

EVIDENCE-BASED PRACTICE

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EDITORIAL

- 2 Spotless

IN DEPTH

- 3 Nonsurgical treatment of mild to moderate ulcerative colitis

DIVING FOR PURLs

- 4 SSRIs for depression after traumatic brain injury
Repeated antenatal steroids for preterm labor

TOPICS IN MATERNITY CARE

- 5 When to induce for late-term pregnancy

HELPDESK ANSWERS

- 6 Safety of ondansetron during pregnancy
7 Cannabis for chronic pain
8 Prevalence of vitamin D deficiency
9 Teeth staining with doxycycline versus tetracycline
10 Evaluation for asymptomatic microscopic hematuria
11 Doxylamine and pyridoxine for nausea and vomiting in pregnancy

- 12 Risks of valproate use during pregnancy

- 13 Physical examination findings in OSA

SPOTLIGHT ON PHARMACY

- 15 H2 blockers for patients with GERD

ONLINE CONTENT

- E1 Effectiveness of HPV vaccine
E2 Caffeine and anxiety
E3 T-SPOT.TB for diagnosing tuberculosis
E4 Psychological therapy for panic disorder
E5 Effect of omega-3 supplementation on cardiac mortality
E6 Sleep-disordered-breathing and poor maternal-fetal outcomes
E7 Mortality and morbidity risks of metabolically healthy obesity
E9 Aquatic aerobic exercise programs for fibromyalgia
E10 CT scans for children and adolescents with cervical spine injury

- E11 Potassium citrate to prevent kidney stone recurrence

Effective methods to reduce operative interventions in pregnant women

- E12 Effectiveness of heat or cold for reducing symptoms of acute muscle strain

- E13 Best treatment for seizures in patients with hyponatremia

- E14 Use of ESR and CRP for management of rheumatoid arthritis

- E15 Pneumococcal vaccinations for patients with COPD

- E16 Risk of concussion in female athletes

Empiric antibiotic use for UTI symptoms

- E18 Psychotherapy for chronic low back pain

- E19 Benefits of folic acid supplementation during pregnancy

Risks associated with using donor breast milk in neonates

- E21 **Diving for PURLs**
Syncope and PE

Acupuncture for constipation

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

Spotless

I have a friend who has a thoughtful approach to dusting her apartment. She cleans only when the dust becomes “thick enough to see without my glasses.” That frees her from obsessively dusting every particle from every stick of furniture every day, while preventing the buildup of enough dust to trigger her allergy symptoms or the formation of dust balls.

There are lots of places in medicine where we search for this kind of balance. High blood pressure is bad, but a pressure of 0/0 is not good either. High blood sugar is diabetes, but low blood sugar is a coma. An overgrowth of *Clostridium difficile* in your bowel is bad, but a sterilized colon is hardly a benefit.

So what about LDL cholesterol? High levels seem to be bad. And now, because we have proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors—which can literally drive LDL levels down to less than 10 mg/dL—we might soon know the effect of very low LDL levels.

We already know some of the costs. PCSK9 inhibitors decreased major cardiovascular events in patients with elevated risk in the FOURIER trial, in which statin therapy was compared with a combination of statins, ezetimibe, and PCSK9 inhibitors. Researchers used that data to calculate the cost-effectiveness of this new medication.¹ The team defined a reasonable cost as about \$100,000 per quality-adjusted life-year (QALY) gained. Their model used an annual cost of \$14,542 for the PCSK9 inhibitor and \$3,818 for ezetimibe. Adding this incremental cost to the incremental benefit of combination therapy seen in the FOURIER trial, the researchers found that the cost for each QALY gained was a whopping \$450,000. In order to hit their price-point of \$100,000 per QALY, the PCSK9 inhibitor’s price needed to come down by 71% (or by about \$10,000 a year).

So it appears that the makers of PCSK9 inhibitors (evolocumab and alirocumab) have positioned themselves to profit enormously by enticing us to keep the apartment spotless. It may be prudent to leave a little dust.



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REFERENCE

1. Kazi DS, Penko J, Coxson PG, Moran AE, Ollendorf DA, Tice JA, et al. Updated cost-effectiveness analysis of PCSK9 inhibitors based on the results of the FOURIER trial [letter]. *JAMA*. 2017; 318(8):748–750.

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What is the most effective nonsurgical medical treatment for adults with mild to moderate ulcerative colitis?

EVIDENCE-BASED ANSWER

Oral 5-aminosalicylic acid (5-ASA) formulations such as mesalamine produce similar remission rates as oral sulfasalazine (SASP) with fewer side effects (SOR: **A**, meta-analysis of RCTs). Mesalamine enemas are more effective than budesonide enemas with fewer side effects (SOR: **B**, single RCT). Combination therapy with rectal and oral mesalamine is more effective than oral mesalamine alone (SOR: **B**, single RCT).

Evidence summary

A 2016 systemic review examined 53 RCTs with parallel design (N=8,548, >18 years of age) comparing oral 5-ASA various other formulations of 5-ASA, SASP, and placebo for the induction of remission in mild to moderate ulcerative colitis as defined by Truelove and Witts' severity index.¹ All treatments were given for at least 4 weeks.

Patients receiving varying dosages of SASP (1–3 g/d) had ulcerative colitis remission rates similar to those seen in patients receiving oral 5-ASA (1.2–4.8 mg/d) (8 trials, n=526; 42% vs 46%; relative risk [RR] 0.90; 95% CI, 0.77–1.0). However, patients receiving 5-ASA were less likely to experience side effects, such as headache, nausea, and abdominal pain, than patients receiving SASP (12 trials, n=909; 15% vs 29% incidence; RR 0.48; 95% CI, 0.37–0.63). No statistically significant difference was noted in improvement of symptoms or remission rates among the various formulations of 5-ASA.¹

A 2010 RCT (N=237) compared the efficacy of the 5-ASA formulation, mesalamine (4 g/60 mL enema daily) with that of budesonide (2 mg/100 mL enema daily) for the treatment of mild to moderate, left-sided ulcerative colitis.² Patients were randomized to receive either budesonide (n=118) or mesalamine enemas (n=119) for 8 weeks. Each patient was evaluated using a clinical activity index (number of stools, bleeding, pain, fever, and inflammatory markers), endoscopic and histological index, and the Inflammatory Bowel Disease Questionnaire (IBDQ) that assessed activities of daily living, symptoms, and general well-being after 4 and 8 weeks.

After 8 weeks of treatment, mesalamine treatment led to a higher clinical remission rate based on the clinical activity

index (77% vs 64%; $P<.05$). However, endoscopic mucosal healing, histological remission, and IBDQ scores were not significantly different. Budesonide resulted in a higher rate of adverse events such as various gastrointestinal disorders or infections than mesalamine (55% vs 34%; $P<.002$). Limitations of this study included small patient group size and short treatment period.²

In 2014, a multinational, double-blind, parallel-group RCT compared the efficacy of adding mesalamine enemas to oral mesalamine in mild to moderate ulcerative colitis.³ Treatment efficacy was based on remission rates using the 12-point Ulcerative Colitis Disease Activity Index (UCDAI), which assesses clinical signs and endoscopic evaluation as well as endoscopic mucosal healing and cessation of rectal bleeding. Patients (N=127) at 43 centers in 6 countries were randomized to receive 2 g oral mesalamine (Pentasa®) BID for 8 weeks, plus either 1 g mesalamine (Pentasa) enema (n=71) or placebo enema (n=56) before bed for 4 weeks.

Patients receiving combination therapy were more likely to have clinical improvement (defined as an UCDAI score decrease of ≥ 2) than patients receiving oral therapy alone at week 2 (65% vs 45%; $P=.03$), week 4 (89% vs 62%; $P=.001$), and week 8 (86% vs 68%; $P=.03$). Combination therapy resulted in significantly higher remission rates (UCDAI < 2) at 8 weeks (64% vs 43%; $P=.03$). No difference was noted in adverse events between the 2 groups. Additionally, no significant differences were noted in mucosal healing, rectal bleeding, or quality of life.³

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REFERENCES

1. Wang Y, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2016; (5):CD000544. [STEP 1]
2. Hartman F, Stein J; BudMesa-Study Group. Clinical trial: controlled, open, randomized multicentre study comparing the effects of treatment in quality of life, safety and efficacy of budesonide or mesalazine enemas in active left-sided ulcerative colitis. *Aliment Pharmacol Ther*. 2010; 32(3):268–376. [STEP 2]
3. Probert CS, Dignass AU, Lindgren S, Oudkerk Pool M, Marteau P. Combined oral and rectal mesalazine for the treatment of mild-to-moderately active ulcerative colitis: rapid symptom resolution and improvements in quality of life. *J Crohns Colitis*. 2014; 8(3):200–207. [STEP 2]

Countering the blow: Effectiveness of sertraline after traumatic brain injury

Jorge RE, Acion L, Burin DI, Robinson RG. Sertraline for preventing mood disorders following traumatic brain injury: a randomized clinical trial. *JAMA Psychiatry*. 2016; 73(10):1041–1047.

This double-blind, placebo-controlled, intention-to-treat RCT evaluated starting sertraline to prevent depression in 94 patients with traumatic brain injury (TBI). Investigators used the Centers for Disease Prevention definition for TBI, which is any injury that causes disruption of normal brain function. Overall, 534 patients (age range 18–85 years) were eligible, but 440 (82%) declined to participate. Ninety-four patients consented to participate: 48 (mean age 50 years) in the sertraline group and 46 (mean age 55 years) in the placebo group.

The patients received sertraline titrated to 100 mg daily or placebo for 24 weeks. The primary outcome was diagnosis of depression using DSM-IV criteria and the Mini-International Neuropsychiatric Interview. Patients were evaluated at 2-week intervals. Most TBIs were mild (78%) as defined by Glasgow Coma Scale and caused by a motor vehicle crash (38%) or fall (59%).

The number needed to treat to prevent development of depression was 6.0 (95% CI, 3.1–71.1). Adverse events consistent with sertraline were more common in the treatment group, including diarrhea (odds ratio [OR] 2.3; 90% CI, 1.0–5.5) and dry mouth (OR 7.2; 90% CI, 1.9–28).

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

Bottom line: Sertraline may be effective for preventing depression in some patients after certain TBIs. However, efficacy may not be established for every patient with TBI, as 82% of eligible patients did not participate and the only patients examined were 50 years old and had sustained their TBI through motor vehicle accidents or falls. How other populations would respond is unknown, such as younger patients or patients with sports- or assault-related TBIs.

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Corticosteroid doses for threatened preterm labor

Crowther CA, Anderson PJ, McKinlay CJ, Harding JE, Ashwood PJ, Haslam RR, et al. Mid-childhood outcomes of repeat antenatal corticosteroids: a randomized controlled trial. *Pediatrics*. 2016; 138(4). pii:e20160947. Epub September 20, 2016.

This RCT was a mid-childhood follow-up of an earlier RCT, which examined the outcomes of women at risk of preterm labor (<32 weeks' gestation) who received an initial course of antenatal corticosteroids and received either weekly corticosteroid injections if an increased risk of preterm birth remained, or saline placebo. The initial trial found repeated corticosteroid injections resulted in reductions in respiratory distress syndrome, severe lung disease, and neonatal morbidity.

This trial examined potential adverse effects in patients 6 to 8 years later. Of the initial 1,146 pregnancies, data were available for 93% of patients in each group.

No difference between groups was seen in the primary outcome of neurosensory disability (defined as cerebral palsy, IQ 1 standard deviation below the mean, blindness or deafness). Nor were differences noted in secondary outcomes such as mortality, lung function, height, weight, attention and executive function, academic achievement, or health-related quality of life.

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

Bottom line: Repeated antenatal corticosteroid doses given to patients at increased risk of preterm labor do not appear to have any adverse effects on children 6 to 8 years later. However, whether a change in practice is warranted is unclear, because a recent meta-analysis on repeated corticosteroid doses was limited by heterogeneity, and some guidelines recommend a rescue dose of corticosteroids after the initial 7 days but do not recommend scheduled repeat doses. **EBP**

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<http://fpin.org/page/WhatarePURLs>

In a woman with a late-term pregnancy, when is the best time to induce?

CASE

A 26-year-old G1P0 at 40 3/7 weeks comes in for routine prenatal care. She has had an uncomplicated pregnancy and desires a low-intervention unmedicated birth. She has become more uncomfortable lately, however, and asks for your guidance regarding at what point induction of labor is indicated.

Bottom line

In a woman with late-term pregnancy, induction of labor at 41 weeks results in a reduction in perinatal mortality and a reduced risk of Cesarean delivery compared with expectant management. The absolute risk of these outcomes is small, and women who prefer to avoid induction may be managed expectantly with twice-weekly antenatal testing to assess fetal well-being. Perinatal mortality continues to rise with increasing gestational age. The American College of Obstetricians and Gynecologists (ACOG) recommends induction of labor by 43 weeks.

Review of the evidence

Late-term pregnancy is defined as pregnancy between 41 0/7 and 41 6/7 weeks' gestation. Postterm pregnancy is defined as a pregnancy that reaches 42 weeks of gestation or longer. Observational studies have shown that perinatal mortality (stillbirth or death within the first week of life) increases with each week that a pregnancy lasts beyond the estimated due date. Fetal mortality increases weekly after 40 weeks' gestation: the odds ratio (OR) at 41 weeks is 1.48 (95% CI, 1.13–1.95), at 42 weeks is 1.77 (95% CI, 1.22–2.56), and at 43 weeks is 2.90 (95% CI, 1.27–6.61).¹

A 2012 systematic review investigated labor induction at a predetermined gestational age versus expectant management in low-risk pregnant women at or beyond term (37 weeks).² This analysis of 22 RCTs (N=9,383) included 5 trials in which labor was induced at less than 41 weeks and 17 trials in which labor was induced at 41 or more weeks. In 20 of the trials, the expectant management protocol included some type

of fetal monitoring (fetal heart rate monitoring and/or assessment of amniotic fluid).

Induction of labor compared with expectant management was associated with fewer all-cause perinatal deaths (risk ratio [RR] 0.31; 95% CI, 0.12–0.88). The number needed to treat to prevent 1 perinatal death was 410 pregnancies (95% CI, 322–1,492). A policy of induction of labor was also associated with a decreased risk of meconium aspiration syndrome (RR 0.59; 95% CI, 0.34–0.73), fewer Cesarean deliveries (RR 0.89; 95% CI, 0.81–0.97), more operative vaginal births (RR 1.10; 95% CI, 1.00–1.21), and a reduced rate of macrosomia (birth weight >4,000 g) (RR 0.73; 95% CI, 0.64–0.84). No significant difference was noted in newborn intensive care unit (NICU) admissions or Apgar score less than 7 at 5 minutes.²

A 2003 systematic review with meta-analysis assessed 16 RCTs (N=6,588) comparing induction of labor with expectant management for uncomplicated, singleton, live pregnancies of at least 41 weeks' gestation.³ Thirteen of the RCTs in this systematic review were among the 22 RCTs included in the systematic review described above. Researchers concluded that women who underwent induction of labor had lower rates of Cesarean delivery (OR 0.88; 95% CI, 0.78–0.99). No significant difference was noted in the perinatal mortality rate (0.09% vs 0.33%; OR 0.41; 95% CI, 0.14–1.18), NICU admissions (OR 0.92; 95% CI, 0.78–1.10), meconium aspiration syndrome (OR 0.46; 95% CI, 0.18–1.21), or abnormal Apgar scores (OR 0.82; 95% CI, 0.51–1.32).

Recommendations from others

A 2014 ACOG practice bulletin recommended induction of labor after 42 0/7 weeks and by 42 6/7 weeks of gestation because of evidence of increased perinatal morbidity and mortality.⁴ They further stated that induction of labor between 41 0/7 and 42 0/7 weeks "can be considered." Cervical ripeness was not incorporated in these recommendations. They suggested starting antepartum fetal surveillance at 41 0/7 weeks.

CONTINUED ON PAGE 14

Is ondansetron safe to use during pregnancy?

EVIDENCE-BASED ANSWER

Ondansetron use in pregnancy is associated with a small increase in risk of renal and cardiac birth defects, but no increase in risk of major malformations. Evidence is conflicting on risk of cleft palate (SOR: **B**, systematic review of observational studies). However, for patients with hyperemesis, ondansetron use is also associated with a lower risk of miscarriage during the first trimester and a higher live birth rate. There is no association with other adverse outcomes (stillbirth, preterm delivery, low birthweight, and small-for-gestational age [SGA]) (SOR: **B**, retrospective cohort studies).

A systematic review of 8 studies (N=3,184,422) examined the association between ondansetron exposure and birth defects in women with hyperemesis gravidarum or nausea and vomiting during pregnancy.¹ The studies (5 registry

reviews, 3 case-control studies, and 1 prospective cohort study) compared infant outcomes in women exposed to ondansetron during pregnancy with infants born to nonexposed mothers.

Six studies found no increased risk of major malformations (not defined) and 2 found a slightly increased risk of cardiac defects (see **TABLE**). Three studies reported on the risk of cleft palate with mixed results: 1 found a slight increase, 1 no difference, and 1 a slight decrease risk of cleft palate when compared with nonexposed infants. One study found a slight risk of renal agenesis or dysplasia.¹

A retrospective cohort study of 608,385 pregnancies in Denmark included in the systematic review above also investigated the risk of adverse maternal as well as additional fetal outcomes associated with ondansetron use during pregnancy compared with pregnancies not exposed to ondansetron.² Ondansetron prescriptions and birth outcomes were identified using national registries. Additional adverse maternal and fetal outcomes (other than major malformations reported in the systematic review) were miscarriage, stillbirth, preterm delivery, low birthweight, and SGA.

