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EVIDENCE-BASED PRACTICE

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Mulligans and gilligans

I have only been out golfing once, but I quickly learned about "taking a mulligan." For those of you who are unfamiliar with the term, a mulligan is a do-over, sometimes allowed when your first shot is gosh awful. Since I'd never golfed before, most of my shots were gosh awful. Fortunately, my golf buddies (by brother and his father-in-law) took pity on me, and allowed me many second (or third) drives off the tee. Their benevolence assured that we all made it home at a reasonable hour, and kept my score from going into 4 digits. One time, to everyone's amazement, I actually hit a ball onto the green with my first stoke. It was probably dumb luck and I'm glad they didn't want me to try that trick a second time.

But they might have! Are you aware that the opposite of a mulligan is called a gilligan?[1] When a gilligan is agreed to, your golf buddies have the right to ask you to replay a shot that appears freakishly lucky, say a ricochet off the grounds keeper's rake for a hole in one. The gilligan, I reckon, takes some of the randomness out of golf and increases the effects of skill on the outcome of the game.

Well, those of us working in evidence-based medicine would also like to get randomness out of our game. Would a few gilligans help?

The Center for Open Science in Charlottesville, Virginia arranged for 270 experienced investigators to rerun high-quality gilligans of 100 landmark psychological studies previously published in 3 major psychology journals.[2] The results were not inspiring. Overall, replicated effects had about half the magnitude as the original effects. Originally, 97% of studies had statistically significant results, whereas on replication, only 36% did. The effect size during replication fell within the original 95% confidence interval only 47% of the time.

So research is a bit like golf in this regard. We probably don't need to issue too many mulligans, but when someone's first paper looks freakishly positive, we really should ask for a gilligan.

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Are bronchodilator nebulizers superior to MDIs for the treatment of acute asthma exacerbations?

EVIDENCE-BASED ANSWER

No. Bronchodilators delivered by metered-dose inhaler (MDI) and spacer or nebulizer result in similar therapeutic benefits for adults and children with acute asthma exacerbation in the emergency department (ED). Children have fewer adverse effects and shorter ED stays with use of MDI and a spacer (SOR: **A**, meta-analysis of RCTs). Furthermore, costs of the delivery system, medication, and personnel are lower for MDI and spacer therapy in adults (SOR: **B**, single small RCT).

Evidence summary

A 2013 meta-analysis of 33 RCTs including 1,690 children and 701 adults in the ED for acute asthma exacerbation compared beta-agonist delivery using MDI with a spacer versus wet nebulization.[1]

Risk of hospital admission after use of MDI with spacer was similar to nebulizer in adults (9 studies, n=582; risk ratio [RR] 0.94; 95% CI, 0.6–1.4) and in children (9 studies, n=757; RR 0.71; 95% CI, 0.47–1.1). The mean duration in the ED for children was longer in the wet nebulizer group (103 minutes) than the MDI with spacer group (3 studies, n=396; mean difference 33 minutes; 95% CI, 24–43), but no difference was noted in adults. In children, pulse rate was 5% lower with MDI with spacer treatment than with nebulizer (9 studies, n=679; 95% CI, 2–8) as well as less risk of tremor (9 studies, n=679; RR 0.64; 95% CI, 0.44–0.95). In both adults and children, measurements of peak flow and forced expiratory volume did not differ between the MDI with spacer and nebulizer groups. An exclusion criterion for all these studies was life-threatening asthma; therefore, the results of this meta-analysis may not be generalizable to these patients.[1]

A 2011 randomized, double-blinded, placebo-controlled trial evaluated MDI with spacer versus nebulizer in 60 adults with acute asthma exacerbation in 2 inner city EDs.[2] This trial was included in the meta-analysis above but also included data on costs of each treatment. Patients were randomized to receive albuterol by 6 puffs of an MDI with spacer followed by nebulized placebo (n=29) or 2.5 mg nebulized albuterol followed by placebo MDI/spacer (n=29). Baseline severity of asthma exacerbation as measured by median peak flows and symptom scores was similar between groups.

After treatment, median peak flow and symptom scores improved similarly in both groups. However, the median cost of the delivery system, medication, and respiratory therapist was $10.11 per MDI patient and $18.26 per nebulizer patient ($P<.001$).[2] EBP

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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

Utility of fetal RhD screening

de Haas M, Thurik FF, van der Ploeg CP, Veldhuisen B, Hirschberg H, Soussan AA, et al. Sensitivity of fetal *RHD* screening for safe guidance of targeted anti-D immunoglobulin prophylaxis: prospective cohort study of a nationwide programme in the Netherlands. *BMJ*. 2016; 355:i5789.

This large observational cohort trial from the Netherlands examined the accuracy with identifying RhD-positive fetuses using fetal *RHD* genotype screening on cell-free DNA isolates in maternal plasma in more than 32,000 RhD-negative women. Fetal *RHD* testing was conducted in week 27 of gestation and results were compared with cord blood analysis at birth.

If the fetal *RHD* genotype test was positive, providers administered 200 µg anti-D immunoglobulin in the 30th week of gestation and within 48 hours after birth. If the fetal *RHD* genotype was negative, providers were told immunoglobulin was unnecessary.

RHD-positive results occurred 62% of the time and *RHD*-negative results occurred 38% of the time. Cord blood samples were available for 25,789 pregnancies (80%). Overall, there were 225 false-positive and 9 false-negative results. The sensitivity for identifying the fetal *RHD* genotype was 99% and specificity was 98%, with a negative predictive value of 99% and a positive predictive value of 99%. In the 9 false-negative results, 6 were due to no fetal DNA in the sample and were found on repeat testing, and 3 were due to technical error. In 22 of the 225 false-positive results, follow-up serology or molecular testing found an *RHD* gene was present, meaning the result of routine cord blood serology in these cases were falsely negative.

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

Bottom line: The use of fetal cell-free DNA in maternal serum is becoming more common for genetic testing during prenatal care. Prior meta-analyses found slightly lower sensitivity and specificity, but timing of testing varied significantly. Fetal *RHD* testing at 27 weeks appears to be highly accurate and evaluating fetal *RHD* at 27 weeks in Rh-negative patients could reduce the unnecessary use of anti-D immunoglobulin when the fetal *RHD* is negative.

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Screening for and treating prediabetes

Barry E, Roberts S, Oke J, Vijayaraghavan S, Normansell R, Greenhalgh T. Efficacy and effectiveness of screen and treat policies in prevention of type 2 diabetes: systematic review and meta-analysis of screening tests and interventions. *BMJ*. 2017; 356:i6538.

This systematic review and meta-analysis assessed current screening and treatment modalities for prediabetes. Three searches were undertaken: 1 for screening tests for prediabetes, another for intervention trials, and a third for the prevention of type 2 diabetes in women with a history of gestational diabetes. A total of 148 articles covering 138 trials assessing screening, and 50 intervention trials assessing treatment, were included. For the screening search, all diagnostic accuracy and prevalence studies using glycosylated hemoglobin (HbA1C) and fasting plasma glucose (FPG) as screening tools were included.

Primary outcomes for screening were the diagnostic accuracy of using HbA1C and FPG versus the "gold standard" oral glucose tolerance test (OGTT).

The diagnostic accuracy of screening tests to detect prediabetes was low. HbA1C was neither sensitive (49%) nor specific (79%). FPG was more specific (94%), but not as sensitive (25%). For intervention studies, trials included participants ≥18 years old and "at risk of prediabetes"—impaired glucose tolerance or fasting glucose, elevated HbA1C, or history of gestational diabetes.

Primary outcomes for the intervention studies included relative risk reduction for development of diabetes, weight reduction, or change in glycemic markers with lifestyle interventions or use of metformin.

Lifestyle interventions reduced the relative risk of developing diabetes by 31% for interventions lasting 6 months to 2 years (95% CI, 23–67; I^2=0%; number needed to treat [NNT]=33) versus 37% for interventions lasting 3 to 6 years (95% CI, 28-46; I^2=45%; NNT=12), with an overall relative risk reduction of 36% (95% CI, 28–43; I^2=30%). Metformin had a relative risk reduction of 26% (95% CI, 16-35; I^2=0%; NNT=14).

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

Bottom line: HbA1C and FPG in isolation are poor screening tests; however, which alternative test to use to screen for prediabetes is unclear. Additional studies are needed,

CONTINUED ON PAGE 5

Is eczema in infancy associated with later food allergy in childhood?

CASE

A 10-month-old white girl presents with dry, erythematous patches over both cheeks and extensor surfaces of her ankles. You diagnose eczema by simple inspection. She is breastfed and her mother has introduced fruits, vegetables, grains, eggs, yogurts, and peanut butter. Her mother is wondering whether the rash could be from a food allergy. Should further testing be done?

Evidence-based answer

Infants who have eczema are more likely to develop food allergy later in childhood than are infants without eczema. Food allergy evaluation can be considered in patients with persistent eczema despite optimal management.

Evidence summary

The association of atopic disease in infancy and food allergy later in childhood is an active area of investigation.[1] Children with atopic disease have had varied estimates of immunoglobulin E (IgE)-mediated food allergy, ranging from 15% to 40%.

A prospective, population-based cohort study investigated the relationship between early-onset atopic disease and food allergy. In this study, 4,453 1-year-old infants were assessed for a history of eczema and then underwent skin prick testing to peanut, egg white, cow milk, and sesame. Those testing positive subsequently underwent an oral food challenge.[1]

The risk of food allergy among infants with eczema was 20.9%. Infants with eczema were 11.0 times more likely to develop peanut allergy (95% CI, 6.6–18.6) and 5.8 times more likely to develop egg allergy (95% CI, 4.6–7.4) by 12 months than infants without eczema. For infants with eczema before 3 months of age, the risk of food allergy was increased significantly (by 50%; 95% CI, 43–59).[1]

In a 2015 prospective study of 1,087 infants with atopic disease (mean age 7.3 months) who had no history of food allergy at baseline, infants were followed for 69 months and serum IgE (sIgE) as a predictor of food allergies was monitored at regular intervals.[2]

Based on a logistic regression model, baseline elevated sIgE values for various common foods were associated with later food allergies: cow's milk (odds ratio [OR] 1.9; *P*<.001), peanut (OR 1.6; *P*<.001), egg white (OR 1.4; *P*<.001), and seafood mix (OR 2.8; *P*=.0013). Wheat and soybean baseline sIgE levels were not significant predictors of clinical allergies. However, despite the increased risk, elevated sIgE had very low positive predictive values for allergy. Therefore, it was recommended that only children with persistent atopic disease despite appropriate management be screened for food allergy.[2]

Evidence does not support an altered diet for children with atopic disease. Experts state that an elimination diet should be considered only after true food allergy has been diagnosed, preferably by oral food challenge. These diets involve removing a specific food for 4 weeks and then reintroducing for 2 days to evaluate for return of atopic disease.[3]

Data suggest that introducing allergenic foods to infants with severe eczema, if tolerable, reduces the risk of allergy later in life.[4]

CASE WRAP-UP

After further discussion about the poor predictive value of laboratory testing, mother opted to not obtain lab work to evaluate for food allergies. She decided to monitor the eczema before considering an elimination diet. EBP

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DIVING FOR PURLs

PRIORITY UPDATES FROM THE RESEARCH LITERATURE

CONTINUED FROM PAGE 4

including revisiting the acceptability and feasibility of the OGTT and validation studies for proposed diagnostic algorithms. EBP

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Do fitness trackers use by adults increase physical activity?

EVIDENCE-BASED ANSWER

Yes. Physical activity monitors decrease sedentary time by about 2 hours per day and increase the number of steps per day by about 2,000 (SOR: **B**, RCTs and case series), but the effect on moderate to vigorous physical activity is inconsistent (SOR: **C**, inconsistent RCTs).

A 2013 RCT of 33 sedentary adults (mean age 27 years) compared the effect of a physical activity monitor worn daily versus no monitor on changes in sedentary time and physical activity over 4 weeks.[1] At baseline, patients had a total sitting time of more than 7 hours a day; 63% of participants were office workers and 37% full-time students.

The intervention included an online personal activity monitor with a wearable device to measure energy expenditures. Key outcomes were changes from baseline in sedentary time and time of vigorous physical activity, as defined by the metabolic equivalent of task (MET) method (details not given).

Participants wearing physical activity monitors reduced sedentary time from 10.9 to 8.6 hours (P<.01) while the control group had a nonsignificant increase in sedentary time from 10.7 to 11.2 hours (P=.55). Participants wearing physical activity monitors increased vigorous activity from 291 to 733 MET-minutes/week (P<.001) while the control group had a nonsignificant increase in vigorous activity from 173 to 193 MET-minutes/week (P=.7).[1]

A 2015 randomized pilot study of 25 healthy inactive women 55 to 70 years old evaluated the effect of an individualized education program including a wearable activity monitor on physical activity over 6 months.[2] The control group attended monthly group education sessions, but had no activity monitor. Both groups wore hip accelerometers to measure steps. Outcomes included steps per day and self-reported moderate to vigorous physical activity in minutes per day.

At 6 months, the intervention group was taking 2,080 more steps per day (95% CI, 704–4,918) than the control group, although no difference was noted in moderate to vigorous physical activity.[2]

A 2015 prospective case series of 25 postmenopausal obese or overweight women examined the effect of wearing an activity monitor for 16 weeks on physical activity measured by accelerometer.[3] Outcomes collected from the device included steps per day, device adherence with total logging time, and days of valid wear at 16 weeks.

The device was worn for at least 10 hours per day on more than 95% of days and participants had an average of 7,540 steps per day compared with a baseline value of 5,906 steps per day.[3]

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Does testing C-reactive protein add important information to standard coronary artery disease risk assessment?

