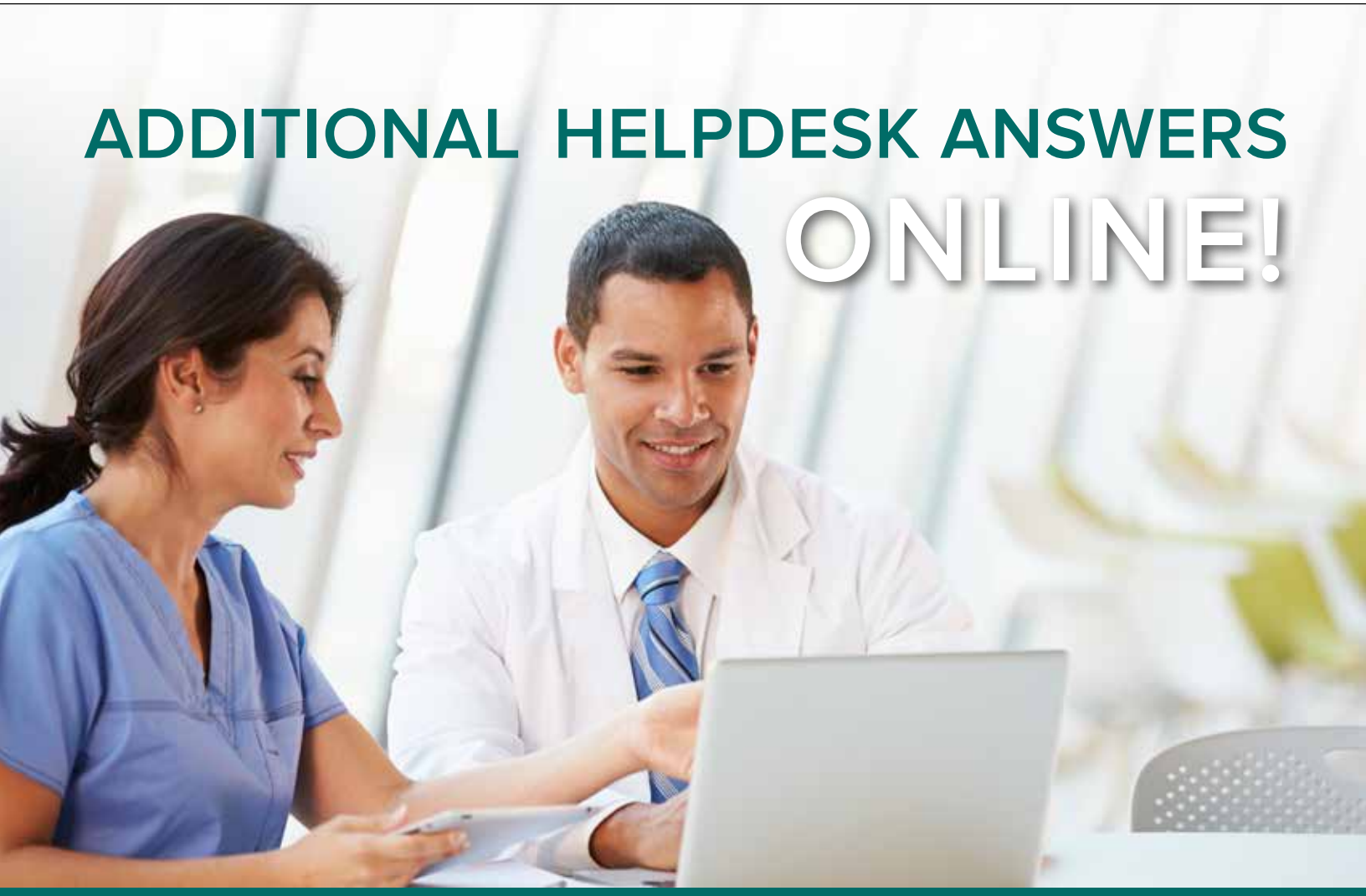
1. Widmer M, Gülmezoglu AM, Mignini L, Roganti A. Duration of treatment for asymptomatic bacteriuria during pregnancy. *Cochrane Database Syst Rev*. 2011; (12):CD000491. **[STEP 1]**
2. Guinto VT, De Guia B, Festin MR, Dowswell T. Different antibiotic regimens for treating asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev*. 2010; (9):CD007855. **[STEP 1]**
3. Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM, et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis*. 2005; 40(5):643–654. **[STEP 3]**

EVIDENCE-BASED PRACTICE

Family Physicians Inquiries Network, Inc.
401 West Boulevard North
Suite D
Columbia, MO 65203

Change Service Requested

ADDITIONAL HELPDESK ANSWERS ONLINE!



To find more pages of HelpDesk Answers content, please visit www.fpin.org/ebparchives and view this month's online edition.

ISSN 1095-4120 (print)
ISSN 2473-3717 (online)

Vol 20 | No. 7 | July 2017 | Electronic Version

EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the
Family Physicians Inquiries Network

For women of average risk, what are the best tests to screen for Down syndrome in the first trimester?

EVIDENCE-BASED ANSWER

In average-risk women, the most accurate combination of traditional tests for first-trimester screening for Down syndrome is combined testing with serum pregnancy-associated plasma-protein-A (PAPP-A), free or total beta-human chorionic gonadotropin (β-hCG), ultrasonographic nuchal translucency measurement, and nasal bone ossification in combination with maternal age. Of note, nasal bone ossification is not available until 11 weeks' gestation (SOR: **A**, meta-analyses of cohort and case-control studies). Of serum-only tests, PAPP-A and β-hCG in combination with maternal age are most accurate (SOR: **A**, meta-analyses of cohort and case-control studies). Cell-free DNA (cfDNA) testing has the highest sensitivity and specificity (SOR: **B**, single cohort study), but further evidence on cost-effectiveness is needed to support its widespread use in average-risk women (SOR: **C**, expert consensus).

A 2015 meta-analysis of 24 studies (23 cohort and 1 case-control, N=375,801) examined various combinations of first-trimester serum and ultrasonographic markers and maternal age to determine their sensitivity and specificity of predicting Down syndrome.[1] Studies included singleton pregnancies of all risk. The reference standard for the diagnosis of Down syndrome was genetic or chromosomal analysis.

The pooled sensitivity and specificity of combined maternal age, nuchal translucency, PAPP-A, and free β-hCG (5 studies, n=62,475) were 0.83 and 0.95. The positive (LR+) and negative likelihood ratios (LR–) were 17.5 and 0.18, respectively. Including nasal bone ossification (7 studies, n=133,335) increased both sensitivity (0.90) and specificity (0.97), improving the likelihood ratios (LR+ 35 and LR– 0.10). However, inclusion of nasal bone ossification is clinically limiting in that the ossification begins at 11 weeks' gestation.[1]

A 2015 systematic review and meta-analysis of 56 case-control studies (N=204,759) evaluated 18 different serum index tests in isolation and in 78 combinations for screening of Down syndrome.[2] Studies included women who were unselected, women of increased risk of Down pregnancy, or multiple gestations. The reference standard for diagnosis of Down syndrome was genetic or chromosomal analysis. This meta-analysis did not include 16 of the 24 studies in the meta-analysis above that included ultrasonographic markers in addition to serum markers.