TABLE

Trials of risk of birth defects in women exposed and not exposed to ondansetron during pregnancy¹

Study type	Outcome	Number of women exposed	Number of women not exposed	Birth defect rate in women exposed	Birth defect rate in women not exposed	Odds ratio of exposed to not exposed (95% CI)
Prospective cohort	Major malformation	169	160	3.6%	1.9%	1.9 (0.4–7.8)
Registry review	Major malformation	65	676,198	0%	3.5%	0
Case-control	Cleft palate	55	4,479	20%	11%	2.4 (1.2–4.8) ^a
Registry review	Major malformation	263	98,062	4.6%	4.1%	1.2 (0.6–2.2)
Registry review	Major malformation	1,233	4,932	2.9%	2.9%	1.1 (0.7–1.8)
Registry review	Major malformation	1,248	895,770	4.6%	3.5%	1.3 (1.0–1.7)
	Cardiac defects			N/A	N/A	2.0 (1.3–3.1) ^a
Registry review	Major malformation	1,349	1,500,085	2.8%	2.9%	1.0 (0.7–1.3)
	Cardiac defects			N/A	N/A	1.6 (1.04–2.14) ^a
Case-control	Cleft palate	111	N/A	N/A	N/A	1.5 (0.9–2.5)
Case-control	Cleft palate	243	N/A	N/A	N/A	0.4 (0.2–0.8) ^a
	Renal agenesis or dysplasia			N/A	N/A	2.3 (1.3–4.0) ^a

N/A=not available.

^aStatistically significant difference.

The risk of miscarriage rate between 7 and 12 weeks was lower among ondansetron users (1.1% vs. 3.7%; hazard ratio [HR] 0.5; 95% CI, 0.3–0.9). No differences were noted in the risk of miscarriage between 13 and 22 weeks (n=8,628; HR 0.6; 95% CI, 0.3–1.2), stillbirth (n=9,575; HR 0.4; 95% CI, 0.1–1.7), preterm delivery (n=8,960; odds ratio [OR] 0.9; 95% CI, 0.7–1.3), low birth weight (n=8,920; OR 0.8; 95% CI, 0.5–1.1), or SGA (n=8,920; OR 1.1; 95% CI, 0.9–1.4) when comparing ondansetron-exposed with unexposed pregnancies.²

A retrospective cohort study collected data via patient survey on 3,396 US pregnancies and categorized them as follows: 1,070 had hyperemesis gravidarum and were exposed to ondansetron with 952 live births; 771 had hyperemesis gravidarum but were not exposed to ondansetron with 441 live births; and 1,555 had neither a history of hyperemesis gravidarum nor ondansetron exposure.³

No difference was noted in the rate of birth defects for the ondansetron group versus the nonexposed group (3.5% vs 3.4%; OR 1.6; 95% CI, 0.9–3.0). Women with hyperemesis who were treated with ondansetron were less likely than women not treated to have a first-trimester miscarriage (n=276; OR 0.1; 95% CI, 0.06–0.13) or termination due to hyperemesis (n=94; OR 0.3; 95% CI, 0.2–0.4). The live birth rate was higher for women given ondansetron compared with women not given ondansetron (n=1,260; OR 3.6; 95% CI, 2.9–4.4), and it was higher compared with women who had neither hyperemesis gravidarum nor ondansetron exposure (n=2,238; OR 1.7; 95% CI, 1.3–2.1). Rates of preterm birth did not differ between the 2 groups with hyperemesis, after adjusting for live births.³

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1. Carstairs S. Ondansetron use in pregnancy and birth defects. *Obstet Gynecol.* 2016; 127(5):878–883. [STEP 2]
2. Pasternak B, Svanstrom H, Hviid A. Ondansetron in pregnancy and risk of adverse fetal outcomes. *N Engl J Med.* 2013; 368(9):814–823. [STEP 3]
3. Fejzo MS, MacGibbon KW, Mullin PM. Ondansetron in pregnancy and risk of adverse fetal outcomes in the United States. *Reprod Toxicol.* 2016; 62:87–91. [STEP 3]

We invite your questions and feedback.
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Is cannabis an effective treatment for chronic pain?

EVIDENCE-BASED ANSWER

Inhaled and ingested cannabis formulations are somewhat effective in reducing chronic neuropathic or cancer-related pain compared with placebo; the numbers needed to treat (NNT) are 4 to 17 patients to result in 1 more patient achieving at least a 30% reduction in pain. Inhaled cannabis may be more effective than ingested cannabis, and pain relief may be dose dependent (SOR: **B**, meta-analyses of lower quality RCTs and 1 small RCT).

A 2015 systematic review of 28 RCTs evaluated the effectiveness of cannabinoids for chronic pain in 2,454 individuals.¹ Eight trials (n=1,370) measured a dichotomous outcome and compared nabiximols or inhaled tetrahydrocannabinol (THC) versus placebo for the treatment of chronic neuropathic (central, peripheral, or unspecified) and cancer pain.

Pain reduction of at least 30% occurred in 37% of patients using inhaled THC (1 trial) or nabiximols (7 trials) compared with 31% using placebo (odds ratio [OR] 1.4; 95% CI, 1.0–2.0; NNT=7). The greatest benefit was observed for inhaled THC versus placebo (1 trial, n=50; 52% vs 24%; OR 3.4; 95% CI, 1.0–11.5; NNT=4). No significant difference was noted in pain reduction between patients with neuropathic or cancer pain.¹

Limitations included small sample size and short duration for each study, and variable cannabis administration routes (altering pharmacokinetics of drug delivery). Additional limitations included the failure of some studies to appropriately address subject dropouts from trials, selective outcome reporting, and inadequate description of randomization methods, allocation concealment, and blinding.¹

A 2015 Bayesian meta-analysis evaluated individual patient data (N=178) from 5 RCTs to determine the efficacy of inhaled cannabis in chronic diabetic, traumatic, or HIV-related painful neuropathy.² All 5 RCTs were included in the previously mentioned systematic review. Administration of cannabis and placebo occurred via pipe, vaporization, and prerolled cigarettes; dose estimates ranged from 1.6 to 96 mg THC per day. Follow-up ranged from 5 hours to 2 weeks.

CONTINUED

Inhaled cannabis was more effective than placebo in achieving more than 30% pain reduction as measured by a visual analog scale (OR 3.2; 95% credible interval, 1.6–7.2; NNT=6). The psychoactive effects of THC may have contributed to a lack of blinding.²

A subsequent double-blind, crossover RCT treated 16 individuals with diabetic peripheral neuropathy with placebo or low (4 mg), medium (16 mg), or high (28 mg) doses of THC via vaporized cannabis.³ Participants inhaled 4 puffs over a single 4-hour session, then crossed to a different treatment arm after a 2-week interval. Pain intensity was measured using a 10-point numerical pain scale and was recorded every 30 minutes for up to 4 hours. Baseline pain intensity was 6.7 (±1.6).

At 4 hours, average pain intensity scores, compared with placebo, were 0.44, 0.42, and 1.2 points lower, respectively, in patients given low-, medium-, and high-dose THC ($P \leq .04$ for each THC vs placebo comparison). High-dose (but not medium- or low-dose) THC resulted in greater pain reduction from baseline compared with placebo (70% vs 53% reduction; $P = .03$). Limitations to this study included the small number of study participants and the occurrence of a higher than normal placebo response. Additionally, the crossover trial design and psychoactive effects of THC may have contributed to a lack of blinding.³

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1. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA*. 2015; 313(24):2456–2473. [STEP 1]
2. Andrae MH, Carter GM, Shaparin N, Suslov K, Ellis RJ, Ware MA, et al. Inhaled cannabis for chronic neuropathic pain: a meta-analysis of individual patient data. *J Pain*. 2015; 16(12):1221–1232. [STEP 1]
3. Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of inhaled cannabis on painful diabetic neuropathy. *J Pain*. 2015; 16(7):616–627. [STEP 2]

What is the prevalence of vitamin D deficiency in the United States?

EVIDENCE-BASED ANSWER

The overall prevalence of vitamin D deficiency (25-hydroxyvitamin D levels <30 nmol/L) in the United States is 8.1% and is slightly higher in females (9.9%) than males (6.3%). Mexican Americans (11%), and non-Hispanic blacks (31%) have a higher prevalence than whites (3.6%). In adolescents, the prevalence is 8.5% to 24.1% using 30 to 37.5 nmol/L cutoffs. Breastfed infants not receiving vitamin supplements have a prevalence of 64%. The data on children are inconsistent, with rates ranging from 0.7% to 40% (SOR: **C**, cross-sectional studies of disease-oriented data).

A 2012 cross-sectional report on data collected from 2003 to 2006 as part of the National Health and Nutrition Examination Survey reported prevalence rates of vitamin D deficiency.¹ This annual survey provided a snapshot of the health and nutrition of the civilian, noninstitutionalized US population. Participants were randomly selected based on US census data (N=16,604).

Vitamin D deficiency, based on serum levels less than 30 nmol/L, was less prevalent in men than women (see **TABLE**). Prevalence was lowest in children 1 to 11 years old. Prevalence rates were similar in the older age groups of 12 to 19 years, 20 to 39 years, 40 to 59 years, and older than 60 years. Among different racial/ethnic groups, prevalence was lowest among non-Hispanic whites compared with Mexican Americans and non-Hispanic blacks.¹

In 2004, a cross-sectional study of a Boston clinic-based sample of 307 healthy adolescents, 11 to 18 years of age, tested vitamin D levels from blood drawn during an annual physical examination.² Exclusion criteria included chronic illness, use of a medication known to affect bone metabolism, ordering of a blood test other than for routine screening, patients being seen for a sick visit, and adolescents not having blood drawn.

Prevalence of vitamin D levels less than 20 nmol/L was 4.6%, less than 37.5 nmol/L was 24%, and less than 50 nmol/L was 42%. Prevalence of vitamin D deficiency (<37.5 nmol/L) was not statistically different between females (26%) and

EVIDENCE-BASED PRACTICE LEARNING OBJECTIVES

- 1** To become knowledgeable about evidence-based solutions to commonly encountered clinical problems.
- 2** To understand how ground-breaking research is changing the practice of family medicine.
- 3** To become conversant with balanced appraisals of drugs that are marketed to physicians and consumers.

TABLE

Prevalence of vitamin D deficiency in the United States¹

Group	n	Patients with 25-hydroxyvitamin D <30 nmol/L, % (95% CI)
Age >1 y (entire cohort)	16,604	8.1 (6.7–9.8)
1–5 y	1,799	0.7 (0.4–1.3)
6–11 y	1,768	1.8 (1.3–2.6)
12–19 y	4,044	8.5 (6.5–11)
20–39 y	3,262	9.5 (7.6–12)
40–59 y	2,660	9.3 (7.4–12)
≥60 y	3,071	8.8 (7.3–11)
Sex		
Male	8,145	6.3 (5.0–7.9)
Female	8,459	9.9 (8.1–12)
Race/ethnicity		
non-Hispanic whites	6,698	3.6 (3.0–4.4)
Mexican Americans	4,275	11 (8.7–15)
non-Hispanic blacks	4,439	31 (27–35)

males (21%). Deficiency prevalence was 36% among African Americans (n=142; odds ratio [OR] 8.6 vs non-Hispanic whites; 95% CI, 2.5–29) and 22% among Hispanics (n=78; OR 4.3 vs non-Hispanic whites; 95% CI, 1.2–16). Rates were not significantly different between Asians at 17% and whites at 6.1%. Compared with a summer prevalence of 12% (n=107), the winter prevalence of 39% (n=66; OR 4.7; 95% CI, 2.2–10), and the spring prevalence of 44% (n=45; OR 5.8; 95% CI, 2.5–13) were significantly higher. No significant difference was noted between summer and fall prevalence rates.²

In 2008, a cross-sectional study of a Boston clinic-based sample of 380 healthy infants (7.6–12 months old) and toddlers (12–24 months old) undergoing routine blood draw evaluated vitamin D status.³ There were 247 infants and 133 toddlers in the study, 192 females and 188 males. Exclusion criteria included presence of a chronic disease and use of medications known to affect vitamin D metabolism during the past 3 months. Vitamin D deficiency was defined as serum levels less than 20 nmol/L.

Overall prevalence of vitamin D deficiency was 12%. When deficiency was defined as serum levels less than 30 nmol/L, the prevalence was 40%.³

Differences in rates of vitamin D deficiency were noted according to vitamin supplementation and breast versus bottle feeding. The 14 breastfed infants not receiving vitamin D supplementation had a 64% prevalence of vitamin D deficiency compared with a prevalence of 33% among the 6 breastfed infants receiving supplementation. The 42 infants fed by both breast and bottle had a 9.5% prevalence, and the 185 bottle-fed infants had a 6.2% prevalence.³

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- Centers for Disease Control and Prevention (CDC). Second national report on biochemical indicators of diet and nutrition in the U.S. population. Hyattsville, MD: CDC; 2012. http://www.cdc.gov/nutritionreport/pdf/Nutrition_Book_complete508_final.pdf. Accessed December 21, 2017. [STEP 1]
- Gordon CM, DePeter KC, Feldman HA, Grace E, Emans SJ. Prevalence of vitamin D deficiency among healthy adolescents. *Arch Pediatr Adolesc Med.* 2004; 158(6):531–537. [STEP 3]
- Gordon CM, Feldman HA, Sinclair L, Williams AL, Kleinman PK, Perez-Rossello J, et al. Prevalence of vitamin D deficiency among healthy infants and toddlers. *Arch Pediatr Adolesc Med.* 2008; 162(6):505–512. [STEP 3]

Is doxycycline more likely to result in teeth staining than tetracycline?

EVIDENCE-BASED ANSWER

Although no studies have been published that directly compare the effects of doxycycline and tetracycline on teeth staining, doxycycline exposure before 8 years of age is not associated with teeth staining in children 8 to 16 years old (SOR: **B**, retrospective cohort, prospective cohort). Conversely, tetracycline exposure during anterior permanent teeth formation is associated with teeth staining in children 8 to 11 years old, especially if the treatment course is longer than 10 days or a dose of more than 3 g is given (SOR: **B**, retrospective cohort).

A 2015 retrospective cohort study involving 271 children between 8 and 16 years old examined the incidence of teeth staining with doxycycline.¹ The exposed group (N=58) received at least 1 dose of doxycycline for Rocky Mountain spotted fever and had at least 1 fully erupted exposed tooth at the time of examination. The average age at time

of exposure was 4.5 years (range 0.2–7.9 years). Mean doxycycline dose was 2.3 mg/kg (range 0.3–2.9 mg/kg). Five dentists, who were blinded to exposure status and trained by 1 dentist, used a handheld spectrophotometer to quantify tooth shade (on a scale of 1–16, with 16 being the darkest).

The average tooth shade in doxycycline-exposed children did not differ from that in unexposed children (9.5 vs 9.0; $P=.2$). Duration of doxycycline treatment was not correlated with average tooth shade, even after controlling for age at examination.¹

A 2007 single-blinded, prospective cohort study evaluated teeth staining in 8 to 16 year olds (N=61) exposed to doxycycline.² Thirty-one children received at least 1 course of doxycycline before the age of 8 years for an asthma attack. Dosing was standardized: doxycycline syrup 4 mg/kg twice daily for the first day and then 2 mg/kg per day for 9 more days. The comparison group had similar asthma severity but did not receive doxycycline. No difference was noted between groups in external factors contributing to possible tooth discoloration. One dentist performed most of the visual inspections, quantifying tooth shade using the Lumin Vacuum Shade Guide (on a scale of 1–16, with 16 being the darkest). The average age of initial exposure was 4.1 years. The average number of treatment courses was 2 (maximum 4).

Of the children exposed to doxycycline, 28% had a tooth shade of 3 to 5, whereas the other 72% had a tooth shade of 6 to 11, which was no different than tooth shade in unexposed children (20% with tooth shade 3–5 and 80% tooth shade 6–11; $P=.53$).²

A 1970 retrospective cohort study observed tetracycline teeth staining in children 8 to 11 years old with partially or fully erupted anterior teeth.³ Children were matched in a 1:2 ratio for those exposed to tetracycline in the hospital during anterior teeth formation versus no exposure. Examiners evaluated teeth staining with ultraviolet light to confirm exposure to tetracycline. The researchers did not determine tetracycline exposure outside of the hospital, potentially introducing bias that would favor the null hypothesis.

Of the children in the control group (n=476), 2.5% had teeth staining compared with 21% of tetracycline-exposed children (n=238; $P<.001$). Teeth staining was not associated with treated condition, sex, age, or weight. The proportion

of teeth staining increased above 33% if the tetracycline treatment course was longer than 10 days or if the total tetracycline dose administered was more than 3 g.³

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1. Todd SR, Dahlgren FS, Traeger MS, Beltrán-Aguilar ED, Marianos DW, Hamilton C, et al. No visible dental staining in children treated with doxycycline for suspected Rocky Mountain Spotted Fever. *J Pediatr*. 2015; 166(5):1246–1251. [STEP 3]
2. Volovitz B, Shkap R, Amir J, Calderon S, Varsano I, Nussinovitch M. Absence of tooth staining with doxycycline treatment in young children. *Clin Pediatr (Phila)*. 2007; 46(2):121–126. [STEP 3]
3. Conchie JM, Munroe JD, Anderson DO. The incidence of staining of permanent teeth by the tetracyclines. *Can Med Assoc J*. 1970; 103(4):351–356. [STEP 3]

Which adult patients with asymptomatic microscopic hematuria require further evaluation to rule out occult malignancy?

