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EVIDENCE-BASED PRACTICE

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FPIN Family Physicians Inquiries Network

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Hand to hand

Back in 1942, Robert A. Heinlein wrote a short story called "Waldo." It introduced the reader to an arrogant genius named Waldo Farthingwaite-Jones who lived in his own space station to mitigate the effects of his myasthenia gravis. This antihero made himself quite rich by developing telerobotic hands that allowed him (or anyone else) to finely and powerfully manipulate objects at a distance. The robotic hands were known as "waldoes."

When laparoscopic cholecystectomies first came on the scene about 25 years ago, I was reminded of those same waldoes and whimsically wondered if Farthingwaite-Jones would be getting any royalties. Since then, laparoscopic procedures have largely proven their worth and replaced open surgical procedures for many indications, and the number of laparoscopic procedures done each year continues to rise.

My hospital recently tried an upgrade in this arena by purchasing a Da Vinci® next-generation robotic surgery device that even more closely resembles the fantastical waldoes described in 1942. The way a Da Vinci transmits a surgeon's subtle hand motions to tools located inside a patient's abdomen is a technological marvel. But is this expensive, newer robot better than standard laparoscopic waldoes?

Someone decided to check, at least in the realm of bowel surgery. Researchers identified 12 (mostly observational) studies with 4,148 patients comparing enhanced robotic and older laparoscopic partial colectomy for a variety of colon diseases.[1] Overall, patients receiving new robotic surgery had slightly fewer postoperative complications (20% vs 25%) and slightly shorter hospital stays (by about half a day on average) than patients treated laparoscopically. Yet, the overall costs with the newer robotics were higher (and the study was strangely vague about that number).

This was not a definitive knockout punch by the latest robotic technology, no Optimus Prime crushing a Decepticon (you are a Transformers fan, aren't you?). Waldo technology, it seems, improves only incrementally in the medical arena. Frankly, I find it humbling to note just how long it is taking for something that shines so vividly in the imagination to be built by hands of sinew and sensation.

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STATEMENT OF PURPOSE

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

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Stepping up our approach to the management of infants with fever without a source

PRACTICE CHANGER

The Step-by-Step approach is the most sensitive algorithm for the management of infants with fevers without a source in the emergency department (ED), allowing providers to decrease invasive testing and antibiotic treatment of low-risk infants.

Strength of recommendation: B, based on a multicenter prospective study

Gomez B, Mintegi S, Bressan S, Da Dalt L, Gervaix A, Lacroix L; European Group for Validation of the Step-by-Step Approach. Validation of the "Step-by-Step" approach in the management of young febrile infants. *Pediatrics*. 2016; 138(2). doi: 10.1542/peds.2015-4381.

CASE

A well-appearing 45-day-old infant presents to the ED with a temperature of 102.1°F. Should you proceed with empiric antibiotics and admit for observation or can you safely monitor a low-risk infant in the outpatient setting?

Clinical context

Viral infection is the most common cause of fever in young infants; however, serious bacterial infection occurs in 12.3% of febrile infants younger than 90 days old.[1] Delaying treatment until the cause of the infection becomes obvious increases the risk of preventable morbidity and mortality.

The goal in the evaluation of a febrile infant is to identify infants who require hospitalization and empiric antimicrobial therapy. Over the past few decades, different criteria have been used (Rochester, Philadelphia, and Boston), but no consensus guideline exists to stratify patients.[2–4] The Rochester criteria (see **TABLE 1**) have been used for identifying febrile infants <90 days old who have an invasive bacterial infection. These criteria require a full history, physical examination, and laboratory and radiographic evaluation if indicated, but no lumbar puncture (setting the Rochester apart from the Philadelphia and Boston criteria). Critics of guidelines for febrile infants have found them to be inconsistently applied and outdated, especially with the decline of invasive bacterial infection, given the introduction of pneumococcal conjugates vaccines.[1] In addition, the epidemiology of bacterial pathogens in infants is changing, with *Escherichia coli* as the leading cause of bacteremia in this population.[2,3] Furthermore, biomarkers, such as C-reactive protein (CRP), now provide additional information not available when older scoring systems were developed. Newer scores, such as the Lab-score, take into account these biomarkers but have not become widely adopted, as many centers do not have instant test results available.[4]

A recent study was designed to validate a new algorithm (Step-by-Step) developed by a group of pediatric emergency physicians in Europe that identifies a low-risk group of infants with fever without source who, after initial examination and blood work, could be managed safely in the outpatient setting without a lumbar puncture or empiric antibiotics. The sensitivity, specificity, and negative predictive algorithm were compared with the Rochester criteria and Lab-score, which are further described in **TABLE 1**.

Study summary

This multicenter prospective study, performed in 11 European pediatric EDs, compared the Step-by-Step approach with the Rochester criteria and the Lab-score for the evaluation of 2,185 infants younger than 90 days of age presenting with fever without a source. Fever without a source was defined as a temperature measured at home or in the ED ≥38.0°C in an infant with a normal physical examination and no respiratory signs/symptoms or diarrhea. Exclusion criteria included a clear source of fever after careful history and physical examination, no fever on arrival at the ED, absence of ≥1 mandatory ancillary tests, and refusal of the parents or caregiver to participate. The Step-by-Step approach takes into account infant appearance (using the pediatric assessment triangle), age, leukocyturia, and procalcitonin (PCT) to identify high-risk infants. CRP and absolute neutrophil count (ANC) are further used to identify intermediate risk patients (see **FIGURE**). The pediatric assessment triangle used in the algorithm is a quick simple approach to evaluating a child based on appearance, work of breathing, and circulation to determine if the child is sick or not sick.[6]

All infants had a urine dipstick, a urine culture collected by an aseptic technique (bladder catheterization or suprapubic aspiration), white blood cell count, CRP, PCT, and a blood

TABLE 1

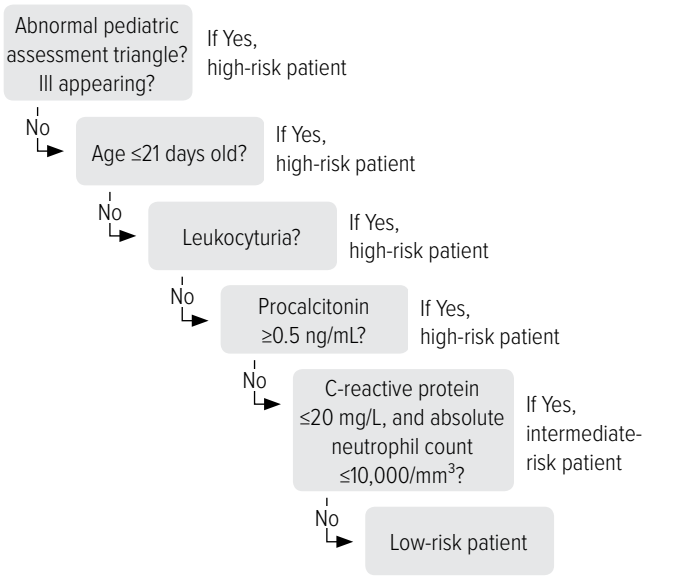
Description of Rochester criteria and Lab-score in infants with a fever without a source

Rochester criteria: reassuring if all criteria are present[5]	Lab-score[4]
a. Infant appears generally well b. Previously healthy: – Born at term – No perinatal antimicrobial therapy – No chronic or underlying illness c. No evidence of skin, soft tissue, bone, joint, or ear infection d. Lab values: – WBC count normal (5,000–15,000 m^3) – Band neutrophils <1,500/mm^3 – If diarrhea present, fecal leukocytes <5 WBC/hpf – Urine WBC <10 WBC/hpf	a. 2 points for: – PCT ≥0.5 ng/mL – CRP ≥40 mg/L b. 4 points for: – PCT ≥2 ng/mL – CRP ≥100 mg/L c. 1 point for positive urine dipstick (ie, positive leukocyte esterase and/or positive nitrate)
If all reassuring criteria present, <1% risk occult bacteremia risk	**Score ≥3 predictive of serious bacterial infection**

CRP=C-reactive protein; PCT=procalcitonin; WBC=white blood cell.

FIGURE

Step-by-Step approach



culture. The decision to perform any other test was left to the discretion of the physician. Patients were admitted and/or received antibiotics according to the provider.

Parents or caregivers of infants managed as an outpatient received a follow-up phone call within 1 month after the initial ED visit. If the caregiver could not be contacted after 3 phone calls, the electronic registries of public health were used to identify or review any follow-up information.

The mean age of infants was 47 days, and 16.7% of patients were ≤21 days old. Bacterial infections were diagnosed in 504 patients (23.1%), which included patients with positive urine culture but no leukocyturia, pneumonia with negative cultures, and acute otitis media with negative cultures. Invasive bacterial infections (positive blood or lumbar puncture cultures) were diagnosed in 4.0% (87 patients) and noninvasive bacterial infections (with a urine or stool confirmation) in 19.1% (417). On initial examination, 87.7% were classified as well-appearing. The number of patients identified as low risk by algorithm was as follows: Step-by-Step, 991 (45.3%); Rochester criteria, 949 (43.4%); and Lab-score 1,798 (82.2%).

The first part of the Step-by-Step algorithm (evaluating general appearance [pediatric assessment triangle], age <21 days, and presence of leukocyturia) identified 79.3% of the cases of invasive bacterial infection (69 of 87 infants) and 98.5% of the cases noninvasive bacterial infection (411 of 417 infants). After further stratification taking into account CRP, PCT, and ANC, a subgroup of the 991 low-risk infants was identified that had a prevalence of invasive bacterial infection of 0.7%.

More patients in the Rochester and Lab-score would have been designated low risk but would have also had a higher prevalence of suspected bacterial infection. The prevalence of suspected bacterial infection in the low-risk groups were Step-by-Step 1.1% (n=11; 95% CI, 0.5–1.8), Rochester criteria

TABLE 2

Sensitivity, specificity, NPV, and LR– of each algorithm for identifying invasive bacterial infection

Algorithm	Sensitivity, % (95% CI)	Specificity, % (95% CI)	NPV (95% CI)	LR– (95% CI)
Step by Step	92 (84–96)	47 (45–49)	99.3 (98.5–99.7)	0.17 (0.08–0.35)
Rochester criteria	82 (72–88)	45 (42–47)	98.3 (97.3–99.0)	0.41 (0.26–0.65)
Lab-score	60 (49–69)	84 (82–86)	98.1 (97.3–98.6)	0.48 (0.37–0.62)

LR–=negative likelihood ratio; NPV=negative predictive value.

2.1% (n=20; 95% CI, 1.2–3.0), and Lab-score 10.8% (n=195; 95% CI, 9.4–12.3).

Overall, Step-by-Step was more sensitive, with a higher negative predictive value and the best negative likelihood ratio compared with the prior gold standard of the Rochester criteria (see **TABLE 2**).

What's new

This study validates the Step-by-Step algorithm as an accurate tool to identify low-risk infants presenting with fever without a source. The algorithm yields fewer infants in the low-risk group with suspected bacterial infection than the gold standard Rochester criteria. It was superior to Rochester and Lab-score in identifying infants with an invasive bacterial infection. The tool takes into account the biomarkers PCT and CRP, which were not previously available or applied in more well-known clinical tools.