In the first trimester of pregnancy, meta-analysis of 31 studies (n=158,878) determined the most accurate test to be the combination of PAPP-A and β-hCG in combination with maternal age, which provided a sensitivity of 0.68 and specificity 0.95 (LR+ 11 and LR– 0.27).[2]

A 2015 prospective, multicenter, blinded cohort study of 18,955 unselected women with singleton pregnancies between 10 and 14 weeks of gestation compared cfDNA screening with combined nuchal translucency, PAPP-A, and total or free β-hCG in screening for Down syndrome.[3] The reference standard was preferentially genetic testing, and if not available, medical records of the newborn physical examination were reviewed by 2 physicians in a blinded fashion.

The sensitivity and specificity of cfDNA was 1.00 (95% CI, 0.907–1.00) and 0.999 (95% CI, 0.999–1.00), respectively, yielding a LR+ of 1,000 (95% CI, 907–∞) and LR– of 0.00 (95% CI, 0–0.09). The sensitivity and specificity of nuchal translucency, PAPP-A, and total or free β-hCG were 0.79 and

0.95, respectively (LR+ 16, LR– 0.22). Stratification by risk did not significantly alter the results.[3]

A 2007 practice bulletin from the American College of Obstetrics and Gynecology (ACOG) recommended first trimester Down syndrome screening with combined nuchal translucency, PAPP-A, and total or free β-hCG.[4] In a 2015 committee opinion summary, ACOG recommended continued use of conventional screening methods over cfDNA in the low-risk obstetric population, citing limited data on cost-effectiveness.[5]

Lamya Khoury, MD, MPH
Grace Shih, MD, MAS
University of Washington FMRP
Seattle, WA

1. Liu Y, Ye X, Zhang N, Zhang B, Guo C, Huang W, et al. Diagnostic value of ultrasonographic combining biochemical markers for Down syndrome screening in first trimester: a meta-analysis. *Prenat Diagn*. 2015; 35(9):879–887. **[STEP 1]**
2. Alldred SK, Takwoingi Y, Guo B, Pennant M, Deeks JJ, Neilson JP, et al. First trimester serum tests for Down's syndrome screening. *Cochrane Database Syst Rev*. 2015; (11):CD011975. **[STEP 1]**
3. Norton ME, Jacobsson B, Swamy GK, Laurent LC, Ranzini AC, Brar H, et al. Cell-free DNA analysis for noninvasive examination of trisomy. *N Engl J Med*. 2015; 372(17):1589–1597. **[STEP 2]**
4. ACOG Committee on Practice Bulletins. ACOG Practice Bulletin No. 77: Screening for fetal chromosomal abnormalities. *Obstet Gynecol*. 2007; 109(1):217–227. **[STEP 5]**
5. ACOG Committee on Genetics. ACOG Committee Opinion Summary No. 640: Cell-free DNA screening for fetal aneuploidy. *Obstet Gynecol*. 2015; 126(3):691–692. **[STEP 5]**

In patients with irritable bowel syndrome, does a diet low in FODMAPs reduce gastrointestinal symptoms?

EVIDENCE-BASED ANSWER

A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) appears to reduce gastrointestinal symptom scores in patients with irritable bowel syndrome (IBS), at least in the short term (SOR: **B**, meta-analysis and systematic review of variable quality RCTs and observational studies).

FODMAPs, present in fruits, juices, onions, wheat, and legumes, are poorly absorbed in the small intestines and are rapidly fermented, resulting in gas production and increased intestinal osmolality.

A 2016 systematic review and meta-analysis, including 6 RCTs and 16 observational studies in the United States, Europe, New Zealand, and Australia, evaluated the effects of FODMAPs on patients with IBS.[1] Patients were 18 to 72 years old except in 1 pediatric study that included patients 7 to 17 years old. Study sizes ranged from 16 to 90 patients (total 934 patients). Interventions consisted of dietary counseling and food diaries, although in 1 study the participants had low FODMAP meals provided. Control groups varied from no intervention, standard IBS dietary counseling, or were provided typical Western diet meals. Adherence was assessed using food diary evaluation or hydrogen breath tests, which detect fermentation from ingested FODMAPs. The primary outcome was IBS Symptom Severity Score (IBS-SSS), a validated 500-point scale assessing 5 domains: severity of abdominal pain, frequency of abdominal pain, severity of bloating, satisfaction with bowel habits, and impact of symptoms on quality of life. A higher score indicates more severe symptoms, and a reduction of 50 points is considered a clinically significant improvement.

In the meta-analysis of RCTs, the mean reduction in IBS-SSS scores was more than 50 points in both groups (a 123-point reduction in FOMAP group and a 69-point reduction in control group). A low FODMAP diet compared with control was reported to result in more patients with a significant decrease in mean IBS-SSS scores (>50 points), but how the given odds ratio (OR) was calculated was unclear (4 trials, n=275; OR 0.44; 95% CI, 0.25–0.76). Similarly, the odds of showing improvement in the IBS-SSS were higher in the low FODMAP diet (4 trials, n=239; OR 1.8; 95% CI, 1.1–3.0). Follow-up for the RCTs varied from 3 to 6 weeks.[1]

For the meta-analysis of observational studies, a low FODMAP diet was also associated with a lower mean IBS-SSS score compared with placebo, but it is unclear what cutoff was used to dichotomize the outcome into an OR (16 studies; n=580; pooled OR 0.03; 95% CI, 0.01–0.2). Follow-up for observational studies varied from 2 days to 35 months. The larger effect size in the observational studies compared with the meta-analysis of RCTs may have reflected confounding among the observational studies.[1]

A 2015 systematic review assessing the effects of a low FODMAPs diet on IBS included 3 RCTs (n=172) and 3 observational studies (n=209).[2] All of the studies included in this review, with the exception of a single RCT, were also included in the meta-analysis above. With similar study inclusion criteria, it is unclear why there was a difference in included studies.

Interventions for the RCTs were FODMAP-restricted diets compared with high FODMAP diets (standard Western diet), and follow-up ranged from 2 days to 6 weeks. Statistically

significant improvements in IBS symptoms (measured variably by Likert scores, visual analog scores, and IBS-SSS) were observed in the FODMAP-restricted diet group compared with control for all 3 RCTs, but outcomes were heterogeneous and the authors could not perform a meta-analysis.[2]

The authors noted multiple limitations, particularly a short follow-up duration, and they suggested that at least 3 months of follow-up was needed for short-term outcomes and 6 to12 months for long-term outcomes. The authors noted that sustainability of diet and duration of effects of a low FODMAP diet had not been established. Additionally, they stated that any significant harms of the diet, such as nutritional deficiency or changes in gut microbiota, were unknown.[2]

Hanh Nguyen, MD
Kathleen Paul, MD, MPH
Kaiser Permanente Washington FMR
Seattle, WA

1. Marsh A, Eslick EM, Eslick GD. Does a diet low in FODMAPs reduce symptoms associated with functional gastrointestinal disorders? A comprehensive systematic review and meta-analysis. *Eur J Nutr*. 2016; 55(3):897–906. **[STEP 1]**
2. Rao SS, Yu S, Fedewa A. Systematic review: dietary fibre and FODMAP-restricted diet in the management of constipation and irritable bowel syndrome. *Aliment Pharmacol Ther*. 2015; 41(12):1256–1270. **[STEP 2]**

Is high-dose influenza vaccine more effective than standard-dose influenza vaccine in elderly patients?