EVIDENCE-BASED ANSWER

High-sensitivity C-reactive protein (hsCRP) may help stratify patients at intermediate risk of coronary artery disease based on standard risk profiling. When hsCRP is added to algorithms using standard risk factors, 5.2% of patients at intermediate risk of cardiovascular disease would be reclassified into a higher-risk group in which statins are recommended (SOR: **B**, predictive modeling of data from a meta-analysis of prospective cohort studies). Checking hsCRP levels may be considered for intermediate-risk and low-risk patients in whom the decision to start a statin is unclear (SOR: **C**, consensus guidelines).

A 2012 meta-analysis of 52 prospective cohort studies of individuals without known coronary artery disease (N=246,669) included 38 studies (n=166,596) examining the

addition of hsCRP to standard risk factors (age, sex, smoking status, history of diabetes, systolic blood pressure, and levels of total and high-density lipoprotein [HDL] cholesterol) to improve prediction of a first cardiovascular event.[1] The mean age was 60 years, 49% were men, 21% were current smokers, and 6% had a history of diabetes. Mean systolic blood pressure was 136 mmHg, and total and HDL cholesterol levels were 227 and 51 mg/dL, respectively.

Researchers calculated the incremental value of adding various risk factors (including hsCRP levels) in predicting first cardiovascular events, defined as myocardial infarction, fatal coronary heart disease, or any stroke. Assuming a population of 100,000 adults with cardiovascular risk profiles similar to those observed in the included trials, standard risk factors alone classified 15,025 individuals as intermediate risk (10%–20% probability of a cardiovascular event over a 10-year period). Of these, 13,199 would not be eligible for statin treatment based on the Adult Treatment Panel-III guidelines.[1]

Assessment of hsCRP levels in these 13,199 intermediate-risk individuals would result in reclassification of 5.2% (n=690) to a high-risk group (predicted cardiovascular event rate risk of >20% over 10 years). Assuming that the reclassified patients would be placed on statin therapy, the researchers predicted that 30 additional cardiac events would be prevented over a 10-year period. In other words, researchers estimated that for every 440 persons screened during a 10-year period, assessment of hsCRP would prevent 1 cardiovascular event and result in initiation of statin therapy for 23 additional individuals.[1]

In their 2013 guidelines on cholesterol treatment, the American College of Cardiology (ACC) and American Heart Association (AHA) stated that hsCRP levels of 2 mg/L or more may be considered in the decision of whether to start a moderate-dose statin in patients at intermediate risk for atherosclerotic cardiovascular disease (ASCVD) (class IIb-Level C; uncertain benefit, based on expert opinion, case studies, or standard of care).[2]

For patients with diabetes, intermediate risk includes age younger than 40 or older than 75 years, or a low-density lipoprotein cholesterol (LDL-C) concentration of less than 70 mg/dL. For patients without diabetes, intermediate risk includes a combination of age 40 to 75 years, LDL-C between 70 and 189 mg/dL, and 10-year ASCVD risk 5% to 7.5%. In addition, statin therapy may be considered if measured hsCRP is 2 mg/L or more in individuals at low risk for ASCVD (nondiabetic patients with LDL-C <190 mg/dL and age <40 years or >75 years, or <5% 10-year ASCVD risk).[2]

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Does alcohol consumption affect blood pressure?

EVIDENCE-BASED ANSWER

Alcohol reduction efforts result in only a small decrease (average 3 mmHg systolic and 2 mmHg diastolic) in blood pressure (SOR: **A**, systematic review of RCTs.) However, moderate to heavy alcohol consumption is associated with an increased risk of hypertension (SOR: **B**, meta-analysis of cohort studies).

A 2001 meta-analysis of 15 RCTs (N=2,234) assessed the effects of reduction of alcohol consumption on blood pressure.[1] In all studies, alcohol reduction was the sole intervention compared with a control group, with most studies using substitution with low alcohol beer as the means to reduce alcohol intake. All but 1 study had at least 95% male subjects with an age range of 27 to 57 years old. Approximately half of the studies involved patients with preexisting hypertension.

The median alcohol reduction was 76% (16% to 100%) over a wide time span of 1 to 104 weeks. Alcohol reduction resulted in a reduction of systolic blood pressure by 3.3 mmHg (95% CI, 2.5–4.1) and diastolic blood pressure by 2.0 mmHg (95% CI, 1.5–2.6).[1]

In a 2012 systematic review and meta-analysis, alcohol consumption and the risk of hypertension in men and women was studied.[2] Data were included from 16 prospective cohort studies, involving 227,656 patients, of which 14.9% were men (age range 24–60 years) and

85.1% were women (age range 30–55 years). Men and women were categorized in 10-g/d increments of alcohol consumption. A standard drink in the United States contains about 14 grams of pure alcohol. Hypertension was defined in various ways in the studies—2 studies used a blood pressure of more than 160/95 mmHg as a threshold.

In men, the risk of developing hypertension was increased with alcohol consumption of 31 to 40 g/d (relative risk [RR] 1.8; 95% CI, 1.4–2.3) and more than 50 g/d (RR 1.6; 95% CI, 1.4–1.9). In women, the risk of developing hypertension was decreased with alcohol consumption of less than 10 g/d (RR 0.87; 95% CI, 0.82–0.92), and the risk of hypertension was increased for consumption of 31 to 40 g/d (RR 1.2; 95% CI 1.1–1.3). Significance was not found for the other increments of alcohol consumption in men or women.[2]

In the process of developing Canadian recommendations on alcohol consumption, a 1999 review of 14 RCTs, involving a total of 2,202 patients, was conducted.[3] These trials assessed the effects of alcohol consumption on the prevention and control of hypertension in both normotensive and hypertensive subjects. The subjects were mostly men, 20 to 80 years old. The subjects reduced their alcohol consumption from 15% to 100%.

In normotensive subjects, blood pressure reductions were found to be statistically significant in all 7 studies for both systolic blood pressure (mean reduction range 2.1–8 mmHg) and diastolic blood pressure (mean reduction range 1.4–8 mmHg). In hypertensive subjects, blood pressure reductions were statistically significant in 5 of 7 studies for systolic blood pressure (mean reduction range 0.9–7.3 mmHg) and in 2 of 7 studies for diastolic blood pressure (mean reduction range 0.7–3.2 mmHg).[3]

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What is the most effective dose and route of misoprostol for labor induction?

EVIDENCE-BASED ANSWER

The answer is unclear. Minimal differences exist among vaginal misoprostol (either <50 µg or ≥50 µg), oral tablets (≥50 µg), and oral titrated solution (<50 µg) in terms of risk of Cesarean delivery or failure to achieve vaginal delivery within 24 hours (SOR: **A**, meta-analyses of RCTs). Compared with vaginal dosing, oral misoprostol has a lower risk of Apgar score less than 7 and postpartum hemorrhage, although a higher risk for meconium-stained fluid (SOR: **A**, systematic review). Vaginal misoprostol at 50 µg leads to vaginal delivery 4.5 hours sooner than oral tablets at the same dose (SOR: **B**, RCT).

A 2015 systematic review and network meta-analysis of 280 RCTs (N=48,068) assessed the relative effectiveness and safety of 12 different regimens of prostaglandins for labor induction.[1] A subset of studies (157 studies, n=29,339) assessed misoprostol in either vaginal or oral form; comparisons included placebo as well as other vaginal prostaglandins. Women had a viable fetus and an indication for induction in the third trimester, although specific inclusion and exclusion criteria varied among studies. The details of misoprostol regimens (dose, frequency, and titration) varied, but most used dosing every 1 to 6 hours.

Titrated oral misoprostol solution (<50 µg/dose) led to the lowest probability of Cesarean delivery compared with placebo, but the differences compared with vaginal and oral misoprostol tablets were small and likely not significant (see **TABLE 1**). Vaginal misoprostol (both <50 µg and ≥50 µg), oral misoprostol tablets (≥50 µg), and titrated oral solution (<50 µg) produced similarly low probabilities of failure to achieve vaginal delivery within 24 hours (see **TABLE 2**).[1]

A 2014 systematic review of 76 RCTs (N=14,412) evaluated oral misoprostol for induction of labor in the third trimester for women with a viable fetus.[2] Most studies used repeated doses of 50 µg, but some included starting doses as low as 10 µg and a few as high as 200 µg.

A pooled analysis of 14 RCTs (n=2,448) demonstrated no difference between oral and vaginal misoprostol in equal doses (25–200 µg) in terms of vaginal delivery not achieved

TABLE 1

Results from direct, pairwise meta-analysis (where possible) and network meta-analysis for treatments' risk of caesarean section relative to placebo[1]

Treatment comparison	Direct comparison	Network meta-analysis		
	OR (95% CrI)	OR (95% CrI)	NNT (95% CrI)	Absolute probability (95% CrI)
Placebo	Reference	Reference	Reference	0.21 (0.05–0.50)
No treatment	—	1.00 (0.74–1.32)	24 (–953 to 1,092)	0.21 (0.05–0.51)
Vaginal misoprostol				
<50 µg	1.09 (0.58–2.06)	0.76 (0.62–0.92)	28 (11–135)	0.17 (0.04–0.44)
≥50 µg	0.86 (0.14–5.57)	0.74 (0.6–0.89)	25 (11–104)	0.17 (0.04–0.43)
Oral misoprostol tablet				
<50 µg	—	1.17 (0.70–1.85)	17 (–488 to 450)	0.21 (0.05–0.55)
≥50 µg	0.59 (0.36–0.95)	0.72 (0.59–0.89)	24 (10–102)	0.16 (0.03–0.43)
Titrated oral misoprostol solution <50 µg	—	0.65 (0.49–0.83)	18 (8–75)	0.15 (0.03–0.40)

CrI=credible interval; NNT=number needed to treat; OR=odds ratio.

TABLE 2

Results from direct, pairwise meta-analysis (where possible) and network meta-analysis for treatments' failure to achieve vaginal delivery within 24 hours relative to placebo[1]

Treatment comparison	Direct comparison	Network meta-analysis		
	OR (95% CrI)	OR (95% CrI)	NNT (95% CrI)	Absolute probability (95% CrI)
Placebo	Reference	Reference	Reference	0.81 (0.23–1.00)
No treatment	—	0.32 (0.09–1.14)	7 (–49 to 285)	0.66 (0.07–0.99)
Vaginal misoprostol				
<50 µg	—	0.07 (0.03–0.16)	2 (2–26)	0.43 (0.02–0.96)
≥50 µg	—	0.06 (0.02–0.12)	2 (1–20)	0.39 (0.01–0.94)
Oral misoprostol tablet				
<50 µg	—	0.16 (0.05–0.48)	4 (2–77)	0.56 (0.04–0.98)
≥50 µg	0.10 (0.03–0.31)	0.08 (0.04–0.18)	3 (2–30)	0.46 (0.02–0.96)
Titrated oral misoprostol solution <50 µg	—	0.06 (0.03–0.15)	2 (1–23)	0.41 (0.02–0.95)

CrI=credible interval; NNT=number needed to treat; OR=odds ratio.

within 24 hours (relative risk [RR] 1.1; 95% CI, 0.86–1.4). Thirty-five RCTs (n=6,326) showed no difference in likelihood of Cesarean delivery (RR 0.93; 95% CI, 0.81–1.1). Compared with vaginal dosing, oral misoprostol was associated with fewer Apgar scores less than 7 at 5 minutes (RR 0.60; 95% CI, 0.44–0.82) and lower risk of postpartum hemorrhage

(RR 0.57; 95% CI, 0.34–0.95), although meconium-stained fluid was more likely with oral dosing (RR 1.2; 95% CI, 1.03–1.4). Pooling of 29 RCTs (n=5,503) revealed no difference in uterine hyperstimulation with fetal heart changes between the oral and vaginal routes (RR 0.71; 95% CI, 0.47–1.1) and no differences in other serious neonatal or maternal morbidity or mortality. However, these events were rare (zero in most trials). The best dose frequency was not analyzed.[2]

A 2015 RCT (N=140) directly compared misoprostol 50 µg administered every 6 hours via oral route versus vaginal route for induction of Nigerian women at term.[3]

The time from start of induction to vaginal delivery was shortest with vaginal dosing (mean difference 4.5 hours; *P*=.02). The oral misoprostol group had a lower risk of tachysystole (RR 0.13; 95% CI, 0.03–0.56). Rates of other maternal complications, Cesarean delivery, neonatal complications, and maternal satisfaction did not differ between groups.[3]

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***EVIDENCE-BASED PRACTICE* LEARNING OBJECTIVES**

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Is development of osteoarthritis more common in patients who did not have surgical repair after complete isolated ACL tear?

EVIDENCE-BASED ANSWER

No. Development of osteoarthritis over 10 to 16 years is similar in patients treated nonoperatively after a complete ACL tear compared with patients who have undergone ACL reconstruction (33% vs 24%–35%) (SOR: **B**, meta-analysis of RCTs and observational studies, 1 small RCT).

A 2014 meta-analysis of 2 RCTs, 2 cohort studies, 7 prospective case series, and 18 retrospective case series examined knee stability, functional outcomes, need for additional surgery, and radiographic evidence of osteoarthritis in adults with ACL tears (N=2,270) to determine if surgical reconstruction leads to improved long-term outcomes.[1] Study inclusion criteria required a minimum of 10 years of follow-up, a sample size of more than 10, and closed growth plates.