Caveats

The study used an age cutoff of 21 days as being high risk. Four of 7 patients aged 22 to 28 days diagnosed with invasive bacterial infection were identified by the algorithm as low risk. Further data need to be collected to assess the safest age cutoff. In addition, 6 of 7 patients were potentially missed because their fever duration was <2 hours, which would be too short of a time for PCT to rise. Extended observation in the ED is important to assist in monitoring clinical course. Although Lab-score is not used often in the United States, this study evaluated the Lab-score, which was developed in Italy to identify severe bacterial infections using CRP, PCT, and a urinary dipstick.[4] Not all hospitals or EDs have PCT or CRP available within the turnaround time required to apply the algorithm. Furthermore, clinicians have not consistently followed previous algorithms so it is unknown if they will use Step-by-Step.

Challenges to implementation

Educating providers about existing algorithms has been difficult, with various surveys by the American Academy of Pediatrics showing only 62% of respondents used some set of published guidelines.[1] The Step-by-Step evaluation still requires blood work and testing, although it continues to avoid unnecessary lumbar punctures. Furthermore, PCT is not readily available at all facilities. In the United States, providers may still be uncomfortable with an age cutoff of 21 days and not 28 days. As some infants may have short fever duration, close observation in the ED is still recommended. This guideline is one of the newest in the setting of changing biomarkers and bacterial pathogens, and may require further validating before broad implementation. EBP

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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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Vitamin D supplementation and asthma exacerbations? Don't hold your breath yet

Martineau AR, Cates CJ, Urashima M, Jensen M, Griffiths AP, Nurmatov U, et al. Vitamin D for the management of asthma. *Cochrane Database Syst Rev*. 2016; (9):CD011511. [Epub ahead of print]

This meta-analysis of 7 RCTs assessed the efficacy of giving vitamin D to 435 children and 658 adults with asthma to reduce the rate of severe exacerbations and improve symptom control. Trials were double-blind, lasted at least 12 weeks, and compared any dose or formulation of vitamin D with placebo.

The primary outcome was incidence of asthma exacerbations requiring administration of systemic corticosteroids. Secondary outcomes included incidence of exacerbation precipitating an emergency department (ED) visit or hospital admission and Asthma Control Test (ACT) scores to assess symptom control.

In the 3 trials for which the primary outcome could be assessed (which included 22 children and 658 adults), vitamin D decreased the risk of asthma exacerbations requiring administration of systemic steroids (relative risk 0.63; 95% CI, 0.45–0.88). Vitamin D also decreased the risk of exacerbations precipitating an ED visit or hospitalization (7 trials, n=963; odds ratio 0.39; 95% CI, 0.19–0.78; number needed to treat=27), but had no significant effect on ACT scores or other secondary outcomes. No serious adverse events were identified.

Vitamin D dosing varied greatly by study (400–4,000 IU/d), and data were insufficient to conduct subgroup analyses by dose, patient age, baseline vitamin D level, or asthma severity. Few patients had severe asthma, and the primary outcome occurred in very few children.

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

Bottom line: Vitamin D for asthma seems promising, but before recommending a change in practice, we need to know which patients benefit from vitamin D, whether some patients may be harmed, and how much vitamin D to give.

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Topical timolol maleate for the treatment of infantile hemangiomas works, but referral is still the standard of care

Püttgen K, Lucky A, Adams D, Pope E, McCuaig C, Powell J, et al; for the Hemangioma Investigator Group. Topical timolol maleate treatment of infantile hemangiomas. *Pediatrics*. 2016; 138(3). Epub 2016 Aug 15.

The off-label use of topical timolol maleate for infantile hemangioma has escalated over the past several years.

This retrospective cohort study evaluated the safety and effectiveness of timolol maleate therapy for infantile hemangioma. Nine vascular anomaly centers in the United States and Spain reported on 731 patients <3 months of age deemed to be candidates to receive timolol maleate by a physician with expertise in vascular anomalies. The most common indication for treatment was the perceived risk of disfigurement. Investigators excluded patients who did not have a baseline photograph and ≥1 follow-up visit with clinical data and a photograph. A meaningful treatment response was defined as a 10% improvement on visual analog scales for color (VAS-C) and for size, extent, and volume (VAS-SEV).

After 1–3 months of timolol maleate therapy, 70% of patients had meaningful improvement on the VAS-C scale, as did 92% after 6–9 months. For the VAS-SEC scale, 77% of patients improved at 6–9 months. Mild adverse events occurred in 3.4% of patients.

Timolol maleate therapy appeared to alter the natural history of the lesions in these children, and the effect was consistent with the documented biological response of infantile hemangioma to oral beta-blockers.

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

Bottom line: Off-label use of timolol maleate was well-tolerated, safe, and showed moderate to good effectiveness in patients with high-risk infantile hemangioma who had been referred to a specialist for treatment. Current standard of care in this situation is referral to a vascular anomaly specialist. This study does not change this practice. EBP

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Are prophylactic antibiotics effective for preventing infection after first-trimester abortion?

EVIDENCE-BASED ANSWER

Antibiotic prophylaxis given preprocedure at the time of first-trimester surgical abortion is an effective strategy for reducing the risk of infection and is recommended (SOR: **A**, meta-analysis). For medical abortions, the routine use of prophylactic antibiotics is not recommended (SOR: **B**, systematic review–based guidelines).

A 2012 meta-analysis of 19 RCTs (N=9,715) compared upper genital tract infection rates after first-trimester surgical abortion between women given prophylactic antibiotics versus placebo, nothing, a different antibiotic, or screening and treating screen-positive women only.[1] Women were included with or without a past pelvic inflammatory disease history or preabortion infection with bacterial vaginosis, *Neisseria gonorrhoeae*, or *Chlamydia trachomatis*. The antibiotics used belonged to 1 of the following classes: nitroimidazole, tetracycline, beta-lactam, fluoroquinolone, macrolide or glycoside. The antibiotics were given before, during, or after the procedure. The frequency varied with the antibiotic used. None of the studies were conducted in low-income countries, where postabortion infections are more common. There was evidence of small study bias.

Antibiotic prophylaxis was more effective than placebo for reducing upper genital tract infections (15 RCTs, n=7,025; relative risk [RR] 0.59, 95% CI, 0.46–0.75). When compared with placebo, nitroimidazoles, tetracyclines, and beta-lactams were each effective for reducing upper genital tract infections (nitroimidazoles: 6 RCTs, n=1,087; RR 0.53; 95% CI 0.37–0.77; tetracyclines: 4 RCTs, n=2,433; RR 0.37; 95% CI, 0.14–0.98; beta-lactams 2 RCTs, n=778; RR 0.52; 95% CI, 0.31–0.88). When fluoroquinolones, macrolides, and glycosides were each compared with placebo, no difference was noted in infection rates.[1]

In 2012, the World Health Organization (WHO) published guidelines on safe abortion policy for healthcare systems.[2] For surgical abortions, the WHO recommended that women receive appropriate prophylactic antibiotics, preoperatively or perioperatively. This recommendation was advised regardless of the patient's risk of pelvic inflammatory infection. Single-dose administration of nitroimidazoles, penicillins, or tetracyclines was suggested. For medical abortions, the WHO guidelines recommended against the routine use of prophylactic antibiotics.

The Society of Family Planning 2010 clinical guideline recommended that preoperative antibiotic prophylaxis be provided to all patients undergoing a surgical first-trimester abortion.[3] The Society further recommended that prophylaxis with the shortest possible course of antibiotics should be given preprocedure for maximal effect and lowest risk of adverse reactions. A single dose of doxycycline is a safe and effective option. In addition to antibiotic prophylaxis, if possible, screening for gonorrhea and chlamydia should be performed. These recommendations were all rated Level A, based on good and consistent scientific evidence.

The Society gave a Level B recommendation (based on limited or inconsistent scientific evidence) to the statement that a 1-week course of doxycycline begun at the time of medical abortion may lower the risk of serious infection at the time of early medical abortion. However, the Society does not consider universal antibiotics a requirement for all women having a medical abortion.[3]

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EVIDENCE-BASED PRACTICE LEARNING OBJECTIVES

1 To become knowledgeable about evidence-based solutions to commonly encountered clinical problems.

2 To understand how ground-breaking research is changing the practice of family medicine.

3 To become conversant with balanced appraisals of drugs that are marketed to physicians and consumers.

In patients with psoriasis, does a gluten-free diet improve outcomes?

EVIDENCE-BASED ANSWER

A gluten-free diet is associated with a slight improvement in psoriasis severity in patients with coexisting celiac disease. However, the diet does not seem to have much effect on patients without celiac disease (SOR: **B**, small crossover trial and case series).

A 2000 nonrandomized crossover trial (N=39) evaluated the effect of gluten-free diet on psoriasis symptoms.[1] Thirty-three of the patients were anti-gliadin antibody (AGA) positive and 6 were AGA negative. The population included 23 men and 16 women with a mean age of 43 years (range 18–70 years) and a mean duration of psoriasis of 20 years (range 1–42 years). The intervention consisted of 3 months of a gluten-free diet, followed by 3 months of the patient's regular diet.

Three AGA-positive patients (with moderate to severe psoriasis) dropped out of the study because of worsening gastrointestinal problems; 2 AGA-negative patients were excluded because of psoriasis medication changes. The Psoriasis Area and Severity Index (PASI) scale was used to determine any improvement. The PASI scale ranks disease from 0 (none) to 72 (maximal disease).[1]

The PASI scores of the 30 remaining AGA-positive patients decreased from 5.5 to 3.6 (*P*=.001) while on the gluten-free diet. The PASI scores of the 4 remaining AGA-negative patients did not significantly change (8.9 to 10.2; *P*=.465), although the power to detect a difference was low.[1]

A 2015 case series (N=9) evaluated the effect of a gluten-free diet on patients with both celiac disease and psoriasis.[2] All 9 patients had serology- and biopsy-proven celiac disease, with complete villous atrophy. The most common symptoms were bloating and diarrhea. The population included 4 women and 5 men with a mean age of 49 years (range 27–71 years). The intervention consisted of 6 months of a gluten-free diet with verification of adherence by a dietician. A dermatologist evaluated the severity of psoriasis using the PASI scale at 3 and 6 months. One patient was lost to follow-up. The key outcome was the change in the PASI scores compared with baseline (initial and final scores were not given).

Two patients had improvement in PASI scores of 50% or more at 3 months; 5 patients had improvement of 75% or more at 3 months, and 1 had no skin lesions. Six patients had at least 75% improvement at 6 months, 1 had no skin lesions, and 1 (who had ≥75% improvement at 3 months) had a worsening of his PASI score.[2]

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Does treatment of mild gestational diabetes reduce adverse neonatal outcomes?

EVIDENCE-BASED ANSWER

Yes. Treatment of mild gestational diabetes with insulin decreases birth weight, the incidence of large-for-gestational age infants, and hyperbilirubinemia requiring phototherapy (SOR: **A**, consistent RCTs). The effect of treatment on perinatal mortality and birth trauma including shoulder dystocia is less clear.