EVIDENCE-BASED ANSWER

Yes. High-dose influenza vaccine reduces laboratory-confirmed influenza by 24% more than standard-dose influenza vaccine in elderly patients (SOR: **B**, single RCT). High-dose vaccine is associated with a lower rate of probable influenza and hospital admission due to influenza (SOR: **B**, retrospective cohort). However, the Centers for Disease Control and Prevention (CDC) does not prefer 1 influenza vaccine formulation over another in patients 65 years and older (SOR: **C**, expert opinion).

A 2014 multicenter, randomized, double-blind, active-controlled trial compared trivalent inactivated high-dose flu vaccine (60 µg of hemagglutinin per strain) with trivalent inactivated standard-dose flu vaccine (15 µg of hemagglutinin per strain) in 31,989 adults aged 65 years and older without moderate or severe acute illness.[1] The trial was conducted in the 2011/2012 and 2012/2013 influenza seasons in the United States and Canada.

Nasopharyngeal swabs were collected from patients who met criteria for protocol-defined influenza-like illnesses (ILI), modified CDC-defined ILI, or respiratory illnesses. Nasopharyngeal swabs were collected within 5 days of symptom onset for 80% with protocol-defined ILI, 74% with modified CDC-defined ILI, and 67% with respiratory illnesses. No significant differences in collection rate were noted for patients who were given a high dose of vaccine versus standard dosage of vaccine. Laboratory-confirmed influenza was defined as a positive culture or polymerase-chain-reaction assay.[1]

In the intention-to-treat analysis, a high dose of vaccine reduced the rate of laboratory-confirmed influenza versus the standard dose of vaccine (1.4% vs 1.9%), with a relative efficacy of 24% (95% CI, 9.7%–37%). The absolute efficacy of a high dose of vaccine could only be inferred and was estimated to be 62% by the trial authors. This level of protection is similar to that seen with standard vaccine dosage in nonelderly patients. The high dose of vaccine was associated with a lower rate of serious adverse events than the standard dose (8.3% vs 9.0%; relative risk [RR] 0.92; 95% CI, 0.85–0.99). Of note, Sanofi Pasteur, the manufacturer of the high-dose influenza vaccine, designed and funded the trial.[1]

A 2015 retrospective cohort studied Medicare beneficiaries aged 65 and older who received a high dose of flu vaccine or standard dose of vaccine from pharmacies offering both vaccines during the 2012/2013 influenza season.[2] Patients were identified via billing codes on Medicare claims. Probable influenza infection was defined as receipt of a rapid influenza test followed by dispensing of oseltamivir.

High-dose vaccination was associated with a lower rate of probable influenza infections versus standard-dose vaccination (1.0 vs 1.3 cases per 10,000 person-weeks), yielding a relative vaccine effectiveness of 22% (95% CI, 15–29). A high-dose vaccine was associated with a lower rate of hospital admission due to influenza (0.86 vs 1.1 admissions per 10,000 person-weeks; relative efficacy 22%; 95% CI, 16%–27%). One limitation of this study was that the authors did not confirm influenza diagnoses with laboratory results.[2]

The CDC and its Advisory Committee on Immunizations Practices has recommended that all patients 65 years and older are immunized annually with an influenza vaccine.[3] They

have not indicated a preference for 1 influenza formulation over another for patients 65 years and older.

Jessica Norman, PharmD
Angela Thompson, PharmD
University of Colorado FMR
Denver, CO

1. DiazGranados CA, Dunning AJ, Kimmel M, Kirby D, Treanor J, Collins A, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N Engl J Med*. 2014; 371(7):635–645. **[STEP 2]**
2. Izurieta HS, Thadani N, Shay DK, Lu Y, Maurer A, Foppa IM, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. *Lancet Infect Dis*. 2015; 15(3):293–300. **[STEP 3]**
3. Fluzone high-dose seasonal influenza vaccine: questions and answers. Centers for Disease Control and Prevention website. http://www.cdc.gov/flu/protect/vaccine/qa_fluzone.htm. Updated August 1, 2016. Accessed June 23, 2017. **[STEP 5]**

In a patient with postdates gestation, when should fetal surveillance be initiated?

EVIDENCE-BASED ANSWER

Oligohydramnios in uncomplicated pregnancies after 39 plus 6 weeks' gestation predicts an increased risk of adverse outcomes (positive likelihood ratio 1.9) (SOR: **B**, cross-sectional study). Use of a screening non-stress test (NST) between 40 and 40 plus 6 weeks' gestation is not associated with improved outcomes (SOR: **B**, retrospective cohort study). Abnormal fetal testing and adverse maternal and perinatal outcomes are increased after 41 weeks' gestation (SOR: **B**, retrospective cohort study). Initiating antenatal surveillance at or beyond 41 weeks of gestation may be indicated (SOR: **C**, expert opinion).

A 2004 cross-sectional study followed 3,050 women carrying uncomplicated singleton gestations with semiweekly monitoring of amniotic fluid index (AFI) starting at 40 weeks until delivery.[1] The women had a mean age of 32 years and 61% were nulliparous. The pregnancy outcome was classified as adverse (167 deliveries with any of the following features: 5-minute Apgar score <7, umbilical artery pH <7.0, Cesarean section for fetal distress, meconium aspiration syndrome, or intrauterine death) or favorable (2,883 deliveries with absence of all adverse features).

Oligohydramnios before delivery (defined as an AFI ≤5 cm) had a 20% sensitivity and 89% specificity for adverse pregnancy outcomes (relative risk [RR] 2.1; 95% CI, 1.4–3.1). Infants who were small for gestational age were more common in pregnancies with adverse outcomes (14% vs 5.8%; *P*<.001); however, oligohydramnios was also associated with increased risk in newborns whose weight was appropriate for gestational age (19% vs 11%; RR 1.9; 95% CI, 1.2–3.1). The study did not separately report outcome for deliveries after 41 weeks' gestation.[1]

A 2015 retrospective cohort study (N=460) compared intrapartum and neonatal outcomes with or without screening NSTs in healthy pregnancies at gestational ages of 40 to 40 plus 6 weeks.[2] This was the first study to evaluate screening NSTs before 41 weeks. Viable singleton pregnancies with no maternal medical complications (diabetes mellitus, hypertension), no obstetric complications (gestational diabetes mellitus, pregnancy-induced hypertension, intrauterine growth retardation), and >3 prenatal appointments were included. Women who received NSTs (N=228) were slightly younger (28 vs 29 years; *P*=.03) and gained slightly more weight in pregnancy (16 vs 15 kg; *P*=.03), but the groups were comparable in body mass index, hematocrit, and multiparity.

The primary outcomes included nonreassuring fetal heart rate (NRFHR) defined as an intrapartum category III tracing (sinusoidal pattern or absent variability plus bradycardia or recurrent late/variable decelerations). Receiving an NST was not associated with improved outcomes versus not receiving an NST for stillbirth (0.4% vs 0%; *P*=.49), neonatal mortality (0.4% vs 0.0%; *P*=.49), neonatal morbidity (including meconium aspiration, asphyxia, and respiratory distress; 0.9% vs 0.9%; *P*=1.0), or NRFHR (3.1% vs 4.3%; *P*=.48).[2]

A 1989 retrospective cohort study compared patients who had NSTs and AFIs starting at 41 weeks' gestation (N=293) with a control group of low-risk patients who also had NSTs and AFIs but delivered between 39 and 41 weeks' gestation (N=59).[3] The control group delivered by spontaneous labor or due to induction of labor for abnormal NST (the presence of recurrent variable or late decelerations or 120 minutes of a nonreactive tracing) or oligohydramnios (defined as largest pocket of <2 cm in vertical depth.)