EVIDENCE-BASED ANSWER

A validated risk index for asymptomatic microscopic hematuria (AMH) that incorporates age, sex, history of gross hematuria, history of smoking, and degree of hematuria (<25 or >25 red blood cells per high-power field [RBC/HPF]) can identify a low-risk group of patients with a 0.2% risk of urinary tract malignancy, suggesting that these low-risk patients may not benefit from further evaluation (SOR: **B**, prospective cohort study). The American Urological Association (AUA) recommends computed tomography (CT) urography as the imaging test of choice, but also acknowledges that serious causes of AMH in younger patients (<35 years) without risk factors are rare, and so suggests ultrasound with or without intravenous urography as an alternative (SOR: **C**, expert opinion).

In a 2013 prospective inception cohort study, researchers developed and validated a Hematuria Risk Index (HRI).¹ High-risk factors were given 4 points when present (gross hematuria and age >50 years). Low-risk factors were given 1 point each if present (history of smoking, male sex, >25 RBC/HPF on recent urinalysis). The HRI had a maximum score of 11. The index stratified patients as low (scores of 0–4), moderate (scores of 5–8), and high

risk (scores ≥ 9). The test cohort contained 2,630 adult patients with AMH.

Of the 872 low-risk patients, 3 (0.3%) had cancer (determined by examination of medical record pathology reports; evaluation methods varied); of the 1,471 moderate-risk patients, 16 (1.1%) had cancer; and of the 237 high-risk patients, 31 (11.6%) had cancer. The HRI was then tested on a validation cohort of 1,784 patients in which no patients in the low-risk group were found to have cancer but 2.5% in the moderate-risk group and 10.7% in the high-risk group had cancer. Overall, out of the 4,414 total patients with AMH, 1,428 patients (32%) were identified as low risk, of whom 3 (0.2%) had cancer; 2,354 (53%) were identified as moderate risk, of whom 38 (1.6%) had cancer; and 632 (14%) were identified as high risk, with 70 (11.1%) having cancer. The strongest predictors of cancer were age older than 50 years (odds ratio [OR] 16.3; 95% CI, 2.2–119) and a history of gross hematuria in the prior 6 months (OR 9.9; 95% CI, 5.2–18.8).¹

The AUA performed a systematic review and included input from an expert panel in their 2012 guidelines on management of AMH.² The AUA reviewed a meta-analysis of 17 heterogeneous, single-cohort observational studies including more than 3,700 patients. The panel was unable to recommend an algorithm based on risk factor stratification because of a lack of published research on this question at the time of publication. Their expert consensus panel recommended cystoscopy and radiologic evaluation with CT urography on all patients with AMH (defined as ≥ 3 RBC/HPF), regardless of age.

This analysis found that among individuals found to have a urinary tract malignancy, 98 (97%) were older than 35 years. The panel recognized that in patients younger than 35 years who had no risk factors for urinary tract malignancies (irritative voiding symptoms, current or past tobacco use, or chemical exposures), ultrasound as an alternative but less optimal imaging modality and cystoscopy could be performed at the physician's discretion.²

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1. Loo RK, Lieberman SF, Slezak JM, Landa HM, Mariani AJ, Nicolaisen G, et al. Stratifying risk of urinary tract malignant tumors in patients with asymptomatic microscopic hematuria. *Mayo Clin Proc.* 2013; 88(2):129–138. [STEP 2]
2. Davis JR, Jones JS, Barocas DA, Castle EP, Lang EK, Leveillee RJ, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. *J Urol.* 2012; 188(6 suppl):2473–2481. [STEP 5]

Is combination doxylamine and pyridoxine effective and safe for nausea and vomiting of pregnancy?

EVIDENCE-BASED ANSWER

Combination therapy with doxylamine and pyridoxine is somewhat effective treating nausea and vomiting of early pregnancy, improving well-being by about 10%. Combination therapy also appears safe for both mother and infant (SOR: **B**, RCT and cohort studies).

A double-blind RCT examined the efficacy of Diclegis® (doxylamine succinate 10 mg/pyridoxine hydrochloride 10 mg) on nausea and vomiting of pregnancy in 256 patients.¹ The average patient was 26 years old and had a body mass index of 29 kg/m². The gestational age at start of treatment was 9.3 weeks in both groups.

Compared with placebo, Diclegis dosed as 2 tablets at bedtime plus 1 additional tablet as needed improved symptoms on the Pregnancy Unique Quantification of Emesis (PUQE) score (a validated quality-of-life measure scored 3–15, in which a lower number denotes less symptoms) (–4.8 vs –3.9 at day 15; $P=.006$). Although the PUQE score incorporates physical symptoms and quality of life, clinical significance is not clearly defined. The global assessment of well-being score improved significantly with treatment compared with placebo (scale 0–10, with 0 being the worst; 2.8 vs 1.8; $P=.005$). No significant difference was noted in lost time from employment in the Diclegis group compared with placebo (0.92 vs 2.37 days, $P=.06$). At the end of the 2-week trial, more women in the Diclegis group requested continued use of their medication (49% vs 33%; $P=.009$).¹

Data from the same RCT assessed maternal safety of Diclegis.² Diclegis did not increase the rate of maternal adverse events compared with placebo (57% vs 51%; $P=.39$). Measured adverse events included gastrointestinal upset, dry mouth, constipation, abdominal pain, fatigue, back pain, dizziness, headache, syncope, and somnolence. Equivalent numbers of patients discontinued the study drug and placebo due to an adverse effect (4.6% vs 3.1%, $P=.75$).

CONTINUED

A 2013 prospective cohort study (N=58) evaluated the efficacy and safety of combination doxylamine 25 to 50 mg daily and pyridoxine 50 mg twice daily compared with metoclopramide 10 mg 3 times a day for nausea and vomiting of pregnancy.³ Mothers who called in to the Beilinson Teratology Information Service reported severity of their nausea and vomiting (mild, moderate, severe) and efficacy of treatment (none, mild, moderate, high) and were followed for up to 2 years. Most women started treatment during the first trimester and the average duration of therapy in the treatment and control group was 6.2 and 3.5 weeks, respectively.

More women in the pyridoxine and doxylamine group initially reported moderate to severe symptoms compared with metoclopramide (97% vs 69%; $P<.01$). No significant differences were noted between the 2 groups for rates of congenital malformations, cesarean section, maternal pregnancy complications, or normal infant development.³

A 2004 prospective cohort study evaluated the teratogenicity of Diclegis in women who called into the Canadian Teratogen Information Service.⁴ The average maternal age was 29 years and 30% of women were primiparous. Women were exposed starting during the first trimester to a standard dose (1–4 tablets per day, n=122, average treatment duration 21 weeks), a high dose (5–12 tablets per day, n=124, average treatment duration 25 weeks), or had no exposure (n=130).

Using ANOVA, no differences were noted in the rates of major malformations, still birth, miscarriage, or birth weight <2,500 g among all groups.⁴

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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 AIR FORCE MEDICAL DEPARTMENT, THE AIR FORCE AT LARGE, OR THE DEPARTMENT OF DEFENSE

Is valproate use during pregnancy associated with an increased risk of developmental delays in childhood?

EVIDENCE-BASED ANSWER

Yes, depending on dose. Compared with untreated controls, carbamazepine, lamotrigine, levetiracetam, and phenytoin, higher doses of valproate (≥ 800 mg/d) are associated with lower IQ scores at age 6 and delays in cognitive development at age 2 (SOR: **B**, based on prospective cohort studies).

In 2013, a prospective cohort study of 224 children born to women with epilepsy compared the effects of valproate, carbamazepine, lamotrigine, or phenytoin monotherapy on IQ at 6 years of age.¹ Median doses were carbamazepine 700 mg/d, lamotrigine 433 mg/d, phenytoin 398 mg/d, and valproate 1,000 mg/d. IQ was determined at age 6 using the Differential Ability Scales, Children's Memory Scale, Behavior Rating Inventory of Executive Function, Developmental Neuropsychological Assessment, expressive 1-word picture vocabulary test, and the Developmental Test of Visual Motor Integration. Mean score for each of these tests is 100 with a standard deviation of 15.

In children exposed to valproate, verbal IQ scores were 97 (n=49; 95% CI, 94–100) compared with 104 with exposure to carbamazepine (n=61; 95% CI, 102–107; $P=.0005$), 105 with exposure to lamotrigine (n=74; 95% CI, 102–107; $P=.0003$), and 106 with exposure to phenytoin (n=40; 95% CI, 102–109; $P=.0005$). Nonverbal IQ scores were 101 in the valproate group (n=49; 95% CI, 98–104) compared with 108 with lamotrigine exposure (n=74; 95% CI, 105–110; $P=.002$). Subgroup analysis showed that valproate doses of less than 1,000 mg/d versus other antiepileptic drugs were not associated with a difference in IQ, whereas valproate doses of more than 1,000 mg/d were associated with a decrease in IQ.¹

In 2015, a prospective cohort study of 243 children born to women with epilepsy examined the effect of valproate, carbamazepine, lamotrigine, and antiepileptic polytherapy on child IQ compared with a control group of children born to women without epilepsy.² IQ at age 6 was measured using the Differential Ability Scales.

1. Koren G, Clark S, Hankins GD, Caritis SN, Miodovnik M, Umans JG, et al. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. *Am J Obstet Gynecol*. 2010; 203(6):571.e1–e7. [STEP 2]
2. Koren G, Clark S, Hankins GD, Caritis SN, Umans JG, Miodovnik M, et al. Maternal safety of the delayed-release doxylamine and pyridoxine combination for nausea and vomiting of pregnancy; a randomized placebo controlled trial. *BMC Pregnancy Childbirth*. 2015; 15:59. [STEP 2]
3. Ashkenazi-Hoffnung L, Merlob P, Stahl B, Klinger G. Evaluation of the efficacy and safety of bi-daily combination therapy with pyridoxine and doxylamine for nausea and vomiting of pregnancy. *Isr Med Assoc J*. 2013; 15(1):23–26. [STEP 3]
4. Boskovic R, Rudic N, Danieliewska-Nikiel B, Navioz Y, Koren G. Is lack of morning sickness teratogenic? A prospective controlled study. *Birth Defects Res A Clin Mol Teratol*. 2004; 70(8):528–530. [STEP 3]

High-dose (>800 mg/d) valproate was associated with an IQ 9.7 points lower than control (95% CI, -15 to -4.9) and an increased risk of impairment (defined as IQ <85) in the child by a relative risk of 8.6 (95% CI, 3.1–19). Polytherapy with any dose of valproate was also associated with an IQ 6.4 points lower than control (95% CI, -12 to -1.2). Neither low-dose (<800 mg/d) valproate nor polytherapy without valproate were associated with a reduced IQ compared with control.²

In 2011, a prospective cohort study of 95 children born to women with epilepsy examined the effect valproate (n=44; average dose 800 mg) compared with levetiracetam (n=51; average dose 1,700 mg) during pregnancy on cognitive development of the child at 24 months old compared with a control group (n=97) of children born to women without epilepsy.³ Cognitive development was measured on the Griffiths Mental Development Scale (GMDS; mean score of 100 and standard deviation of 15).

Valproate exposure was associated with a significantly lower GMDS quotient (88; 95% CI, 83–93) than control (99; 95% CI, 96–102) and levetiracetam (100; 95% CI, 97–103). Valproate exposure compared with control was associated with lower GMDS scores in locomotor skills: 85 (95% CI, 79–91) versus 95 (95% CI, 92–98); hearing and language: 90 (95% CI, 84–97) versus 101 (95% CI, 98–104); and performance 89 (95% CI, 83–94) versus 101 (95% CI, 98–105). No significant difference was noted between overall development quotients of children whose mothers did and did not have seizures during pregnancy.³

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1. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol.* 2013; 12(3):244–252. [STEP 2]
2. Baker GA, Bromley RL, Briggs M, Cheyne CP, Cohen MJ, García-Fiñana M, et al; for the Liverpool and Manchester Neurodevelopment Group. IQ at 6 years after in utero exposure to antiepileptic drugs: a controlled cohort study. *Neurology.* 2015; 84(4):382–390. [STEP 2]
3. Shallcross R, Bromley RL, Irwin B, Bonnett LJ, Morrow J, Baker GA. Child development following in utero exposure: levetiracetam vs sodium valproate. *Neurology.* 2011; 76(4):383–389. [STEP 2]

What physical examination findings are most predictive of a diagnosis of obstructive sleep apnea?

EVIDENCE-BASED ANSWER

In patients referred for a sleep study, Mallampati class and pharyngeal narrowing are slightly predictive of obstructive sleep apnea (OSA) (SOR: **B**, systematic review of observational studies). A 4-item score using neck circumference plus clinical features is moderately predictive of OSA (SOR: **C**, cohort studies). Neck circumference, body mass index (BMI), and waist circumference are all moderately associated with OSA in a high-risk referral group (SOR: **C**, cross sectional study).

A 2013 systematic review investigated the accuracy of symptoms and signs for predicting the diagnosis of OSA using nocturnal polysomnography.¹ Forty-two observational studies were included, but the number of patients was not reported for any analysis. Patient characteristics that were somewhat predictive of OSA included Mallampati class III/IV (apnea-hypopnea index [AHI] threshold >15; 2 studies; positive likelihood ratio [LR+] 1.6; 95% CI, 1.1–2.2) and undefined pharyngeal narrowing (AHI >10; 4 studies; LR+ 1.4; 95% CI, 1.1–1.7). Jaw overjet of at least 3 mm was not predictive of OSA in a single study. This review did not evaluate neck circumference as a predictive variable.

A 1994 prospective cohort study used a combination of risk factors, symptoms, and signs to create a model to predict the probability of the diagnosis of OSA in patients referred for a sleep study (N=200).² Overall, 82 patients were diagnosed with OSA with an AHI ≥10 on polysomnography. Characteristics assessed included weight, BMI, neck circumference, chest circumference, waist circumference, waist/hip ratio, and waist/thigh ratio. The final Sleep Apnea Clinical Score (SACS) included neck circumference along with history of hypertension, snoring, and witnessed apnea. Patients are given a SACS score of 0 to 110 based on the combination of these 4 factors, in which high scores indicate greater likelihood of OSA, then are stratified by AHI >10 or >20 to determine final probability.

A SACS score of <5 moderately decreases the likelihood of OSA (AHI >10, LR+ 0.25, 95% CI, 0.15–0.42; AHI >20,

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LR+ 0.21, 95% CI, 0.10–0.46) while a SACS score >15 moderately increases the likelihood of OSA (AHI >10, LR+ 5.17, 95% CI, 2.54–10.51; AHI >20, LR+ 3.74, 95% CI, 2.20–6.37).²

A 2016 prospective cohort study of patients with clinical suspicion for OSA referred for sleep study reexamined the accuracy of the SACS to diagnose OSA (N=191).³ A SACS score >15 was moderately predictive of OSA diagnosed by polysomnography with AHI >10 (LR+ 4.03; 95% CI, 2.16–7.56). A SACS score <5 was slightly predictive of the absence of OSA (LR+ 0.46; 95% CI, 0.31–0.7).

A 2014 Korean cross-sectional study examined 383 middle-aged patients (72% male), referred for a sleep study based on clinical suspicion, to assess physical examination signs associated with OSA.⁴ Examiners assessed BMI, neck circumference, and waist circumference in all patients. OSA, defined by AHI ≥5, was diagnosed in 316 patients.

After adjusting for age, sex, alcohol consumption, and smoking, the researchers found BMI, waist circumference,

and neck circumference were moderately associated with OSA in men (LR+ was 4.88 for BMI; 1.91 for waist circumference; and 4.54 for neck circumference). Adjusted associations in women were similar (LR+ was 3.33 for BMI; 2.25 for waist circumference; and 2.86 for neck circumference).⁴ **EBP**

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1. Myers K, Mrkobrada M, Simel D. Does this patient have obstructive sleep apnea? The Rational Clinical Examination systematic review. *JAMA*. 2013; 310(7):731–741. **[STEP 1]**
2. Flemons WW, Whitelaw WA, Brant R, Remmers J. Likelihood ratios for a sleep apnea clinical prediction rule. *Am J Respir Crit Care Med*. 1994; 150(5 pt 1):1279–1285. **[STEP 2]**
3. Grover M, Mookadam M, Chang Y, Parish J. Validating the diagnostic accuracy of the Sleep Apnea Clinical Score for use in primary care populations. *Mayo Clin Proc*. 2016; 91(4):469–476. **[STEP 2]**
4. Kang HH, Kang JY, Ha JH, Lee J, Kim SK, Moon HS, et al. The associations between anthropometric indices and obstructive sleep apnea in a Korean population. *PLoS One*. 2014; 9(12):e114463. **[STEP 2]**

CONTINUED FROM PAGE 5

TOPICS IN MATERNITY CARE

CASE WRAP-UP

You counsel your patient regarding the small, but statistically significant increased risk of fetal mortality with each week beyond 40 weeks' gestation. When presented with the option of induction of labor at 41 weeks or expectant management with twice-weekly nonstress test and amniotic fluid index monitoring, she chooses induction of labor at 41 weeks. **EBP**

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REFERENCES

1. Divon MY, Haglund B, Nisell H, Otterblad PO, Westgren M. Fetal and neonatal mortality in the postterm pregnancy: the impact of gestational age and fetal growth restriction. *Am J Obstet Gynecol*. 1998; 178(4):726–731. **[STEP 3]**
2. Guelmezoglu AM, Crowther CA, Middleton P, Heatley E. Induction of labour for improving birth outcomes for women at or beyond term. *Cochrane Database Syst Rev*. 2012; (6):CD004945. **[STEP 1]**
3. Sanchez-Ramos L, Olivier F, Delke I, Kaunitz AM. Labor induction versus expectant management for postterm pregnancies: a systematic review with meta-analysis. *Obstet Gynecol*. 2003; 101(6):1312–1318. **[STEP 1]**
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]**

GLOSSARY

ARR=absolute risk reduction
 CDC=Centers for Disease Control and Prevention
 CI=confidence interval
 CT=computed tomography
 FDA=US Food and Drug Administration
 HR=hazard ratio
 LOE=level of evidence
 MRI=magnetic resonance imaging
 NNH=number needed to harm
 NNT=number needed to treat
 NSAID=nonsteroidal anti-inflammatory drug
 OR=odds ratio
 RCT=randomized controlled trial
 RR=relative risk
 SOR=strength of recommendation
 SSRI=selective serotonin reuptake inhibitor
 WHO=World Health Organization

In adult patients with GERD, do histamine (H2) blockers reduce symptoms and improve quality of life?