In 2009, a multicenter RCT involving 958 ethnically diverse women (between 24 0/7 and 30 6/7 weeks' gestational age) with mild gestational diabetes examined the effect of treatment with insulin and home blood glucose monitoring compared with routine prenatal care on neonatal outcomes.[1] Mild gestational diabetes was defined as a fasting glucose of less than 95 mg/dL and 2 or 3 timed glucose measurements that exceeded thresholds (1-hour: 180 mg/dL; 2-hour: 155 mg/dL; 3-hour: 140 mg/dL) on a 3-hour 100-g glucose tolerance test performed after 24 weeks' gestation. The treatment group received insulin if most of their daily self-monitored glucose test results were elevated (fasting >95 mg/dL or 2-hour post-prandial >120 mg/dL). Women in the control group received routine prenatal care with random blood glucoses at the discretion of their providers. The primary outcome was a composite of perinatal mortality, neonatal

hypoglycemia, hyperbilirubinemia, hyperinsulinemia, and birth trauma (brachial plexus injury and clavicular, humeral, or skull fracture).

No difference was noted in the frequency of the composite outcomes between the treatment and control groups (32.4% and 37%, respectively; *P*=.14). The treatment group had reductions in the secondary outcomes of neonatal overgrowth (mean birth weight 3,302 g vs 3,408 g; *P*<.001), percent of infants large-for-gestational age (7.1% vs 14.5%; *P*<.001), percent with birth weight more than 4,000 g (5.9% vs 14.3%; *P*<.001), and percent of deliveries with shoulder dystocia (1.5% vs 4.0%; *P*=.02).[1]

Another multicenter RCT from 2005 involving 1,000 women with "glucose intolerance of pregnancy" and gestational age between 24 and 34 weeks studied the effect of treatment of maternal hyperglycemia compared with routine prenatal care on neonatal outcomes.[2] Glucose intolerance of pregnancy was defined as having oral glucose levels between 140 and 198 mg/dL on a 75-g fasting oral glucose tolerance test performed between 24 and 34 weeks' gestational age. The treatment group received nutrition counseling, blood glucose monitoring, and insulin therapy. The primary outcome was a composite measure of neonatal death, shoulder dystocia, fractures, nerve palsy, admission to the neonatal nursery, and jaundice requiring phototherapy.

The composite primary outcome was significantly lower in the treatment group than in the routine-care control group (1% vs 4%, respectively; *P*=.01). The number needed to treat to prevent a primary outcome in an infant was 34 (95% CI, 20–103). Infants born to women in the treatment group had significantly lower mean birth weights than infants born to women in the control group (3,335 g vs 3,482 g; 95% CI for difference, –219 to –70) and no statistically significant difference in rates of shoulder dystocia (relative risk [RR] 0.46; 95% CI, 0.19–1.10) or jaundice requiring phototherapy (RR 0.93; 95% CI, 0.63–1.37).[2]

In 2008, a blinded longitudinal study involving 23,316 women at 15 centers in 9 countries examined the correlation between maternal hyperglycemia and neonatal outcomes.[3] Primary neonatal outcomes studied were birth weight above the 90th percentile for gestational age and neonatal hypoglycemia. Participants (age >18 years, singleton pregnancies) underwent a 75-g oral glucose-tolerance test at 24 to 32 weeks and were excluded from the study if their blood glucose test results were diagnostic for gestational diabetes (fasting glucose >105 mg/dL or 2-hour glucose >200 mg/dL).

Odds ratios (ORs) demonstrated strong association between maternal hyperglycemia not high enough to meet criteria for gestational diabetes and increased birth weight. Every 1 standard deviation increase in fasting glucose level (6.9 mg/dL), 1-hour glucose level (30.9 mg/dL), and 2-hour glucose level (23.5 mg/dL) was associated with an increased birth weight greater than 90th percentile with an OR of 1.4 (95% CI, 1.3–1.44), 1.5 (95% CI, 1.4–1.54), and 1.4 (95% CI, 1.3–1.4), respectively.[3]

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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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In patients with anxiety or depression, does yoga reduce symptoms?

EVIDENCE-BASED ANSWER

Practicing yoga, compared with usual care and a variety of other interventions, results in a moderate reduction in symptoms of depression and an inconsistent effect on symptoms of anxiety (SOR: **B**, meta-analyses and a systematic review of heterogeneous RCTs).

A 2013 meta-analysis of 12 RCTs (N=619) of adults with depressive disorders compared the effect of yoga versus other treatments on symptoms of depression and anxiety.[1] The mean age of patients in each study ranged from 22 to 67 years, and 37% to 100% of patients in each study were women.

A variety of yoga interventions were included (eg, Hatha, Sudarshan Kriya, Savasana), and the intervention length

ranged from 3 days to 12 weeks (mean 8 weeks). Control groups varied among studies and included usual care, a relaxation intervention (progressive muscle relaxation, music, partial yoga, or sitting quietly), and aerobic exercise. Outcome measures included a variety of standardized psychometric scores, so results were given as standardized mean difference (SMD, where 0.2–0.5 is considered a small, 0.5–0.8 a medium, and >0.8 a large clinical effect).[1]

Yoga, compared with usual care, decreased depressive symptoms (5 RCTs, n=99; SMD –0.69; 95% CI, –0.99 to –0.39) but had no effect on symptoms of anxiety (2 RCTs, n= 43; SMD 0.00; 95% CI, –0.44 to 0.44). Yoga, compared with relaxation, decreased depressive symptoms (3 RCTs, n=46; SMD –0.62; 95% CI, –1.03 to –0.22) and symptoms of anxiety (2 RCTs, n=30; SMD –0.79; 95% CI, –1.32 to –0.26). Yoga, compared with aerobic exercise, decreased depressive symptoms (2 RCTs, n=66; SMD –0.59; 95% CI, –0.99 to –0.18), but anxiety symptoms were not reported. The results of this meta-analysis were limited by the heterogeneity of patients, yoga interventions, and control groups.[1]

A 2011 meta-analysis of 10 RCTs (N=373) involving patients with psychiatric disease compared the effect of yoga versus a variety of treatments other than yoga on psychiatric symptoms.[2] Eight of these studies evaluated patients with anxiety and depression (n=301). Four of these RCTs were also included in the 2013 meta-analysis cited above.

Interventions included various forms of yoga and yoga with meditation. Mean intervention length was 7 weeks (range 2–12 weeks). Control groups were exposed to various interventions, including wait list, education, antidepressants, and electroconvulsive therapy. Again, multiple standardized psychometric tests were used.[2]

Nine of the 10 studies demonstrated that yoga significantly reduced psychiatric symptoms, including symptoms of anxiety and depression, compared with controls. In pooled analysis, yoga decreased psychiatric symptoms (10 studies, n= 373; SMD –3.25; 95% CI, –5.36 to –1.14). The analysis did not separate out type of symptoms. The studies were significantly heterogeneous, but the authors noted that 212 null studies would need to be added to the aggregate data in order to negate the effect observed.[2]

A 2013 systematic review of 16 RCTs involving patients with neuropsychiatric disorders compared the effect of yoga versus other treatments on psychiatric symptoms.[3] Three of these RCTs were included in the 2013 meta-analysis cited above, and 4 of these RCTs were included in the 2011 meta-analysis cited above.

The 4 RCTs examining yoga in depression included 227 patients 18 to 80 years old who were assigned to different yoga practices (Sudarshan Kriya, Iyengar, and laughter yoga) for study periods ranging from 2 to 24 weeks. Control groups varied and included wait list, exercise, Ayurveda, and usual care. Data were not pooled, but the effect of yoga in each of the 4 trials was reported separately. In all 4 RCTs, yoga compared with controls significantly reduced symptom scores across all mental health inventories, but numerical data were not reported.[3]

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Is pulmonary rehabilitation helpful in decreasing exacerbations or improving quality of life in patients with COPD?

EVIDENCE-BASED ANSWER

Pulmonary rehabilitation improves health-related quality of life in patients with stable chronic obstructive pulmonary disease (COPD) and in patients with recent COPD exacerbations. Furthermore, pulmonary rehabilitation following an exacerbation significantly reduces hospital readmissions (number needed to treat [NNT]=4) and overall mortality (NNT=6) (SOR: **A**, meta-analyses of RCTs).

A meta-analysis of 65 nonblinded RCTs involving 3,822 patients with stable COPD compared the effects of pulmonary rehabilitation versus usual care on health-related quality of life.[1] Patients had a clinical diagnosis of COPD with FEV1/FVC of less than 0.7 and no exacerbation within

TABLE

Effect of pulmonary rehabilitation vs usual care on health-related quality of life in stable COPD in 19 RCTs with >1,100 patients[1]

Outcome	Mean difference (95% CI)
CRQ domains (clinically significant >0.5)	
Dyspnea	0.79 (0.56–1.03)
Fatigue	0.68 (0.45–0.92)
Emotional function	0.56 (0.34–0.78)
Mastery	0.71 (0.47–0.95)
SGRQ (clinically significant <–4)	
Total score	–6.9 (–9.3 to –4.5)

COPD=chronic obstructive pulmonary disease; CRQ=Chronic Respiratory Disease Questionnaire (7-point scale for each domain); SGRQ=St George's Respiratory Questionnaire (100-point scale).

4 weeks of starting pulmonary rehabilitation. Usual care was defined as conventional care without any exercise or formal education component.

The duration of rehabilitation ranged from 4 weeks to 1 year (8 and 12 weeks most common) and consisted of exercise therapy with or without additional education or psychological support. Health-related quality of life was measured by the Chronic Respiratory Disease Questionnaire (CRQ) or St George's Respiratory Questionnaire (SGRQ) before and after pulmonary rehabilitation (median follow-up of 12 weeks). The CRQ assesses 4 domains: fatigue, dyspnea, emotional function, and mastery, each on a 7-point scale; an improvement of more than 0.5 points is considered a minimal clinically important difference. The SGRQ assesses similar domains on a 100-point scale, and a decrease of more than 4 points is considered clinically significant.[1]

Compared with usual care, pulmonary rehabilitation resulted in improvement in all 4 CRQ domains and total SGQC score (see **TABLE**). Subanalysis found no significant difference in quality of life between exercise-only pulmonary rehabilitation and pulmonary rehabilitation consisting of exercise plus additional education or psychological report.[1]

Another meta-analysis of 9 nonblinded RCTs involving 432 patients with COPD recovering from an acute exacerbation evaluated the effect of pulmonary rehabilitation versus usual care on future hospital readmissions, health-related quality of life, and overall mortality.[2] The rehabilitation programs were initiated within 3 weeks of an exacerbation, varied in duration, and consisted of endurance exercise with or without education. Usual care was defined as conventional community care without exercise, except for 1 study that included a low-intensity walking component.

Patients who participated in pulmonary rehabilitation, compared with usual care, had a lower risk of readmission over 25 weeks (5 trials, n=250; odds ratio [OR] 0.22; 95% CI, 0.08–0.58; NNT=4) and a lower risk of mortality over 107 weeks (3 trials, n=110; OR 0.28; 95% CI, 0.10–0.84; NNT=6). They also had a clinically significant improvement in the total SGQC score of 9.9 (3 trials, n=128; 95% CI, 5.4–14). Limitations to the study included a relatively small sample size and heterogeneity among the interventions.[2]

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Is female-to-male transgender status a barrier to adequate cervical cancer screening with Pap smear?

EVIDENCE-BASED ANSWER

It appears so. Female-to-male transgender patients are less likely to have timely screening, more likely to have an inadequate Pap smear samples, and less likely to receive regular medical care (SOR: **B**, retrospective cross-sectional studies).