Delivery between 41 and 42 weeks' gestation was associated with increased rates of abnormal NSTs, oligohydramnios, and adverse outcomes compared with delivery between 39 and 41 weeks; however, only the rate of abnormal NSTs was increased with delivery between 41

TABLE

Antenatal surveillance, perinatal and maternal outcomes at term and postterm[3]

Perinatal outcome	Rate of adverse outcome with delivery between the following number of weeks (%)			*P* value for between-group differences	
	39–41 weeks (n=59)	41–42 weeks (n=139)	After 42 weeks (n=154)	41–42 vs 39–41 weeks	41–42 vs after 42 weeks
Abnormal nonstress test	6.8	24	14	<.01	<.05
Oligohydramnios	0	14	10	<.02	NS
Cesarean section for fetal distress	1.7	10	9.1	<.05	NS
Apgar score ≤6 at 5 min	0	0	0.1	NS	NS
NICU admissions	0	6.5	3.9	<.05	NS
Perinatal deaths	0	0	0	NS	NS

NICU=neonatal intensive care unit; NS=not statistically significant.

and 42 weeks compared with delivery after 42 weeks (see **TABLE**). Women with abnormal NSTs between 41 to 42 weeks were induced, a strategy that likely reduced the rate of abnormal NSTs after 42 weeks.[3]

The 2014 American College of Obstetricians and Gynecologists practice guideline for the management of late-term and postterm pregnancies states that, based on expert opinion, initiating antenatal surveillance at or beyond 41 weeks of gestation may be indicated.[4]

Thai-Hao Nguyen, MD
Ashley Hildebrand, MD
In His Image FMRP
Tulsa, OK

1. Locatelli A, Zagarella A, Toso L, Assi F, Ghidini A, Biffi A. Serial assessment of amniotic fluid index in uncomplicated term pregnancies: prognostic value of amniotic fluid reduction. *J Matern Fetal Neonatal Med*. 2004; 15(4):233–236. **[STEP 2]**
2. Kiettisanpipop P, Phupong V. Intrapartum and neonatal outcome of screening non-stress test (NST) compared with no screening NST in healthy women at 40–40 (+6) weeks of gestation. *J Obstet Gynaecol Res*. 2015; 41(1):50–54. **[STEP 3]**
3. Guidetti DA, Divon MY, Langer O. Postdate fetal surveillance: is 41 weeks too early? *Am J Obstet Gynecol*. 1989; 161(1):91–93. **[STEP 3]**
4. American College of Obstetricians and Gynecologists. Practice bulletin no. 146: Management of late-term and postterm pregnancies. *Obstet Gynecol*. 2014; 124(2 pt 1):390–396. **[STEP 5]**

What is the risk of esophageal adenocarcinoma in patients with Barrett's esophagus?

EVIDENCE-BASED ANSWER

The risk of esophageal adenocarcinoma (EAC) in patients with Barrett's esophagus (BE) is estimated to be 0.12% to 0.63% annually (SOR: **A**, meta-analysis of longitudinal studies and 2 population-based studies). Risk factors for progression to EAC include male sex, more than 3 cm of Barrett's mucosa, and dysplasia or metaplasia on index biopsy (SOR: **B**, 1 population-based study).

A systematic review and meta-analysis in 2010 studied the incidence of EAC and mortality due to EAC in patients with BE described in 51 longitudinal studies (N=14,109 with 61,804 person-years).[1] The studies were from Europe (33), the United States (16), and Australia (2) and were included if they were written in English, had histologically proven BE as manifested by columnar-lined esophagus or specialized intestinal metaplasia, and EAC cases on surveillance that were histologically proven. The surveillance schedules used in the individual studies were not reported.

The overall incidence of EAC in patients with BE was 6.3 cases per 1,000 person-years of follow-up (95% CI, 4.7–8.4). Assuming roughly equal risk per year, this incidence would translate to an annual risk of 0.63%. The pooled incidence

of fatal EAC in 19 studies (n=7,930 with 33,022 person-years) was 3.0 per 1,000 person-years (95% CI, 2.2–3.9). Twelve studies (n=4,207 with 24,959 person-years and 921 deaths) reported on cause-specific mortality in patients with BE and found cardiovascular disease (including stroke) to be the most common cause of death (35%). The other leading causes of death were pulmonary disease (20%) and other malignancies (16%), with EAC being the cause of death in only 7% of patients with BE.[1]

A 2011 population-based study using the Northern Ireland Barrett's esophagus Register examined the risk of adenocarcinoma or high-grade dysplasia in patients with BE and determined risk factors for progression to malignancy.[2] This study included a total of 8,522 patients with a mean follow-up of 7 years.

The overall incidence of EAC in patients with BE was 0.13% per year (95% CI, 0.10–0.16). Progression to malignancy was greater in men (0.17% per year; 95% CI, 0.13–0.22) than in women (0.08%; 95% CI, 0.05–0.12). Patients with metaplasia at index biopsy had greater risk (0.23% per year (95% CI, 0.18–0.29) than patients with columnar-lined epithelium alone (0.04% per year; 95% CI, 0.02–0.08). Patients with low-grade dysplasia had greater risk (0.92% per year; 95% CI, 0.60–1.4) than patients without (0.10% per year; 95% CI, 0.08-0.13). Patients with >3 cm of Barrett's mucosa had greater risk (0.22% per year; 95% CI, 0.13–0.37) than patients with <3 cm (0.07% per year; 95% CI, 0.02–0.20).[2]

A 2011 population-based study performed in Denmark aimed to calculate the incidence of adenocarcinoma or high-grade dysplasia among patients with BE who had metaplasia.[3] This study included a total of 11,028 patients who were followed between 1992 through 2009. Cases of EAC diagnosed during the first year of follow-up were excluded.

The absolute annual risk of EAC in patients with BE (with metaplasia) was 0.12% (95% CI, 0.09–0.15).[3]

Brandon Ganzer, DO
Charles Powell, MD
In His Image FMR
Tulsa, OK

1. Sikkema M, de Jonge PJ, Steyerberg EW, Kuipers EJ. Risk of esophageal adenocarcinoma and mortality in patients with Barrett's esophagus: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2010; 8(3):235–244. **[STEP 1]**
2. Bhat S, Coleman HG, Yousef F, Johnston BT, McManus DT, Gavin AT, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. *J Natl Cancer Inst*. 2011; 103(13):1049–1057. **[STEP 2]**
3. Hvid-Jensen F, Pedersen L, Drewes AM, Sørensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med*. 2011; 365(15):1375–1383. **[STEP 2]**

Do you need to monitor liver function tests in patients taking statins for hypercholesterolemia?

EVIDENCE-BASED ANSWER

No, at least not in patients with a baseline aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <3 times the upper limit of normal (ULN) (SOR: **A**, based on 2 high-quality RCTs). The American College of Cardiology/American Heart Association (ACC/AHA) guidelines and the National Lipid Association's Statin Safety Task Force recommend checking ALT prior to starting statin therapy, and only if clinically indicated thereafter (SOR: **C**, based on consensus guidelines).