Bottom line

Yes. Patients with reflux symptoms treated with H2 blockers are 16% to 23% more likely to have heartburn remission, 20% to 25% more likely to have pain-free days, and 28% to 69% more likely to have improvement in overall symptoms compared with patients treated with placebo (SOR: **A**, systematic review of RCTs). H2 blockers can be used for maintenance therapy in patients without esophageal erosions who receive heartburn relief, in patients with night-time reflux symptoms, and in patients seeking quicker relief than can be found with proton-pump inhibitors (SOR: **C**, expert opinion).

Evidence summary

A 2013 systematic review (6 RCTs, N=2,273) examined the effectiveness of H2 blockers for both empiric treatment of gastroesophageal reflux disease (GERD) symptoms (without endoscopy) and treatment of reflux symptoms with negative endoscopy.¹ In each case, H2 blockers (ranitidine 150 mg orally once daily, ranitidine 150 mg orally twice daily, cimetidine 200 mg orally 4 times daily, or famotidine 20 mg orally twice daily) were compared with placebo. Participants were followed for 2 to 6 weeks.

The primary efficacy variable of this review was remission of heartburn, defined as no more than 1 day with mild heartburn per week. Other secondary outcomes included pain-free days, pain-free nights, and overall symptom improvement, but these outcomes were not defined.¹

In 2 empiric treatment trials (n=1,013), ranitidine (150 mg once or twice daily) was more likely than placebo to lead to remission of heartburn symptoms (risk ratio [RR] 0.77; 95% CI, 0.60–0.99). In 2 endoscopy-negative reflux disease trials (n=514), cimetidine 200 mg 4 times a day, famotidine 20 mg twice a day, or famotidine 40 mg daily were also more likely to lead to remission of heartburn symptoms (RR 0.84; 95% CI, 0.74–0.95). Patients treated with H2 blockers, compared with placebo, were more likely to be pain-free during the day with empiric treatment (4 trials, n=696; RR 0.80; 95% CI, 0.71–0.89) and treatment for endoscopy-negative reflux disease (1 trial, n=381; RR 0.75;

95% CI, 0.61–0.93). Similarly, H2 blockers were more likely to lead to pain-free nights with empiric treatment (3 trials, n=642; RR 0.77; 95% CI, 0.63–0.94) but not in treatment of endoscopy-negative reflux disease (1 trial, n=312; RR 0.80; 95% CI, 0.59–1.1). In 4 RCTs (n=1,635) involving empiric treatment, ranitidine was more likely to lead to overall improvement (RR 0.72; 95% CI, 0.63–0.81). Finally, in 2 endoscopy-negative RCTs (n=514), H2 blockers were also more likely to lead to overall improvement (RR 0.41; 95% CI, 0.13–1.3).¹

Two major gastroenterological societies in the United States recommend the use of H2 blockers for specific populations of adult patients with GERD. The American College of Gastroenterology concluded that in the absence of esophageal erosions, H2 blockers could be used for maintenance therapy in patients who receive heartburn relief and in patients with night-time reflux symptoms (conditional recommendation based on low-quality evidence).²

The American Gastroenterological Association Institute's management guidelines for GERD concluded that although proton-pump inhibitors are more effective than H2 blockers, the onset of action for H2 blockers is quicker and they will be adequate for the treatment of some individuals with reflux (recommendation based on moderate-quality evidence).³

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REFERENCES

1. Sigterman KE, van Pinxteren B, Bonis PA, Lau J, Numans ME. Short-term treatment with proton-pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Cochrane Database Syst Rev.* 2013; (5):CD002095. [STEP 1]
2. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol.* 2013; 108(3):308–328. [STEP 5]
3. Kahrilas PJ, Shaheen NJ, Vaezi MF; American Gastroenterological Association Institute; Clinical Practice and Quality Management Committee. American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. *Gastroenterology.* 2008; 135(4):1392–1413. [STEP 5]

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EVIDENCE-BASED PRACTICE

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How effective are the first and second doses of HPV vaccine in providing protection against cervical dysplasia?

EVIDENCE-BASED ANSWER

The clinical efficacy of 1 and 2 doses of bivalent vaccine is similar to that of 3 doses in protecting against human papillomavirus (HPV) infection (SOR: **B**, post hoc analysis of 2 RCTs). Two doses 6 months apart appear to elicit similar immunogenicity as 3 doses in the short term; however, the data are conflicting on how long the antibody titers remain comparable (SOR: **C**, heterogenous RCTs of immune response).

A post hoc analysis of 2 RCTs evaluated the efficacy of 1, 2, or 3 doses of bivalent HPV-16/18 vaccine in preventing HPV infection in nulliparous women 15 to 25 years old.¹ Participants were administered either HPV vaccine or control (hepatitis A vaccine) at 0, 1, and 6 months and monitored for incident HPV infection over 4 years.

Vaccine efficacy (equivalent to relative risk reduction) of 1 dose compared with control was 86% (n=543; 95% CI, 71–94), of 2 doses was 76% (n=1,185; 95% CI, 62–85), and of 3 doses was 77.0% (n=22,327; 95% CI, 75–79), failing to demonstrate a significant trend between number of doses administered and incident cervical HPV infections ($P=.36$). The study also found that cross-protection was increased against HPV-31/33/45 when spacing a 2-dose regimen of the vaccine by 6 months rather than 1 month (68.1% vs 10.1%; $P=.029$).¹

A prospective, multicenter, age-stratified RCT (N=830) compared immunogenicity of 2 doses (0 and 6 months) with 3 doses (0, 1, and 6 months) of quadrivalent HPV-6/11/16/18 vaccine in girls aged 9 to 13 years.²

At 1 month postvaccination, the geometric mean titer (GMT) ratios (2 doses/3 doses) demonstrated noninferiority, defined as the lower bound of 95% CI greater than 0.5, for HPV-6 (1.1; 95% CI, 0.85–1.5), HPV-11 (1.1; 95% CI, 0.91–1.3), HPV-16 (0.95; 95% CI, 0.73–1.2), and HPV-18 (0.68; 95% CI, 0.54–0.85). However, as time progressed, the 2-dose regimen had inferior antibody response to HPV-18 by 24 months and HPV-6 by 36 months; HPV-11 and HPV-16 GMT ratios remained noninferior throughout the 3-year study.²

A 2015 partially blind RCT compared immunogenicity of bivalent HPV-16/18 vaccine in girls 9 to 14 years old (n=240) receiving 2 doses (0 and 6 months) with that in women aged 15 to 25 years (n=239) receiving 3 doses (0, 1, and 6 months).³ This trial was a follow-up to a trial originally designed to demonstrate noninferiority at 7 months.

Comparable GMT ratios (3 doses/2 doses) sustainable for 5 years were reported for both HPV-16 (1.1; 95% CI, 0.82–1.5) and HPV-18 (1.1; 95% CI, 0.74–1.5). Furthermore, statistical modelling projected sustained immunogenicity in both dosing groups above natural immunity levels for more than 21 years. This study was limited in that its participants were predominantly healthy Caucasian females.³

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1. Kreimer AR, Struyf F, Del Rosario-Raymundo M, Hildesheim A, Skinner SR, Wacholder S, et al; for the HPV PATRICIA Principal Investigators/Co-Principal Investigator Collaborators; GSK Vaccines Clinical Study Support Group. Efficacy of fewer than three doses of an HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica Vaccine and PATRICIA trials. *Lancet Oncol*. 2015; 16(7):775–786. [STEP 1]
2. Dobson SR, McNeil S, Dionne M, Dawar M, Ogilvie G, Kraiden M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. *JAMA*. 2013; 309(17):1793–1802 [STEP 2]
3. Romanowski B, Schwarz TF, Ferguson L, Peters K, Dionne M, Behre U, et al. Sustained immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine administered as a two-dose schedule in adolescent girls: five-year clinical data and modelling predictions from a randomized study. *Hum Vaccin Immunother*. 2016; 12(1):20–29. [STEP 2]

Does daily caffeine intake increase the risk of anxiety?

EVIDENCE-BASED ANSWER

Caffeine increases self-rated anxiety more than placebo, but the dose-response relationship is inconsistent (SOR: **B**, 2 small RCTs). This effect may be exclusive to men (SOR: **C**, small RCT). Patients with generalized anxiety disorder are more sensitive to the anxiogenic effects of caffeine than patients with panic disorder or no psychiatric illness (SOR: **B**, small RCT).

A 2002 double-blinded RCT of 24 men (19–23 years old) examined the effects of multiple versus single doses of caffeine on outcome measures of anxiety, alertness, and cognitive performance.¹ Participants underwent a series of computer-based performance tasks, and then received four doses of caffeine 65 mg (or placebo) at 1-hour intervals or a single dose of caffeine 200 mg (or placebo) and repeated the performance tasks. Each day over 4 days, participants received a different intervention or placebo.

Assessment of anxiety using multiple visual analog scales (maximum score of 150 indicating no anxiety) showed worse anxiety after caffeine (80 points for single dose and 79 points for multiple dose) than after placebo (86 points for single dose and 84 points for multiple dose; $P < .05$ for both comparisons). The degree of anxiety in both intervention groups receiving caffeine was comparable regardless of the dosing regimen.¹

A 1997 randomized, double-blinded, single-dose crossover study examined dose-dependent effects of caffeine in 12 men and women (20–46 years old).² Participants were given each of 3 treatment conditions on different days (placebo, caffeine 250 mg, caffeine 500 mg) with at least 1 week elapsing between trials. Participants rated anxiety on a 100-mm visual analog scale 7 times in 4 hours after dosing, and change compared with baseline score was plotted for each assessment.

The 4-hour area under/above the baseline showed placebo decreased anxiety (4-hour effect area of –23) while 250 mg caffeine (4-hour effect area of 16) and 500 mg caffeine (4-hour effect area of 74) increased anxiety. Anxiety after high-dose caffeine was significantly different from that after low-dose caffeine and placebo ($P < .001$), but the difference between low-dose caffeine and placebo was not significant.²

A 2003 randomized, placebo-controlled, single-blinded study of adults examined the association between coffee intake and increased anxiety.³ Study participants (N=99) included 39 men and 60 women (18–31 years old). Participants received placebo, decaffeinated coffee (caffeine 3 mg), or coffee with caffeine (75, 150, or 300 mg) and filled out the State-Trait Anxiety Inventory 30 minutes after consumption.

Women receiving any of the 3 coffee doses rated anxiety no different from women receiving placebo. Men receiving 150 and 300 mg caffeine rated anxiety significantly higher than men receiving placebo and women receiving the same doses ($P < .05$, magnitude of effect not reported).³

A 1992, double-blinded, triple crossover, placebo-controlled study examined the anxiogenic effects of caffeine in 12 adults with generalized anxiety disorder, 12 adults with panic disorder, and 12 normal controls.⁴ Participants included men and women who were free of substance abuse and psychoactive drug use. Participants were given 1 of 3 treatment conditions (placebo, 250 mg, and 500 mg caffeine) on 3 separate days and tested on a variety of measures in 2-hour intervals. Results were given using *F*-score, which is a number representing the ratio of variance between groups.

All patients (generalized anxiety disorder, panic disorder, and normal controls) had increased self-rated anxiety on the State-Trait Anxiety Inventory after caffeine (numerical results not reported). Compared with normal controls receiving caffeine, patients with generalized anxiety disorder receiving caffeine had higher self-ratings of anxiety, $F(1,108)=5.5$; $P < .05$. Patients with panic disorder had lower self-ratings of anxiety than patients with generalized anxiety disorder, $F(1,108)=9.5$; $P < .01$, and similar ratings as normal controls.⁴

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1. Brice CF, Smith AP. Effects of caffeine on mood and performance: a study of realistic consumption. *Psychopharmacology (Berl)*. 2002; 164(2):188–192. [STEP 2]
2. Kaplan GB, Greenblatt DJ, Ehrenberg BL, Goddard JE, Cotreau MM, Harmatz JS, et al. Dose-dependent pharmacokinetics, and psychomotor effects of caffeine in humans. *J Clin Pharmacol*. 1997; 37(8):693–703. [STEP 2]
3. Botella P, Parra A. Coffee increases state anxiety in males but not in females. *Hum Psychopharmacol*. 2003; 18(2):141–143. [STEP 2]
4. Bruce M, Scott N, Shine P, Lader M. Anxiogenic effects of caffeine in patients with anxiety disorders. *Arch Gen Psychiatry*. 1992; 49(11):867–869. [STEP 2]

Is T-SPOT.*TB* (tuberculosis-specific ELISPOT assay) useful for diagnosing tuberculosis in high-risk populations?

EVIDENCE-BASED ANSWER

The degree of usefulness of T-SPOT.*TB* for diagnosing tuberculosis in high-risk populations varies with the specific population. Concordance between T-SPOT.*TB* and tuberculin skin testing (TST) is 69% in children referred to a tuberculosis clinic (SOR: **B**, prospective cohort study). T-SPOT.*TB* is slightly better than TST in predicting subsequent development of active tuberculosis in patients with silicosis (SOR: **B**, prospective cohort study). T-SPOT.*TB* can lead to discordant results up to half of the time in samples drawn 2 weeks apart from healthcare workers being screened, but is less likely than TST to be positive in patients with prior BCG vaccine (SOR: **B**, longitudinal study). T-SPOT.*TB* is a good test for differentiating active tuberculosis patients from healthy controls but is less useful for differentiating among patients with other pulmonary diseases (SOR: **B**, case-control study).

A 2011 prospective cohort trial (N=210) of children 1 month to 18 years old in a pediatric tuberculosis clinic in Texas compared TST with T-SPOT.*TB* for diagnosing tuberculosis.¹ Children were classified as uninfected (normal examination, normal radiograph, and negative TST), latent TB infection (LTBI; positive TST and negative radiograph), or tuberculosis infection (positive culture, radiographic, or clinical findings). Overall concordance between TST and T-SPOT.*TB* (in the 193 available paired results) was 69%.

No statistical difference was noted in sensitivity between TST and T-SPOT.*TB* (77% vs 92%; $P=.59$) in the 13 children with tuberculosis. Overall concordance rates for BCG- (n=66) and non-BCG-vaccinated (n=127) children were 47% and 81%, respectively. Of 71 children at high risk for LTBI, defined as contact with a known source case, 34 had a positive TST and 30 had a positive T-SPOT.*TB*. Concordance for the high-risk children not immunized with BCG was 95%, compared with 88% for BCG-immunized children (no P value available).¹

A 2010 prospective cohort trial of 308 male patients (mean age 61 years) with silicosis from Hong Kong compared

T-SPOT.*TB* with TST for predicting development of active tuberculosis.² Patients with silicosis (a known risk factor for tuberculosis) but without a history of active tuberculosis or LTBI were followed for 1 to 5 years. Active tuberculosis was diagnosed by bacteriologic confirmation or clinical, radiographic, or histologic findings. Clinicians were blinded from T-SPOT.*TB* results.

Active tuberculosis occurred in 7.4% of T-SPOT.*TB*-positive patients and 1.9% of T-SPOT.*TB*-negative patients compared with 6.4% of 10-mm TST-positive patients and 3.9% of TST-negative patients. The relative risk of patients with a positive T-SPOT.*TB* developing active tuberculosis was 4.5 (95% CI, 1.0–20) while a 10-mm positive TST was not associated with a significant increased risk of developing tuberculosis (RR 1.6; 95% CI, 0.53–5.0) in these patients.²

A 2014 longitudinal study (N=2,418) compared the performance of 2 interferon gamma release assays (IGRAs), T-SPOT.*TB*, and QuantiFERON-TB Gold In-Tube with TST at baseline, 6, 12, and 18 months in US healthcare workers 18 years old or older.³

There was a higher prevalence of baseline positive tests with T-SPOT.*TB* than with TST (5% vs 1.8%; $P<.001$). IGRA groups had 6 to 9 times higher cumulative conversions than TST over 18 months. T-SPOT.*TB* tests drawn 2 weeks apart changed from positive to negative in 53% of samples, and discordant results from samples drawn at the same time occurred in 6.5%. Baseline positive TST with negative IGRAs was far more common with prior BCG vaccination than without BCG vaccination (odds ratio [OR] 25; 95% CI, 16–41).³

The authors stated that absence of cross-reactivity with BCG is an advantage of IGRAs over TST, hence supporting a role for IGRAs in accurately determining tuberculosis infection status in BCG-vaccinated healthcare workers.³

A 2014 case-control study assessed T-SPOT.*TB* in a high prevalence setting in southern China.⁴ Participants (N=413) included 202 patients with active tuberculosis, 106 patients with other pulmonary diseases randomly selected from a pulmonary hospital, 20 medical staff from the same hospital, and 85 healthy volunteers. Other pulmonary disease patients were defined as patients with lung disease including pneumonia, bronchitis, and lung cancer, but no history of tuberculosis and no bacteriologic or clinical manifestations of tuberculosis.