A 2014 cross-sectional study of 5,232 HIV-negative patients 21 to 64 years old with a cervix who had a medical visit in 2012 compared 4,882 non-transgender female patients with 350 female-to-male (FTM) transgender patients for rates of

up-to-date cervical cancer screening with Pap testing based on 2012 US Preventive Services Task Force recommendations.[1]

FTM patients were less likely than non-transgender female patients to have up-to-date Pap test screening (adjusted odds ratio [aOR] 0.63; 95% CI, 0.47–0.85). Limitations of the study were recall bias, tests conducted at the outside facilities not reported to the center, overreporting, and the possible lack of generalizability.[1]

Another 2014 cross-sectional study (by the same research team) conducted between 2006 and 2012 evaluated the prevalence of unsatisfactory Pap screening within an electronic health record.[2] A total of 3,625 female and 233 FTM patients were included. Patients had to be active patients for at least 1 year, were 21 to 64 years old, and had at least 2 medical appointments at least 1 year apart. Prescription of any testosterone medication was also recorded. Self-reported Pap results without lab report were not included.

Compared with non-transgender female patients, FTM patients had much higher odds of having inadequate Pap because of a lack of sufficient cells (aOR 11; 95% CI, 6.8–17). Risk factors for inadequate cells included increased age, increased weight, and testosterone therapy. When the analysis was adjusted for use of testosterone, a correlation persisted between Pap inadequacy and transgender identity (aOR 6; 95% CI, 3–12).[2]

Another 2014 cross-sectional study of health care access with more than 6,000 transgender and nonbinary people was conducted by using the National Transgender Discrimination Survey from 2008 to 2009.[3] Non-transgender persons were not included. Convenience sampling had to be used due to difficulty of reaching this group for research purposes. FTM patients were more likely to postpone access of care than male-to-female transgender persons (OR 1.4; $P<.001$). This study did not address cervical cancer screening with Pap directly.

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How effective is caffeine plus an analgesic for treating acute postoperative or postpartum pain in adults?

EVIDENCE-BASED ANSWER

Caffeine at doses of 100 mg or more as an adjunct to analgesics may be slightly more effective than analgesics alone for acute postoperative or postpartum pain in adults and is significantly better than placebo alone (SOR: **A**, based on systematic reviews RCTs and a subsequent RCT).

A 2014 systematic review analyzed 10 RCTs (N=2,139) of adults older than 16 years with acute postoperative (dental extraction) or postpartum (postepisiotomy, postsurgical, or uterine cramping) pain and examined the effectiveness of caffeine plus an analgesic compared with analgesic alone.[1] The trials combined caffeine (dose range 65–260 mg) with acetaminophen (dose range 500–2,000 mg), ibuprofen (dose range 100–400 mg), or aspirin (dose 650 mg), and measured pain relief compared with a control analgesic alone. Participants' mean ages ranged from 21 to 44 years, although not every study reported a mean age. Outcomes included pain relief measured by a variety of pain scales at time intervals ranging from 1 to 8 hours after the intervention.

Pooled analysis of these 10 RCTs showed that 60% of participants treated with analgesic plus caffeine reported at least a 50% reduction in pain intensity, compared with only 51% for participants who took an analgesic alone (relative risk [RR] 1.2; 95% CI, 1.1–1.3; number needed to treat [NNT]=10). No drug-induced adverse events occurred. Most of the trials had fewer than 150 patients and were at risk for size bias.[1]

A subsequent systematic review in 2015 further analyzed the 4 RCTs (N=908) that compared single-dose oral ibuprofen plus caffeine (n=332) against either placebo (n=160) or ibuprofen alone (n=416) for treating acute postoperative pain.[2] Patients were at least 15 years old and the mean age ranged from 22 to 25 years. All were recovering from either dental surgery (n=459) or episiotomy (n=449). The caffeine dose ranged from 50 to 200 mg, and the ibuprofen dose ranged from 100 to 200 mg when given in combination with caffeine, or 50 to 400 mg when given alone. The primary outcome was the achievement of at least 50% pain relief

over 4 to 6 hours, measured using a variety of pain intensity scales.

Oral ibuprofen 200 mg with caffeine 100 mg resulted in 59% of patients achieving a 50% or more reduction in pain versus 10% of patients with placebo (4 trials, n=334; NNT=2.1; 95% CI, 1.8–2.5). Side effects were low and no serious adverse events occurred. The reviewers did not calculate the effectiveness of combination ibuprofen plus caffeine versus ibuprofen alone.[2]

A 2012 double-blind RCT assessed pain control effectiveness in 100 patients after root canal surgery; patients received 1 of 3 oral analgesics (1 of which contained caffeine) or placebo alone.[3] Patients were not pregnant, had no systemic diseases, and were between 20 and 60 years old; the mean ages in the 4 treatment groups ranged from 28 to 31 years. Patients requiring additional analgesics were excluded. The 3 active intervention groups received 100 mg tramadol, 500 mg naproxen, or 1 Novafen (a combination of 325 mg acetaminophen, 200 mg ibuprofen, and 40 mg caffeine anhydrous) while the control group received placebo. Pain intensity was measured at 6, 12, and 24 hours postprocedure using a self-administered 10-point visual analog scale.

After 6 hours, mean pain scores dropped from 5.8 to 0.8 with Naproxen, from 5.8 to 0.6 with Novafen, from 5.1 to 3.2 with tramadol, and from 5.7 to 4.8 by placebo. No difference was noted between Naproxen and Novafen ($P>.05$), but tramadol was less effective than the other 2 active drugs ($P<.05$). Harms of the intervention were not reported. This trial was limited by small sample size and did not compare caffeine plus analgesic with the same analgesic alone.[3]

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Do mental activities such as crossword puzzles, playing games, and reading reduce the risk of developing dementia?

EVIDENCE-BASED ANSWER

Performing mental activities such as crossword puzzles, playing games, and reading is associated with a reduced risk and delayed onset of dementia (SOR: **B**, systematic reviews of cohort and case-control studies and single cohort study). Of course, association is not proof of effect.

A 2012 systematic review found 9 longitudinal cohort studies (N=11,968) investigating the association of engaging in mental activities such as reading, playing games, puzzles, or studying with the risk of developing dementia.[1] These studies included mostly older persons from North America and Europe, except 1 study from China; baseline cognitive function was not reported. The development of dementia among patients who self-reported participation (not further defined) in mental activities was compared with patients who did not report such participation over 4 to 40 years. No meta-analysis was performed due to variability in study design.

All 9 studies showed that participation in mental activities was associated with a reduced risk of developing dementia or Alzheimer disease (see **TABLE**). Many studies in the review did not control for confounding variables such as educational level, occupation, or baseline cognition.[1]

A systematic review of 8 cohort studies (n=12,486) and 5 case-control studies (759 cases and 2,220 controls) investigated the relationship between cognitive leisure activities and development of dementia.[2] Six of the 8 cohort studies were also included in the 2012 systematic review above. Studies involved participants at least 60 years old, with or without a clinical diagnosis of dementia. The definition of cognitive leisure activities varied; the most common were reading, playing cards, playing games, or doing crossword puzzles. Because of this variance, as well as heterogeneity in study design and the stage of life at which participants were evaluated, statistical pooling was not feasible.

Eleven of the 13 studies showed a positive association between participation in cognitive leisure activities and reduced risk of developing dementia, whereas 2 showed no significant effect. Of the 2 cohort studies that were

TABLE

Risk, hazard, or odds ratio of developing dementia in people who participated in mental activities such as reading, playing games, or studying[1]

Year of study	No. of patients	Age, years	Years of follow-up	Outcome	Results (95% CI)
2001	1,772	65+	7	Dementia	RR=0.8 (0.6–0.9)
2002	732	75+	6	Dementia	RR=0.5 (0.3–0.9)
2002	842	65+	4.2	Alzheimer disease	OR=0.4 (0.2–0.7)
2002	801	65+	4.5	Alzheimer disease	HR=0.7 (0.5–0.9)
2003	469	75–85	5.1	Dementia	RR=0.9 (0.9–0.98)
2006	732	75+	6	Dementia	RR=0.7 (0.5–1.0)
2007	775	65+	5	Alzheimer disease	RR=0.6 (0.4–0.8)
2008	147	44.7	20–40	Dementia	OR=0.7 (0.6–0.9)
2009	5,698	65+	4	Dementia	HR=0.5 (0.3–0.8)
				Alzheimer disease	HR=0.4 (0.2–0.7)

Data from cohort studies in a systematic review.

CI=confidence interval; HR=hazard ratio; OR=odds ratio; RR=relative risk.

not included in the above-mentioned systematic review, 1 showed an 80% risk reduction of dementia in people older than 65 years who self-reported participating in at least 3 leisure activities over 3 years, as compared with patients who did not report such participation (n=2,043; relative risk [RR] 0.20; 95% CI, 0.04–0.87). The other cohort study of people older than 55 years (n=5,055) demonstrated an increased risk of dementia over a 10-year period in people who did not report participating in reading or writing activities (RR 4.2; 95% CI, 2.4–7.2). Many of the included studies did not control for confounding variables such as educational level, occupation, or baseline cognition.[2]

A 2011 cohort study examined the association between doing crossword puzzles and speed of cognitive decline in the 101 participants who developed dementia out of 488 people followed for up to 30 years.[3] Participants were between 75 and 85 years old, were cognitively normal at baseline (assessed by the Buschke Selective Reminding Test), and were living independently. Researchers followed participants over a 27- to 30-year period and assessed cognitive function every 12 to 18 months; the mean time to dementia diagnosis was 5 years (no statistical analysis provided).

Seventeen of the 101 participants who developed dementia reported doing crossword puzzles, ranging in frequency from less than once a week to daily, and were noted to have a 2.5-year (95% CI, 0.88–4.2) delay in the beginning of accelerated memory decline compared with participants who did not report doing crossword puzzles.[3] EBP

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What is the most effective management for *H pylori* gastritis?

Bottom line

The most effective treatments include 7–14 days of quadruple therapy, 10–14 days of standard triple therapy plus probiotics, and 10–14 days of levofloxacin plus amoxicillin/clarithromycin plus a proton-pump inhibitor (PPI) (SOR: **A**, meta-analyses of RCTs). In areas where resistance to either metronidazole or clarithromycin is >80%, clarithromycin, amoxicillin, metronidazole, and a PPI for 10 days preserves eradication rates (SOR: **A**, meta-analysis of RCTs).

Evidence summary

A 2015 systematic review and network meta-analysis of 143 RCTs (N=32,056; mean age 47) compared 14 therapies for *H pylori* infection.[1] Patients had no comorbid conditions. Eradication testing occurred 4–14 weeks after treatment.

Four treatment regimens yielded ≥90% eradication rates: (1) 7 days of concomitant therapy; (2) 10–14 days of concomitant therapy; (3) 10–14 days of standard triple therapy plus a probiotic; and (4) 10–14 days of a PPI plus levofloxacin and another antibiotic (see **TABLE**).[1]

The rates of adverse drug events among the above rates of adverse drug events among the above regimens were not statistically different from rates seen with 7 days of standard triple therapy (mean occurrence 0.21; 95% CI, 0.18–0.26).[1]

A 2007 meta-analysis of 93 RCTs (4 included in the above meta-analysis) and unblinded trials (N=10,178) examined the effect of emerging drug resistance on the efficacy of first-line treatment regimens for *H pylori*.[2] Resistance rates were stated to be 80% to 100% in developing countries and 30% to 45% in industrialized nations. Treatments lasted 3 to 16 days.