From the 29 studies, 27 patient cohorts had surgical reconstruction (n=1,585), with a mean sample size of 59 (range 22–181) and a mean follow-up of 13 years. The most common type of ACL reconstruction used a patellar tendon autograft with arthroscopic technique and occurred a mean of 21 months after injury. Thirteen patient cohorts were treated nonoperatively (n=685) with a mean sample size of 53 (range 18–94) and a mean follow-up of 16 years. Nonoperative treatments were not described. Meniscal damage before surgery was equivalent in both groups.[1]

Osteoarthritis, diagnosed using radiographic criteria, was observed in a similar number of patients in the operative and nonoperative groups (35% vs 33%; *P*=.77).[1]

A 2016 RCT of 32 men with isolated ACL ruptures compared operative (n=17) and conservative (n=15) treatments for the occurrence of osteoarthritis.[2] Inclusion criteria included isolated ACL injury, body mass index less than 30, no previous major injury or surgery of the knee, and patients who successfully completed the final follow-up. Mean follow-up time was 10 years (range 10–11 years) and mean age was 31 years (range 20–36 years).

Patients were randomly assigned to the operative or conservative treatment group. Treatment began a mean

of 6 weeks (range 4–8 weeks) after initial injury. Operative treatment was performed via arthroscopic technique using a semitendinosus-gracilis tendon autograft. Both the operative and conservative treatment groups participated in the same rehabilitation program. This program included range of motion exercises followed by targeted muscle group strengthening and, lastly, activities including jogging, swimming, and bicycling. No patients required surgical revision. Presence of osteoarthritis was measured by clinical examination, radiological findings, and pain scores.[2]

Evidence was noted of cartilage degeneration in all of the patients, but the overall incidence of osteoarthritis between the 2 groups did not differ (24% treatment group vs 33% conservative group, *P* reported as nonsignificant).[2]

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Is vaginal estrogen safe in patients with a history of venous thromboembolism caused by estrogen?

EVIDENCE-BASED ANSWER

Vaginal estrogen medications do not appear to increase risk of recurrent venous thromboembolism (VTE) in patients with a history of estrogen-related VTE when used in low doses (SOR: **C**, case-control study and consensus guidelines).

Nonoral estrogen products such as transdermal or vaginal preparations produce lower circulating levels of clotting factors and triglycerides than oral estrogen medications, as these products do not undergo first-pass metabolism.[1–3]

A 6-year, Swedish nationwide case-control study evaluated VTE risk associated with various hormone therapies and routes of administration.[4] A total of 838 patients between 40 and 64 years old with a history of VTE were matched to 891 women of the same age without a history of VTE. Both groups self-reported their VTE risk factors including exposure to hormone therapy. Patients who were prescribed hormone therapy 3 months prior to the index date were considered current users.

Forty-two (5%) of the 838 patients who reported VTE were current users of topical estrogen treatment for local vaginal effects compared with 73 (8%) of the 891 controls. Logistic regression analysis did not demonstrate an increased risk of VTE in the current localized estrogen therapy group versus the control group (adjusted odds ratio 0.69; 95% CI, 0.43–1.1).[4]

The 2015 evidence-based Endocrine Society clinical practice guidelines on menopause categorized vaginal estrogens as either low, intermediate, or high systemic dose and recommend using the lowest effective dose to minimize systemic absorption (strong recommendation, based on low-quality evidence).[1] However, these guidelines noted that studies in high-risk patients were lacking. The 2 US-available low-dose vaginal estrogen options are a twice-weekly 10-µg estradiol vaginal tablet and a 2-mg estradiol ring that delivers 7.5 µg/d over 90 days.

The 2013 evidence and expert consensus-based guidance statement by The North American Menopause Society (NAMS) on vulvovaginal atrophy acknowledged the overarching VTE risk with all forms of estrogen therapy, but suggested a "very low [VTE] risk" for low-dose vaginal estrogen products because they produced estrogen levels similar to that in an average postmenopausal woman (Level C strength of recommendation, based primarily on expert opinion).[2,3] Although NAMS noted that clinical trials have not demonstrated increasing VTE risks with vaginal estrogen, these studies excluded women with a history of VTE.[2]

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What is the best treatment for plantar warts?

EVIDENCE-BASED ANSWER

Topical salicylic or lactic acid leads to slightly higher clinical cure rates (66% vs 50%) compared with placebo/no treatment for the treatment of plantar warts (SOR: **A**, meta-analysis of RCTs) and is recommended first-line treatment (SOR: **C**, expert opinion). Cryotherapy and placebo both have a 25% cure rate (SOR: **B**, RCT), yet cryotherapy is also recommended as first-line treatment of plantar warts (SOR: **C**, expert opinion). Combining salicylic acid and cryotherapy does not improve cure rates (SOR: **A**, meta-analysis of RCTs). Alternative interventions include laser, topical 5-fluorouracil, topical immunotherapy, hyperthermia, dithranol, formaldehyde, glutaraldehyde, photodynamic therapy, and podophyllotoxin (SOR: **C**, expert opinion).

A 2012 meta-analysis of 85 RCTs with 8,815 patients evaluated the efficacy of local treatments for cutaneous nongenital warts in healthy, immunocompetent adults and children.[1] Most of these studies (77 RCTs) were completed in secondary care locations. Refractory warts—those that have failed standard treatment—were included in 18 studies, while 26 studies included warts without prior treatment.

Treatments of plantar/foot warts included topical salicylic acid/lactic acid (SA), cryotherapy, and combinations of SA/cryotherapy (treatment protocols were not reported). Assessment of cure occurred between 6 weeks and 6 months after treatment, but the definition of cure was not reported.[1]

For plantar/foot warts, SA demonstrated significant increase in cure rates compared with placebo or no treatment (2 RCTs, n=239; 66% vs 50%; relative risk [RR] 1.3; 95% CI, 1.1–1.6). The remainder of the treatments showed no difference in cure rates: cryotherapy versus placebo/no treatment (2 trials, n=110; 25% vs 25%; RR 0.9; 95% CI, 0.26–3.1), cryotherapy versus SA (3 trials, n=357; 24% vs 22%; RR 1.1; 95% CI, 0.76–1.6), cryotherapy plus SA versus SA alone (1 trial, n=47; 56% vs 41%; RR 1.4; 95% CI, 0.74–2.5), and cryotherapy plus SA versus cryotherapy alone (1 trial, n=51; 56% vs 58%; 95% CI, 0.6–1.6). Harms of the interventions included pain, blistering, and scarring, which were not consistently reported but were thought to be more common with cryotherapy. Many of the trials within this analysis had limitations of blinding and allocation concealment due to the nature of treatments such as cryotherapy.[1]

In 2014, the British Association of Dermatologists published a guideline for cutaneous warts based on a systematic review.[2] The above meta-analysis was cited by this guideline.

The guideline recommends salicylic acid (15%–40% daily; strength of recommendation A: directly applicable, high-quality meta-analysis, systematic review, or RCT) or cryotherapy (every 2 weeks for 3–4 months; strength of recommendation B: extrapolated evidence from meta-analysis, systematic review, RCT) for the treatment of plantar warts with combination treatment optional. Other treatment options based on lower levels of evidence include laser (several treatment protocols reported), topical 5-fluorouracil applied with or without occlusion daily for 4 to 12 weeks, topical immunotherapy with squaric acid dibutyl ester twice weekly for 10 weeks, hyperthermia with red light up to 44°C for 30 minutes on 3 consecutive days, dithranol applied daily for up to 10 months, formaldehyde, glutaraldehyde, photodynamic therapy, and podophyllotoxin applied topically with prolonged occlusion.[2]

The guideline cautioned that each patient should be considered on a case-by-case basis due to risk of harms of the intervention including spread of human papillomavirus infection, pain, blistering, and secondary infection.[2]

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Does vaginal douching cause bacterial vaginosis?

EVIDENCE-BASED ANSWER

Vaginal douching is associated with a 20% higher incidence of bacterial vaginosis, although causation remains unclear (SOR: **B**, cohort studies with consistent findings). Cessation of douching for 4 weeks does not decrease the risk of bacterial vaginosis (SOR: **C**, small cohort study).

A 2010 multicenter cross-sectional cohort study (N=3,620) examined nonpregnant women 15 to 44 years old recruited from 12 clinics in Alabama for the effect of douching on the risk of bacterial vaginosis.[1] Participants were followed quarterly for up to 1 year, with vaginal swabs and interviews regarding personal hygiene, sexual behaviors, and vaginal symptoms performed at each visit. Swabs were tested for bacterial vaginosis and sexually transmitted infections. Bacterial vaginosis was defined by a gram stain Nugent score of 7 to 10 with 0 to 4 points for the presence of each bacterial morphotype—*Lactobacillus*, *Gardnerella*, or *Bacteroides*—and curved gram-variable rods.

Of all feminine hygiene behaviors studied, douching at least weekly was significantly associated with bacterial vaginosis (prevalence ratio 1.2; 95% CI, 1.1–1.3). This study was limited by its 50% loss to follow-up.[1]

In a 2008 prospective cohort study using the same database described above, the authors applied a marginal structural model to remove the confounder of women douching in response to bacterial vaginosis–associated vaginal symptoms versus bacterial vaginosis as a result of douching.[2] There were a total of 12,349 eligible visits. The percentage of study visits involving bacterial vaginosis for women who douched at least once in every study interval was compared with those who had not.

Douching was associated with a higher risk of bacterial vaginosis (relative risk 1.2; 95% CI, 1.1–1.4). However, the researchers may not have accounted for all possible covariates including douching frequency, douche ingredients, or reinfection versus relapse.[2]

A 2008 observational crossover cohort study (N=39) evaluated the risk of bacterial vaginosis in a douching cessation trial.[3] Reproductive-aged non¬pregnant women who reported douching in the prior 2 months were recruited through ads, fliers, and referrals. Participants underwent a 4-week douching observation phase (during which they douched at least once) followed by 12 weeks of douching cessation, then a 4-week self-chosen phase of either douching or cessation (11 of 33 women chose to resume douching). Patients returned for visits at 4 and 16 weeks. Patients filled out daily diaries and submitted self-collected vaginal swabs twice weekly in the first 16 weeks with a final sample in week 20. Bacterial vaginosis was diagnosed with the Nugent criteria. Univariable analysis compared any diagnosis of bacterial vaginosis during the douching cessation versus the observation phase.

Compared with the douching observation phase, douching cessation did not decrease the odds of developing bacterial vaginosis (adjusted odds ratio 0.76; 95% CI, 0.33–1.8).[3]

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What is the prognosis of microscopic hematuria in children?

EVIDENCE-BASED ANSWER

Hypercalciuria and familial microscopic hematuria are the most commonly identified etiologies of microscopic hematuria in children and are considered benign. In contrast, when associated with proteinuria or intermittent gross hematuria, microscopic hematuria has the potential to progress to pathologic renal disease. Patients with microscopic hematuria without proteinuria are unlikely to develop pathologic renal disease (SOR: **C**, based on observational studies with disease-oriented outcomes).

A 2013 prospective cohort study (N=351) followed children in China who had undergone renal biopsy for asymptomatic microscopic hematuria.[1] The study population was divided into 2 groups—1 with isolated microscopic hematuria (n=215) and the other with microscopic hematuria and intermittent gross hematuria or proteinuria (n=136). Patients with idiopathic hypercalciuria or other known urologic or nonglomerular diseases were excluded. Participants were followed for 2 to 10 years (median follow-up 3.7 years) to assess for adverse renal events defined as proteinuria of more than 0.5 g/d, development of hypertension, or decreased glomerular filtration rate to less than 60 mL/min for 3 months.

On initial biopsy, 71% (152 of 215) of the microscopic hematuria group had normal or minor histopathologic lesions compared with only 29% (39 of 136) of the gross hematuria and proteinuria group. On follow-up, 6% (13 of 215) of the microscopic hematuria group had adverse renal events compared with 23% (31 of 136) of the gross hematuria and proteinuria group (P<.001). This study was limited by a relatively short follow-up period.[1]

A 2005 cross-sectional study assessed the clinical significance of microscopic and gross hematuria with a thorough diagnostic protocol including history, physical examination, complete blood count, creatinine, C3 levels, and urine calcium and protein excretion as well as ultrasound or intravenous pyelogram.[2] Indication for renal biopsy was persistent high-grade hematuria (>100 red blood cells [RBCs] per hpf) or association with hypertension, decreased renal function or proteinuria.

Of 342 subjects with microscopic hematuria, 16% (56) had hypercalciuria without nephrolithiasis, 1.5% (5) had benign urologic structural abnormalities, 1.2% (4) had poststreptococcal nephritis, and 0.3% (1) had immunoglobulin A (IgA) nephropathy (the only pathologic finding in this group). By contrast, of the 228 subjects in the gross hematuria group, 22% (51) had hypercalciuria without nephrolithiasis, 15% (34) had IgA nephropathy, and 9% (21) had poststreptococcal nephritis.[2]

A large retrospective cohort study on adolescents entering military service in Israel assessed risk for end-stage renal disease (ESRD) among subjects with persistent microscopic hematuria without proteinuria.[3] Of 1,203,626 subjects included, 3,690 (0.3%) had persistent microscopic hematuria, defined as 5 or more RBCs per hpf on 3 separate occasions.

Over a mean 21-year follow-up period, 26 (of 3,690) persons with and 539 (of 1,199,936) persons without microscopic hematuria progressed to ESRD, yielding incidence rates of 34 and 2.1 per 100,000 person-years, respectively, and a hazard ratio of 20 (95% CI, 13–29). The mean age at recruitment was 17.6 years, so generalizability to the pediatric population may be limited.[3]

A retrospective cohort study in 1998 assessed the clinical significance of microscopic hematuria in children referred to a pediatric nephrology office.[4] Of 325 patients referred, all had normal creatinine and electrolyte values and lacked proteinuria. Eleven percent (29 of 263 tested) had hypercalciuria and 25% (66 of 263) had reported a positive family history of hematuria.