T-SPOT.*TB* false-positive rates were higher in the other pulmonary diseases population than in healthy controls (34%

vs 8.2%). Combining the active tuberculosis and healthy control populations, the positive likelihood ratio (LR+) and negative likelihood ratio (LR-) for diagnosing active tuberculosis with T.SPOT.TB were 10.4 (95% CI, 5.1–21) and 0.16 (95% CI, 0.11–0.22), respectively. When combining the active tuberculosis and other pulmonary disease populations, LR+ and LR- for diagnosing active tuberculosis were 2.5 (95% CI, 1.9–3.3) and 0.22 (95% CI, 0.15–0.31), respectively.⁴

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1. Cruz AT, Geltemeyer AM, Starke JR, Flores JA, Graviss EA, Smith KC. Comparing the tuberculin skin test and T-SPOT.TB blood test in children. *Pediatrics*. 2011; 127(1):e31–e38. [STEP 3]
2. Leung CC, Yam WC, Yew WW, Ho PL, Tam CM, Law WS, et al. T-SPOT.TB outperforms tuberculin skin test in predicting tuberculosis disease. *Am J Respir Crit Care Med*. 2010; 182(6):834–840. [STEP 3]
3. Dorman SE, Belknap R, Graviss EA, Reves R, Schluger N, Weinfurter P, et al; FOR THE Tuberculosis Epidemiologic Studies Consortium. Interferon-γ release assays and tuberculin skin testing for diagnosis of latent tuberculosis infection in healthcare workers in the United States. *Am J Respir Crit Care Med*. 2014; 189(1):77–87. [STEP 3]
4. Zhu C, Liu Z, Li Z, Mei S, Hu Z. The performance and limitation of T-SPOT.TB for the diagnosis of TB in a high prevalence setting. *J Thorac Dis*. 2014; 6(6):713–719. [STEP 3]

What are the most effective office-based psychological interventions for patients with panic disorder?

EVIDENCE-BASED ANSWER

The most effective psychological interventions for panic disorder appear to be cognitive-behavioral therapy and exposure therapy with relaxation/breathing training. Sparse evidence also suggests supportive psychotherapy may be one of the more effective interventions (SOR: **B**, meta-analyses of RCTs with low- to very-low-quality evidence).

A 2016 systematic review (54 RCTs, N=3,021) compared various psychological interventions for panic disorder and panic disorder with agoraphobia.¹ These interventions included physiological therapies such as breathing retraining and progressive muscle relaxation, supportive psychotherapy, behavioral therapy such as exposure, cognitive therapy, third-wave cognitive-behavioral therapy such as mindfulness approaches, psychodynamic therapies

to reveal and resolve intrapsychic or unconscious conflicts, and cognitive-behavioral therapy using both cognitive and behavioral therapy with or without physiologic therapy. These interventions were compared with no treatment, “wait list” with education given in the interim, and placebo treatment.

The reviewers performed a network meta-analysis for direct and indirect comparisons among therapies. The primary outcome was short-term remission (defined as having reached a satisfactory endpoint in the judgment of the original investigators) at 3 months posttreatment.¹

Cognitive-behavioral therapy was by far the most-studied intervention (42 of 54 analyzed studies), with wait-list control the most common comparison. Cognitive-behavioral therapy had the most consistent evidence for benefit in short-term remission compared with wait-list control when adjustments were made for publication bias (18 studies, n=903; odds ratio [OR] 3.0; 95% credible interval [CrI], 1.5–6.3). The review found no significant benefit from active treatment versus control in 11 other comparisons; 1 comparison (supportive psychotherapy vs wait list) was statistically significant, but deemed unreliable due to a limited number of trials.¹

In cross-comparisons, cognitive-behavioral therapy was found to be more effective than behavioral therapy alone (10 studies, n=460; OR 1.8; 95% CrI, 1.0–3.1), and cognitive-behavioral therapy was more effective than physiological therapy (4 studies, n=266; OR 1.9; 95% CrI, 1.0–4.0).¹

Using the surface under the cumulative ranking curve (40 trials, n=2,491), the researchers ranked treatments, in terms of short-term remission, from best to worst, as supportive psychotherapy, cognitive-behavioral therapy, psychodynamic therapy, cognitive therapy, behavioral therapy, and physiological therapy, with the caveat that the evidence supporting supportive psychotherapy was very low due to the small number of trials assessing this treatment modality. Overall evidence quality was low with unclear or high risk for bias related to poor methodological quality (including allocation and blinding), and unclear risk for selective reporting.¹

A 2010 systematic review and meta-analysis examined 42 controlled trials (N=2,839) of psychological treatment for panic disorder and panic disorder with agoraphobia; 15 studies (n=802) were also in the systematic review described above.² The modalities included exposure therapy, relaxation or breathing training, and cognitive therapy, all of which were compared with combined controls of wait-list, no

treatment, and placebo. Treatment durations ranged from 8 to 12 weeks. The included studies used various symptom scoring instruments; therefore, results were reported using standardized mean differences (SMD).

Exposure therapy, alone or in combination with either relaxation/breathing training or cognitive therapy, had the largest SMDs for panic-related symptoms (excluding agoraphobia) compared with control: 1.5 for exposure alone (4 studies, n=119; 95% CI, 0.9–2.1), 1.8 for exposure plus relaxation/breathing training (4 studies, n=142; 95% CI, 1.2–2.4), 1.2 for exposure plus cognitive therapy (19 studies, n=832; 95% CI, 1.0–1.5) (SMD of 0.2 is small, 0.6 is moderate, and >0.8 is large). Comparisons between modalities and control for agoraphobia measures did not show significant differences.²

This study differs from the 2016 systematic review described above in that it explicitly excluded studies with medication use while the 2016 systematic review allowed concurrent medication treatment if equivalent between study arms. Also, this review did not include trials from the June 2007 to March 2015 date range of the later systematic review. Limitations of this study included substantial heterogeneity of results and variable study quality.²

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1. Pompili A, Furukawa TA, Imai H, Tajika A, Efthimiou O, Salanti G. Psychological therapies for panic disorder with or without agoraphobia in adults: a network meta-analysis. *Cochrane Database Syst Rev.* 2016; (4):CD011004. [STEP 2]
2. Sánchez-Meca, J, Rosa-Alcázar A, Marín-Martínez F, Gómez-Conesa A. Psychological treatment of panic disorder with or without agoraphobia: a meta-analysis. *Clin Psychol Rev.* 2010; 30(1):37–50. [STEP 2]

Does omega-3 supplementation reduce cardiac mortality?

EVIDENCE-BASED ANSWER

No. Omega-3 fatty acid supplementation does not reduce cardiac mortality in primary or secondary prevention (SOR: **A**, meta-analysis of RCTs and 2 RCTs).

In 2012, a meta-analysis of 20 RCTs (N=68,680) investigated the effect of omega-3 fatty acid intake on all-cause mortality,

cardiac death, and sudden death.¹ The median age of participants was 68 years and the median treatment duration was 2 years. Four trials evaluated a mixed primary and secondary prevention population, the others addressed secondary prevention. All supplements were omega-3 polyunsaturated fatty acid (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), with a mean dose of 1.51 g/d. Statistical significance was assumed at a *P* value 0.0063 because of adjustment for the number of subgroup analyses performed.

Omega-3 supplementation did not reduce cardiac deaths compared with placebo (13 trials, n=3,480; risk ratio [RR] 0.91; 95% CI, 0.85–0.98; *P*=.01). Similarly, no statistically significant reduction was noted in all-cause mortality or sudden death.¹

A 2013 double-blind RCT followed a cohort of 12,513 patients (mean age 64 years) randomly assigned to either omega-3 fatty acid supplementation with 1 gram combined EPA plus DHA daily or olive oil (placebo) for approximately 5 years.² All patients had known cardiac risk factors, defined as clinical evidence of atherosclerotic vascular disease excluding myocardial infarction, or at least 4 of the following characteristics: older than 65 years, male sex, hypertension, hypercholesterolemia, current smoking, body mass index of 30 or more, or a family history of premature cardiovascular disease (CVD).

Initially, the primary endpoint was the cumulative rate of death, nonfatal myocardial infarction, and nonfatal stroke, but the event rates were lower than anticipated and the primary endpoint was revised to time to death from cardiovascular causes or admission to the hospital for cardiovascular causes.²

Death from cardiac causes occurred in 2.3% of patients receiving omega-3 fatty acids as compared with 2.2% taking placebo (hazard ratio [HR] 1.0; CI 95%, 0.82–1.3). Rates of hospital admission for cardiovascular causes were similarly unaffected and no difference was noted in the combined outcome. Subgroup analysis, however, found a statistically significant reduction of the primary endpoint among women—but not men—who received omega-3 fatty acids compared with placebo (hazard ratio [HR] 0.82; 95% CI, 0.6–0.99). Specific data on cardiac death in this subgroup analysis were not available.²

In 2014, a 4-arm RCT evaluated the effect of long-chain omega-3 polyunsaturated fatty acids or macular xanthophylls on CVD over a median of 4.8 years.³ Participants (N=4,203)

were 50 to 85 years old (mean 74 years), with 96% non-Hispanic white, 56% female, 19% with a history of CVD, and 44% taking a statin. After a 30-day run-in period, participants who consumed 75% of supplements were eligible for randomization to 1 of the following daily supplementation arms: long-chain omega-3 polyunsaturated fatty acids (350 mg DHA + 650 mg EPA), macular xanthophylls (10 mg lutein + 2 mg zeaxanthin), combination of the 2, or placebo.

The primary endpoint was a composite of CVD mortality (sudden cardiac death and death due to MI, stroke, or heart failure) and CVD morbidity (myocardial infarction, stroke, unstable angina, coronary and carotid revascularization, congestive heart failure hospitalization, or resuscitated cardiac arrest).³

No significant difference was noted in the primary outcomes between the supplement and control groups (1.9 vs 2.0 events per 100 person-years; HR 0.95; 95% CI, 0.78–1.2). Specific cardiac mortality data were not available, but no significant difference was noted in total mortality between DHA plus EPA versus placebo.³

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1. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *JAMA*. 2012; 308(10):1024–1033. [STEP 1]
2. Risk and Prevention Study Collaborative Group. N-3 fatty acids in patients with multiple cardiovascular risk factors. *N Engl J Med*. 2013; 368(19):1800–1808. [STEP 2]
3. Writing Group for the AREDS2 Research Group. Effect of long-chain ω-3 fatty acids and lutein + zeaxanthin supplements on cardiovascular outcomes: results of the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA Intern Med*. 2014; 174(5):763–771. [STEP 2]

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Is sleep-disordered-breathing associated with poor maternal-fetal outcomes?

EVIDENCE-BASED ANSWER

Moderate-to-severe sleep-disordered-breathing (SDB) in pregnant women is associated with various maternal and fetal morbidities: gestational diabetes mellitus, pregnancy-related hypertension, preterm delivery, intrauterine growth restriction, low birth weight, and neonatal intensive care unit (NICU) admission (SOR: **B**, meta-analysis of limited-quality observational studies). Limited evidence suggests a positive SDB screen with the Berlin Questionnaire is associated with hypertensive disorders of pregnancy (SOR: **B**, cohort study).

A 2014 meta-analysis of 12 prospective cohort studies (n=5,794) and 12 nonprospective observational studies (retrospective cohort, cross-sectional, and case control, n=8,283) evaluated SDB during pregnancy and maternal-fetal outcomes.¹ SDB was defined as either frequent snoring (15 studies) or obstructive sleep apnea (OSA, 7 studies). Further information on the patients was not reported. The authors defined the most severe SDB in each eligible study as “moderate-to-severe SDB,” whereas no SDB or the least severe group was defined as “no or mild SDB.”

Compared with no or mild SDB, maternal moderate-to-severe SDB was significantly associated with a higher risk of gestational diabetes mellitus, pregnancy-related hypertension, preeclampsia, preterm delivery, low birth weight, NICU admission, intrauterine growth restriction, and an Apgar score of <7 at 1 minute (see **TABLE**). The quality of studies included were limited because some studies did not adjust for potential confounders.¹

A 2014 prospective cohort study screened 1,509 pregnant women for OSA with the Berlin Questionnaire and the Epworth Sleepiness Scale to evaluate the association between positive screens and maternal-neonatal outcomes.²

The 10 Berlin questions are in 3 sections: snoring, sleepiness during daily activities, and medical risk factors. Testing positive in 2 of 3 sections indicates a positive screen. The 8 Epworth questions evaluate tendencies to doze on a scale of 0 to 3. Scoring 10 or more is considered a positive screen.

TABLE

Associations between sleep-disordered breathing in pregnancy and maternal-fetal outcomes¹

Outcomes	No. of studies ^a	No. of patients	Odds ratio (95% CI)	Study heterogeneity, I ²
Gestational diabetes mellitus	12	11,335	1.8 (1.3–2.5)	55% ^b
Pregnancy-related hypertension	12	9,807	2.4 (1.6–3.5)	53% ^b
Preeclampsia	12	9,962	2.2 (1.7–2.8)	34%
Preterm delivery	7	6,804	2.0 (1.6–2.5)	43%
Low birth weight	3	6,057	1.8 (1.3–2.3)	33%
NICU admission	4	844	2.4 (1.6–3.7)	0.0%
Intrauterine growth restriction	11	8,923	1.4 (1.2–1.7)	27%
Apgar score <7 at 1 minute	6	1,362	1.8 (1.1–2.9)	50% ^b

NICU=neonatal intensive care unit.

^aBased on 12 prospective cohort studies (n=5,794) and 12 nonprospective studies (cross-sectional, case-control, and retrospective cohort; n=8,283).

^bSignificant heterogeneity among studies.

Of the 383 women with final outcomes available who tested positive on the Berlin (178 of 1,152) or the Epworth (205 of 1,081), 44 underwent testing with polysomnography or a type 3 unattended home sleep testing device. Eight women of these 44 were diagnosed with OSA. In this limited sample, no correlation was noted between a positive screen on either screen and polysomnography-confirmed OSA and no association between polysomnography or home testing-confirmed OSA and maternal, perinatal, or neonatal outcomes. A positive Berlin screen was associated with hypertensive disorders of pregnancy (adjusted relative risk 1.9; 95% CI, 1.5–2.4) but a positive Epworth screen was not significantly associated with any perinatal or neonatal outcomes. Adjustments were made for maternal age, ethnicity, smoking, parity, BMI, hypertension, gestational age, and pregestational and gestational diabetes.²

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1. Ding XX, Wu YL, Xu SJ, Zhang SF, Jia XM, Zhu RP, et al. A systematic review and quantitative assessment of sleep-disordered breathing during pregnancy and perinatal outcomes. *Sleep Breath*. 2014; 18(4):703–713. [STEP 2]
2. Antony KM, Agrawal A, Arndt ME, Murphy AM, Alapat PM, Guntupalli KK, et al. Association of adverse perinatal outcomes with screening measures of obstructive sleep apnea. *J Perinatol*. 2014; 34(6):441–448. [STEP 3]

Do metabolically healthy obese individuals have the same mortality and morbidity risks as normal-weight metabolically healthy individuals?

EVIDENCE-BASED ANSWER

The answer is unclear. Cardiovascular (CV) events and mortality are increased inconsistently in metabolically healthy obese individuals compared with metabolically healthy normal-weight individuals, depending on duration of follow-up and the criteria used to define metabolic health (SOR: **B**, meta-analysis of cohort studies and single cohort study).

A meta-analysis of 8 prospective cohort studies (N=61,386) compared CV events and mortality in normal-weight, overweight, and obese adults with and without metabolic syndrome as defined by Adult Treatment Panel (ATP) III criteria.¹ Patients were categorized by body mass index (BMI) into normal-weight (BMI ≥18 and <25 kg/m²), overweight (BMI ≥25.0 and <30 kg/m²), and obese (BMI ≥30 kg/m²).