In 2009, long-term detailed safety data were reported from a 2002 RCT in the United Kingdom (N=20,536) that compared simvastatin 40 mg daily with placebo.[1] Patients (75% male, mean age 64 years) were at high risk for cardiovascular events (due to occlusive arterial disease or diabetes, or were men ≥65 years old receiving treatment for hypertension). Exclusion criteria included total cholesterol <135 mg/dL, clear indication or contraindication for statin per their primary care provider, chronic liver disease, or ALT >1.5×ULN. ALT was checked at 4, 8, and 12 months after trial entry, and then every 6 months for a total mean follow-up of 5 years.

An ALT >3×ULN was measured at least once in 77 simvastatin and 65 placebo patients (0.75% vs 0.63%; *P*=.35). However, on repeat testing, an ALT >3×ULN persisted in 21 simvastatin versus 9 placebo patients (0.20% vs 0.09%; *P*=.045; number needed to treat to harm=909). The number of discontinuations because of liver or muscle enzyme abnormalities was no different between simvastatin and placebo (57 vs 46; *P*=.32).[1]

In 2010, long-term safety data were reported from a 2002 open-label RCT of 1,600 patients with coronary artery disease that compared statin therapy versus primarily nonstatin therapy in Greece.[2] Patients younger than 75 years (78% men, mean age 58 years) were enrolled if they had a baseline low-density lipoprotein (LDL) concentration >100 mg/dL plus AST and ALT <3×ULN. Atorvastatin (10–80 mg daily), simvastatin (10–40 mg), pravastatin

(20–40 mg), and fluvastatin 40 mg were titrated every 6 weeks to target an LDL <100 mg/dL. Patients in the control group were treated by their primary care physicians and statin therapy was not forbidden. AST and ALT were checked at 6 weeks, and then every 6 months during 3 years of follow-up.

A total of 437 patients had baseline AST and ALT levels greater than the ULN. In these patients, from baseline to the end of the study, ALT dropped by 35% (*P*<.0001) and AST dropped by 47% (*P*<.0001) in patients treated with statins (n=227), while ALT increased by 12% (*P*=.003) and AST increased by 12% (*P*=.01) in patients treated with placebo (n=210). An AST or ALT >3×ULN was observed in 10 of the 880 patients who were treated with statins. AST or ALT normalized in 3 patients after a 50% statin dose reduction and statins were stopped in the other 7 patients. Statins did not increase the withdrawal rate due to liver-related adverse effects versus placebo (0.79% vs 0.42%; *P*=.6).[2]

The 2014 National Lipid Association's Statin Safety Task Force recommended obtaining liver enzymes before initiating statin therapy, based on expert opinion.[3] The task force also affirmed their 2006 recommendation that routine liver enzyme monitoring was not required after starting treatment, unless clinically indicated.

The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults recommended baseline measurement of ALT before initiating statin therapy ("class I recommendation; level of evidence: B").[4] They suggested further testing if symptoms consistent with hepatotoxicity arise ("class IIa recommendation; level of evidence C").

Aarti Aggarwal, MD
Gina G. Glass, MD, FAAFP
Inspira FMRP
Woodbury, NJ

1. Armitage J, Bowman L, Collins R, Parish S, Tobert J. Effects of simvastatin 40 mg daily on muscle and liver adverse effects in a 5-year randomized placebo controlled trial in 20,536 high-risk people. *BMC Clin Pharmacol*. 2009; 9:6. **[STEP 2]**
2. Athyros VG, Tziomalos K, Gossios TD, Griva T, Anagnostis P, Kargiotis K, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. *Lancet*. 2010; 376(9756):1916–1922. **[STEP 2]**
3. Bays H, Cohen D, Chalasani N, Harrison S. An assessment by the Statin Liver Safety Task Force: 2014 update. *J Clin Lipidol*. 2014; 8(3 suppl):S47–S57. **[STEP 5]**
4. Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014; 129(25 suppl 2):S1–S45. **[STEP 5]**

Is the Edinburgh Postnatal Depression Scale an effective way to screen for postpartum depression?

EVIDENCE-BASED ANSWER

In some settings. The Edinburgh Postnatal Depression Scale (EPDS) screens for postpartum depression with a sensitivity of 59% to 100% and a specificity of 44% to 97%, with variation due to geographic location of studies, cutoff scores chosen, and reference standards used for diagnosis (SOR: **B**, systematic reviews of diagnostic cohort studies and 2 diagnostic cohort studies with inconsistently applied reference standards).

The EPDS is a 10-item instrument with responses scored 0, 1, 2, or 3 and a maximum score of 30. Scores of ≥10 and ≥12 are typically used as cutoffs for identifying women with postpartum depression.

A 2013 systematic review and meta-analysis included 10 diagnostic cohort studies (N=2,170) that assessed the reliability and validity of EPDS in screening for postpartum depression in numerous countries in Africa.[1] The reference standards varied among the studies and included the Clinical and Structured Interview, Present State Examination (PSE), Comprehensive Psychopathological Rating Scale, and the Mini International Neuropsychiatric Interview (MINI). One study did not use a reference standard. Using a cutoff score of ≥9 yielded the highest sensitivity for diagnosis of postpartum depression.

Pooled results of 8 studies (n=1,548) found the EPDS had a sensitivity of 0.94 (95% CI, 0.68–0.99) and a specificity of 0.77 (95% CI, 0.59–0.88).[1]

A 2009 systematic review of 34 diagnostic cohort studies (N=10,067) assessed the validity of using the EPDS to diagnose postpartum major and minor depression.[2] Four studies were in common with the review above. Studies were excluded if the population was <1 week postpartum or if >24 hours existed between the EPDS questionnaire and clinical interview. The reference standard varied among the included studies: 6 used the International Classification of Diseases (ICD); 2 used the PSE; and 1 study did not state the reference used. The cutoff of ≥10 points and ≥13 points on the EPDS were used to differentiate between minor and major depression, respectively.

CONTINUED

Using the cutoff of ≥10 points on the EPDS, the sensitivity ranged from 59% to 100% and the specificity ranged from 44% to 97%. The median positive predictive value (PPV) was 50%; the median negative predictive value (NPV) was 97%; and the median positive likelihood ratio (LR+) was 5.9. Using the cutoff of ≥13 points on the EPDS, the sensitivity ranged from 34% to 100%; specificity ranged from 49% to 100%; the median PPV was 61%; and the NPV 96%.[2]

A 2008 prospective cohort study evaluated 123 women between 6 and 8 weeks' postpartum comparing the effectiveness of the EPDS along with Postpartum Depression Screening Scale (PDSS) and Patient Health Questionnaire (PHQ-9).[3] Exclusion criteria included women <18 years old, delivery before 29 weeks' gestation, or a history of bipolar disorder or abusing drugs or alcohol. Women were interviewed over the telephone between 6 and 8 weeks' postpartum with all 3 questionnaires. If all questionnaires were negative they were contacted at 3 and 6 months. If at any interval the patient had a positive screening questionnaire, they were asked to participate in a home visit where they completed the Diagnostic Interview Schedule module, which was considered the gold standard for diagnosis. Using cutoffs of ≥10 on the EPDS, ≥14 on the PDSS, or ≥10 on the PHQ-9, a total of 29 home visits were accepted out of a total of 40 home visits offered. Of all the 29 home visits, 13 patients were diagnosed with depression on the diagnostic interview.

Using a cutoff point of ≥10, the sensitivity of the EDPS was 62% (8 of 13) and specificity was 88% (14 of 16). A limitation of this study was that not all patients underwent the reference standard interview, which could have overestimated sensitivity.[3]

A 2006 prospective cohort study including 815 women evaluated the validity of EPDS at days 3 to 5 postpartum.[4] Patients were excluded if they refused to participate, were illiterate, or were diagnosed with schizophrenia. Patients were included if they gave birth on the maternity unit during the study period. A total of 758 questionnaires were completed; 227 scored >8 and were compared with a control group of 200 randomly selected patients with a score of <8.