On imaging work-up 6% (18 of 283) had abnormal findings on renal ultrasound, but none which required intervention; 10% (9 of 90) had voiding cystourethrograms showing low-grade reflux. The study was limited in that no renal biopsies were performed and therefore early renal disease may have been missed.[4] EBP

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Are immediate- and extended-release oral metformin formulations absorbed in patients after gastric bypass?

Bottom line

Absorption of immediate-release metformin may be increased after gastric bypass (SOR: **C**, single pharmacokinetic study). No studies describe absorption characteristics of metformin extended-release (ER) after gastric bypass. Guidelines recommend against the use of any ER oral mediations after gastric bypass because absorption may be decreased (SOR: **C**, expert opinion).

Evidence summary

In healthy individuals, the absorption of metformin occurs slowly and incompletely in the duodenum. The most common bariatric procedure in the United States is the roux-en-Y, which reduces the size of the stomach, and bypasses the duodenum and most of the proximal small intestine.[1]

A nonblinded, single-dose pharmacokinetic study in 16 patients without diabetes after gastric bypass evaluated immediate-release metformin absorption 3 months after surgery.[2] Patients were administered a single dose of metformin 1 g and compared with sex- and body mass index–matched controls.

Metformin's area under the curve was nonsignificantly increased in gastric bypass subjects by 21% (mean difference 2.3 µg/h per milliliter; 95% CI, –1.3 to 5.9) and bioavailability was significantly increased by 50% (mean difference 14.0%; 95% CI, 4.1–23.9).[2]

An open-label, multidose, 5-regimen, 2-sequence clinical trial of 14 healthy volunteers who had not undergone bariatric procedures assessed the steady-state pharmacokinetic absorption of metformin ER tablets.[3] One-week regimens of metformin ER 500, 1,000 and 1,500 mg daily were administered sequentially. Subjects were then given immediate-release metformin 1,000 mg twice a day or metformin ER 2,000 mg daily for the last 2 weeks. The steady-state pharmacokinetic measurements of metformin ER were compared with metformin.

Maximum plasma concentrations after metformin ER 2,000 mg once daily were 36% higher than that seen after the evening dose of metformin 1,000 mg twice daily.[3]

Recommendations from others

A 2013 evidence-based guideline by the American Association of Clinical Endocrinologists, the Obesity Society, and the American Society for Metabolic & Bariatric Surgery for the perioperative support of the bariatric surgery patient recommended against using any ER medications.[4]

This recommendation was given a grade D evidence rating, based on a systematic literature review of 26 studies on drug absorption after bariatric surgery that identified no published data of any ER formulation medications.[5] EBP

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What is the best treatment for chronic anal fissures in adults?

EVIDENCE-BASED ANSWER

For medical treatments, topical nitroglycerin, topical calcium channel blockers, and botulinum toxin injections are effective in about half of patients but nitroglycerin has more adverse effects than the other agents and has a high recurrence rate in chronic anal fissure. Lateral internal sphincterotomy results in long-term cure rates of more than 90% and less than a 5% risk of incontinence (SOR: **A**, meta-analyses of RCTs). Medical therapies are usually recommended first, but lateral internal sphincterotomy is the treatment of choice for refractory anal fissures (SOR: **C**, expert opinion).

A 2012 meta-analysis of nonsurgical versus surgical treatment of anal fissures included 75 RCTs with 5,031 patients using 17 different agents.[1] Agents used included nitroglycerin ointment 0.05% to 0.5% 1 to 3 times daily for up to 8 weeks; botulinum toxin injections 10 to 100 units once; calcium channel blockers (CCBs) including diltiazem ointment 2% once or twice daily for 6 to 8 weeks; nifedipine ointment 0.2% to 0.5% 2 or 3 times daily for 3 to 8 weeks; and nifedipine 20 mg orally once or twice daily for 3 to 8 weeks. Adverse outcomes assessed included incontinence, headache, anaphylaxis, and infection.

Nitroglycerin was marginally better than placebo in percentage of patients with healed anal fissures (18 trials, n=1,315; 49% vs 36%; *P*<.0009). However, recurrence rates were between 51% and 67% for chronic anal fissures treated with nitroglycerin, and the risk of significant headache from nitroglycerin was 30%. Botulinum and CCBs were equivalent to nitroglycerin in healing rates, but botulinum had a lower occurrence of headaches than nitroglycerin (5 trials, n=284; odds ratio [OR] 0.22; 95% CI, 0.10–0.49) and nitroglycerin had a higher occurrence of all adverse outcomes than CCBs (2 trials, n=140; OR 3.6; 95% CI, 1.3–10). Nonhealing with any surgery was significantly less common than with any medical therapy (15 trials, n=979; OR 0.11; 95% CI, 0.06–0.23).[1]

A 2011 meta-analysis update of operative procedures for anal fissures evaluated 27 RCTs of 13 surgical procedures involving 2,056 patients.[2] The outcomes studied were persistence of the anal fissure and incontinence to flatus and feces. Seven trials compared manual anal stretch with some form of internal sphincterotomy.

When 2 studies with very high bias risk were removed from analysis, fissure persistence was more common with anal stretch than internal sphincterotomy (5 trials, n=328; OR 3.4; 95% CI, 1.6–7.3). Anal stretch also resulted in greater risk of incontinence (7 trials, n=385; OR 4.0; 95% CI, 2.0–8.0). The authors concluded that manual anal stretch should be abandoned. Open and closed partial lateral internal sphincterotomy appeared to be the most effective techniques, providing less than 10% persistence of anal fissure and less than 5% incontinence.[2]

In 2010, the American Society of Colon and Rectal Surgeons developed evidence-based practice parameters for the management of anal fissures.[3] Nonoperative treatments were recommended as the first step in therapy for anal fissures (1B, strong recommendation, moderate-quality evidence). Topical nitrates (1A, strong recommendation, high-quality evidence) and botulinum injections (1C, strong recommendation, low-quality evidence) were listed as effective nonoperative treatments.

The practice parameters stated that the effectiveness of topical CCBs compared with placebo had not been established, but CCBs did have fewer adverse effects than

nitroglycerin (1B). Surgery was noted to be consistently superior to medical therapy. Lateral internal sphincterotomy (either open or closed) was the surgical treatment of choice for refractory anal fissures (1A).[3]

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What are the risks of surgical adverse outcomes in newborn boys undergoing circumcision?

EVIDENCE-BASED ANSWER

The overall rate of complications with newborn circumcision is low, ranging between 0% and 3%, although the rate of complications is as high as 16% in some settings around the world. Serious complications, including partial amputation of the glans and urethral laceration, occur in 0% to 2% of circumcisions (SOR: **C**, systematic review of case series and single case series). Meatal stenosis can be a late complication and is associated with 2.7% of circumcisions (SOR: **C**, case-control study).

A 2010 systematic review (16 prospective case series, N=26,645) evaluated complications of circumcision performed in newborn and infant boys up to 13 months of age.[1] Studies were completed in 12 countries and involved Gomco®, Plastibell®, freehand, sleeve, and ritual techniques performed by doctors, nurses, midwives, and traditional providers. The Plastibell was used most frequently.

The median frequency of any adverse event—including severe adverse events (partial amputation of glans, urethral lacerations) and minor events (bleeding, infection, meatal stenosis)—was 1.5% (but ranged from 0% to 16% across studies). The median rate of severe adverse events was 0% (ranging from 0% to 2%). Studies from Canada in 1961–1962 using Plastibell and Gomco clamps and Nigeria using Plastibell or freehand techniques reported the highest complication rates. Of note, the severe events were reported only in circumcisions that were nonshielded. In contrast, a study from Israel done freehand by Mohels revealed just 0.1% complications. Studies with no complications came from Oman, Nigeria, and the United States with the procedure performed by physicians.[1]

A 1976 case series conducted at the University of Washington reviewed a 10-year history of 5,521 newborn male circumcisions.[2] Plastibell (52%) and Gomco (48%) circumcisions were performed by medical students or residents under supervision or by attending physicians.

A total of 174 (3.2%) complications occurred. Adverse events included hemorrhage, infection, injury to glans, excess skin removal, dehiscence, circumcision of hypospadias, cyanosis, and edema of the glans requiring early removal of the Plastibell. No significant difference was noted in adverse events among the circumcision techniques.[2]

A 2006 case-control study evaluated the incidence of meatal stenosis in boys aged 2 to 18 years who required genital examination for sports physicals, well-child checks, or sick visits in a rural primary care practice (N=1,100).[3] Patients were diagnosed with meatal stenosis if they had dysuria, voiding complaints, stream abnormalities, or abdominal discomfort and a meatal opening of less than 2 mm.

Evidence of circumcision was assessed by visual inspection; 1,009 of the boys in the study were circumcised, and 28 (2.7%) were diagnosed with meatal stenosis compared with no cases of meatal stenosis in the 91 uncircumcised boys. The study did not have sufficient power to demonstrate a difference in development of meatal stenosis between circumcised and uncircumcised boys. Nearly all cases of meatal stenosis required surgical correction.[3]

A 2005 prospective case series that was included in the 2010 systematic review above compared neonatal male circumcisions performed by medical versus nonmedical providers.[4] The study was conducted in Israel where virtually all newborn boys are circumcised, usually by a nonmedical provider (a Mohel) using a knife, with or without a clamp.

In the 19,478 boys born at 4 tertiary care hospitals over 1 year, 66 (0.34%) circumcision complications were documented: 16 bleeding; 2 infection; 1 partial amputation of glans; 38 excess skin removal; 5 penile torsion; and 4

shortage of skin, phimosis, or inclusion cysts. Mohels had performed 83% of the circumcisions with complications and physicians had performed 11%, but the total percentage of circumcisions performed by Mohels and physicians was not reported.[4]

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Are in-office breathing exercises effective for adults presenting to primary care with anxiety or panic disorders?

EVIDENCE-BASED ANSWER

Perhaps. Breathing exercises assisted by capnography have similar efficacy for anxiety and panic symptoms as cognitive restructuring techniques and, as a standalone treatment, are generally associated with better symptom relief than control interventions (SOR: **C**, single small RCT and systematic review of small observational studies). Furthermore, breathing exercises, as a component of cognitive behavioral therapy (CBT) and medication management by trained clinicians, improve anxiety symptoms more than usual care (SOR: **B**, RCT).

A 2010 RCT compared respiratory training with cognitive restructuring techniques in 41 adults with diagnoses of agoraphobia and panic disorder.[1] Treatment consisted of 5 weekly skill training sessions of 1-hour duration and twice-daily home sessions of 17-minute duration for capnometry-assisted respiratory training (CART) or cognitive restructuring techniques focused on panic. Outcome measures were the combined Body Sensations Questionnaire and Anxiety Sensitivity Index (BSQ/ASI), the Anxiety Control Questionnaire (ACQ), and the Panic Disorder Severity Scale (PDSS).

Both CART and cognitive restructuring led to moderate reductions in anxiety symptoms on the BSQ/ASI (standardized mean difference [SMD] 0.74 and 0.75, respectively) and the ACQ (SMDs 0.66 and 0.61, respectively) and large reductions in panic symptoms on the PDSS (SMDs 2.7 and 2.3, respectively; $P<.05$ for all comparisons to baseline). However, the differences between groups were not significant. Limitations were methodological in nature, as different time lags occurred between intervention and measurement.[1]

A 2003 systematic review examined the efficacy of breathing training among adults being treated for panic disorder in 9 small studies (5 cohort studies, 3 case series, and 1 case report; N=175) with marked heterogeneity.[2] The breathing training occurred between 1 and 5 sessions over 2 to 4 weeks.

According to the review authors, breathing training alone showed promise as a brief standalone treatment for panic attacks, as evidenced by improved physiological and psychological outcome measures. However, not all studies reached the same conclusion: 2 of the 9 showed no effect, and 1 showed questionable effect. Noted limitations were that reviewed studies did not assess a consistent breathing technique, outcome measures were not psychometrically sound, treatment settings were not delineated, and numerical results and statistical analysis were not reported.[2]

A 2010 RCT examined the effectiveness of the Coordinated Anxiety Learning and Management (CALM) program compared with usual care for the management of anxiety within a primary care setting.[3] The sample consisted of 1,004 adults with anxiety (67% with comorbid major depression), aged 18 to 75 years, who were followed longitudinally for 18 months.

CALM consists of CBT or medication, or both, supervised by specially trained clinicians (nurses, psychologists, or social workers). CBT, including breathing training, was conducted over 6 to 8 weekly sessions by the trained clinicians. Usual care was defined as medication and physician counseling. Anxiety was measured with the 12-item Brief Symptom Inventory (BSI-12) with scores ranging from 0 (no symptoms) to 12 (severe symptoms).[3]

Patients who received the CALM intervention had greater reductions in symptoms reported on the BSI-12 (responders ≥50% reduction from pretreatment BSI-12 score; remitters

with total BSI-12 score <6) than the usual-care group at 6 months (mean difference [MD] 2.5 points; 95% CI, 1.4–3.6), 12 months (MD 2.6 points; 95% CI, 1.5–3.7), and 18 months (MD 1.6 points; 95% CI, 0.53–2.7). The number needed to treat with CALM versus usual care for 12 months for 1 more response (≥50% reduction from pretreatment BSI-12) was 5 and for 1 more remission (total BSI-12 score <6) was 6.[3]

Limitations of this study were primarily methodological in nature, as outcomes could not be isolated to a single component of CALM, and outcome measures relied heavily on subjective information.[3]

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Does checking lactic acid have any benefit in conditions other than sepsis?