In the initial analysis, metabolically healthy obese persons had a similar rate of combined outcome of CV events and all-cause mortality compared with

TABLE

Various criteria for “metabolic health”^{1,2}

Model	Components	Cutoff for “metabolically healthy”
Homeostasis Model Assessment (HOMA) index	Fasting plasma glucose/plasma insulin levels	≤1.70 for men ≤1.52 for women
Adult Treatment Panel-III	<ul style="list-style-type: none"> • TG <150 mg/dL • HDL ≥40 mg/dL male, ≥50 mg/dL female • BP <130/85 mmHg • Fasting glucose <110 mg/dL 	≥3 of the components
Wildman	<ul style="list-style-type: none"> • TG <150 mg/dL • BP <130/85 mmHg • Fasting glucose <110 mg/dL • HOMA ≤90th percentile • CRP ≤90th percentile 	≥4 of the components
Karelis	<ul style="list-style-type: none"> • TG <150 mg/dL • HDL ≥50 mg/dL • LDL ≤100 mg/dL • HOMA ≤2.7 • CRP ≤3 mg/L 	≥4 of the components
Matsuda index	10,000 ÷ square root of (fasting glucose × fasting insulin × mean glucose × mean insulin)	Upper quartile of results during oral glucose tolerance test

BP=blood pressure; CRP=high-sensitivity C-reactive protein; HDL=high-density lipoprotein cholesterol; LDL=low-density lipoprotein cholesterol; TG=triglycerides.

metabolically healthy normal-weight individuals (relative risk [RR] 1.2; 95% CI, 0.98–1.4). After the analysis was restricted to 4 studies (n=11,181) with at least 10 years of follow-up, metabolically healthy obese patients had a higher risk of CV events and all-cause mortality than the metabolically healthy normal-weight group (RR 1.2; 95% CI, 1.0–1.6). Individuals who were metabolically healthy and overweight—but not obese—did not show an increase in CV events or mortality (RR 1.2; 95% CI, 0.91–1.6).¹

The analysis was limited by variables including effects of medications prescribed to control risk factors, duration of exposure to BMI and metabolic factors, and smoking and physical activity, although the researchers noted that in other studies smoking occurred at a higher rate in normal-weight participants than in obese participants.¹

A 2013 cohort study (N=5,269) compared the all-cause and CV mortality of metabolically healthy obese (BMI >30 kg/m²) London civil servants 35 to 55 years old with normal-weight individuals.² The same BMI ranges were

used to stratify individuals into 3 groups: 45% of the participants were normal weight, 43% were overweight, and 12% were obese. Individuals were classified as metabolically healthy or unhealthy based on 1 of 5 models (see **TABLE**). Of 638 obese participants, 260 (41%) using the Homeostasis Model Assessment (HOMA) index, 236 (37%) were classified as metabolically healthy by ATP-III criteria, 146 (23%) by the Wildman criteria, 119 (19%) by the Karelis criteria, and 57 (9.0%) by the Matsuda index. During a median follow-up of 17.7 years, 413 deaths occurred in the total study population.

Compared with metabolically healthy normal-weight individuals, metabolically healthy obese individuals had higher all-cause mortality using all models except the HOMA index, with hazard ratios (HR) ranging from 2.3 (95% CI, 1.1–4.7) for the Matsuda model to 1.8 (95% CI, 1.2–2.8) for the ATP-III model. For CV mortality, only metabolically healthy obese patients identified using the ATP-III criteria had higher mortality (HR 2.5; 95% CI, 1.1–5.9). The study was

limited by an ethnically homogeneous, predominantly male population, and by some classifications of metabolic health using population quartile distribution rather than set cutoffs.²

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1. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions? A systematic review and meta-analysis. *Ann Intern Med.* 2013; 159(11):758–769. [STEP 2]
2. Hinnouho G, Czernichow S, Dugravot A, Batty GD, Kivimaki M, Singh-Manoux A. Metabolically healthy obesity and risk of mortality: does the definition of metabolic health matter? *Diabetes Care.* 2013; 36(8):2294–2300. [STEP 3]

Are aquatic aerobic exercise programs effective in decreasing pain levels in patients with fibromyalgia?

EVIDENCE-BASED ANSWER

Aquatic aerobic exercise programs reduce pain scores by up to 33% compared with no exercise for patients with fibromyalgia; however, aquatic programs are no more effective at reducing pain than land-based therapy (SOR: **A**, meta-analysis of RCTs and 2 RCTs).

A 2014 systematic review of 16 RCT with 881 patients compared the use of aquatic aerobic exercise programs with land-based aerobic exercise programs (and control) in mostly female patients with fibromyalgia.¹ Aquatic aerobic exercise programs were defined as vertical exercises in an aquatic environment with depths between shoulder and waist height. No restrictions were given for time duration, water temperature, or type of exercise equipment used. Control groups received treatment as usual or nonexercise interventions. The review evaluated multiple functional aspects of fibromyalgia, with 13 studies focused specifically on pain.

Mean pain scores for participants in aquatic exercise improved 6.6 points (on a 0–100 scale) more than control over an average of 17 weeks (7 trials, n=382; 95% CI, 2.5–11). No difference was noted for improvement in pain scores between aquatic and land-based programs (4 trials, n=169; –0.75 points; 95% CI, –11 to 9.2). Reviewers rated the risk of bias—including selection, attrition, reporting, and detection bias—as low, but comparisons among studies were limited

by imprecision, high statistical heterogeneity, and wide confidence intervals.¹

A 2015 RCT compared the effectiveness of home-based isometric stretching and strengthening exercises versus a gym-based aerobic exercise program versus an aquatic aerobic exercise program over a period of 12 weeks for 75 women with fibromyalgia.² Patients were 18 to 50 years old and recruited from a physical medicine and rehabilitation clinic in Turkey. Twice per week, the aquatic group participated in aquatic group exercises, which increased in duration over the course of 12 weeks. Pain was rated on a 100-point visual analog scale (VAS).

Mean VAS pain scores in the aquatic group decreased significantly from baseline to 12 weeks (72 vs 48; $P<.01$). Participants in the gym-based group also demonstrated similar improvement in their mean VAS pain score (70 vs 48; $P<.01$). No significant difference was noted in pain improvement between aquatic and gym-based exercise. Participants in the isometric group had a small increase in mean VAS pain score (68 vs 70; $P<.01$).²

A 2013 RCT compared the effectiveness of aquatic aerobic exercise versus control on perception of pain in 64 female patients older than 50 years with fibromyalgia.³ Patients were recruited via local media in Brazil and randomized to aquatic aerobic exercise or no exercise intervention. Patients in the aquatic group participated in 45-minute sessions biweekly for 15 weeks. Sessions took place in a 33°C heated pool and time was divided into 5 minutes of warm up exercises; 35 minutes of exercises designed to develop strength, mobility, balance, coordination and agility; and 5 minutes of stretching and relaxation.

At the end of 15 weeks, participants in the aquatic group decreased their mean VAS pain scores (0–100 scale) by 17 points compared with baseline (60 vs 43; $P<.001$). No significant change in pain scores was noted in the control group.³

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1. Bidonde J, Busch AJ, Webber SC, Schachter CL, Danyliw A, Overend TJ, et al. Aquatic exercise training for fibromyalgia. *Cochrane Database Syst Rev.* 2014; (10):CD011336. [STEP 1]
2. Sevimli D, Kozanoglu, E, Guzel R, Doganay A. The effects of aquatic, isometric strength-stretching and aerobic exercise on physical and psychological parameters of female patients with fibromyalgia syndrome. *J Phys Ther Sci.* 2015; 27(6):1781–1786. [STEP 2]
3. Letieri RV, Furtado GE, Letieri M, Góes SM, Pinheiro CJ, Veronez SO, et al. Pain, quality of life, self perception of health and depression in patients with fibromyalgia treated with hydrokinesiotherapy. *Rev Bras Reumatol.* 2013; 53(6):494–500. [STEP 2]

When is a CT scan necessary in children and adolescents with cervical spine injury?

EVIDENCE-BASED ANSWER

Imaging of the cervical spine should be obtained if the patient has neurologic signs or symptoms or mechanism of injury suggests cervical spine injury. Plain x-rays should be done first, with computed tomography (CT) of the cervical spine reserved for cases of diagnostic uncertainty or to confirm abnormal plain films (SOR: **B**, based on a systematic review of retrospective case-control studies and case series, and an individual retrospective case-control study).

In 2011, The Trauma Association of Canada Pediatric Committee created guidelines for evaluating cervical spine injury based on a systematic review of the literature.¹ The consensus guidelines recommended that published decision tools such as the National Emergency X-Radiography Utilization Study (NEXUS) be used to clinically clear the pediatric cervical spine, but other factors such as age, pain on range-of-motion exercises of the neck, and mechanism of injury needed to be considered when deciding on imaging (Grade recommendation: strong literature review, LOE low to moderate, based on 5 retrospective case-control studies and a prospective observational study). The guidelines recommended using plain radiographs as the initial imaging of choice (Grade recommendation: conditional literature review). Additional CT was recommended when the neurologic examination was abnormal or unreliable or when suspected injuries required further investigation (Grade recommendation: Strong literature review, LOE low to moderate, based on 6 case-control studies, 1 case series, and a survey of radiologists).

One case-control study (n=190) found that the sensitivity for plain cervical x-rays was 75% in children younger than 8 years compared with 93% in children 8 years of age or more. Adding occiput-C3 CT of the neck increased the sensitivity in the younger and older age groups to 94%, and 97%, respectively. Another retrospective case-control study (n=27) reported that of 23 patients with cervical spine injury who had plain films, 18 had their cervical spine injury

detected on plain films, while the other 5 false-negative results were found only with CT scan.¹

A 2016 retrospective case-control review of 2 pediatric trauma center registries (N=220) identified risk factors for cervical spine injury in children aged 1 month to 17 years (mean age 10 years) to help develop a protocol for C-spine clearance.² Patients with documented radiographic cervical spine injury were compared with trauma patients who had cervical spine injury symptoms but no cervical spine injury on CT. Variables analyzed included age, sex, Glasgow Coma Scale (GCS) score, Injury Severity Score (ISS), loss of consciousness, neck tenderness, and mechanism of injury. Of the 220 children, 46 (21%) had cervical spine injury (27 of 158 boys and 19 of 62 girls).

The only variables found to be significantly associated with cervical spine injury were male sex (59% cervical spine injury vs 75% no cervical spine injury; $P<.026$), ISS >25 (16 points cervical spine injury vs 8.7 points no cervical spine injury; $P<.001$), and neck tenderness (83% cervical spine injury vs 24% no cervical spine injury; $P<.0001$).²

The authors recommended imaging children who had a NEXUS risk factor (midline tenderness, altered level of consciousness, distraction injury, focal neurologic deficit, or intoxication) or the additional criteria of: GCS <14, GCSeye=1, or motor vehicle accident. An AP/lateral cervical spine film was recommended for children ≤ 8 years old and CT cervical spine or AP/lateral film for children >8 years, with CT or magnetic resonance imaging done if the first film was abnormal or neurologic symptoms or signs persist.²

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1. Chung S, Mikrogianakis A, Wales PW, Dirks P, Shroff M, Singhal A, et al. Trauma Association of Canada Pediatric Subcommittee National Pediatric Cervical Spine Evaluation Pathway: consensus guidelines. *J Trauma*. 2011; 70(4):873–884. [STEP 1]

2. Chaudhry AS, Prince J, Sorrentino C, Fasanya C, McGinn J, Atanassov KD, et al. Identification of risk factors for cervical spine injury from pediatric trauma registry. *Pediatr Neurosurg*. 2016; 51(4):167–174. [STEP 4]

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Is potassium citrate effective for preventing kidney stone recurrence in patients with calcium-containing stones?

EVIDENCE-BASED ANSWER

Potassium citrate and other potassium-containing citrate salts reduce kidney stone recurrence by 75% in patients with calcium-containing stones (SOR: **A**, meta-analysis and systematic review). The optimal formulation, dosing, and duration of potassium-containing citrate salt therapy is not clear.

A 2015 meta-analysis of 7 RCTs (N=477) explored the efficacy of potassium-containing citrate salts to prevent the recurrence of calcium-containing renal stones.¹ Interventions included various preparations and doses of potassium-containing citrate salts compared with placebo or no intervention for 1 to 2 years.

Potassium-containing citrate salts significantly reduced new stone formation with high heterogeneity (7 RCT, n=324; relative risk [RR] 0.26; 95% CI, 0.10–0.68). The high heterogeneity was due to a single study that also had attrition bias. When this study was removed, the subanalysis had similar results (6 RCTs, n=286; RR 0.24; 95% CI, 0.15–0.41). The reviewers rated the quality of the included studies as moderate to poor. No difference was noted in rates of adverse events (nausea, bloating, and abdominal pain) between the groups.¹

The American College of Physicians (ACP) 2014 guideline on preventing recurrent nephrolithiasis was based on a systematic review of 6 trials with 385 patients (5 RCTs included in the above meta-analysis).²

Citrates (potassium citrate, potassium-magnesium citrate, and potassium-sodium citrate) reduced the risk for composite stone recurrence (4 trials, n=197; RR 0.25; 95% CI, 0.14–0.44; number needed to treat=2.5) compared with placebo or no treatment. The authors noted that there was insufficient statistical power to compare the type of potassium-containing citrate salts used among the studies.²

The American Urologic Association (AUA) 2014 guideline for the medical management of kidney stones was based on the same studies of potassium-containing citrate salts that were included in the ACP guideline's systematic

review.³ The AUA guideline recommended potassium citrate therapy for patients with calcium stones and low or relatively low urinary levels of citrate.

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1. Phillips R, Hanchanale VS, Myatt A, Somani B, Nabi G, Biyani CS. Citrate salts for preventing and treating calcium containing kidney stones in adults. *Cochrane Database Syst Rev*. 2015; (10):CD010057. [STEP 1]
2. Fink HA, Wilt TJ, Eidman KE, Garimella PS, MacDonald R, Rutks IR, et al. Medical management to prevent recurrent nephrolithiasis in adults: a systematic review for an American College of Physicians Clinical Guideline. *Ann Intern Med*. 2013; 158(7):535–543. [STEP 1]
3. Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR, et al. Medical management of kidney stones: AUA guideline. *J Urol*. 2014; 192(2):316–324. [STEP 1]

What methods are effective to reduce operative interventions and maternal morbidity in women during the second stage of labor?

EVIDENCE-BASED ANSWER

Delayed pushing decreases the risk of operative vaginal delivery by 23% and time spent pushing by 11 minutes in nulliparous women with epidural anesthesia (SOR: **A**, meta-analysis of RCTs). Forceps use leads to 35% fewer failed vaginal deliveries compared with vacuum but increases maternal morbidity (third/fourth degree lacerations, vaginal trauma, flatus incontinence) (SOR: **A**, meta-analysis of RCTs). Use of a dental support device may reduce the rate of operative vaginal delivery and Cesarean delivery in nulliparous women without altering the duration of second-stage labor (SOR: **C**, single small RCT).

In 2008, a meta-analysis of 7 RCTs (N=2,827) analyzed the effect of immediate pushing versus delayed pushing (1–2 hours after full dilation) during the second stage of labor in healthy, full-term, nulliparous women with epidurals.¹

Delayed pushing reduced the risk of assisted vaginal delivery (forceps and vacuum) by 23% (7 trials, N=2,827; relative risk [RR] 0.77; 95% CI, 0.71–0.85). Delayed pushing also decreased overall pushing time by 11 minutes (6 trials, n not reported; mean difference 0.19 hours; 95% CI, 0.12–0.27). Limitations included the exclusion of women who had

no epidural and lack of data collection on maternal fatigue, maternal morbidity, and long-term effects on health and quality of life.¹

A 2010 systematic review of 13 RCTs including 3,338 women (parity not defined), evaluated maternal and neonatal outcomes between forceps and vacuum (both soft and metal cup) devices used during vaginal delivery.² All studies included singleton pregnancies at more than 34 weeks' gestation.

Forceps use was associated with fewer failed vaginal deliveries than vacuum (7 trials, n=2,419; RR 0.65; 95% CI, 0.45–0.94). The use of any assisted vaginal delivery device did not significantly increase the risk of Cesarean delivery (4 RCTs, n=1,222; RR 1.8; 95% CI, 0.95–3.2). However, forceps use was associated with an increase incidence of third and fourth degree lacerations (10 trials, n=2,810; RR 1.9; 95% CI, 1.5–2.4), vaginal trauma (8 trials, n=2,443; RR 2.5; 95% CI, 1.6–3.9), and flatus incontinence (1 trial, n=130; RR 1.8; 95% CI, 1.2–2.6). All studies were randomized, although blinding is not possible for either the patient or the forceps or vacuum operator.²

In 2016, a RCT evaluated the use of a dental support device by nulliparous women (N=93) at 37 to 41 weeks 3 days gestation during the second stage of labor.³ The dental support device was made from injection-molded plastic elastomer and approved by the US Food and Drug Administration for use during labor to relax the jaw and promote more effective breathing. The control group consisted of 98 women who did not use the device.

The duration of the second stage of labor was similar between the groups, but the intervention group had significantly lower rates of operative vaginal delivery (12% vs 28%; $P=.004$) and Cesarean delivery (1.2% vs 6.4%; $P=.004$).³

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1. Brancato RM, Church S, Stone PW. A meta-analysis of passive descent versus immediate pushing in nulliparous women with epidural analgesia in the second stage of labor. *J Obstet Gynecol Neonatal Nurs*. 2008; 37(1):4–12. [STEP 1]
2. O'Mahony F, Hofmeyr GJ, Menon V. Choice of instruments for assisted vaginal delivery. *Cochrane Database Syst Rev*. 2010; (11):CD005455. [STEP 1]
3. Aviram A, Ashwal E, Hiersch L, Hadar E, Wiznitzer A, Yogev Y. The effect of intrapartum dental support use among nulliparous during the second stage of labor—a randomized control study. *J Matern Fetal Neonatal Med*. 2016; 29(6):868–871. [STEP 2]

In patients with significant acute muscle strain, is heat or cold more effective for reducing symptoms?

EVIDENCE-BASED ANSWER

Either heat and cold therapy applied for 30 minutes combined with ibuprofen provides mild yet similar immediate relief of acute back or neck strains (SOR: **C**, small RCT). Heat and cold are equivalent in the treatment of acute and chronic low back pain (SOR: **B**, nonrandomized trial).