Metronidazole resistance reduced eradication rates of triple therapy (metronidazole, tetracycline, and bismuth) by 26% (95% CI, 14–38), but rates were reduced only 14% (95% CI, 5–23) when combined with a PPI. In areas of dual resistance, quadruple therapies containing both clarithromycin and metronidazole were associated with a 13% (95% CI, –22 to 49) reduced rate of efficacy. In areas with resistance to either metronidazole or clarithromycin, efficacy of quadruple therapy remained at 97% (95% CI, 94–99). The inclusion of unblinded trials lowers the level of evidence of this meta-analysis.[2] EBP

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TABLE

Network meta-analysis results of eradiation rates for antibiotic regimens for the treatment of *H pylori* gastritis[1]

Treatment	Network meta-analysis risk ratio (95% CI)	Direct comparison risk ratio (95% CI)	Eradication rate (95% CI)
7 days triple therapy (amoxicillin, clarithromycin, PPI)	Reference standard	Reference standard	0.73 (0.71–0.75)
7 days concomitant/quadruple therapy (amoxicillin, clarithromycin, metronidazole, and PPI)	1.29 (1.22–1.35)	1.39 (1.16–1.67)	0.94 (0.89–0.98)
10 or 14 days concomitant/quadruple therapy (amoxicillin, clarithromycin, metronidazole, and PPI)	1.24 (1.19–1.29)	N/A	0.91 (0.87–0.94)
10 or 14 days triple therapy plus probiotic	1.24 (1.17–1.29)	1.13 (0.69–1.84)	0.90 (0.85–0.94)
10 or 14 days levofloxacin, PPI, and amoxicillin or clarithromycin	1.23 (1.16–1.29)	N/A	0.90 (0.84–0.94)

N/A=not available; PPI=proton-pump inhibitor.

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EVIDENCE-BASED PRACTICE

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How can physicians promote exercise in adolescents?

EVIDENCE-BASED ANSWER

Use of smartphone apps may not improve teen cardiorespiratory fitness, but motivational interviewing added to usual care appears to increase physical activity time. Computer-generated exercise plans seem to decrease sedentary behavior (SOR: **B**, small RCTs).

A 2015 RCT of 51 adolescents 14 to 17 years old compared use of both interactive (immersive, n=17) and noninteractive (nonimmersive, n=16) smartphone applications with usual behavior without applications (control, n=18) to increase cardiorespiratory fitness over 8 weeks.[1] Patients in New Zealand who owned a smartphone and were not spending at least 60 minutes a day in physical activity were recruited through advertising.

Three times per week use of an immersive or nonimmersive fitness training application did not significantly decrease time to complete a 1-mile walk/run fitness test (immersive app mean –28.4 sec; 95% CI, –66.5 to 9.8; *P*=.20; nonimmersive app mean –24.7 sec; 95% CI, –63.5 to 14.2; *P*=.32). Self-reported scores on the Physical Activity Questionnaire (a survey of physical activity time with 8 items rated 1–5) for the app groups did not differ from those for usual behavior (immersive app adjusted mean difference 0.14, *P*=.78; nonimmersive app adjusted mean difference 0.23; *P*=.42).[1]

A 2013 RCT of 54 obese adolescents 11 to 18 years old compared the effectiveness of 6 motivational interviewing telephone sessions added to a standard weight-loss program (n=26) versus the weight-loss program alone (n=28) over 6 months.[2] Patients were recruited at a French hospital through general practice referrals.

After 6 months, self-reported physical activity time per day was numerically higher for adolescents who received motivational interviewing, but the difference was not significant (1.3 vs 0.9 h/d; *P*=.22). However, a significant increase was noted in objective physical activity time measured with an accelerometer for adolescents who received motivational interviewing (2.01 vs 1.62 h/d; *P*<.01). This study was underpowered.[2]

A 2006 RCT of 878 adolescents 11 to 15 years old, some obese, examined use of a primary care office computer kiosk that assessed nutrition and physical activity and generated diet and physical activity progress plans (n=424) versus a control group (n=395) that received information about sunscreen protection.[3] Adolescents were volunteered by their parents. Trained staff provided patients with 5 sessions of supplemental telephone counseling per 6 months.

Self-reported sedentary behaviors decreased by 21% for girls and 24% for boys after 12 months (*P*<.001). However, self-reported active days per week significantly improved for boys (0.3 days; *P*=.01) but not for girls (0.1 days; *P*=.88).[3]

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Do daycare facilities adhere to exercise recommendations for preschool age children?

EVIDENCE-BASED ANSWER

Not generally. Less than 15% of daycare facilities adhere to the current recommendations by the Society of Health and Physical Educators for preschool-aged children (SOR: **B**, systematic review of observational studies and 2 observational studies).

In 2009, the Society of Health and Physical Educators recommended 120 minutes of physical activity daily for preschool-aged children that included both free play (unstructured) and adult-led structured activities.[1]

A 2010 systematic review of 13 observational studies from 2000 to 2008 evaluated moderate to vigorous-intensity physical activity (MVPA) in 1,900 children 3 to 6 years old attending 96 childcare centers in the United States (7 studies) and 5 European countries (6 studies).[2] MVPA was measured over 1 to 6 days by Actigraph accelerometer (7 studies, n=994) or with observation or pedometers (6 studies, n=1,295).

In 1 study (n=122) using actigraphy, 8% of children had MVPA longer than 60 minutes. In the remaining 6 actigraphy studies (n=872), the MVPA extrapolated to an 8-hour day was less than 60 minutes. Using direct observation, the average MVPA extrapolated over 8 hours was 64 minutes or less (3 studies, n=946). In the studies using a pedometer, the children took up to 10,000 steps in an 8-hour day (3 studies, n=359), but the intensity of the exercise was not measured. A key weakness of the systematic review was inconsistent MVPA definitions or a lack thereof for each of the studies.[2]

A 2015 observational study of 10 childcare facilities in Washington investigated activity in 98 children 3 to 5 years old over 4 full days (8:00 AM to 5:00 PM) through observation and while wearing an Actigraph accelerometer.[3] Observed physical activity included structured and unstructured "active play opportunities."

The average daily physical activity time measured by observation was 49 minutes per day, made up of teacher-led structured active play opportunities of 9 minutes and unstructured play time of 40 minutes. An average of 12% of total care time was spent in some type of physical activity. The Actigraph accelerometer data were categorized as sedentary, light, or MVPA (specific definitions not given), and only 34% of the 98 children had more than 60 minutes of MVPA.[3]

A 2009 observational study examined physical activity in children 3 to 5 years old (total number of children not given) at 96 childcare centers representative of North Carolina's demographics.[4] The observation took place over 1 day. Physical activity in this study was defined as active play (unstructured or teacher-led structured nonsedentary activity inside or outside). Only 14% of centers had an average physical activity time longer than the recommended 120 minutes; 59% of centers had physical activity time longer than 60 minutes.

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Does vitamin B_{12} supplementation improve outcomes for patients taking metformin?

EVIDENCE-BASED ANSWER

Administration of routine vitamin B_{12} supplementation may protect against biochemical B_{12} deficiency in adults with type 2 diabetes who take metformin, but the clinical significance of this therapy is unknown (SOR: **C**, cross-sectional and case-control studies with disease-oriented outcomes).

A cross-sectional study used data from adults at least 50 years old queried by the 1999 to 2006 National Health and Nutrition Examination Survey to determine the effect

of vitamin B_{12} supplementation on prevalence of vitamin B_{12} deficiency among 3 groups: patients with type 2 diabetes taking metformin for an average of 5 years (n=575), patients with diabetes not taking metformin (n=1,046), and patients without diabetes (n=6,867).[1] The prevalence of B_{12} deficiency (defined as a serum level <149 pmol/L) in the 3 groups was 5.8%, 2.2%, and 3.3%, respectively. Diet histories were reviewed for vitamin B_{12} intake.

Of the 209 (41%) metformin users taking a supplement containing vitamin B_{12}, 33% were taking 0 to 6 µg/d and 61% were taking more than 6 µg/d; data were unavailable on the supplement dose for the remaining 6%. Although supplement use overall was not associated with a decrease in the prevalence of B_{12} deficiency (5.6% vs 5.3%; *P*=.9), higher supplement doses trended toward protection against B_{12} deficiency. The prevalence of B_{12} deficiency was 14% for those taking 0 to 6 µg/d and 1.8% for patients taking more than 6 µg/d (*P*<.03 for linear trend).[1]

A case-control study evaluated the relationship between metformin-induced vitamin B_{12} deficiency, hyperhomocysteinemia, and vascular complications in 100 patients with type 2 diabetes, 62 of whom were taking metformin.[2] Of those 62 patients, 13% had B_{12} deficiency (serum level ≤150 pmol/L), and 29% had borderline B_{12} deficiency (serum level 150–220 pmol/L). Conversely, of the 38 patients not on metformin, 8% had B_{12} deficiency, and 13% had borderline B_{12} deficiency.

Overall, 42% of patients in the metformin-treated group had low B_{12} levels versus 21% in the non–metformin-treated group (*P*<.05). Researchers randomly selected 46 patients from the metformin group to evaluate the relationship among metformin use, serum B_{12} levels, homocysteinemia, and vascular complications. Hyperhomocysteinemia (serum level ≥10 µmol/L) was higher in the metformin-treated patients versus non–metformin-treated patients (46% vs 34%; statistical analysis not provided). B_{12} levels were lower in metformin users than the nonusers (serum levels 250 and 318 pmol/L, respectively; *P*=.03). However, neither hyperhomocysteinemia nor vitamin B_{12} deficiency were associated with either stroke or coronary heart disease.[2]

Ten patients in the metformin group were given oral B_{12}, 1,500 µg/d, for an average of 2.2 months; the mean serum B_{12} level rose from 152 to 299 pmol/L (*P*<.01). However, no corresponding change was noted in homocysteine levels. This study was limited by its small total number of patients, its observational nature, the short period of follow-up, and the lack of assessment of clinical impact of B_{12} supplementation.[2]

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Should the varicella-zoster virus be given to all children to prevent chicken pox?

EVIDENCE-BASED ANSWER

The administration of the varicella vaccination to healthy, nonimmunized children greatly decreases the incidence of varicella (SOR: **B**, double-blind placebo-controlled efficacy trial). Such vaccination has resulted in an 87% reduction in varicella-related mortality. The use of the vaccine in immunocompromised children has not been approved by the US Food and Drug Administration.

A double-blind controlled efficacy trial of the live attenuated Oka/Merck varicella vaccine was conducted among 956 children between 1 and 14 years old with a negative clinical history of varicella.[1] Of the 914 who were serologically confirmed to be susceptible to varicella, 468 received the vaccine and 446 received the placebo.