EVIDENCE-BASED ANSWER

A lactic acid level of 2.5 mmol/L or higher is associated with increased mortality in geriatric patients with trauma (SOR: **C**, retrospective case series). Higher lactic acid levels in patients with out-of-hospital cardiac arrest, in an intensive care unit (ICU), or with acute heart failure are associated with lower survival (SOR: **C**, prospective and retrospective case series).

In a 2013 retrospective case series, 1,987 trauma patients 65 years old and older admitted to an urban level 1 trauma center from 2009 to 2011 had serum lactate levels checked on admission to evaluate whether venous lactate levels predicted mortality better than traditional vital signs (systolic blood pressure and heart rate).[1]

Occult hypoperfusion (defined as lactate ≥2.5 mmol/L with or without abnormal traditional vital signs) was associated with a higher risk in mortality versus abnormal traditional vital signs alone (odds ratio [OR] 2.6; 95% CI, 1.5–4.6). Compared with normal vital signs, abnormal vital signs without occult hypoperfusion (OR 1.7; 95% CI, 0.7–3.9) did not predict mortality.[1]

A 2014 prospective case series study measured the lactate change at 0, 12, and 24 hours in adult patients with out-of-hospital cardiac arrest (N=100; median age 63 years).[2] Patients surviving at 0, 12, and 24 hours had statistically significant lower median lactate levels than nonsurvivors (0 hour: 4.1 vs 7.3 mmol/L; 12 hours: 2.2 vs 6 mmol/L; 24 hours: 1.6 vs 4.4 mmol/L). Patients with good neurologic outcome, defined as a modified Rankin scale of 0 to 3, also had statistically significant lower median lactate levels than patients with poor functional outcome as described by a Rankin scale of 4 to 6 (0 hours: 3.9 vs 7 mmol/L; 12 hours: 2.2 vs 5.1 mmol/L; 24 hours: 1.5 vs 3.9 mmol/L).

A 2014 retrospective case series of 754 patients with acute decompensated heart failure admitted to the ICU correlated lactate levels taken on admission with in-hospital mortality.[3] Eighty-eight patients (12%) in the study group died during hospitalization.

As an independent predictor of in-hospital death, patients with a lactate level more than 3.2 mmol/L had a greater risk of death than patients with a lactate level of less than 3.2 (OR 2.1; 95% CI, 1.1–4.2). Patients who survived with elevated lactate levels had a longer admission than patients without elevated lactate (median 25 vs 18 days; $P<.0001$).[3]

A 2011 retrospective case series of 5,041 patients admitted to the ICU for any diagnosis compared the lactate levels in survivors versus nonsurvivors in the first 24 hours of admission.[4] Patients had a minimum of 2 lactate levels collected over the first 24 hours. Multiple lactate analyses were done, including studying static lactate levels (minimum and maximum lactate) and dynamic levels (change in lactate, time-weighted lactate).

The dynamic lactate level changes versus simple static lactic level best predicted hospital mortality. A 1-unit increase in time weighted lactate based on a formula calculation

increased the risk of hospital death (OR 1.37; 95% CI, 1.3–1.5) as did a 1-unit increase in change in lactate (OR 1.15; 95% CI, 1.1–1.2).[4]

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In women desiring postpartum contraception with an IUD, does immediate IUD insertion after delivery increase continued IUD use at 6 months compared with delayed IUD insertion?

EVIDENCE-BASED ANSWER

Immediate IUD insertion after delivery probably increases the rate of continued use at 6 months postpartum compared with delayed insertion 6 to 8 weeks after delivery. While the risk of IUD expulsion is higher with immediate insertion, the risk of failure to follow-up for delayed IUD placement at 6 to 8 weeks postpartum leads to a higher overall rate of IUD use at 6 months with immediate insertion (SOR: **A**, meta-analysis of RCTs).

A 2015 systematic review of 15 trials included a meta-analysis of 4 RCTs (N=243) examining IUD continuation at 6 months postpartum with immediate insertion within 10 minutes of placenta delivery compared with delayed (standard) insertion at 6 to 8 weeks postpartum.[1] Women aged 18 years and older delivering both by vaginal and Cesarean section desiring a copper or levonorgestrel IUD for postpartum contraception were included. Exclusion criteria were allergy to the IUD, contraindication for IUD placement, gestational age less than 34 weeks, prolonged rupture of membranes, intrapartum chorioamnionitis, postpartum hemorrhage, or surgical complication preventing IUD placement within 10 minutes of placental removal. The control group received their IUD at 6 to 8 weeks if they still desired the IUD, were not pregnant, and had no contraindications.

Compared with the delayed insertion group, the immediate insertion group had a borderline significantly increased rate of use at 6 months, with a Mantel-Haenszel odds ratio of 2.0 (95% CI, 1.0–4.1). The I^2 test showed low degrees of heterogeneity. Risk of bias in these 4 studies was low.[1]

A 2015 nonblinded RCT (N=112) randomized women undergoing Cesarean delivery to IUD placement through the hysterotomy within 10 minutes after placental delivery compared with delayed insertion at 6 weeks postpartum.[2] English- and Spanish-speaking women 18 to 45 years of age desiring a copper or levonorgestrel IUD delivering by scheduled and unplanned Cesarean section at more than 24 weeks' gestation were included. Exclusion criteria were allergy to the IUD, contraindication for IUD placement, gestational age less than 24 weeks, intrapartum chorioamnionitis or fever, or prolonged rupture of membranes of more than 24 hours.

At the 6-month follow-up, women in the intra-Cesarean IUD insertion group had higher, but marginally statistically significant, continued use when compared with the delayed insertion group (relative risk 1.3; 95% CI, 1.0–1.7). Statistical analysis controlled for age, parity, race, educational status, marital status, monthly income, prior IUD use, indication for Cesarean delivery, and cervical dilation at time of delivery. The authors noted that a higher proportion of women randomized to the delayed insertion group did not attend their 6-week postpartum visit or receive their IUD.[2]

Guidelines from the American College of Obstetricians and Gynecologists in 2011 recommended immediate postpartum insertion of IUDs within 10 minutes of placental separation, as women may be highly motivated to use contraception at this time.[3] Expulsion rates for immediate postpartum IUD insertions were cited as 10% to 27% in various studies.

Copper IUDs were considered Category 1 (no restriction) in the United States Medical Eligibility Criteria for contraception, and levonorgestrel IUDs were considered Category 2

(benefits of insertion may outweigh the risks), with exclusion criteria including chorioamnionitis, endometritis, or puerperal sepsis.[3]

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Are neonatal mortality rates increased in stand-alone birthing center births compared with hospital births?

EVIDENCE-BASED ANSWER

Neonatal mortality rates do not differ when low-risk patients deliver in an alternative birthing setting within a hospital or in a stand-alone birthing center compared with a hospital-based obstetric unit (SOR: **B**, meta-analysis of RCT and quasi-RCTs and 2 cohort studies). However, when home births are grouped with stand-alone birthing centers there is an associated increase of 1.5 perinatal deaths per 1,000 deliveries (SOR: **B**, cohort study).

A 2010 meta-analysis of 9 randomized or quasi-randomized controlled trials of variable quality with 10,684 low-risk obstetric patients (single/multiple gestation not specified) compared alternative institutional birth environments with conventional maternity ward care.[1] Alternative environments were defined as home-like bedrooms within hospital labor wards or home-like birthing units adjacent to labor wards. No trials of stand-alone birth centers were found. Eight of the 9 trials used adequate methods of sequence generation, concealment was adequate in 6 trials, and selective reporting was problematic in 3 trials.

No difference was found in neonatal mortality in alternative birthing settings compared with conventional maternity wards (7 trials, n=10,095; relative risk [RR] 1.7; 95% CI, 0.93–3.0). However, many women (number unreported) were transferred to standard care either before or during labor because they no longer met eligibility criteria for the alternative setting. Reasons for transfer included failure to progress in labor, fetal distress, and desire for pharmacologic anesthesia.[1]

A 2011 prospective cohort study of 64,538 women who gave birth between April 2008 and April 2010 compared perinatal mortality or intrapartum neonatal morbidity in low-risk, singleton, term gestations with planned delivery at a hospital, a midwife-attended birthing center, or a home birth.[2]

Compared with a hospital-based obstetric unit, no significant difference was noted in composite outcome of neonatal morbidity and perinatal mortality in a midwife center not located on a hospital site (odds ratio [OR] 0.92; 95% CI, 0.58–1.5) or a midwife-led unit on a hospital site (OR 0.92; 95% CI, 0.60–1.4). In subgroup analysis, no difference was noted in neonatal morbidity/mortality in either nulliparous women or multiparous women delivering in birthing centers compared with hospital-based obstetric units.[2]

A 2015 population-based, retrospective cohort study of all the births in the state of Oregon from 2012 to 2013 analyzed perinatal mortality according to the planned birth setting (out of hospital vs hospital).[3] Planned out-of-hospital settings included births at home or at a stand-alone birthing center.

A higher rate of perinatal death was associated with planned out-of-hospital birth than with planned in-hospital birth (3.9 vs 1.8 deaths per 1,000 deliveries; OR 2.4; 95% CI, 1.4–4.3). After adjustment for maternal race/ethnicity, age, parity, and medical conditions associated with greater risk, the risk difference was 1.5 deaths per 1,000 deliveries (95% CI, 0.51–2.5).[3]

A 2010 retrospective cohort study from 2001 to 2005 examined perinatal mortality (including stillbirths and neonatal deaths of live-born babies up to 28 days) in 822,955 women in 4 jurisdictions of Australia who gave birth during that period.[4] Of all the patients, 2.7% (n=22,222) intended to give birth in a stand-alone birth center at the onset of labor.

Perinatal mortality for women intending to give birth in a birth center was 1.3 per 1,000 births (99% CI, 0.66–2.0)

compared with 1.7 per 1,000 births (99% CI, 1.5–1.8) for women intending to give birth in a hospital, a difference that was not statistically significant (OR 0.79; 99% CI, 0.48–1.3).[4]

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Are N-methyl-D-aspartate receptor antagonists or acetylcholinesterase inhibitors more effective in slowing cognitive decline in Parkinson's disease dementia?

EVIDENCE-BASED ANSWER

Currently, no head-to-head trials have compared the efficacy of acetylcholinesterase inhibitors with N-methyl-D-aspartate receptor antagonists for Parkinson's disease dementia. Acetylcholinesterase inhibitors minimally slow cognitive decline and improve language and memory function, although these changes may not be clinically significant (SOR: **B**, meta-analysis of RCTs and an RCT). N-methyl-D-aspartate receptor antagonists do not slow cognitive decline (SOR: **B**, RCT).

A 2015 meta-analysis of 4 double-blind RCTs lasting 10 to 24 weeks compared the effects of acetylcholinesterase inhibitors with placebo in patients (N=941; average age range 68–74 years) with Parkinson's disease dementia, by evaluating changes in the Mini-Mental Status Examination (MMSE, range 0–30, with higher scores indicating less cognitive impairment).[1] Secondary outcomes included (1) language and memory functions, as measured by Alzheimer Disease Assessment Scale-Cognitive Subscale (maximum 70 points, higher scores indicate worsened severity); and (2) global assessment, as measured by Alzheimer Disease Cooperative Study Clinician's Global Impression of Change (maximum 7 points, higher scores indicate worsened severity) or the Clinician's Interview-Based Impression of Change Plus Caregiver Input (maximum 7 points, higher scores indicate worsened severity). Studies used donepezil 10 mg/d or rivastigmine 12 mg/d. The average baseline MMSE ranged from 19 to 28 (reflecting mild impairment to normal cognition).

Acetylcholinesterase inhibitors compared with placebo significantly slowed decline in MMSE (4 studies, n=941; mean difference [MD] –1.1; 95% CI, –1.6 to –0.61) and improved language and memory functions (3 studies, n=918; standardized mean difference [SMD] –0.27; 95% CI, –0.4 to –0.13) and global assessment (4 studies, n=941; SMD –0.29; 95% CI, –0.42 to –0.15). Although these differences were statistically significant, they may not represent clinically meaningful improvement. Additionally, this study was conducted over 10 to 24 weeks, a timeframe that is not representative of disease progression for Parkinson's disease dementia.[1]

A 2009 double-blind RCT analyzed with intention to treat (N=25) compared 20 mg/d memantine (an N-methyl-D-aspartate receptor antagonist) versus placebo in patients with Parkinson's disease dementia.[2] Patients taking acetylcholinesterase inhibitors were not excluded. The average age in the memantine group was 78 years versus 75 years in the placebo group. Men comprised 36% of the patients in the memantine group versus 64% in the placebo group. Dementia Rating Scale (maximum score 144, lower scores indicate worsened severity), MMSE, and Clinician's Interview-Based Impression of Change Plus Caregiver Input scores were assessed at baseline, after 16 weeks of treatment, and 22 weeks (6 weeks after discontinuation of drug). Baseline MMSE and Dementia Rating Scale scores were 19 and 94, respectively, in the memantine group versus 19 and 88 in the placebo group.