A 2010 single-center RCT (N=60) involving men and women older than 18 years (mean age 38 years) with acute back or neck strains compared 30 minutes of a heating pad (n=31) or cold pack (n=29) applied to the strained area.¹ Patients had neck or back pain for less than 24 hours caused by a minor injury. Exclusion criteria included any association with radiculopathy, neurological findings, spinal fracture, any contraindication to NSAIDs, or any aggravation of a previous injury. Groups were similar in baseline demographic and pain characteristics.

Participants were given 400 mg ibuprofen, then randomized to either cold pack or heat delivered by heating pad for 30 consecutive minutes. Outcomes included pain severity before and after treatment as measured on a 0-to-100 visual analog pain scale (VAS) (0=no pain, 100=most pain), the percentage of patients requiring additional pain relief, and the subjective reporting of pain relief on a verbal rating scale.¹

No differences were noted between treatment groups in the VAS scores before or after treatment. Nor were differences noted in the need for additional pain relief. Overall 16 (51.6%) patients in the heat group and 18 (62.1%) patients in the cold group reported their pain to be better or much better ($P=.27$). The authors suggested that pain relief could have been a result of the ibuprofen alone.¹

A systematic review of 9 randomized and nonrandomized controlled trials (N=1,117) examined the effect of superficial heat or cold application for low back pain.² However, only 1 nonrandomized trial (n=117) in the systematic review directly compared the effectiveness of heat versus cold therapies for pain relief in hospitalized

patients, and all trials included a mix of acute and chronic low back pain. Patients were excluded if they had a definite diagnosis of disk herniation.

One group received hot packs for 20 minutes twice daily over the lumbosacral area (n=59). The other group had ice massage for 10 to 12 minutes over the lumbosacral area until numb (n=58). All participants also performed flexion exercises. Duration of treatment and follow-up were not reported. The primary outcome of pain symptoms was self-reported as a minimal, moderate, marked increase or decrease, or no change.²

No significant difference was noted in pain between ice massage and hot pack therapy. The authors concluded that both therapies appeared equally effective (numerical data not available).²

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1. Garra G, Singer AJ, Leno R, Taira BR, Gupta N, Mathaikutty B, et al. Heat or cold packs for neck and back strain: a randomized controlled trial of efficacy. *Acad Emerg Med.* 2010; 17(5):484–489. [STEP 2]
2. French SD, Cameron M, Walker BF, Reggars JW, Esterman AJ. Superficial heat or cold for low back pain. *Cochrane Database Syst Rev.* 2006; (1):CD004750. [STEP 1]

What is the best treatment for seizures in patients with hyponatremia?

EVIDENCE-BASED ANSWER

In the setting of severe hyponatremia symptoms, including seizure, the best treatment is an infusion of 3% hypertonic saline until symptoms resolve (SOR: **B**, based on systematic review of consensus practice guidelines). The rate and volume recommended varies, ranging from continuous infusion to bolus doses, but correction should not exceed 10 mmol/L in the first 24 hours (SOR **C**, based on consensus guidelines).

A 2014 systematic review identified 5 clinical practice guidelines and 5 consensus statements, 6 which were based on systematic literature reviews and 4 based on expert opinion, regarding treatment of severe hyponatremia.¹ Despite inconsistencies in approaches, all

recommended treatment of patients with severe symptoms, including seizures, with an infusion of 3% hypertonic saline until symptom resolution.

Three evidence-based studies in the review stated a continuous infusion rate, and 3 evidence-based guidelines and 3 expert opinion statements used various fixed doses scheduled for correction. Three studies set a strict limit of less than 8 mmol/L correction in the first 24 hours if the patient was deemed at high risk for osmotic demyelination, 2 of which were evidence-based guidelines and 1 of which was based on expert opinion. One evidence-based guideline and 1 opinion-based consensus statement made no recommendation to limit correction rates, although the remainder suggested a daily maximum correction of 8 to 12 mmol/L to avoid adverse events such as osmotic demyelination.¹

A 2014 clinical practice guideline from the European Society of Intensive Care Medicine, the European Society of Endocrinology, and the European Renal Association-European Dialysis and Transplant Association made recommendations for diagnosis and treatment of hyponatremia based on a systematic literature review.²

For hyponatremia with severe symptoms, the guideline recommended infusing 150 mL of 3% hypertonic saline over 20 minutes. At 20 minutes, serum sodium should be checked while infusing another 150 mL of 3% hypertonic saline over the next 20 minutes. Infusions should be repeated until a goal of a 5-mmol/L increase in serum sodium levels is achieved. If symptoms are improved, further steps should be geared toward treating the specific cause of hyponatremia, taking care not to exceed a 10-mmol/L increase in serum sodium in the first 24 hours. The guideline recommends hospital pharmacies carry prepared 150-mL bags of 3% hypertonic saline.²

In a 2015 consensus statement, senior experienced physicians from the United Kingdom created an algorithm for in-hospital assessment and management of hyponatremia based on published data, current practice, and guidelines.³

In the case of hyponatremia with acute neurologic symptoms (including seizure) the statement recommended a 150-mL infusion of 3% hypertonic saline over 15 minutes. Treatments should be repeated after 20 minutes if there is no clinical improvement. Measurement of serum sodium levels should be repeated at 6, 12, 24, and 48 hours to ensure there is no overcorrection. Serum sodium levels should not

correct more than 10 mmol/L in the first 24 hours. Correction after this point should be guided by the underlying cause of hyponatremia.³

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1. Nagler EV, Vanmassenhove J, van der Veer SN, Nistor I, Van Biesen W, Webster AC, et al. Diagnosis and treatment of hyponatremia: a systematic review of clinical practice guidelines and consensus statements. *BMC Med.* 2014; 12:1. [STEP 2]
2. Spasovski G, Vanholder R, Alloioet B. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Intensive Care Med.* 2014; 40(3):320–331. [STEP 1]
3. Grant P, Ayuk J, Bouloux PM, Cohen M, Cranston I, Murray RD, et al. The diagnosis and management of inpatient hyponatraemia and SIADH. *Eur J Clin Invest.* 2015; 45(8):888–894. [STEP 5]

Can ESR and CRP be used interchangeably in the management of rheumatoid arthritis?

EVIDENCE-BASED ANSWER

Yes. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have a concordance of 69% in patients with rheumatoid arthritis (RA). The measures are nearly equal in predicting swollen joint count but both are poorly correlated with clinical disease activity (SOR: **A**, meta-analysis of RCTs). Evidence is conflicting about whether ESR and CRP can predict radiographic progression of RA (SOR: **C**, disease-oriented data from systematic review of conflicting RCTs and cohort studies).

A 2009 meta-analysis evaluated the clinical utility of ESR versus CRP in assessing disease progression in patients with active RA treated with golimumab with or without methotrexate.¹ The authors used data from 3 RCTs with 1,247 patients and 2,417 patient visits. Inclusion criteria were active RA and at least 2 positive findings from a list of 6 laboratory and clinical abnormalities. The average patient age at enrollment was 51 years and 82% were female.

ESR and CRP values were moderate to strongly correlated with each other (n=2,417 patient visits, Pearson $r=0.59$, $P<.001$) and concordance was 69%. In patients with

no swollen joints, 131 (74%) had normal CRP and ESR values. ESR and CRP were significantly but poorly correlated with clinical disease activity index in patients with and without swollen joints (n=2,394 patient visits; Pearson $r=0.28$ for ESR vs 0.29 for CRP; $P<.001$ for each). CRP and ESR had similar sensitivity and specificity for predicting whether swollen joint count was ≤ 4 or >4 , based on area under the curve calculations (area under the curve for CRP: 67%; 95% CI, 65–70; area under the curve for ESR 66%; 95% CI, 64–69).¹

A 2015 systematic review investigated the relationship between several indices of disease activity and radiographic progression in patients with RA.² Only prospective or retrospective cohort studies or RCTs were eligible; of the 57 studies that were included, 37 studies reported results for ESR and 35 for CRP. The use of different outcome assessments and statistical analyses precluded meta-analysis.

Six of 14 studies using univariable analysis and 10 of 12 studies using multivariable analysis demonstrated a significant correlation between baseline ESR and radiographically visible disease progression. Nine of 11 studies evaluating the relationship between time-integrated ESR and radiographic disease progression were statistically significant. A similar comparison using CRP demonstrated that 8 of 17 studies with univariable analysis and 5 of 8 studies using multivariable analysis found statistically significant correlation between baseline CRP and radiographic disease progression. Four of 6 studies using univariable analysis and 2 of 4 studies using multivariable analysis found statistically significant correlation between time-integrated CRP and radiographic disease progression. The authors concluded that ESR is a better measure of radiographic disease progression, because 25 of 37 studies showed significant correlation between ESR and progression, whereas only 19 out of 35 studies showed significant correlation between CRP and progression. Limitations of this study included the lack of evaluation of study sample size and quality.²

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1. Crowson C, Rahman M, Matteson E. Which measure of inflammation to use? A comparison of erythrocyte sedimentation rate and C-reactive protein measurements from randomized clinical trials of golimumab in rheumatoid arthritis. *J Rheumatol.* 2009; 36(8):1606–1610. [STEP 1]
2. Navarro-Compan V, Gherge AM, Smolen JS, Aletaha D, Landewe R, Heijde D. Relationship between disease activity indices and their individual components and radiographic progression in RA: a systematic literature review. *Rheumatology (Oxford).* 2015; 54(6):994–1007. [STEP 1]

For patients with COPD, does pneumococcal vaccination reduce the incidence of pneumococcal pneumonia?

EVIDENCE-BASED ANSWER

Pneumococcal vaccination in patients with chronic obstructive pulmonary disease (COPD) does not reduce pneumonia of any etiology (SOR: **A**, meta-analysis of 3 RCTs), but does lead to a slight reduction in incidence of pneumonia due to pneumococcus (SOR: **B**, RCT). Pneumonia of any etiology may be reduced in patients younger than 65 years (SOR: **B**, RCT).

A 2006 systematic review of 3 RCTs (N=748) analyzed the use of pneumococcal vaccines for preventing COPD exacerbations in patients with COPD.¹ A secondary outcome was the number of cases of pneumococcal pneumonia. The patients were aged in their mid to high 60s.

Severity of COPD varied among the trials: 1 trial had approximately 50% of patients with FEV1 both more and less than 40%, in another trial patients had an FEV1 of 44% to 50%, and in the third trial the FEV1/FVC was 41% to 69%. Two trials (n=645) compared the 23-polyvalent pneumococcal polysaccharide vaccine (PPSV23) to no vaccine while the other trial (n=103) compared the 14-valent pneumococcal polysaccharide vaccine with a placebo control. The diagnostic criteria for pneumonia in 2 trials were lower respiratory tract infection with fever and imaging findings, with pneumococcal pneumonia diagnosed by isolating *Streptococcus pneumoniae* in blood, pleural fluid, or bronchial samples. In the third trial, the diagnostic criteria for pneumonia included only radiological evidence and no other criteria were stated.¹

Pooled analysis of all 3 trials found pneumococcal vaccine compared with control over 6 to 51 months had no effect on the risk of pneumonia (odds ratio [OR] 0.89; 95% CI, 0.58–1.4).¹

A 2012 meta-analysis included only 1 double-blind RCT that evaluated the effectiveness of PPSV23 versus no vaccine over 3 years in 596 patients with COPD stratified by age (either <65 years or ≥65 years) and severity of airflow obstruction (FEV1 <40% of expected or ≥40% of expected).^{2,3} This study was the largest of the 3 trials included in the above meta-analysis. The diagnosis of pneumonia was based on

fever, symptoms of lower respiratory tract infection, and chest x-ray findings. Pneumococcal pneumonia was diagnosed with isolated *S pneumoniae* in blood, pleural fluid, or bronchial samples.

No cases of pneumococcal pneumonia were found in the PPSV23-vaccine group compared with 5 cases in the no-vaccine group (P=.03). Subgroup analysis found that the PPSV23 vaccine reduced all pneumonia in patients younger than 65 years (hazard ratio [HR] 0.2; 95% CI, 0.06–0.66; number needed to treat=10) but not in patients older than 65 years (HR 1.5; 95% CI, 0.6–2.2).

The US Centers for Disease Control and Prevention recommends the use of both pneumococcal vaccines for all adults older than 65 years (PPSV23 and 13-valent conjugated vaccine) and in adults 19 to 64 years old with underlying medical conditions such as COPD that put them at greater risk of serious pneumococcal infection.⁴

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1. Granger R, Walter J, Poole PJ, Lasserson TJ, Mangtani P, Cates CJ, et al. Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2006; (4):CD001390. [STEP 1]
2. Sehatzadeh S. Influenza and pneumococcal vaccinations for patients with chronic obstructive pulmonary disease (COPD): an evidence-based review. *Ont Health Technol Assess Ser*. 2012; 12(3):1–64. [STEP 1]
3. Alfageme I, Vazquez R, Reyes N, Muñoz J, Fernández A, Hernandez M, et al. Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. *Thorax*. 2006; 61(3):189–195. [STEP 2]
4. Centers for Disease Control and Prevention. Vaccines and preventable diseases: pneumococcal vaccine resources. <https://www.cdc.gov/vaccines/vpd/pneumo/hcp/references-resources.html>. Last updated December 6, 2017. Accessed December 29, 2017. [STEP 5]

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For female athletes, what sports are at high risk for concussion?

EVIDENCE-BASED ANSWER

Sports with the highest risk of concussion in female high school athletes are soccer and lacrosse with about 0.35 concussions for every 1,000 athletes participating in 1 game. In college sports, ice hockey has the highest risk at nearly 1 concussion for every 1,000 athletes participating in 1 game, followed by soccer (SOR: **B**, descriptive epidemiologic studies).

A 2012 descriptive epidemiologic study compared concussion rates among US high school athletes for 20 sports.¹ Female and male athlete concussion incidence was collected using High School RIO™ (High School Reporting Information Online) during the 2008 to 2010 academic years that included 7,780,064 athletic exposures, defined as 1 athlete participating in 1 practice or game. For all sports, 1,936 concussions were reported. Female sports included were lacrosse, basketball, field hockey, softball, gymnastics, cheerleading, volleyball, swimming and diving, and track and field.

Lacrosse and soccer had the highest concussion rate among female sports, at 0.35 per 1,000 athletic exposures and 0.34 per 1,000 athletic exposures, respectively. Field hockey had the next highest rate, at 0.22 per 1,000 athletic exposures.¹

A 2007 descriptive epidemiologic study was conducted comparing female and male athlete injury incidence among 15 college sports.² The study used the National Collegiate Athletic Association (NCAA) Injury Surveillance System to obtain the rates from 1988 to 2004 seasons. More than 9,000 concussions were reported. Female sports studied were basketball, field hockey, gymnastics, ice hockey, lacrosse, soccer, softball, and volleyball.

Of the female sports, ice hockey had the highest rate of concussions, at 0.91 per 1,000 athletic exposures. Soccer and lacrosse followed with rates of 0.41 and 0.25 per 1,000 athletic exposures, respectively. Ice hockey data collection did not begin until 2000; the authors suggested ice hockey data need further attention because of the shorter study period.²

Another 2007 descriptive epidemiologic study reported injury rates from 100 randomly sampled US high schools over the 2005 to 2006 academic year.³ The data were collected through High School RIO and compared with the NCAA Injury Surveillance System for the same year and sports. The female sports included in the study were soccer, basketball, volleyball, and softball.

The total number of concussions in female high school and college sports was 107 and 135, respectively, for an overall rate of 0.18 and 0.38 per 1,000 athletic exposures, respectively. Soccer had the highest concussion rates, at 0.36 per 1,000 athletic exposures in high school female athletes. Soccer also had the highest rate of concussion for female collegiate athletes in this study, at 0.63 per 1,000 athletic exposures.³

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1. Marar M, McIvain NM, Fields SK, Comstock RD. Epidemiology of concussions among United States high school athletes in 20 sports. *Am J Sports Med.* 2012; 40(4):747–755. [STEP 2]
2. Hootman JM, Dick R, Agel J. Epidemiology of collegiate injuries for 15 sports: summary and recommendations for injury prevention initiatives. *J Athl Train.* 2007; 42(2):311–319. [STEP 2]
3. Gessel LM, Fields SK, Collins CL, Dick RW, Comstock RD. Concussions among United States high school and collegiate athletes. *J Athl Train.* 2007; 42(4):495–503. [STEP 2]

Before urinalysis and culture, in which patients would starting empiric antibiotics be appropriate?

EVIDENCE-BASED ANSWER

In nonpregnant adult women presenting with symptoms of urinary tract infection (UTI), the combination of dysuria and no vaginal discharge or irritation yields a 90% chance of a UTI. Individual signs and symptoms do not significantly change the probability of UTI (SOR: **B**, 2 meta-analyses of cohort, case-control, cross-sectional, and case-series studies).