Approximately 8 weeks after vaccination, 94% of the children who were seronegative initially had antibodies to varicella. During the 9-month surveillance period after the vaccination, 39 cases of varicella occurred, 38 of them confirmed by laboratory tests. All 39 cases occurred in placebo recipients. The vaccine was 100% efficacious in preventing varicella in this population of healthy children. There was no recorded disease spread from vaccinated children to siblings.[1]

A cohort study of 35 children with chronic renal insufficiency (25 on dialysis) evaluated the efficacy of 2 doses

of high-dose live attenuated varicella vaccine.[2] All children seroconverted with no adverse effects. Of the surviving recipients, 82% had protective immunity at the 20-month follow-up.

A population-based study between 2005 and 2009 included 322 children younger than 18 years with a confirmed diagnosis of varicella-zoster.[3] Varicella-zoster virus typing revealed 84% were wild-type, 15% were vaccine-type, and 2% were a possible wild/vaccine recombinant type. One third of the associated patients were vaccinated and two-thirds were unvaccinated.

Vaccinated children had a 79% lower incidence of herpes zoster than unvaccinated children ($P<.001$). Lower incidence rates were present in the 3–9 and 10–17 years age groups. Among children aged 1 to 2 years, the incidence of vaccine-type herpes zoster was higher among vaccinated children, at 100 per 100,000 person-years ($P=.01$). The incidence rate for wild-type varicella infection in unvaccinated 1- to 2-year-old children was unavailable for comparison. The incidence of herpes zoster was higher in girls than in boys and among immunosuppressed than nonimmunosuppressed children, but the significance of these findings was uncertain.[3]

The annual average age-adjusted mortality rate attributed to varicella was 0.05 per million population after the initiation of the routine 2-dose varicella vaccine program from 2008–2011.[4] This represented an 87% reduction compared with the prevaccine years. Since 1996, the Centers for Disease Control and Prevention has received reports of 5 varicella-related deaths among children and adolescents who previously received 1 dose of varicella vaccine. Four patients were taking high-dose steroids or had an underlying immunocompromising condition.

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Do OTC remedies relieve cough in acute URIs?

EVIDENCE-BASED ANSWER

Honey and diphenhydramine improve ratings of cough frequency compared with baseline by 2.0 and 1.7 points, respectively, on a 7-point Likert scale in children (SOR: **B**, meta-analysis of small RCTs). Dextromethorphan provides decrease in cough frequency and cough ratings in adults, but no changes in cough frequency for children (SOR: **A**, meta-analyses). Sesame seed oil is not effective for cough symptoms in children (SOR: **B**, RCT).

A 2014 meta-analysis of 3 RCTs compared honey with no treatment, placebo, diphenhydramine, or dextromethorphan in children 1 to 18 years old in the ambulatory setting with cough from acute upper respiratory tract infections (URI).[1] Patients (N=568) were given 1 dose of either honey or 1 of 4 comparators (no treatment, placebo, dextromethorphan, or diphenhydramine) and then followed for 24 hours. The first study compared 10 g honey with placebo, the second study compared honey with diphenhydramine, dextromethorphan, or no treatment (doses not reported), and the third study compared honey with dextromethorphan or no treatment (doses not reported). Caregivers rated cough symptoms on a 7-point Likert scale (ranging from 0, not at all; to 6, extremely) before and after the intervention.

Overall, compared with baseline, honey significantly reduced ratings of cough frequency (3 trials, n=300; mean difference [MD] 2.0; 95% CI, 1.3–2.7), as did dextromethorphan (2 trials, n=74; MD 1.5; 95% CI, 0.88–2.1) and diphenhydramine (1 study, n=40; MD 1.7; 95% CI, 0.74–2.7). The honey group had a significant decrease in caregivers' ratings of cough frequency when compared with no treatment (2 trials, n=154; MD 1.1; 95% CI, 0.62–1.5), placebo (1 trial, n=300; MD 1.9; 95% CI, 0.33–3.4), and diphenhydramine (1 trial, n=80; MD 0.57; 95% CI, 0.24–0.90), but no significant difference was seen when honey was compared with dextromethorphan (2 trials, n=149).[1]

A 2014 systematic review of 29 clinical trials (19 in adults, 10 in children) with 4,835 total patients with acute cough due to URIs (3,799 adults and 1,036 children) evaluated oral cough medications.[2] Six trials involved antitussive treatment

in adults, 3 of which compared dextromethorphan 30 mg in a single dose with placebo and measured cough counts using microphone acoustic signals through the nose.

One RCT (n=451) measured significantly fewer cough counts among participants using dextromethorphan, with a net difference of 8 to 10 coughing bouts every 30 minutes compared with placebo (P<.05). A second RCT (n=44) demonstrated improvement at 3 hours in each group from 50 to 19 coughs per 10-minute period in the active group and from 42 to 21 in the placebo arm, but no difference between groups (P=.38), although there was greater decline in cough scores versus placebo at 180 minutes (P=.08). A third study (a meta-analysis of 6 international RCTs, n=710) demonstrated improvement in cough bouts by 12% to 17% over placebo (P<.001). Four trials involved children giving varying doses of dextromethorphan, ranging from a single age-based dose nightly to 5 mg 3 times daily, versus placebo for 3 nights, and showed no change in cough score reduction versus placebo.[2]

A 2006 RCT compared the use of sesame seed oil with placebo in children 2 to 12 years old, with cough from the common cold, presenting to a primary care clinic.[3] Patients (N=107) were given either 5 mL sesame seed oil or 5 mL of similarly flavored placebo each night, and were followed for 3 days. Parents evaluated symptoms by a 4-point Likert scale, with 1 indicating absent and 4 indicating severe for each symptom 2 hours before and after the intervention.

On day 1, no significant difference was noted in decrease of cough frequency from baseline with sesame oil versus placebo (effect size 0.26; 95% CI, –0.64 to 0.12) or decrease in cough strength from baseline (effect size 0.15; 95% CI, –0.53 to 0.23). Cough symptoms on day 3 improved in both the sesame seed oil and placebo groups, but again, no significant difference was noted between the interventions.[3]

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Does maternal position during delivery affect the incidence of neonatal shoulder dystocia?

EVIDENCE-BASED ANSWER

Apparently not. Although underpowered, studies show that mothers delivering in McRoberts position (flexion and abduction of hips) with or without early suprapubic pressure or alternative positions (such as lateral, hands-knees, or squatting) do not have a reduced incidence of shoulder dystocia compared with mothers delivering in the standard lithotomy position (SOR: **B**, underpowered RCTs, quasi-RCT, and cohort study).

A 2003 RCT of 128 pregnant women at risk for shoulder dystocia (ie, estimated fetal weight >3,800 g) compared the effect of McRoberts maneuver and suprapubic pressure before delivery of the fetal head (prophylactic) versus the same maneuvers after delivery of the fetal head (usual care controls) on head-to-body delivery time.[1] Head-to-body delivery times were similar between the prophylactic and control groups (24 vs 27 seconds; P=.38). The incidence of shoulder dystocia, defined as head-to-body delivery time longer than 60 seconds, was similar in both groups (5% vs 7%; P>.99).

A 2007 quasirandomized controlled trial, compared rates of shoulder dystocia during vaginal delivery in 200 mothers (>37 weeks' gestation) alternately assigned to maternal squatting position versus lithotomy during the second stage of labor.[2] No significant difference was noted between the squatting and supine positions in the incidence of shoulder dystocia (0% vs 2%; P=.25).

A 2013 retrospective cohort study compared obstetric outcomes including shoulder dystocia in vaginal deliveries performed by 2 physicians allowing mothers to adopt alternative positions based on their preference (either lateral, hands-knees, or squatting, n=95) versus deliveries by 2 other physicians using the dorsal recumbent position (n=181).[3] No difference was noted in the rates of shoulder dystocia between alternative and dorsal recumbent positions (4.6% vs 5.3%; reported as not statistically significant but P value not reported). No difference was noted when data were adjusted for gestational age and labor induction (odds ratio 1.0; 95% CI,

0.29–3.4). The study was limited by no objective definition of the shoulder dystocia outcome.

A 2004 RCT compared the efficacy of prophylactic McRoberts position versus no intervention in decreasing the force applied to the fetus during vaginal delivery in full-term, multiparous, singleton pregnancies.[4] Twenty-seven patients were randomized to the McRoberts position or to the lithotomy position without McRoberts. Force on the fetal head was measured via sensors on the physician's glove.

The primary outcome of peak force on the fetal head was similar in both groups (McRoberts 8.0 lb vs lithotomy 7.2 lb; *P*=.5). The secondary outcome of shoulder dystocia was equal in both groups: 1 case in 14 with McRoberts and 1 case in 13 with lithotomy position (*P*=1.0).[4]

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Is poor periodontal oral health in pregnant women a risk factor for preterm delivery and low birth weight?

EVIDENCE-BASED ANSWER

Maternal periodontitis is associated with increased risk of low birth weight (<2,500 g) (SOR: **B**, prospective cohort study). Maternal periodontitis may be associated with shorter gestation (SOR: **B**, conflicting prospective cohort and cross-sectional studies, with better quality evidence favoring an association). Treatment of periodontal disease in early pregnancy has not been shown to affect birth weight or preterm labor (SOR: **C**, underpowered RCT).

In a 2015 prospective cohort study of 340 pregnant women 18 to 28 years old, researchers collected data on health habits and medical and reproductive history through a questionnaire, and performed a periodontal examination during the second trimester of pregnancy.[1] Participants had no history of systemic medical problems, obstetric problems, malnourishment, or history of periodontal disease in the current pregnancy, and had a minimum of 20 natural permanent teeth.

Logistic regression analyses assessed the association of periodontitis with pregnancy outcomes, specifically preterm birth (<37 weeks' gestation) and low birth weight (<2,500 g). Oral examination was performed using the Community Periodontal Index developed by the World Health Organization (WHO) guidelines for screening of periodontal disease and measures of clinical attachment loss.[1]

After adjusting for relevant risk factors and covariates such as socioeconomic status, parity, history of prior preterm birth, and smoking exposure, maternal periodontitis was associated with an increased risk of preterm birth (odds ratio [OR] 4.54; 95% CI, 1.98–5.46) and low birth weight (OR 5.32; 95% CI, 2.01–6.79).[1]

A 2014 cross-sectional study of mothers aged 18 to 35 years with a singleton pregnancy (N=770) investigated the association between maternal periodontal disease and its effect on maternal hemoglobin levels and incidence of low birth weight and length of gestation.[2] All participants were selected from the maternity ward of a single hospital in India, currently healthy, of similar socioeconomic status (status not given), and had no history of multiple pregnancies. Periodontal disease was categorized according to probing pocket depth using the WHO Community Periodontal Index.

Prevalence of low birth weight (<2,500 g) increased with the severity of periodontal disease, with a significantly higher incidence in the worst periodontitis category compared with the healthy category (31.3% of births vs 17.1%; *P*=.032). Periodontal disease did not affect length of gestation.[2]

A 2014 RCT of pregnant women with chronic generalized periodontitis (N=20) examined the effect of phase I periodontal therapy prior to 28 weeks of gestational age on birth weight, incidence of preterm birth, and IgM/IgG antibody levels in cord blood at delivery compared with no prenatal treatment of periodontitis.[3] Patients were 18 to 35 years old with a singleton pregnancy between 12 and 24 weeks' gestation, had periodontitis that had not been treated in the

previous 6 months, were not current smokers, and did not have a history of alcohol consumption.