No significant change was noted in Dementia Rating Scale scores (MD 0.1; 95% CI, –19 to 20), MMSE (MD –1.5; 95% CI, –4.9 to 1.3), or Clinician's Interview-Based Impression of Change Plus Caregiver Input (MD 17%; *P*=.07) at the end of the treatment period. However, deterioration was noted 6 weeks after discontinuation of therapy in the memantine group compared with placebo, although this difference may

not be clinically meaningful (mean Clinician's Interview-Based Impression of Change Plus Caregiver Input score 5.4 vs 4.4, *P*=.004). The study was funded by industry.[2]

A 2004 double-blind RCT (N=16) compared donepezil with placebo in patients with Parkinson's disease dementia.[3] Participants were titrated from a starting dose of donepezil 2.5 mg/d up to 10 mg/d as tolerated. The mean tolerated dose of donepezil was 6.4 mg/d. The average age in the donepezil group was 66 years versus 71 years in the placebo group. Patients were assessed for global cognition using the MMSE and Dementia Rating Scale, and for memory using the Dementia Rating Scale-Memory subscore (maximum score 25, lower scores indicate worsened severity). Baseline MMSE and Dementia Rating Scale scores were 26 and 128, respectively, in the donepezil group versus 25 and 132 in the placebo group. Participants were evaluated 5 times at 6-week intervals during the study period.

No significant difference was noted in MMSE scores between the groups at the final visit (MD –1.1; 95% CI, –2.9 to 0.70), nor was a significant difference noted in total Dementia Rating Scale scores (MD –0.68; 95% CI, –7.6 to 6.3). A statistically significant improvement was noted in Dementia Rating Scale-Memory subscores in the donepezil group compared with placebo, although this change in scores may not be clinically meaningful (MD 3.3; 95% CI, 0.35–6.3).[3]

Limitations of this RCT included its small sample size and that the mean tolerated dose of donepezil was 6.4 mg, which is lower than the recommended therapeutic dose.[3]

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We invite your questions and feedback.
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Do Southeast Asian immigrants have a higher incidence of cervical cancer than the general population of Western countries?

EVIDENCE-BASED ANSWER

The incidence rates of cervical cancer in Southeast Asian immigrants in the United States are higher than that of non-Hispanic whites in the United States, but they appear to be decreasing. Among Southeast Asian immigrants in the United States, the incidence rates are highest in the Laotian population, followed by Vietnamese and Filipina populations (SOR: **C**, 2 cross-sectional studies).

A 2010 cross-sectional study compared the incidence of cervical cancer among 6 Asian groups residing in the United States with the incidence in Hispanics, non-Hispanic whites, and non-Hispanic blacks, between 1996 and 2004 (number of patients not provided).[1] The study used 5 registries within the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, which is considered to be a well-maintained, reliable data source. Two of the Asian groups included were Southeast Asian, namely Vietnamese and Filipino groups. Only primary invasive cases were included. Incidence rates were expressed per 100,000 woman-years.

Total cervical cancer incidence rates were highest among Vietnamese women—19 per 100,000 woman-years (95% CI, 16–22), followed by Hispanic at 17 per 100,000 woman-years (95% CI, 16–17), Filipino at 10 per 100,000 woman-years (95% CI, 9.1–11), black at 9.9 per 100,000 woman-years (95% CI, 9.2–11), and non-Hispanic white at 7.1 per 100,000 woman-years (95% CI, 6.9–7.3). Among Vietnamese immigrants in the United States, their cervical cancer incidence is similar to that of women living in Vietnam. Filipina women in the United States have lower cervical cancer incidence rates than women remaining in the Philippines.[1]

A 2013 cross-sectional study evaluated a large variety of cancer incidence trends among 8 Asian American populations in the United States between 1990 and 2008, 3 of which were Southeast Asian (Vietnamese, Filipino, and Laotian).[2] The data were compared with rates for non-Hispanic whites and obtained from 13 SEER registries. Incidence rates were calculated as cases per 100,000 patients, age-adjusted to the 2000 US standard population, and expressed as 5-year

average annual rates for the following time periods: 1990–1994, 1998–2002, and 2004–2008.

For cervical cancer incidence rates, the Laotian population had the highest rate of 49 (95% CI, 35–67) in 1990 to 1994, which then decreased to 23 (95% CI, 15–34) in 1998 to 2002, and 17 (95% CI, 10–26) in 2004 to 2008. The Vietnamese population followed closely with a rate of 39 (95% CI, 33–45) in 1990 to 1994 and 17 (95% CI, 14–19) in 1998 to 2002.[2]

Cervical cancer incidence rates for 2004 to 2008 for Vietnamese, and all time periods for Filipina and non-Hispanic whites were not included in the report because cervical cancer was not among the top 5 cancers for these populations during these time periods.[2]

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Is acetaminophen safe to use in patients with cirrhosis?

EVIDENCE-BASED ANSWER

Maybe. Acetaminophen use of 2 to 3 g/d for an average of 2 to 3 days or 1 g/d for 25 days in cirrhotic patients is not associated with an increased risk of hospitalization for acute liver decompensation (SOR: **C**, 2 case-control trials).

A 2010 prospective case-control study assessed the correlation between nonexcessive use of over-the-counter (OTC) analgesics and hospitalization for liver-associated events in patients with cirrhosis.[1] Analgesics included acetaminophen up to 4,000 g/d, aspirin up to 4,000 mg/d, and ibuprofen up to 1,200 mg/d.

Patients with cirrhosis (n=90) as diagnosed by clinical, biochemical, ultrasound, and/or histologic criteria, admitted with liver-associated events (hepatic encephalopathy, ascites, or variceal hemorrhage) were compared with nonhospitalized control patients with cirrhosis (n=126). The average age of all patients was 56 years, 67% of cirrhotics were male, and more than 80% were Caucasian. The etiology of cirrhosis was most commonly viral, alcoholic, or cryptogenic.[1]

In the 30 days before study enrollment, 19% of hospitalized patients had used acetaminophen compared with 26% of nonhospitalized controls, with an average acetaminophen daily dose of 2 g for an average of 3 days. Acetaminophen use in the past 30 days was not associated with hospitalization for liver-associated events (odds ratio [OR] 0.68; 95% CI, 0.35–1.3).[1]

A 2009 case-control study (N=333) evaluated whether the use of OTC analgesics in the past 30 days was associated with acute liver decompensation in 91 patients with cirrhosis hospitalized with acute liver decompensation compared with 153 nonhospitalized patients with cirrhosis and 89 hospitalized patients without cirrhosis.[2]

Groups were 54% to 67% male with an average age of 53 to 59 years, and had acetaminophen usage that did not exceed a maximum dose of 3 g/d for up to 2 days or a daily dose of 1 g/d for up to 25 days. Acute decompensation was defined as hospitalization due to anasarca, refractory ascites, spontaneous bacterial peritonitis, hepatic hydrothorax, fever/bacteremia without a clear source, jaundice, portal hypertensive bleeding, renal insufficiency, dehydration, electrolyte abnormalities, or portosystemic encephalopathy. Cirrhosis was diagnosed by either an imaging study documenting cirrhosis, a clinical event consistent with cirrhosis (portal hypertension bleed, spontaneous bacterial peritonitis, etc), or physical examination findings consistent with cirrhosis.[2]

More hospitalized controls without cirrhosis self-reported acetaminophen use in the past 30 days than nonhospitalized controls with cirrhosis and hospitalized patients with cirrhosis and acute liver decompensation (42%, 25%, and 19%, respectively; *P*=.001 for each comparison).[2]

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Are antivirals effective in treating Bell's palsy?

EVIDENCE-BASED ANSWER

Antivirals alone are no better than placebo for the treatment of Bell's palsy. Antivirals in addition to corticosteroids result in a modest improvement in full recovery rates compared with corticosteroids alone (SOR: **B**, meta-analysis of lower quality RCTs). Clinical practice guidelines recommend offering antivirals only in conjunction with oral steroids to appropriate patients with Bell's palsy (SOR: **C**, clinical guidelines).

A 2015 meta-analysis including 10 RCTs (N=2,280) compared treatment outcomes in patients with Bell's palsy given oral antivirals with and without corticosteroids versus control therapies.[1] Intervention groups were given antivirals and all participants were followed for 3 to 12 months to determine full recovery of facial muscle function based on a House-Brackmann Scale score measuring residual asymmetric facial muscle function.

Antivirals alone produced no significant benefit compared with placebo (see **TABLE**). A significant benefit was found with the addition of antivirals to corticosteroids compared with corticosteroids alone; however, the quality of evidence was low because of high heterogeneity, risk of bias, and wide confidence intervals that included the possibility of minimal effect. Corticosteroids alone were more effective then antivirals alone, and corticosteroids plus antivirals were more effective than placebo. Due to variation in study design, the optimal dose and timing of antiviral and corticosteroid medication administration was not made clear.[1]

A 2012 clinical guideline by the American Academy of Neurology stated that antiviral agents (in combination with steroids) may be offered to patients with Bell's palsy.[2] The guideline stated that this regimen would minimally increase the possibility of recovery (risk difference < 7%) (Class IV, level of evidence C: based on data with a high risk of bias).

Additionally, the 2013 clinical guideline from the American Academy of Otolaryngology recommended against the use of oral antiviral therapy alone for patients with new-onset Bell's palsy (strong recommendation, Grade A, high confidence in evidence).[3] The guideline stated that antiviral therapy may be offered in conjunction with oral steroids, based on clinical context (Grade B, medium confidence in evidence).

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TABLE

Risk of incomplete recovery[a] in a systematic review of antiviral treatment for Bell's palsy[1]

Intervention	Comparator	No. of trials	No. of patients	Relative risk (95% CI)	Quality
Antiviral alone[b]	Placebo	2	658	1.1 (0.87–1.4)	Low
Antiviral plus corticosteroid[c]	Corticosteroid alone	8	1,315	0.61 (0.39–0.97)	Low
Antiviral	Corticosteroids	3	768	2.8 (1.1–7.3)	Low
Antiviral plus corticosteroid	Placebo	2	658	0.56 (0.41–0.76)	Low

[a]Incomplete recovery was defined as findings consistent with or worse than "obvious but not disfiguring difference between sides, with noticeable but not severe synkinesis (undesired facial movements after nerve regeneration)."

[b]Antivirals included oral acyclovir 2–4 g/d, valacyclovir 1–3 g/d, or famciclovir 750 mg/d, for 5–10 days.

[c]Corticosteroid included prednisone 1 mg/kg per day, prednisolone 60–64 mg/d, or prednisolone 1 mg/kg per day, for 5–21 days inclusive of taper.

CI=confidence interval.

Do continuous glucose monitors result in better A1C control than conventional glucose monitoring in patients with type 2 diabetes?

EVIDENCE-BASED ANSWER

In patients with type 2 diabetes using insulin, continuous glucose monitoring is associated with glycosylated hemoglobin (HbA1C) reductions of 0.7% over self-monitoring (SOR: **C**, meta-analysis with disease-oriented outcomes). In a more diverse population of patients using a variety of management methods for their type 2 diabetes (diet, oral agents, basal insulin), continuous glucose monitoring lowers the HbA1C by 1.3% and self-monitoring blood glucose lowers the HbA1C by 0.5% (SOR: **C**, single RCT with disease-oriented outcome).

A 2011 systematic review of 19 RCTs examined glycemic control in 1,801 adults and children with diabetes who used continuous glucose monitoring or intermittent self-monitoring of blood glucose in the outpatient setting.[1] Three of the RCTs (n=128) looked exclusively at glycemic control in adults (45%–70% male, mean ages 56–57) with type 2 diabetes taking insulin who had an HbA1C of more than 8.5%. Both continuous glucose monitoring and intermittent self-monitoring groups carried out their routine diet and exercise. Glucose monitoring was not standardized and patients were allowed to check their blood sugars as directed by their physician. The continuous glucose monitoring groups showed variability in the frequency of its use during the full 12-week study period. About 12% of the continuous glucose monitoring group patients were lost to follow-up.

The continuous glucose monitoring group had a greater reduction in HbA1C over 12 weeks than the intermittent self-monitoring group (3 trials, n=128; weighted mean difference –0.70%; 95% CI –1.1 to –0.27). Weaknesses of the meta-analysis included a small number of participants, the high loss to follow-up, and the use of different continuous glucose monitors.[1]

A 2012 RCT examined the effect of continuous glucose monitoring versus intermittent self-monitoring of blood glucose to improve glycemic control in adults with type 2 diabetes.[2] One hundred patients were recruited from the military Walter Reed Health Care System and were followed prospectively for 52 weeks. Patients were older than 18 years, had type 2 diabetes longer than 3 months, had an initial HbA1C from 7% to 12%, and were not using prandial insulin, but could be managing blood sugars with diet and exercise, oral medications alone, oral medication plus exenatide, and basal insulin alone or in combination with oral agents. Study participants were on average 55 to 60 years old, 44% to 66% male, with a body mass index of 32.

One group used continuous glucose monitoring for 4 cycles of 2 weeks on followed by 1 week off over 12 weeks, then weeks 13 to 52 they continued with routine self-monitoring of blood glucose. The self-monitoring group checked blood glucoses 4 times daily for the entire study. Both groups continued routine management of their diabetes with their primary care providers and had HbA1C measured at 12, 24, 38, and 52 weeks. Both groups attended the same American Diabetes Association self-management education program. The study retrospectively analyzed both groups based on compliance with recommended glucose monitoring protocols.[2]

Within the continuous glucose monitoring group, patients who successfully wore their device more than 48 days had the most reduction of HbA1C, by 1.3% from a baseline mean of 8.4% (P<.0001). The continuous glucose monitoring group individuals who wore their device fewer than 48 days reduced their HbA1C by 0.76% from their baseline of 8.2% (P=.008). The self-monitoring of blood glucose group reduced their mean HbA1C by 0.5% from a baseline of 8.2% (P=.002).[2]

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Does the use of finasteride lead to sexual dysfunction?