In 2010, a meta-analysis of 16 cross-sectional and cohort studies set out to determine the diagnostic accuracy of signs and symptoms in women presenting with concern for UTI.¹ Patients were symptomatic, nonpregnant women presenting

TABLE

Meta-analyses of likelihood ratios of various clinical signs and symptoms for diagnosis of UTI^{1,2}

Finding	Threshold for diagnosing UTI (CFU/mL)	No. of pooled studies	No. of patients	Positive likelihood ratio (95% CI)
Dysuria ¹	10 ⁵	7	1,584	1.2 (1.1–1.3)
Dysuria ²	10 ⁴ –10 ⁵	7	2,247	1.5 (1.2–2.0)
Frequency ¹	10 ⁵	6	1,333	1.1 (1.0–1.2)
Frequency ²	10 ⁴ –10 ⁵	8	2,331	1.8 (1.1–3.0)
Hematuria ¹	10 ³	6	854	1.7 (1.1–2.7)
Hematuria ²	10 ⁴ –10 ⁵	4	719	2.0 (1.3–2.9)
Back pain ¹	10 ³	4	635	0.90 (0.71–1.1)
Back pain ²	10 ⁴ –10 ⁵	2	506	1.6 (1.2–2.1)
Nocturia ¹	10 ³	5	1,492	1.4 (1.1–1.7)
Costovertebral angle tenderness ²	10 ⁴ –10 ⁵	1	452	1.7 (1.1–2.5)
Urgency ¹	10 ⁵	4	1,039	1.2 (1.0–1.3)
Absence of vaginal irritation ²	10 ⁴ –10 ⁵	2	1,013	2.7 (0.9–8.5)
Absence of vaginal discharge ¹	10 ²	6	1,261	1.1 (1.0–1.2)
Absence of vaginal discharge ²	10 ⁴ –10 ⁵	2	644	3.1 (1.0–9.3)
Dysuria and frequency present, vaginal discharge and irritation absent ²	10 ⁴ –10 ⁵	8	2,331	25 (CI not calculated)

CFU=colony-forming units; UTI=urinary tract infection.

with suspected UTI (N=3,711). UTI was defined as 100, 1,000, or 100,000 CFU/mL on culture.

The summary prevalence of UTI was 65% at 102 CFU/mL, 55% at 103 CFU/mL, and 45% at 105 CFU/mL. Individual signs and symptoms such as dysuria, frequency, hematuria, nocturia, and urgency only slightly increase the likelihood of UTI, with positive likelihood ratios of less than 2 (see **TABLE**). Vaginal discharge modestly decreased the likelihood of a UTI.¹

In 2002, a meta-analysis of 9 cohort, case-control, cross-sectional, and retrospective case-series studies reviewed the accuracy of history and physical examination for the diagnosis of UTI.² Patients were nonpregnant women 15 years old and older with symptoms suggestive of UTI or vaginal infection (N=2,331). Six studies reported the accuracy of 1 or more symptoms in the diagnosis of UTI, 2 studies reported the accuracy of symptoms and physical examination signs, and 1 study reported the accuracy of self-diagnosis. Five of these studies were also included in the 2010 meta-analysis discussed previously. UTI was defined

by the presence of at least 10,000 or 100,000 CFU/mL of a single uropathogen in all the studies, except for 1 study, which used a cutoff of at least 100 CFU/mL.

Most of the individual signs and symptoms (dysuria, frequency, hematuria, back pain, costovertebral angle tenderness) had a positive likelihood ratio of 2 or less. The combination of dysuria and frequency but no vaginal discharge or irritation was highly correlated with the presence of a UTI (see **TABLE**). Using the summary prevalence as the pretest probability of disease (48%), this combination raised the posttest probability of UTI to more than 90%.²

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- Giesen LG, Cousins G, Dimitrov BD, van de Laar FA, Fahey T. Predicting acute uncomplicated urinary tract infection in women: a systematic review of the diagnostic accuracy of symptoms and signs. *BMC Fam Pract.* 2010; 11:78. [STEP 2]
- Bent S, Nallamotheu BK, Simel DL, Fihn SD, Saint S. Does this woman have an acute uncomplicated urinary tract infection? *JAMA.* 2002; 287(20):2701–2710. [STEP 2]

Is psychotherapy effective in decreasing chronic low back pain?

EVIDENCE-BASED ANSWER

Behavioral therapies such as progressive relaxation, biofeedback, operant therapy, and cognitive-behavioral therapy (CBT) slightly to moderately reduce chronic low back pain over the short term (SOR: **B**, meta-analysis of RCTs). Mindfulness-based stress reduction and CBT added to other medical treatments are modestly better at reducing chronic low back pain, but the effect of CBT diminishes at 1 year (SOR: **B**, RCTs).

A 2010 meta-analysis of 30 RCTs evaluated behavioral therapies in 3,438 patients 18 to 65 years old with chronic low back pain of 12 weeks' duration or more without pathologic causes such as infection, neoplasm, or fractures.¹ Behavioral therapies included respondent therapies (progressive relaxation and biofeedback), operant therapy (decreasing reinforcement of pain behaviors and rewarding healthy behaviors), and CBT (changing maladaptive thoughts along with respondent and operant strategies). Frequency of therapy sessions and follow-up durations were not reported consistently or specifically.

Progressive muscle relaxation training decreased pain by 20 points more than waiting list controls on a 100-point scale (3 trials, n=74; 95% CI, 5.2–34) over 1 month. Compared with waiting list controls as measured on various scales, biofeedback moderately decreased pain (3 trials, n=44; standard mean difference [SMD] 0.8; 95% CI, 0.28–1.3) in the short term and operant therapy modestly decreased pain (SMD 0.43; 95% CI, 0.11–0.75) over 8 weeks but this difference disappeared by 6 to 12 months. CBT also decreased pain moderately more than waiting list controls (5 trials, n=239; SMD 0.6; 95% CI, 0.22–0.97) over the short term. Most trials were rated as low or very low quality predominantly because of inadequately described randomization and allocation concealment.¹

A 2016 RCT evaluated the effectiveness of mindfulness-based stress reduction, CBT, and usual care in 342 patients 20 to 70 years old with nonspecific back pain of at least 3 months' duration.² All groups received usual medical care, which was not detailed. CBT was aimed at changing pain-

related thoughts and behaviors. Mindfulness-based stress reduction consisted of mindfulness meditation and yoga. Both were done in a group format for 2 hours a week over 8 weeks. Pain was assessed on a 0 (not at all bothersome) to 10 (extremely bothersome) scale and a 30% improvement from baseline was considered clinically meaningful.

At 26 weeks, similar percentages of patients in the mindfulness-based stress reduction group (44%) and the CBT group (45%) had clinically meaningful improvement in pain and both treatments were significantly better than usual care (27%) ($P=.01$ for both comparisons). At 52 weeks, the percent of patients in the mindfulness-based stress reduction group (49%; $P=.02$) but not the CBT group (40%) remained significantly better than usual care (31%). Both therapy groups had a 20% dropout rate.²

A 2014 RCT evaluated the effectiveness of group CBT for pain tolerance in 103 patients with an average age of 50 years and back pain for at least 6 months.³ Patients were admitted to an inpatient orthopedic rehabilitation unit and received regular physician visits, medications, exercise, massage, electrotherapy, occupational therapy, and education over 21 days. Patients in the CBT arm received group sessions 3 times a week aimed at changing dysfunctional thoughts, stress reduction, and problem solving. The control group received additional occupational therapy sessions focused on positive leisure activities. Pain was rated on a 10-cm visual analog scale 3 times a day.

At 3 weeks, CBT decreased mean pain score slightly more than control (3.0 vs 1.8 points; $P=.002$).³

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1. Henschke N, Ostelo RW, van Tulder MW, Vlaeyen JW, Morley S, Assendelft WJ, et al. Behavioral treatment for chronic low-back pain. *Cochrane Database Syst Rev.* 2010; (7):CD002014. [STEP 1]
2. Cherkin DC, Sherman KJ, Balderson BH, Cook AJ, Anderson ML, Hawkes RJ, et al. Effects of mindfulness-based stress reduction cognitive-behavioral therapy or usual care on back pain and functional limitations among adults with chronic low back pain: a randomized clinical trial. *JAMA.* 2016; 315(12):1240–1249. [STEP 2]
3. Linden M, Scherbe S, Cicholas B. Randomized controlled trial on the effectiveness of cognitive behavioral group therapy in chronic back pain patients. *J Back Musculoskelet Rehabil.* 2014; 27(4):563–568. [STEP 2]

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What are the benefits of folate consumption during pregnancy?

EVIDENCE-BASED ANSWER

Maternal folic acid supplementation taken from before conception through the first trimester reduces primary and recurrent neural tube defects (NTDs) by more than 65%. Folic acid supplementation during pregnancy decreases maternal megaloblastic anemia at the time of delivery by about 80%. Folic acid supplementation does not reduce rates of cleft palate, cleft lip, congenital heart defects, miscarriage, preterm delivery, or stillbirth, or affect mean birthweight (SOR: **A**, meta-analyses of RCTs).

A 2015 meta-analysis of 5 double-blinded RCTs of 7,391 reproductive age females (2,033 with prior delivery affected by an NTD) compared the effect of folic acid supplementation with no folic acid or placebo on birth defects including NTD, cleft palate, cleft lip, or congenital heart defects.¹ Women began supplementation prior to conception (specific time not defined) and discontinued supplementation after 12 weeks' gestation. Trials used 0.36, 0.8, or 4.0 mg supplemental folic acid daily.

Folic acid supplementation reduced primary occurrences of NTDs (5 RCTs, n=6,708 births; relative risk [RR] 0.31; 95% CI, 0.17–0.58) as well as recurrence compared with placebo or control independent of the dose used (4 RCTs, n=1,846 births; RR 0.34; 95% CI, 0.18–0.64). This study did not evaluate for a possible dose response. No difference was noted between folic acid supplementation and placebo or control in cleft palate, cleft lip, congenital heart defects, or miscarriages. All studies demonstrated adequate blinding, but 4 of the 5 studies did not detail randomization methods and the authors noted a risk of selection bias.¹

A 2013 meta-analysis of 31 RCT or quasi-randomized trials (no overlapping studies with previous meta-analysis) of 17,771 women (any age or parity) assessed the effect of folic acid supplementation on maternal and pregnancy outcomes including preterm birth, low birth weight, miscarriage, and perinatal mortality.² Patients were given between 0.1 and 15 mg folate daily, often in combination with iron and occasionally with vitamin B₁₂ or zinc. Controls included placebo and micronutrients that included various vitamins and minerals.

Patients started medication no earlier than the eighth week of pregnancy and had varying lengths of continuity prior to delivery.

Folic acid supplementation decreased maternal megaloblastic anemia at the time of birth compared to placebo/controls (4 trials, n=3,839; RR 0.21; 95% CI, 0.11–0.38). No difference was noted in preterm births, stillbirth/neonatal death, or mean birthweight in patients receiving folic acid compared with placebo or controls. Most of these studies were from the 1960s and the authors expressed concern about selection bias, randomization, and allocation concealment.²

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1. De-Regil LM, Pena-Rosas JP, Fernandez-Gaxiola AC, Rayco-Solon P. Effects and safety of periconceptual oral folate supplementation for preventing birth defects. *Cochrane Database Syst Rev.* 2015; (12):CD007950. [STEP 1]
2. Lassi ZS, Salam RA, Haider BA, Bhutta ZA. Folic acid supplementation during pregnancy for maternal health and pregnancy outcomes. *Cochrane Database Syst Rev.* 2013; (3):CD006896. [STEP 1]

What are the risks of using donor breast milk in preterm or low-birth-weight neonates?

EVIDENCE-BASED ANSWER

Neonates receiving donor breast milk gain about 2.6 g/kg less per day and grow about 1.4 mm less per week in length and 1.2 mm less per week in head circumference than formula-fed infants in the hospital but have about one-third the risk of necrotizing enterocolitis compared with formula-fed neonates (SOR: **A**, meta-analysis of RCTs). Donor breast milk-fed neonates are about 20% more likely to receive some breastfeeding on discharge from the neonatal intensive care unit (NICU) (SOR: **B**, meta-analysis of cohort studies and single RCT).

A 2014 systematic review (9 RCTs, N=1,070) evaluated the effect of formula feeding versus donor breast milk on growth and development in preterm or low-birth-weight infants.¹ Inclusion criteria for the study were either a preterm infant (<37 weeks' gestation) or low birth weight (<2.5 kg). Most of

the trials specifically excluded infants who were small for gestational age at birth and infants with congenital anomalies, or with gastrointestinal or neurologic problems.

Formula-fed infants had higher rates of increase in weight (8 studies, n=702; mean difference [MD] 2.6 g/kg per day; 95% CI, 2.0–3.7), length (7 studies, n=492; MD 1.4 mm/wk; 95% CI, 0.87–1.9), and head circumference (7 studies, n=568; MD 1.2 mm/wk; 95% CI, 0.75–1.7) compared with donor breast milk-fed infants. Formula-fed infants had a higher incidence of necrotizing enterocolitis (6 studies, n=869; risk ratio [RR] 2.8; 95% CI, 1.4–5.5; number needed to harm=25) than donor breast milk-fed infants.¹

A 2016 systematic review (9 retrospective and prospective cohort studies and 1 RCT, N=2,381) investigated the effects of donor breast milk versus formula milk on maternal breastfeeding rates upon discharge from the NICU.² Infants all either weighed less than 1.5 kg or were less than 32 weeks' gestation at time of birth. Reasons for the use of

donor breast milk varied among the studies and included new NICU policies, introduction of milk banks, and attempts to increase use of human milk. Average length of NICU stay or duration of donor milk use was not provided.

Donor breast milk-fed infants had a higher rate of any breastfeeding, which was not specifically defined (4 trials, n=704; RR 1.2; 95% CI, 1.1–1.4) compared with formula-fed infants. No significant difference was noted for exclusive breastfeeding, which was also not specifically defined (2 trials, n=259; RR 1.1; 95% CI, 0.91–1.4).²

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1. Quigley M, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. *Cochrane Database Syst Rev.* 2014; (4):CD002971. [STEP 1]
2. Williams T, Nair H, Simpson J, Embleton N. Use of donor human milk and maternal breastfeeding rates: a systematic review. *J Hum Lact.* 2016; 32(2):212–220. [STEP 2]

GLOSSARY		
ARR=absolute risk reduction	HR=hazard ratio	OR=odds ratio
CDC=Centers for Disease Control and Prevention	LOE=level of evidence	RCT=randomized controlled trial
CI=confidence interval	MRI=magnetic resonance imaging	RR=relative risk
CT=computed tomography	NNH=number needed to harm	SOR=strength of recommendation
FDA=US Food and Drug Administration	NNT=number needed to treat	SSRI=selective serotonin reuptake inhibitor
	NSAID=nonsteroidal anti-inflammatory drug	WHO=World Health Organization

Is there a pulmonary embolus causing that syncope?

Prandoni P, Lensing AW, Prins MH, Ciammaichella M, Perlati M, Mumoli N, et al. Prevalence of pulmonary embolism among patients hospitalized for syncope. *N Engl J Med.* 2016; 375(16):1524–1531.

This prospective cohort study evaluated the incidence of pulmonary embolus (PE) in 2,584 patients presenting with syncope to 11 emergency departments in Italy. Syncope was defined as loss of consciousness for less than 1 minute with no obvious cause. Patients were excluded if they had recurrent syncope, were taking oral anticoagulation agents, or had atrial fibrillation. Patients (N=560) had a mean age of 76 years old, 40% were male, 5% had a previous venous thromboembolism, and 10% had signs of a deep vein thrombosis (DVT).

The diagnosis of PE was excluded in 330 patients with a low Wells score and a negative D dimer. Patients with a positive Wells score or high D dimer (n=230) had imaging for a PE with a CTPA or VQ scan and 42% of these were diagnosed with a PE. More than 50% of patients with a PE had a significantly large PE (in the main or lobar pulmonary artery) and 13% of patients had additional explanation for their syncope (eg, cardiac arrhythmia).

PE was diagnosed in 17% (97 of 560) of the original cohort, which is a higher number than in similar studies because they excluded and discharged home a higher proportion (72%) of the presenting patients than most studies. The study cohort included patients who were older, had signs of a DVT, and had abnormal vital signs; in addition, the researchers did not include oxygen saturation in their assessment of these patients, all factors that could increase the likelihood of a PE.

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

Bottom line: Although PE may be a missed diagnosis in some patients presenting with syncope, in this study various selection biases increased that proportion. Indiscriminate application of the Wells score could lead to overdiagnosis and overtreatment of clinically irrelevant PEs. A more relevant and clinically meaningful outcome would be morbidity and mortality from PE.

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Consider acupuncture for chronic constipation

Liu Z, Yan S, Wu J, He L, Li N, Dong G, et al. Acupuncture for chronic severe functional constipation: a randomized trial. *Ann Intern Med.* 2016; 165(11):761–769.

This multicenter, randomized, sham-controlled trial compared electroacupuncture versus sham acupuncture for the treatment of chronic, functional constipation. Electroacupuncture uses the same acupoints as traditional acupuncture but also generates continuous electrical impulses that can be adjusted by the practitioner. Functional constipation was diagnosed by gastrointestinal and anorectal physicians in 15 centers in China; most centers (13 of 15) were traditional Chinese medicine hospitals.

Adult patients (n=1,075) were randomly assigned to receive either 28 sessions of electroacupuncture at traditional acupoints or sham acupuncture at non-acupoints. The study lasted 8 weeks.

In the electroacupuncture group, the change from baseline in mean bowel movements per week was 1.8 (95% CI, 1.6–1.9) compared with a change of 0.87 (CI, 0.73–0.97) in the sham acupuncture group (between-group mean difference, 0.90; 95% CI, 0.74–1.1). Common adverse reactions were hematoma, sleeplessness, and sharp pain, but only discomfort after acupuncture was significantly more common in the electroacupuncture group. No serious reactions occurred in either group.

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

Bottom line: In adult patients with chronic, severe functional constipation, electroacupuncture provided an increase in complete spontaneous bowel movements compared with sham acupuncture and was well tolerated. Access to acupuncture is the primary barrier to implementing this change in practice; however, local healthcare systems are increasingly offering this service to patients with both private and public health insurance. Local knowledge of available resources will be necessary for clinicians to implement this change in practice. EBP

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