No difference was noted in normal births (defined as delivery after 37 weeks' gestation and birth weight >2,500 g) between the untreated and treated groups (70% vs 100%, respectively; *P*=.23). The study was likely underpowered to detect a difference.[3]

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Are neonatal mortality rates higher in birthing centers than in hospitals?

EVIDENCE-BASED ANSWER

No. Neonatal mortality rates of freestanding and hospital-based birth centers are not significantly different from those of hospitals (SOR: **A**, systematic review of RCTs and consistent cohort studies).

A 2012 systematic review (5 RCTs, N=6,385) evaluated rates of perinatal mortality and serious perinatal morbidity (defined as birth asphyxia, neonatal encephalopathy, severe respiratory distress syndrome, and other conditions predictive of long-term disability) in conventional versus alternative institutional birth settings.[1] The alternative institutional settings were characterized by a philosophy of labor and birth as a normal experience and existed to serve low-risk pregnant women who expressed a preference for little to no medical intervention. The study settings varied in layout within the hospital and degree of midwife involvement. Of note, no trials in freestanding birth centers were included in this review.

Overall, perinatal mortality and serious perinatal morbidity of women at low risk for obstetric complications were not significantly increased in hospital birth centers compared with conventional labor wards (relative risk [RR] 1.17; 95% CI, 0.51–2.67). Significant heterogeneity (I^2= 66%) was identified in analysis of the study results.[1]

A 2007 retrospective cohort study (N=1,002,249) used data from the Australian national database to evaluate the rates of perinatal mortality in all births performed in a birth center or hospital in Australia between the years 1999 and 2002.[2] Of these women, 21,800 (2.18%) gave birth in a freestanding birth center, 972,664 (97.14%) gave birth in a hospital, and 6,785 (0.68%) were excluded because of missing place of birth data or because they gave birth in another location.

The study compared 28-day mortality in term infants born in birth centers with term infants of low-risk women born in the hospital (defined as vertex-presentation infants at 37–41 weeks' gestation with birth weight ≥2,500 g, in women between 20 and 34 years of age with no preexisting or gestational hypertension or diabetes).[2]

Neonatal mortality was significantly lower among women who gave birth in birth centers than among women with low-risk hospital births, even when adjusted for maternal age, indigenous status, and public/private accommodation status. For primiparas, the adjusted odds ratio (aOR) was 0.25 (99% CI, 0.9–0.65); for multiparas, the aOR was 0.09 (99% CI, 0.2–0.31). Women who intended to give birth in a birth center but were transferred to a hospital were counted as giving birth in a hospital and the effect of transfer was not accounted for in study results.[2]

A 2010 retrospective cohort study of 827,955 Australian women looked at the data from the Australian birth registry from 2001 to 2005 in a similar fashion as the 2007 retrospective cohort study, but instead counted infants born in a hospital among the birth center group if their mothers intended to give birth in a birth center.[3] Birth centers in this study included both freestanding and "alongside hospital" birth centers. Of the total number of women, 22,222 women (2.7%) intended to give birth in a birth center, while 822,955 (96.8%) intended to give birth in the hospital; 0.5% of women intended to give birth at home or in other settings.

The neonatal mortality rate was significantly lower among women who intended to give birth in a birth center, regardless of actual place of birth, compared with low-risk women who intended to give birth in the hospital. However, when adjusted for maternal age, indigenous status, and public/private accommodations, no significant difference was noted

in neonatal mortality (primipara aOR 1.00; 99% CI, 0.61–1.65; multipara aOR 1.00; 99% CI, 0.62–1.61).[3]

A 2011 nationwide prospective cohort study in the United Kingdom of 64,538 women with low-risk pregnancies evaluated rates of maternal and neonatal morbidities, including stillbirth and neonatal death.[4] Women were grouped based on the setting in which they intended to give birth; data were collected on women giving birth in birth centers and obstetric units between April 2008 and April 2010. A total of 19,706 women gave birth in the obstetric unit, versus 11,282 in the freestanding birth center and 16,710 in the "alongside hospital" birth center.

The study found no significant difference in adverse perinatal events in births in either freestanding (OR 0.82; 95% CI, 0.52–1.28) or alongside (OR 0.84; 95% CI, 0.54–1.30) birth centers compared with obstetric units.[4]

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Does chewing gum promote return of bowel function after colorectal surgery?

EVIDENCE-BASED ANSWER

Chewing gum decreases time to first flatus and time to first bowel movement by less than a day. It also decreases the incidence of postoperative ileus on post-operative day 5 with a general trend towards reducing length of hospital stay by up to 1 day. However, when early refeeding protocols are used as a comparator, this effect diminishes (SOR: **A**, meta-analyses of RCTs and single RCT).

A 2015 meta-analysis of 81 RCTs (N=9,072) evaluated the effects of chewing gum as a form of sham feeding on return of bowel function after any abdominal surgery.[1] Investigators included a subgroup analysis of 22 RCTS (n=1,668) of colorectal surgeries in adults. Commercially available, predominantly sugarless gum was given 3 to 4 times per day and chewed an average of 10 to 30 minutes at a time.

Compared with standard postoperative care (not described), chewing gum reduced time to first flatus by 12.5 hours (22 studies, n=1,668; 95% CI, –17.2 to –7.8) and time to first bowel movement by 18.1 hours (20 studies, n=1,470; 95% CI, –25.3 to –10.9). Length of hospital stay was reduced by 1.0 day (18 studies, n=1,523; 95% CI, –1.6 to –0.4). In a subgroup of 4 studies (n=724) using early postoperative feeding regimens (within 24 hours) for all patients, chewing gum showed a reduction in time to first bowel movement by 21.1 hours (4 studies, n=635; 95% CI, –33.1 to –9.2), but the differences in time to first flatus and hospital stay became nonsignificant.[1]

Another meta-analysis from 2014 with the same inclusion criteria involved only 10 RCTs (N=612), which were all included in the meta-analysis above.[2] Nine other studies included in the meta-analysis above and published before the search dates of this meta-analysis were not included for reasons not reported. This smaller group of studies demonstrated a much smaller magnitude of effect.

Compared with standard postoperative care (not described), chewing gum reduced time to first flatus by 0.52 hours (10 studies, n=612; 95% CI, −0.86 to −0.18), time to first bowel movement by 0.50 hours (10 studies, n=612; 95% CI, −0.99 to −0.012), and length of stay (LOS) by 0.5 days (8 studies, n=462; 95% CI, −0.86 to −0.14). Subgroup analysis of 2 studies (n=271) using early postoperative feeding showed no statistical difference in time to first flatus or bowel movement.[2]

A 2015 RCT evaluated the effect of chewing gum as a form of sham feeding on return of bowel function in 120 adults after elective open hemicolectomy or rectal resection.[3] The control group wore an inert dermal patch, but were led to believe the patch would possibly increase gut motility. The intervention group received commercially available sugarless gum 3 hours before surgery and patients were encouraged to chew a new piece 3 times per hour starting 3 hours after surgery. The refeeding protocol used was not reported.

The mean LOS was not statistically different between the groups: the intervention group LOS was 9.5 days (median 9 days) and the control group LOS was 14.0 days (median 9 days;

P=.07). A significant reduction was noted in postoperative ileus (lack of passage of flatus or stool and intolerance to oral intake for 24 hours on postoperative day 5), which occurred in 27% of the intervention group compared with 48% of the control group (*P*=.02).[3]

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Is duct tape therapy effective as a single agent for treating nongenital warts?

EVIDENCE-BASED ANSWER

Duct tape is no better than nonmedicated dressing or cryotherapy for the treatment of nongenital warts (SOR: **A**, meta-analysis of RCTs).

A 2012 meta-analysis identified 3 RCTs (254 patients aged 3 years to adult) on the use of duct tape compared with placebo (2 studies) or cryotherapy (1 study) for treatment of warts.[1] Clear duct tape was used in 2 of the studies and opaque duct tape was used in the comparison with cryotherapy.

The duct tape was applied to cover 1 or more warts per patient for as long as 8 days, then the wart was debrided and left open overnight and the duct tape was reapplied the next day. The tape was kept in place until resolution of the wart or for as long as 2 months. Liquid nitrogen was applied weekly for up to 6 treatments. Placebo was either nonmedicated materials such as mole skin or a corn pad. The primary endpoint in each of the studies was wart resolution as determined by the investigators.[1]

Pooled results of clear duct tape versus placebo found no difference in wart resolution (2 trials, n=193; relative risk [RR] 1.4; 95% CI, 0.51–4.1). Individual results for wart resolution found clear duct tape was no better than a corn pad (n=103; 16% vs 6%, respectively; *P*>.05) or moleskin (n=90; 21% vs 22%, respectively; *P*>.05). These studies were rated as low risk of bias, but due to their small size may have been underpowered to detect a difference. Opaque duct tape was equivalent to cryotherapy in wart resolution (1 study, n=61; RR 1.5; 95% CI, 0.99–2.3). This study was subject to bias from high attrition and lack of blinding.[1]

In 2011, another meta-analysis of the same 3 RCTs (N=254) also assessed the effectiveness of duct tape as a treatment for warts.[2] This meta-analysis pooled the data from the study comparing opaque duct tape versus cryotherapy with the data from the other 2 studies. Pooled results of duct tape (all types) versus placebo or cryotherapy found no difference in wart resolution (RR 1.4; 95% CI, 1.0–1.9).

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How effective is cinnamon in improving blood glucose control in individuals with diabetes?

EVIDENCE-BASED ANSWER

Cinnamon therapy, in general, likely does not alter glycosylated hemoglobin (HbA1C), although the supplement might possibly lower fasting plasma glucose (FPG) in patients with diabetes (SOR: **C**, meta-analyses of heterogeneous RCTs with inconsistent results). Evidence is insufficient to support the use of cinnamon in diabetes (SOR: **C**, practice guideline).

A 2013 systematic review and meta-analysis identified 10 RCTs (N=543) that examined the effectiveness of oral cinnamon supplementation for glycemic control in patients with type 2 diabetes mellitus.[1] Patients were included regardless of other interventions for control of their

diabetes. Eight RCTs (n=499) evaluated HbA1C reduction over a period of 4 to 18 weeks and 9 trials (n=474) reported results for FPG. Cinnamon doses ranged from 120 mg to 6 g per day in aqueous cinnamon extract or raw cinnamon powder and were compared with placebo.

The pooled results demonstrated no significant reduction of HbA1C (mean difference [MD] –0.16%; 95% CI, –0.39 to 0.02) with cinnamon use compared with placebo. A moderate to high degree of heterogeneity (I^2=66.5%) was noted for HbA1C reduction studies. Cinnamon use was associated with reductions in FPG compared with placebo (MD –24.6 mg/dL; 95% CI, –40.5 to –8.7 mg/dL). A high degree of heterogeneity (I^2=92.0%) was noted among the FPG studies.[1]

A 2012 systematic review and meta-analysis identified 10 RCTs (N=577) that examined the effectiveness of oral cinnamon in patients with type 1 or type 2 diabetes based on HbA1C, FPG, serum insulin, or postprandial glucose.[2] Eight of these trials were included in the 2013 review; 2 additional trials were identified in this review. The average daily dose of cinnamon was 2 g for a mean duration of 11 weeks.