EVIDENCE-BASED ANSWER

Patients treated with finasteride are up to twice as likely to experience ejaculation disorder, decreased libido, and impotence than patients not taking finasteride (SOR: **A**, meta-analysis of RCTs). The incidence of sexual dysfunction is greatest during the first year of treatment; and almost a quarter of patients will experience 1 or more sexual adverse effects during 4 years of treatment (SOR: **B**, RCT).

A 2010 meta-analysis of 12 RCT (N=13,194) evaluated the risk of ejaculation disorders, decreased libido, and impotence with taking finasteride (5 mg daily) versus placebo.[1] Men with benign prostatic hyperplasia (BPH) based on urinary symptoms or symptom-based scoring were included, whereas men presenting with or treated for hematuria were excluded.

Compared with men taking placebo, men (age range 40–94 years, mean 65 years) using finasteride for up to a year experienced greater risk of decreased libido (5 RCTs, n=3,782; risk ratio [RR] 2.1; 95% CI, 1.4–3.2), ejaculatory disorders (5 RCTs, n=4,700; RR 2.9; 95% CI, 1.8–4.7), and impotence (6 RCTs, n=4,278; RR 2.0; 95% CI, 1.4–3). An additional 2 RCTs (n=6,208), which followed men past a year (average study length 3 years), found that men continuing to take finasteride reported more ejaculatory disorder than men taking placebo (RR 3.3; 95% CI, 1.7–6.4). Men who remained on finasteride past a year (average study length 1.6 years) also continued to experience more impotence compared with men taking placebo (3 RCTs, n=4,396; RR 1.8; 95% CI, 1.3–2.7).[1]

A 2003 RCT, not included in the meta-analyses above (because it was a subsidiary study of 1 of the previous RCTs), randomized men (N=3,040, age range 45–78 years) with symptomatic BPH and no evidence of prostate cancer to receive placebo or finasteride 5 mg daily for 4 years.[2]

During the first year of treatment, 15% of the finasteride-treated patients and 7% of the placebo-treated patients reported sexual adverse events including decreased libido, ejaculatory disorder, and decreased ejaculate volume (P<.001). During the following 3 years of the study, the cumulative incidence of sexual adverse events was 7% for both treatment groups and no difference was noted in the incidence of new sexual adverse events between groups. The drug-related sexual adverse events were similar for men with or without a history of sexual dysfunction. Of the men who had sexual adverse events, 12% of the finasteride group and 19% of the placebo group had resolution of the adverse events. During the 4-year study, 22% of the finasteride group and 14% of the placebo group reported at least 1 drug-related sexual adverse event (P<.0001).[2]

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Are subacromial NSAID injections as effective as subacromial corticosteroid injections for treatment of rotator cuff impingement syndrome?

EVIDENCE-BASED ANSWER

Maybe. In patients with rotator cuff impingement syndrome, a ketorolac injection appears to be superior to a corticosteroid injection for improvement in pain and function (SOR: **C**, small RCT). A single steroid injection appears to be superior to a single tenoxicam injection, but a series of 3 tenoxicam injections may outperform a single corticosteroid injection (SOR: **C**, small RCTs).

A 2013 double-blind RCT of 32 patients, aged 21 to 58 years, with a clinical diagnosis of shoulder impingement syndrome, examined the effect of 1 subacromial injection of ketorolac 60 mg compared with 1 subacromial injection of

triamcinolone 40 mg.[1] Outcomes measured were pain and function on the UCLA shoulder scale (range 2–35, with 35 best), visual analog pain scale (VAS, 0–10, with 0=no pain), and range of motion in abduction and forward flexion.

At 4-week follow-up, the NSAID group compared with the steroid group had a greater mean improvement on the UCLA scale (7.1 vs 2.1; *P*=.028) and a greater improvement in active abduction versus the steroid group (+22 vs –3 degrees; *P*=.030). No difference was noted in the VAS. One patient in the steroid group had an episode of fainting that resolved in 5 minutes, but no other complications were noted. Study limitations were small sample size and a short follow-up.[1]

A 2010 double-blind RCT with 58 patients, aged 36 to 88 years, with a clinical diagnosis of subacromial impingement, studied the effect of 1 subacromial injection of tenoxicam 20 mg (n=31) compared with 1 subacromial injection of methylprednisolone 40 mg (n=27).[2] Outcome measurements were pain and function as measured on the Constant-Murley Shoulder Score (range 0–100, with 100 best), Disabilities of the Arm, Shoulder, Hand Scale (DASH, range 0–100, with 0 best), and the Oxford Shoulder Score (range 12–60, with 12 best).

At 6-week follow-up, the steroid group compared with the NSAID group had a greater median improvement on the Constant-Murley (19.5 vs 6.5; *P*=.003) and a greater median improvement on the DASH scale (13.3 vs 2.9; *P*=.020). No significant difference was noted between groups on the Oxford scale at the 6-week follow-up. No major complications were reported. Study limitations included use of median instead of mean scores and a short follow-up.[2]

A 2015 RCT of 40 adults, aged 29 to 73 years, with rotator cuff tendinitis or subacromial bursitis based on clinical examination and magnetic resonance imaging, examined the effectiveness of treatment with either 3 subacromial injections of tenoxicam given weekly (n=20) or 1 subacromial injection of methylprednisolone (n=20).[3] Outcomes included change in pain measured on a VAS, change in DASH scale, and change in degrees of active range of motion.

At 1-year follow-up, the tenoxicam group had a greater mean improvement in VAS scores (5.2 vs 2.6; *P*=.009) and DASH scores (44.7 vs 38.6; *P*=.014) than the methylprednisolone group. Both groups had substantial mean improvement in degrees of active range of motion (tenoxicam 67° vs steroid 69°; *P*=.695). Although no major complications were reported, 2 patients in the tenoxicam group had temporary hypotension. Study limitations included lack of clarity regarding blinding, lack of a baseline demographics table, and no description of medication dosing.[3]

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What sideline tests help diagnose concussion in athletes?

EVIDENCE-BASED ANSWER

In patients suspected of having a concussion after a nontrivial head injury, the presence of headache alone has a sensitivity of 0.76 to 1.0 and a specificity of 0.83 to 0.94 (positive likelihood ratio [LR+] 4.5–17, negative likelihood ratio [LR–] 0–0.29). The Concussion Symptom Inventory and the symptom score portion of the Sport Concussion Assessment Tool 2 (SCAT2) likely have similar accuracy. The King-Devick test, an oculomotor test, has a sensitivity of 0.75 to 1.0 and a specificity of 0.91 to 1.0 (LR+ 8.3 to "rule in" and LR– 0 to 0.27). A 3.5-point decrease compared with baseline on the full SCAT2 multimodal test is 0.96 sensitive and 0.81 specific (LR+ 5 and LR– 0.05) (SOR: **B**, systematic reviews of low-quality cohort studies).

A 2017 systematic review of 21 prospective and retrospective cohort studies (N=2,902) evaluated the diagnostic accuracy of sideline screening tests, either alone or in combination, to identify suspected sports-related concussion.[1] Inclusion criteria for the review included any published or unpublished studies, excluding case reports, of athletes older than 12 years competing in a sporting activity and sustaining a nontrivial

head impact, with any sideline assessment used to detect concussion. The reference standard for concussion was a clinical diagnosis by a registered medical practitioner. However, the review did not report the cutoff values used to determine positive or negative sideline tests.

The sideline tests included common concussion symptom lists (Concussion Symptom Inventory, Graded Symptom Checklist, SCAT2 symptom checklist), oculomotor testing (King-Devick test), balance testing (Balance Error Scoring System), cognitive tests (Standardized Assessment of Concussion, Maddocks), and multimodal assessments (SCAT2 and various combinations of balance and cognitive tests). A meta-analysis was not performed due to the absence of studies at low risk of bias and significant heterogeneity among studies.[1]

Three studies (n=406) showed that headache had a sensitivity of 0.76 to 1.0, and 1 study (n=56) showed a specificity of 0.83 to 0.94. Additionally, 1 study (n=90) reported the Concussion Symptom Inventory had a sensitivity of 0.84 to 0.99 and a specificity of 0.55 to 0.85, while the SCAT2 symptom score (1 study, n=263) had a sensitivity of 0.57 to 0.95 and a specificity of 0.85 to 1.0. Based on 10 studies (n=1,434) the King-Devick test had a sensitivity ranging from 0.75 to 1.0 and a specificity ranging from 0.91 to 1.0. For the multimodal assessments, the SCAT2 had a sensitivity of 0.78 to 1.0 based on 2 studies (n=290) and a specificity of 0.96 based on 1 study (n=263). Balance testing and cognitive testing demonstrated lower sensitivity but similar specificity. One prospective cohort study (n=49) of professional rugby athletes demonstrated that sideline video review identified only 61% of significant head impacts.[1]

Despite a lack of high-quality evidence, the authors of this systematic review recommended a multimodal assessment tool such as the SCAT2 (SCAT5 is the current version) in the setting of suspected concussion.[1]

A 2016 systematic review evaluated any iteration of the SCAT, the Standardized Assessment of Concussion, or modified Balance Error Scoring System and included the same studies as the systematic review above for diagnosis of concussion.[2] However, this systematic review reported the cutoff values used to determine a positive SCAT test.

One of the prospective cohort studies (n=263) evaluating the SCAT2, reported in the systematic review above, found 0.96 sensitivity and 0.81 specificity in detecting concussion using a 3.5-point decrease from baseline, and a 0.83 sensitivity and 0.93 specificity using a cutoff score of 74.5.[2]

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Do pumpkin seeds or pumpkin supplements reduce symptoms of BPH?

EVIDENCE-BASED ANSWER

Pumpkin seed oil and pumpkin seeds appear to reduce obstructive urinary symptom scores in patients with symptomatic benign prostatic hypertrophy (BPH), while pumpkin seed extract is not better than placebo. Pumpkin seed oil is equivalent to saw palmetto and prazosin in decreasing BPH symptom scores (SOR: **C**, small low-quality RCTs).

A 2009 double-blind RCT (N=47) evaluated the effect of pumpkin seed oil and saw palmetto on BPH symptoms in Korean men with an International Prostate Symptom Score (IPSS) of 8 or higher.[1] Patients were randomized to 320 mg daily of pumpkin seed oil, saw palmetto oil, combined pumpkin seed and saw palmetto oils, or placebo for 2 months. Primary outcomes were changes in the IPSS (range 0–35, higher scores equate with worse symptoms) and IPSS Quality-of-Life subscale (IPSS-QoL, range 0–6, higher scores equate with lower quality of life) measured every 3 months.

After 12 months, IPSS scores decreased significantly from baseline in all the active treatment groups but not in the placebo group: pumpkin seed oil by 58%, saw palmetto oil by 50%, combined pumpkin seed and saw palmetto oils by 75% ($P<.05$ for all active treatments vs baseline), and placebo by 39%. The authors stated that the reduction of IPSS after 12 months were statistically equivalent in active treatment groups, although no statistical analysis was reported. IPSS-QoL scores after 12 months improved significantly compared with baseline in all active treatment groups but

not placebo: 41% for pumpkin seed oil, 39% for saw palmetto oil, 58% for combined pumpkin seed and saw palmetto oils (*P*<.05 for all active treatments vs baseline), and 12.5% for placebo. No statistical analysis was reported for comparison among groups. Study limitations included small sample size with no power calculations reported, unknown generalizability to other populations, and baseline age differences among the groups.[1]

A 2015 partially blinded RCT (N=1,431) evaluated change in BPH symptoms in men between 50 and 80 years of age with BPH and lower urinary tract symptoms after receiving 5 g twice daily of pumpkin seeds, 500 mg twice daily of pumpkin seed extract capsules (Granu Fink®), or placebo for 12 months.[2] Patients had not received any 5α-reductase inhibitors or α-blocking agents for 6 months before enrollment. Patients taking pumpkin seed were not blinded. The primary outcome was the response rate, defined as at least a 5-point decrease in the IPSS at 12 months. Secondary outcomes were IPPS scores and IPSS-QoL scores.

Placebo was less likely to lead to response than pumpkin seeds (odds ratio [OR] 0.65; 95% CI, 0.50–0.84) but placebo had an equivalent response rate compared with pumpkin seed extract (OR 1.1; 95% CI, 0.82–1.4). At 12 months, IPSS scores decreased from baseline in all groups: placebo by 4, pumpkin seed by 5.4, and pumpkin seed extract by 4.2 to scores of 11.7, 10.3, and 11.2, respectively (no statistical analysis reported).[2]

A 2014 RCT (N=92) evaluated the effects of 2 capsules daily of pumpkin seed oil (Prostafit®) and 2 capsules daily of prazosin (doses not reported) on IPSS and IPSS-QoL scores over 6 months in men with symptomatic BPH.[3]

At 6 months, pumpkin seed oil decreased IPSS scores by 64% and prazosin by 56% (*P*<.001 for each comparison with baseline). The differences between pumpkin seed oil and prazosin were not significant (*P*<.28). The study did not include a power analysis.[3]

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Does vitamin D supplementation for adults with mild to moderate asthma decrease incidence of exacerbations requiring systemic corticosteroids?

EVIDENCE-BASED ANSWER

No. In adult patients with mild or moderate asthma (forced expiratory volume in 1 second [FEV1] >60%), vitamin D_3 supplementation does not decrease the number of patients experiencing an exacerbation over 6 months or increase the time to first asthma exacerbation over 12 months (SOR: **A**, 2 RCTs with consistent findings).