Of the 427 participants, 363 (unable to contact 60 and 4 were excluded due to schizophrenia) were via telephone at 6 to 8 weeks' postpartum, using the MINI as the reference standard by 2 physicians blinded to the previous EPDS score. Using a cutoff score of ≥10, sensitivity and specificity of the EPDS was 0.82 (95% CI, 0.78–0.86) and 0.68 (95% CI, 0.63–0.73), respectively. The NPV was 95% and the PPV was 43%.[4]

Jonathan Novotney, DO
Douglas Maurer, DO, MPH, FAAFP
Madigan Army Medical Center
Joint Base Lewis-McChord, WA
The opinions and assertions contained herein are those of the authors and are not to be construed as official o r as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.

1. Tsai AC, Scott JA, Hung, KJ, Zhu JQ, Matthews LT, Psaros C, et al. Reliability and validity of instruments for assessing perinatal depression in African settings: systematic review and meta-analysis. *PLos One*. 2013; 8(12):e82521. **[STEP 1]**
2. Gibson J, Mckenzie-McHarg K, Shakespeare J, Price J, Gray R. A systematic review of studies validating the Edinburgh Postnatal Depression Scale in antepartum and postpartum women. *Acta Psychiatr Scand*. 2009; 119(5):350–364. **[STEP 1]**
3. Hanusa BH, Scholle SH, Haskett RF, Spadaro K Wisner KL. Screening for depression in the postpartum period: a comparison of three instruments. *J Womens Health (Larchmt)*. 2008; 17(4):585–596. **[STEP 2]**
4. Jardi R, Pelta J, Maron M, Thomas P, Delion P, Codaccioni X, et al. Predictive validation study of the Edinburgh Postnatal Depression Scale in the first week after delivery and risk analysis for postnatal depression. *J Affect Disord*. 2006; 93(1–3):169–176. **[STEP 2]**

In pediatric patients on antibiotic therapy, do probiotics prevent antibiotic-associated diarrhea?

EVIDENCE-BASED ANSWER

Yes, co-administering probiotics at high doses with antibiotics in children younger than 18 years old is associated with a 48% reduction in the incidence of antibiotic-associated diarrhea (SOR: **B**, meta-analysis of RCTs at risk of bias). Probiotic administration with antibiotic therapy also results in a 60% reduction in the incidence of *Clostridium difficile*-associated diarrhea (CDAD) (SOR: **B**, extrapolated from a meta-analysis including adults and children).

A 2011 meta-analysis of 16 RCTs studied the use of probiotics versus other therapies (placebo, diosmectite, infant formula, or no treatment) in 3,432 children 0 to 18 years old receiving antibiotics.[1] Probiotic treatment ranged from 10 days to 3 months (included *Bacillus* spp, *Bifidobacterium* spp, *Lactobacilli* spp, *Lactococcus* spp, *Leuconostoc cremoris, Saccharomyces* spp, or *Streptococcus* spp). Antibiotic treatment ranged from 3 to 30 days and administration was predominantly in oral form, although 3 of the studies included intravenous antibiotics. Antibiotic regimens varied and included cephalosporins, macrolides, beta-lactams/penicillins, aminoglycosides, and

clindamycin. The probiotics were given concurrently with the antibiotics.

Antibiotic-associated diarrhea was less frequent in the probiotic group (all dosages) than in the control groups (15 trials, n=2,874; 9% vs 18%; relative risk [RR] 0.52; 95% CI, 0.38–0.72). The use of low-dose probiotics (defined as <5 billion CFU/d) did not demonstrate statistically significant benefits. Antibiotic-associated diarrhea occurred in 8% of the high-dose (>5 billion CFU/d) probiotic therapy group and 22% of the control group (7 RCTs, n=1,474; RR 0.4; 95% CI, 0.29–0.55; number needed to treat=7). The risk of bias was high due to loss to follow-up in many studies. Minor side effects reported included rash, nausea, flatulence, increased phlegm, chest pain, constipation, taste disturbance, and low appetite; however, no serious side effects were reported.[1]

A 2012 meta-analysis of 20 RCTs evaluated the incidence of CDAD in 3,818 adults and children receiving antibiotics.[2] The intervention was the administration of probiotics (*Lactobacillus acidophilus, L casei, L rhamnosus, Saccharomyces boulardii*, or other mixed species) for the duration of the antibiotic therapy while the control group either received placebo or no intervention. Reasons for antibiotic therapy included respiratory tract infection, *Helicobacter pylori* infection, meningitis, and septicemia. Antibiotics given included cephalosporins (cefotaxime, cefprozil, cefuroxime), macrolides (clarithromycin, erythromycin, azithromycin), beta-lactams/penicillins (amoxicillin, augmentin, unasyn), aminoglycosides, tetracycline, and furazolidone. Daily dosage of probiotics varied from 100 million to 40 billion CFU/d. The follow-up period was 7 days to 3 months.

The incidence of CDAD was significantly lower in the children treated with probiotics compared with children without probiotics (20 RCTs, n=3,818 including 605 children, RR 0.40; 95% CI, 0.17–0.96). There was no increase in clinically significant adverse events.[2]

Ehab Molokhia, MD, MPH
Amy Kayl, DO
Huy Lam, MD
Ashlen Aggen, MD
Brandi Robinson, MD
University of South Alabama FMRP
Mobile, AL

1. Goldenberg JZ, Lytvyn L, Steurich J, Parkin P, Mahant S, Johnson BC. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Cochrane Database Syst Rev*. 2015; (12):CD004827. **[STEP 1]**
2. Johnson BC, Ma SS, Goldenberg JZ, Thorlund K, Vandvik PO, Loeb M, et al. Probiotics for the prevention of Clostridium difficile–associated diarrhea: a systematic review and meta-analysis. *Ann Intern Med*. 2012; 157(12):878–888. **[STEP 1]**

Is vitamin D effective in preventing stress fractures?

EVIDENCE-BASED ANSWER

Vitamin D supplementation with calcium likely reduces the risk of stress fractures by 20% in female military recruits (SOR: **B**, single RCT). There is a weak association with high vitamin D intake and reduced risk of stress fractures in adolescents (SOR: **B**, based on a single prospective cohort). Low serum 25-(OH) vitamin D levels are associated with an increased risk of stress fractures (no SOR given).

A 2008 double-blind RCT evaluated daily calcium (2000 mg) and vitamin D (800 IU) oral supplementation and the incidence of stress fractures in US female navy recruits 17 to 35 years old.[1] In a 24-month period, groups of recruits were followed during their 8-week-long basic training. A total of 3,700 women completed the study and 309 women were diagnosed with stress fractures.

The supplementation group had a 20% reduction in stress fractures compared with the placebo group (relative risk 0.80; 95% CI, 0.64–0.99). Vitamin D supplementation alone was not evaluated.[1]

A 2012 prospective cohort of 6,712 predominantly white adolescent girls 9 to 14 years old assessed vitamin D, calcium, and dairy intake and the development of stress fractures annually over a 7-year period.[2] During the study, 90% of stress fractures occurred in girls who participated in ≥1 hour/d of high-impact activity.