The pooled results of 8 trials (n=338) with high heterogeneity (I^2=82%) found no significant difference in FPG between cinnamon and placebo (MD –0.83 mmol/L; 95% CI, –1.7 to 0.02). Among the 6 trials (n=405) focused on HbA1C, the pooled analysis found no significant difference in HbA1C between cinnamon and control groups (MD –0.06%; 95% CI, –0.29 to 0.18). No significant heterogeneity was noted in the trials focused on HbA1C (I^2=0).[2]

A 2014 American Diabetes Association nutrition guideline stated that evidence was insufficient to support the use of cinnamon or other herbs/supplements for the treatment of diabetes, with a level of recommendation C (evidence from poorly controlled or uncontrolled studies or there is conflicting evidence).[3]

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Do manual therapies to the perineum during the second stage of labor reduce the incidence of genital tract trauma during vaginal deliveries?

EVIDENCE-BASED ANSWER

Warm compresses and perineal massage in the second stage of labor each reduce incidence of third- and fourth-degree lacerations compared with usual care (SOR: **A**, systematic review of RCTs). "Hands off" reduces the incidence of episiotomy (SOR: **B**, systematic review and single RCT). Perineal massage does not reduce the incidence of postpartum perineal pain (SOR: **B**, single RCT). The modified Ritgen maneuver does not reduce perineal trauma (SOR: **B**, systematic review containing a single RCT).

A 2017 systematic review of 7 RCTs and 1 quasirandomized clinical trial (N=11,651) of pregnant women with singleton, cephalic, healthy term pregnancies examined the effectiveness of perineal techniques in the second stage of labor to reduce genital tract trauma at delivery.[1] Interventions included warm compresses, perineal massage, lubrication with petroleum jelly, hands off (or poised), perineal stretching with contractions, and modified Ritgen maneuver. Comparison techniques were hands off, standard hands on, or usual care. Perineal massage was performed at the vaginal introitus for 1 second, during and between pushes. Modified Ritgen maneuver involved using the fingers of 1 hand to reach for the fetal chin and placing the other hand to control delivery of the fetal head.

Both warm compress and perineal massage interventions showed a reduction in third- or fourth-degree lacerations (see **TABLE**). "Hands off (or poised)" positioning was less likely to result in episiotomy. Modified Ritgen maneuver did not affect the incidence of third- and fourth-degree lacerations or episiotomy. No harms were reported for any of the perineal techniques. Trials were heterogeneous because of the variety of perineal techniques and differences within specific techniques. Bias included lack of blinding (performance and detection bias) and selective reporting.[1]

A single hospital RCT (N=396) examined the effectiveness of perineal massage for 10 minutes at least once during

TABLE

Effectiveness of various perineal techniques in the second stage of labor to reduce perineal trauma at delivery[1]

No. of studies	No. of patients	Intervention	Comparison	Outcome	Relative risk	95% Confidence interval	Number needed to treat
2	1,525	Warm compress	Hands off or no warm compress	3rd- or 4th-degree laceration[a]	0.48	0.28–0.84	40
				Episiotomy	0.93	0.62–1.4	—
				Intact perineum	1.1	0.86–1.3	—
2	2,147	Perineal massage	Hands off or usual care	3rd- or 4th-degree laceration[a]	0.52	0.29–0.94	73
				Episiotomy	1.4	0.42–4.9	—
				Intact perineum	1.0	0.90–1.2	—
3	6,617	Hands off or poised	Hands on	3rd- or 4th-degree laceration	0.73	0.21–2.6	—
2	6,547	Hands off or poised	Hands on	Episiotomy[a]	0.69	0.50–0.96	2,500
				Intact perineum	1.0	0.95–1.1	—
1	1,423	Ritgen's maneuver	Hands on	3rd- or 4th-degree laceration	1.2	0.78–2.0	—
				Episiotomy	0.81	0.63–1.0	—

[a]Statistically significant.

the second stage compared with control.[2] Patients were primigravidas, 18 to 35 years old, with a gestational age of 37 to 42 weeks and healthy singleton vertex pregnancies, who presented to a Turkish hospital. Perineal massage was initiated when cervical dilation was at least at 8 cm, and consisted of fingers within the vagina, moving from the perineal floor toward the lateral aspect in half circles during 1 second and pressing the perineum downward toward the rectum.

Perineal massage resulted in fewer episiotomies (52% vs 61%; odds ratio [OR] 0.71; 95% CI, 0.50–0.99; number needed to treat [NNT]=12) and fewer episiotomies with lacerations (7.6% vs 16%; OR 0.44; 95% CI, 0.23–0.83; NNT=12). However, no difference was noted in women with intact perineum; spontaneous lacerations; or perineal pain on the first day, third week, or first year postpartum. No harms were reported. Study quality was limited by a high baseline rate of episiotomy in the institution, lack of blinding, incomplete outcome data, selective reporting, and an institutional practice of suturing all spontaneous lacerations, which could have affected reporting of postpartum pain.[2]

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Is the addition of fish oil to statin therapy in patients with persistent hypertriglyceridemia more effective than statins alone?

EVIDENCE-BASED ANSWER

Yes. Adding prescription-strength fish oil, or omega-3 fatty acids (OM3FA), to statin therapy is associated with an additional 20% to 30% reduction in triglyceride (TG) concentrations, but the effect on cardiovascular disease outcomes is not known (SOR: **C**, RCTs with disease-oriented evidence). Addition of OM3FA is recommended if TG concentrations remain significantly elevated despite statin therapy (SOR: **C**, expert opinion).

A large RCT evaluated the efficacy of adding OM3FA to statin therapy in 627 primary prevention patients at high cardiovascular risk due to diabetes (72%) and hypertension (86%) in 96 US clinics.[1] The study population was predominantly non-Hispanic white (92%) and male (59%), with a mean age of 61 years and TG values between 200 and 499 mg/dL. After 6 weeks of maximum-tolerated statin therapy, patients were randomized to 1 of 3 study groups: placebo, OM3FA 2 g/d, or OM3FA 4 g/d for 6 weeks.

Both doses of OM3FA caused greater reductions from baseline in TG values than placebo (OM3FA 4 g/d: 21% vs 5.9%, $P<.001$; OM3FA 2 g/d: 15% vs 5.9%, $P<.001$).[1]

A second RCT evaluated the effect of OM3FA in 254 patients (mean age 60 years) without coronary artery disease (CAD) from 41 US clinical sites.[2] Patients (96% white and 58% male) with fasting TG concentrations between 200 and 499 mg/dL after 8 weeks of simvastatin 40 mg/d, were randomized to OM3FA 4 g/d or matching placebo for an additional 8 weeks.

At 8 weeks, OM3FA added to statin therapy resulted in greater TG reduction from baseline than adding placebo (30% vs 6.3%; $P<.001$).[2]

A third RCT evaluated the TG-lowering effects of OM3FA 4 g/d compared with placebo in 59 patients (73% male, mean age 55 years) with established CAD, and TG of more than 200 mg/dL on simvastatin 10 to 40 mg/d (mean 32 mg/d).[3] The primary endpoint was change from baseline in TGs at 12 weeks.

OM3FA significantly reduced TGs from baseline at 12 weeks (28% decrease vs 2.6% increase; $P<.005$) and 24 weeks (24% decrease vs 2.6% increase; $P<.005$) compared with placebo. Baseline TG values were higher in the OM3FA group (407 mg/dL) than the placebo group (337 mg/dL).[3]

The 2011 American Heart Association guidelines for managing dyslipidemia stated that additional therapy may be used in patients with TG concentrations of more than 500 mg/dL to lower the risk of pancreatitis, but noted that the cardiovascular benefit is unknown (no strength of recommendation given).[4]

European guidelines updated in 2016 recommended statin therapy as the first agent to treat hypertriglyceridemia based on the ability of statins to reduce cardiovascular risk and lower TG concentrations.[5] The guidelines stated that prescription-dose OM3FA may be added to statins if further TG lowering is necessary (no strength of recommendation given). EBP

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Folic acid supplementation and prevention of chronic kidney disease

Xu X, Qin X, Li Y, Sun D, Wang J, Liang M, et al. Efficacy of folic acid therapy on the progression of chronic kidney disease: The renal substudy of the China Stroke Primary Prevention Trial. *JAMA Intern Med*. 2016; 176(10):1443–1450.

In this RCT, 15,104 Chinese adults with hypertension (a subset of a large stroke prevention trial) were randomized to 10 mg enalapril alone or 10 mg enalapril plus 0.8 mg folate to evaluate the effectiveness of folic acid and prevention of chronic kidney disease (CKD).

Over 4 years, patients in the folate group had a lower rate of CKD progression (defined as a decrease in creatinine clearance of ≥5 mL/min/1.73 m^2; 2.5% vs 2.1%; *P*=.05, number needed to treat [NNT]=250).

When the patients were divided into groups with and without baseline CKD, no outcomes were different among patients without CKD at baseline. Among the subset of patients with CKD at baseline, the folate group had a lower rate of CKD progression (6.8% vs 3.3%; *P*=.003, NNT=29). This patient population did not eat a diet fortified with folic acid.

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

Bottom line: Folate supplementation of 0.8 mg daily added to 10 mg enalapril reduced the likelihood of a rapid decline in creatinine clearance in patients with CKD. However, whether these findings would apply to a population that routinely eats a diet fortified with folic acid is not known. These findings may not prompt a change in the care of patients with hypertension in countries that fortify their food supply with folic acid.

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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.

Pediatric pneumonia: scan or x-ray

Jones BP, Tay ET, Elikashvili I, Sanders JE, Paul AZ, Nelson BP, et al. Feasibility and safety of substituting lung ultrasonography for chest radiography when diagnosing pneumonia in children: a randomized controlled trial. *Chest*. 2016; 150(1):131–138.

This RCT evaluated the effectiveness of point-of-care lung ultrasound compared with chest x-ray in 191 pediatric emergency department (ED) patients with suspected pneumonia. Patients (median age 3 years) presented to the ED with a clinical suspicion of having pneumonia and clinically requiring a chest x-ray.

Patients were randomly assigned to the lung ultrasound group, completing a chest x-ray only in the event of clinical uncertainty or if the admitting team or parent requested, or to the chest x-ray group, which was always followed by lung ultrasound.

Pneumonia was diagnosed in 14 of 103 (13.6%) patients in the lung ultrasound group and 12 of 88 (13.6%) patients in the chest x-ray group. There was a 39% reduction in chest x-rays in the lung ultrasound group, resulting in a number needed to scan of 2.5 (meaning 2.5 patients would need to undergo lung scan to prevent 1 chest x-ray).

Novice sonologists had a 30% reduction in chest x-ray use, whereas experienced sonologists had a 61% reduction. There were no missed pneumonias in either group and no difference in antibiotic use, unscheduled healthcare visits, or hospital admission. The lung ultrasound group had a reduction in cost of $9,200 during the study period.

This trial did not include a gold standard to diagnose pneumonia; a diagnosis of pneumonia could be made in the lung ultrasound group without confirmation as long as certain sonographic criteria were met (lung consolidation with air bronchograms).

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

Bottom line: Point-of-care lung ultrasound may be effective in diagnosing pneumonia and limiting chest x-ray use, but is not more diagnostically accurate than chest x-ray. Provider training, credentialing, and obtaining the required equipment may be barriers to implementation. EBP

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