A 2014 double-blinded, parallel RCT (N=408) of adult patients with asthma and low vitamin D_3 levels (<30 ng/mL) examined the effect of vitamin D supplementation versus placebo on time to asthma treatment failure over 28 weeks.[1] Asthma exacerbations were also examined as a secondary outcome. The patients were at least 18 years of age on standardized asthma controller therapy during the run-in period, with a predicted FEV1 of at least 50%.

Patients were randomized to inhaled ciclesonide and oral vitamin D_3 100,000 IU once followed by 4,000 IU/d versus inhaled ciclesonide plus placebo. Treatment failure was defined as a decline in lung function based on FEV1 and peak expiratory flow measurements; an increase in the use of levalbuterol, systemic corticosteroids, or inhaled corticosteroids; an emergency department visit or hospitalization with use of systemic corticosteroids; participant lack of satisfaction with treatment; or physician clinical judgment for safety reasons. Asthma exacerbation was defined similarly but with more pronounced FEV1, levalbuterol, or systemic corticosteroid criteria.[1]

Vitamin D supplementation compared with placebo did not affect the percent of patients with treatment failure (28% vs 29%; *P*=.54), percent of patients with first asthma exacerbation (13% vs 19%; *P*=.17), or the overall rate of asthma exacerbations (0.26 vs 0.4/person-year; *P*=.05). In the analysis of 9 prespecified secondary outcomes, the only difference was that the total dose of inhaled ciclesonide to maintain asthma control was significantly less in the vitamin D group compared with the placebo group (111.3 vs 126.2 µg/d; *P*<.05). Possible treatment effects may have been obscured

by insufficient treatment and follow-up periods, and by insufficient dosing of vitamin D_3.[1]

A 2015 double-blinded multicenter RCT (N=250) of adult patients with asthma evaluated the effectiveness of vitamin D_3 3 mg every 2 months for 6 doses compared with placebo for prevention of asthma exacerbation and upper respiratory infection.[2]

Patients were between 16 and 80 years old with an FEV1 of 80.6% to 81.6%, a smoking history of 15 or fewer pack-years, and no diagnosis of chronic obstructive pulmonary disease. An asthma exacerbation was defined as deterioration in asthma requiring oral corticosteroids, treatment by the emergency department, hospital admission, or a decrease in the peak expiratory flow rate to more than 25% below the mean run-in value on 2 or more consecutive days.[2]

Vitamin D_3 had no effect on time to first asthma exacerbation (median 136 days in the vitamin D_3 group vs 192 days in the placebo group; adjusted hazard ratio 1.02; 95% CI, 0.69–1.5). A subgroup analysis found that the baseline vitamin D_3 level had no effect on the primary outcomes.[2]

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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 Army Medical Department, the Army at large, or the Department of Defense.

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Which medication is more effective as a first-line agent for status epilepticus, midazolam or lorazepam?

EVIDENCE-BASED ANSWER

In a mixed population of adults and children requiring prehospital treatment, intramuscular (IM) midazolam is more effective than intravenous (IV) lorazepam for cessation of seizures, prevention of hospitalization, and prevention of intensive care unit (ICU) admissions (SOR: **B**, 1 large RCT). However, in studies limited to children, midazolam (IV or IM) is equivalent to IV lorazepam for the same outcomes (SOR: **B**, 2 small RCTs). IM midazolam is recommended in adults without pre-established IV access, but either midazolam or lorazepam are appropriate in other situations (SOR: **C**, expert opinion).

A 2014 systematic review of 18 RCTs (N=2,755) compared the effectiveness of different anticonvulsants for status epilepticus in children and adults.[1] Two trials compared midazolam with lorazepam.

One 2012 RCT (n=893) compared paramedic-administered IM midazolam (5 mg if 13–40 kg, 10 mg if >40 kg) and IV lorazepam (2 mg if 13–40 kg, 4 mg if >40 kg) in children and adults for status epilepticus in the prehospital setting. Status epilepticus was defined as continuous or intermittent convulsions lasting longer than 5 minutes without regaining consciousness. Participants were 43 years old on average, and 55% were male.[1]

IM midazolam was more effective than IV lorazepam for the cessation of seizures (73% vs 63%; risk ratio [RR] 1.2; 95% CI, 1.1–1.3; number needed to treat [NNT]=10), prevention of hospitalizations (58% vs 66%; RR 0.88; 95% CI, 0.79–0.97; NNT=13), and ICU admissions (29% vs 36%; RR 0.79; 95% CI, 0.65–0.96; NNT=15).[1]

A 1999 RCT (n=27) compared midazolam (0.2 mg/kg IV) and lorazepam (0.1 mg/kg IV) in children 1 month to 15 years of age for the initial treatment of status epilepticus. No difference was noted in rate of seizure cessation (RR 0.20; 95% CI, 0.03–1.6) or requirement of ventilator support (RR 0.4; 95% CI, 0.04–3.9). This second study was limited by small sample size. There was no difference in adverse events in either study.[1]

A 2015 subgroup analysis from the 2012 RCT noted above assessed the effectiveness of IM midazolam versus IV lorazepam for the subgroup of 120 pediatric patients (<18 years old and weight ≥13 kg) with status epilepticus in the prehospital setting.[2] The mean age was 6.7 years, and 41% were female. Key outcomes included seizure cessation and recurrence, hospitalization, ICU admission, and intubation.

No difference was noted between midazolam and lorazepam for termination of the seizure prior to arrival in the emergency department (68% vs 72%; risk difference [RD] –3.3%; 99% CI, –25 to 18), hospitalization (43% vs 52%; RD 9%; 99% CI, –32 to 15), ICU admission (13% vs 22%; RD 9%; 99% CI, –29 to 9), intubation (8% vs 15%; RD 7%; 99% CI, –22 to 8), and recurrent seizure (3% vs 10%; RD 7%; 99% CI, –18 to 5). The study was limited by small sample size, lack of a power calculation, and potential type 1 error.[2]

The 2016 evidence-based report from the Guideline Committee of the American Epilepsy Society states that IM midazolam and IV lorazepam are effective in treating status epilepticus in adults (level A: based on 1 well-done RCT).[3] In adults without pre-established IV access, IM midazolam is more effective than IV lorazepam (level A: based on 1 well-done RCT). In children, IV lorazepam is efficacious at stopping status epilepticus (level A: based on 2 well-done RCTs), whereas IM, intranasal, and intrabuccal midazolam are probably effective (level B: based on multiple small or noncontrolled trials).

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Is ferric carboxy maltose more effective than iron sucrose for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD)?

EVIDENCE-BASED ANSWER

Ferric carboxy maltose is at least as effective as iron sucrose in increasing hemoglobin levels in patients with iron deficiency anemia who have CKD. Ferric carboxy maltose and iron sucrose are both more effective than oral iron supplementation in increasing hemoglobin levels (SOR: **C**, RCTs of disease-oriented outcomes).

A 2014 randomized, active-controlled, multicenter, noninferiority, open-label trial compared the efficacy of ferric carboxy maltose with iron sucrose for the treatment of iron deficiency anemia in 2,561 patients with impaired renal function.[1] Patients had hemoglobin ≤11.5 g/dL and CKD, with a glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 or a GFR <90 mL/min/1.73 m^2 and either documented kidney damage or an elevated risk of cardiovascular disease.

Ferric carboxy maltose was administered at a dose of 15 mg iron/kg (max cumulative dose of 750 mg) on days 0 and 7, for a max total dose of 1,500 mg. Iron sucrose was administered at the current FDA-approved dose of five 200-mg infusions on days 0, 7, and 14, with 1 additional dose given between days 0 and 7, and 1 additional dose given between days 7 and 14 (total cumulative dose of 1,000 mg).[1]

In the 8 weeks of follow-up, the mean increase in hemoglobin was higher in the ferric carboxy maltose group than in the iron sucrose group (1.13 vs 0.92 g/dL; mean difference 0.21; 95% CI, 0.13–0.28). A key weakness of the study was that patients assigned to the ferric carboxy maltose group received a higher cumulative dose of iron than patients in the iron sucrose group (1,500 vs 1,000 mg). The study was further limited by its short follow-up.[1]

A 2005 RCT compared the efficacy of iron sucrose with oral ferrous sulfate in 161 patients with anemia and CKD with or without erythropoietin therapy.[2] Patients were included in the study if they had CKD stages 3 to 5, hemoglobin ≤11 g/dL, transferrin saturation ≤25%, and ferritin ≤300 ng/mL.

Patients received either IV iron sucrose 1 g in divided doses over 14 days or oral ferrous sulfate 325 mg 3 times

daily for 56 days. The primary measure of efficacy was an increase in hemoglobin of at least 1.0 g/dL from baseline.[2]

The proportion of patients with an increase in hemoglobin of at least 1.0 g/dL was significantly higher in the iron sucrose group than in the oral ferrous sulfate group (44% vs 28%; *P*=.034).[2]

In 2014, a multicenter RCT compared the efficacy of IV ferric carboxy maltose with oral ferrous sulfate in patients with iron deficiency anemia.[3] Patients were included if they had hemoglobin ≤11 g/dL, ferritin ≤100 or ≤300 ng/mL, and a transferrin saturation ≤30%.

All patients received a 14-day run-in of oral ferrous sulfate 325 mg 3 times daily. Patients who responded inadequately to oral iron therapy (hemoglobin increase <1 g/dL from baseline) were randomly assigned to either receive IV ferric carboxy maltose (15 mg iron/kg) for a maximum of 750 mg on days 0 and 7 (group A) or to continue oral iron 325 mg 3 times daily for an additional 14 days (group B).[3]

The mean change in hemoglobin from baseline to the highest value was significantly greater in the ferric carboxy maltose group than in the oral iron group (1.6 vs 0.80 g/dL; *P*=.001).[3] EBP

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Is one enough? Frequency of checking hemoglobin in hospitalized patients

Rajkomar A, McCulloch CE, Fang MC. Low diagnostic utility of rechecking hemoglobins within 24 hours in hospitalized patients. *Am J Med*. 2016; 129(11):1194–1197.

This retrospective cross-sectional analysis examined the frequency of a clinically significant decrease in hemoglobin (defined as ≥1 g/dL) when repeat hemoglobin tests were collected on the same calendar day in hospitalized adult patients. During the study period, 88,722 hemoglobin tests were collected from 12,877 patients, who contributed to a total of 86,859 hospitalization days, with 2 tests obtained in a single day on 8,143 (9.4%) hospital days.

This study analyzed a cohort of 4,106 patients who underwent 2 hemoglobin tests and no transfusions on 6,969 hospitalization days. The mean of the initial hemoglobin was 10.5 g/dL and the mean of the second value was 10.4 g/dL.

Of those 6,969 repeat tests, 949 (13.5%) had a value ≥1 g/dL lower and 260 (3.7%) had a value ≥2 g/dL lower.

After adjusting for age, sex, race, hours between tests, and hospital service, variables associated with a ≥1 g/dL decrease in hemoglobin level in a single day were admission to the intensive care unit (adjusted odds ratio [aOR] 1.4; 95% CI, 1.2–1.7) and whether the test was performed on the day of admission (aOR 3.5; 95% CI, 2.8–4.2), but not if the discharge diagnosis was bleeding (aOR 1.3; 95% CI, 0.99–1.7).

This study did not provide a breakdown of admission diagnoses to indicate the frequency of repeat testing based on diagnosis or the indication for the repeat blood test.

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

Bottom line: Repeat hemoglobin in the same calendar day revealed a decrease of ≥1 g/dL in only 14% of patients. However, this study did not specify diagnoses among the patients undergoing repeat testing nor the reasons for the repeat testing, so it is difficult to know when repeat hemoglobin tests are advisable.

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Nasal saline irrigation may reduce rhinosinusitis symptoms in adults

Little P, Stuart B, Mullee M, Thomas T, Johnson S, Leydon G, et al; SNIFS Study Team. Effectiveness of steam inhalation and nasal irrigation for chronic or recurrent sinus symptoms in primary care: a pragmatic randomized controlled trial. *CMAJ*. 2016; 188(13):940–949.

This UK pragmatic RCT examined the effectiveness of brief advice to use nasal saline irrigation or steam inhalation in routine primary care for patients with chronic or recurrent rhinosinusitis. Eligible patients (N=961) at 1 of 72 primary care practices were randomly assigned to 1 of 4 groups: usual care plus nasal saline irrigation, steam inhalation, both, or neither. Patients assigned to nasal saline irrigation were given a Neti pot and a link to an online video describing how to use it.

The primary outcome measure was the validated Rhinosinusitis Disability Index (RSDI), a 30-item questionnaire, with each question graded on a 5-point Likert scale. The scores on the RSDI range from 0 to 120 (higher scores representing worse symptoms), and a 10-point reduction was considered clinically important for this study. Several other measures (the Sino-Nasal Outcome Test [SNOT-20], severity of respiratory symptoms, use of over-the-counter medications, report of headache, and the belief in the need for antibiotics or to see a physician, among others) were secondary outcomes.

At 6 months, significantly more patients maintained a 10-point clinically important improvement in the RSDI score with nasal saline irrigation than patients using steam inhalation or usual care alone (44% vs 37%; risk ratio 1.38; 95% CI, 1.01–1.87). Steam inhalation showed no effect on its own.

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

Bottom line: Advice to use nasal saline irrigation appears to decrease chronic or recurrent rhinosinusitis symptoms compared with usual care or steam inhalation, when patients were given a Neti pot and a link to a video demonstrating its use. Steam inhalation shows no benefit on its own. Because patients in the nasal irrigation arms were given Neti pots, the Neti pots themselves, rather than the brief advice intervention, may be the cause of the difference. Many family physicians are already advising patients to try nasal saline irrigation for rhinosinusitis symptoms, so this information is likely not practice changing. EBP

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