Among these girls, those who consumed vitamin D in the highest quintile (mean 663 IU/d) did not have lower risk of developing stress fractures compared with girls consuming vitamin D in the lowest quintile (mean 107 IU/d) (hazard ratio 0.48; 95% CI, 0.22–1.02), but the trend for decrease in risk from lowest to highest quintiles was significant (*P*trend=.04). No evidence suggested that dairy or calcium intake was protective.[2]

A 2015 systematic review and meta-analysis included 6 prospective cohort studies and 2 case-control studies of 2,634 military personnel 18 to 30 years old undergoing basic training or on active duty who were evaluated for lower extremity stress fractures and serum 25-(OH) vitamin

D levels (1,153 men, 1,481 women; 761 stress fracture cases, 1,873 controls).[3] Study durations ranged from 3 months to 6.5 years with 1 study conducted in United States, 1 in Greece, 4 in Israel, and 2 in Finland.

The mean serum 25-(OH) vitamin D level was significantly lower in participants with stress fracture cases than in controls, with a mean difference of –2.4 ng/mL (95% CI, –4.1 to –0.84). Significant study heterogeneity was noted, likely from variations in ethnicity, sex, location, season, diet, and methods of serum 25-(OH) vitamin D measurement.[3]

A 2016 prospective cohort of British Royal Marine recruits compared serum 25-(OH) vitamin D levels measured at weeks 1, 15, and 32 with stress fracture incidence.[4] The study followed 1,082 male recruits ages 16 to 32 years old over a 32-week training period and found a higher incidence of stress fractures in recruits with serum 25-(OH) vitamin D <50 nmol/L (odds ratio [OR] 1.6; 95% CI: 1.0–2.6). A case-control subanalysis was completed on 75 stress fracture cases retrospectively matched for age, body weight, height, and aerobic fitness with recruits who did not endure stress fractures. Serum 25-(OH) vitamin D <50 nmol/L at week 1 had a higher incidence of stress fracture (OR 2.3; 95% CI, 1.1–4.8).

Melissa Lao, MD
UC Davis Medical Group
Sacramento, CA

Kara Mayes, MD
Mercy FMR
St. Louis, MO

1. Lappe J, Cullen D, Haynatzki G, Recker R, Ahlf R, Thompson K. Calcium and vitamin D supplementation decreases incidence of stress fractures in female navy recruits. *J Bone Miner Res*. 2008; 23(5):741–749. **[STEP 2]**
2. Sonneville KR, Gordon CM, Kocher MS, Pierce LM, Ramappa A, Field AE. Vitamin D, calcium, and dairy intakes and stress fractures among female adolescents. *Arch Pediatr Adolesc Med*. 2012; 166(7):595–600. **[STEP 3]**
3. Dao D, Sodhi S, Tabasinejad R, Peterson D, Ayeni OR, Bhandari M, et al. Serum 25-hydroxyvitamin D levels and stress fractures in military personnel: a systematic review and meta-analysis. *Am J Sport Med*. 2015; 43(8):2064–2072. [STEP 2]
4. Davey T, Lanham-New SA, Shaw AM, Hale B, Cobley R, Berry JL, et al. Low serum 25-hydroxyvitamin D is associated with increased risk of stress fracture during Royal Marine recruit training. *Osteoporos Int*. 2016; 27(1):171–179. **[STEP 3]**

What is the best treatment for adult somatization disorder?

EVIDENCE-BASED ANSWER

Psychological therapies, cognitive behavioral therapy (CBT), and enhanced care by the primary care physician (PCP) all have small positive effects on adults with somatization disorder (SOR: **B**, systematic review of low-quality RCTs). Yet, when compared with enhanced care, psychological therapies generally were not more effective. Selective serotonin reuptake inhibitors (SSRIs)/ selective norepinephrine reuptake inhibitors (SNRIs) and St. John's wort have moderate positive effects in reducing the severity of physical symptoms (SOR: **B**, systematic review of low-quality RCTs).

A 2014 systematic review of 21 RCTs (N=2,658 adults) evaluated nonpharmacological interventions for somatoform disorders and medically unexplained physical symptoms in adults.[1] All studies evaluated the effectiveness of psychological therapy. Three separate analyses were described in this review. First, psychological therapy was compared with usual care (not defined). Second, psychological therapy was compared with enhanced care. Enhanced care is the care provided by the PCP that includes patient education or structured counseling moments with the goal of providing the patient with tools for self-management. And finally, CBT was compared with behavioral therapy. Fourteen studies (n=1,440) evaluated forms of CBT; the remainder evaluated behavior therapies. The duration of interventions and specific techniques varied widely among the studies. Only 1 study (n=173) compared CBT with behavior therapies.

For all studies comparing some form of psychological therapy with usual care, psychological therapy resulted in less severe somatic symptoms at the end of treatment, as measured by various self-reporting instruments (10 studies, n=1,081; standardized mean difference [SMD] –0.34; 95% CI, –0.53 to –0.16). This effect was small to moderate and the quality of evidence was considered low due to study heterogeneity. Subgroup analysis comparing CBT with usual care yielded similar results (6 studies, n=593; SMD –0.37; 95% CI, –0.69 to –0.05). The authors stated only CBT had

been studied well enough for conclusions to be drawn about its efficacy. However, when compared with enhanced care, CBT was not more effective in terms of reducing somatic symptoms (3 studies, n=307; SMD –0.34; 95% CI, –0.71 to 0.03). Limitations of this review include small effect sizes, study heterogeneity, and inherent bias toward a favorable outcome because all participants in these studies were willing to receive psychological treatment.[1]

A separate 2014 systematic review examined pharmacological interventions for somatoform disorders in adults (26 RCTs, N=2,159).[2] Studies were rated as low quality secondary to concerns of bias and small sample sizes. SMDs were reported secondary to various somatization rating scales used in the different studies.

SSRIs and SNRIs (various medications and doses) compared with placebo were moderately effective in treating physical symptoms, anxiety, and depression in somatization disorders (3 studies, n=243; SMD –0.91; 95% CI, –1.36 to –0.46). SSRIs/SNRIs were no more effective than tricyclic antidepressants (TCAs) (3 studies, n=177; SMD –0.16; 95% CI, –0.55 to 0.23). TCAs were no more effective than placebo (2 studies, n=239; SMD –0.13; 95% CI, –0.39 to 0.13). In comparison with placebo, St. John's wort was effective in reducing symptom severity (2 studies, n=322; SMD –0.74; 95% CI, –0.97 to –0.51).[2]

Roxanne Smith, MD, MPH
Advocate Christ Medical Center FMRP
Hometown, IL

1. van Dessel N, den Boeft M, van der Wouden JC, Kleinstäuber M, Leone SS, Terluin B, et al. Non-pharmacological interventions for somatoform disorders and medically unexplained physical symptoms (MUPS) in adults. *Cochrane Database Syst Rev*. 2014; (11):CD011142. **[STEP 1]**
2. Kleinstäuber M, Witthöft M, Steffanowski A, van Marwijk H, Hiller W, Lambert MJ. Pharmacological interventions for somatoform disorders in adults. *Cochrane Database Syst Rev*. 2014; (11):CD010628. **[STEP 1]**

In adults with patent foramen ovale (PFO) who have had a stroke, is transcatheter closure of the PFO better than medical therapy for secondary stroke prevention?

EVIDENCE-BASED ANSWER

Transcatheter device closure (TDC) for PFO after a stroke is not better than medical therapy for secondary stroke prevention. Furthermore, TDC increases the risk of new-onset atrial fibrillation (SOR: **B**, systematic review of RCTs with high risk of bias). A clinical practice guideline does not recommend TDC over medical therapy for secondary stroke prevention in patients with PFO and cryptogenic stroke (SOR: **C**, consensus opinion).

A 2015 systematic review included 3 RCTs (N=2,303) comparing the effect of TDC versus medical therapy for secondary stroke prevention in adults (18–60 years old) with PFO.[1] One study used the STARflex® septal closure system while the others used the Amplatzer® PFO occluder. Medical therapies were not standardized within the studies—with regimens including aspirin, warfarin, clopidogrel, or a combination of aspirin and clopidogrel—and were determined at the discretion of the respective site investigators.

The reviewers defined 2 primary outcomes: (1) recurrent ischemic stroke and (2) a composite endpoint defined as ischemic stroke (fatal or nonfatal) or transient ischemic attacks (TIAs). Secondary endpoints included all-cause mortality and adverse events defined as atrial fibrillation, myocardial infarction, and bleeding.[1]

No statistically significant difference was noted in the primary outcome of stroke. A total of 58 nonfatal strokes or TIAs occurred: 22 (1.9%) in the TDC group and 36 (3.1%) in the medical therapy group (risk ratio [RR] 0.61; 95% CI, 0.29–1.3). No fatal strokes occurred in the studies. Two studies (n=1,323) reported on the composite outcome of stroke or TIA, also with no difference in outcome (RR 0.73; 95% CI, 0.45–1.2). The secondary endpoints of all-cause mortality, myocardial infarction, and bleeding were similar between both groups. The risk of new-onset atrial fibrillation in the intervention group was higher regardless of device used (RR 3.5; 95% CI, 1.5–8.4), although this risk was higher when the STARflex septal closure system was used (RR 7.9; 95% CI, 2.4–26).[1]

CONTINUED

Overall, the reviewers deemed the risk of bias in the studies as high. In light of the low event rates, the data quality was diminished by high dropout rates in both groups, as well as different dropout rates among groups. Dropout rates ranged were 1.8% to 15% in the PFO closure groups and 0.7% to 20% in the medical therapy groups. The largest and most recent trial had discordant dropout rates of 9% in the closure group and 17.3% of the medical therapy group. Furthermore, neither patients nor personnel were blinded (although outcome assessors were), and follow-up periods were <5 years in all 3 studies.[1]

A 2014 clinical practice guideline from the American Heart Association and American Stroke Association concluded that available data did not support a benefit for PFO closure by TDC for secondary stroke prevention in patients with PFO and cryptogenic stroke without deep vein thrombosis (DVT) (Class III; Level of Evidence A: the procedure is not useful or effective, and may be harmful; based on data derived from multiple RCTs).[2] They allowed that closure of PFO might be considered in patients with stroke secondary to DVT, depending on the risk of recurrent DVT (Class IIb; Level of Evidence C: the procedure may be considered; based on data derived from expert opinion). EBP

John R. Stevens, MD
Swedish Family Medicine – First Hill
Seattle, WA

Sarah Maitre, MD
Valley Family Medicine
Renton, WA

1. Li J, Liu J, Liu M, Zhang S, Hao Z, Zhang J, et al. Closure versus medical therapy for preventing recurrent stroke in patients with patent foramen ovale and a history of cryptogenic stroke or transient ischemic attack. *Cochrane Database Syst Rev*. 2015; (9):CD009938. **[STEP 1]**
2. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014; 45(7):2160–2236. **[STEP 5]**

Depressed patients with heart failure may not improve with escitalopram

Angermann CE, Gelbrich G, Störk S, Gunold H, Edelmann F, Wachter R, et al. Effect of escitalopram on all-cause mortality and hospitalization in patients with heart failure and depression: the MOOD-HF randomized clinical trial. *JAMA*. 2016; 315(24):2683–2693.

This RCT compared escitalopram with placebo in 372 adults with symptomatic heart failure who had reduced ejection fraction and depression. Patients were eligible for enrollment after being screened with the 9-question Patient Health Questionnaire and subsequently confirmed to be depressed by a psychiatrist or psychosomatic specialist. Patients successfully treated for depression in the past were excluded.

Investigators titrated the dosage of escitalopram over a 3- to 6-week period to the optimum dosage of escitalopram or placebo. Heart failure treatment was also optimized. The primary outcome was the time to the first event of either all-cause death or rehospitalization. Secondary outcomes included depression symptoms, anxiety symptoms, quality-of-life measurements, ejection fraction, and other disease-oriented cardiac outcomes as well as adverse drug effects.

The trial was stopped after a mean of 18 months of the planned 24-month trial because the data monitoring committee assessed the trial as futile. The escitalopram group experienced the primary outcome at a similar rate as the placebo group (63% vs 64%; hazard ratio 0.99; 95% CI, 0.76–1.3). Depression scores decreased similarly in both groups with a between-group difference of –0.9 (95% CI, –2.6 to 0.7).

Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	Yes	Clinically meaningful	Yes

Bottom line: Escitalopram does not decrease mortality, rehospitalization rates, or depression symptoms among depressed patients with heart failure. This conclusion may not apply to all depressed patients and the study population was not large enough to definitively rule out a benefit in depression symptoms.

Review and Summary Author: Janice L. Benson, MD, University of Chicago/NorthShore University Health System, Chicago, IL

Low-dose vitamin K reduces INR excursions, but may not improve outcomes

Boonyawat K, Wang L, Lazo-Langner A, Kovacs MJ, Yeo E, Schnurr T, et al. The effect of low-dose oral vitamin K supplementation on INR stability in patients receiving warfarin. A randomised trial. *Thromb Haemost.* 2016; 116(3):480–485.

This multicenter RCT randomized 253 patients on warfarin to receive either 150 µg low-dose vitamin K or placebo for 6 months. Outcomes included impact on time in therapeutic range, INR excursions <1.5 or >4.5, significant bleeding, myocardial infarction, cerebral vascular accident or systemic embolism, and pulmonary embolism or deep vein thrombosis. Exclusion criteria consisted of conditions known to affect vitamin K metabolism, INR out of range (<1.8 or >3.4) on the day of screening, or if the warfarin dose was likely to change. The study was stopped after enrollment of 253 patients due to insufficient study drug supply.

The absolute difference in the mean time in therapeutic range between the vitamin K and placebo groups was insignificant at –0.8% (95% CI, –7.0 to 5.4). During the 6-month study period, no thromboembolic or major bleeding events occurred in either group. INR excursions dropped to 5.4% in the low-dose vitamin K group, down from 9.4% (P<.001); INR excursions trended lower in the placebo group (10.1% before and 7.8% during the study period; P=.06). The low-dose vitamin K group had fewer INR excursions than the placebo group during the study period (absolute difference 2.4%; 95% CI, 0.2–4; P=.03).

Relevant	No	Medical care setting	Yes
Valid	Yes	Implementable	No
Change in practice	Yes	Clinically meaningful	No

Bottom line: Low-dose vitamin K reduces INR excursions, but does not improve time in therapeutic range. This study did not have an adequate sample size to establish whether clinically meaningful outcomes would be affected, and low-dose vitamin K is not widely available in a commercial formulation with reliable dosages. EBP

Review and Summary Author: Miriam Whiteley, MD, University of Chicago (Northshore) FMR, Glenview, IL