Is cryotherapy effective for acute management of ankle sprain?

**Evidence-based answer**
Cryotherapy in combination with exercise may be slightly more effective than other treatments for acute ankle sprain (SOR: B, systematic review with significant study heterogeneity). Intermittent cryotherapy may be more effective for pain relief than standard cryotherapy during the first week (SOR: B, single RCT).

**Evidence summary**
A 2004 systematic review of 6 RCTs with 267 patients with ankle injuries evaluated cryotherapy as a part of treatment. Eight different cryotherapy regimens were studied. Study quality was rated by a 10-point Physiotherapy Evidence Database Scoring Scale. Study characteristics and quality along with intervention effect-size estimates for outcomes are summarized in the TABLE. Ice therapy was generally associated with less swelling than heat or contrast therapy and was better at pain relief than no therapy. Cryotherapy was also associated with a small improvement in function when combined with compression compared with compression alone.

A single RCT published after the systematic review above compared 2 cryotherapy protocols for treatment of grade 1 or 2 acute ankle sprains in 89 patients aged ≥16. A standard cryotherapy regimen of melted ice water in 20×20-cm plastic bags applied for 20 minutes every 2 hours for the first 72 hours after injury was compared with an intermittent cryotherapy regimen of application for 10 minutes, followed by removal for 10 minutes, then reapplication for 10 minutes; this strategy was repeated every 2 hours as above. Measures of function, pain, and swelling were recorded for 6 weeks after injury.

Pain with activity, as measured by a 10-cm visual analog scale, was lower in the intermittent cryotherapy group during the first week only (2.8 vs 4.0; P<.05). No differences were noted between...
groups in function, swelling, or pain at rest at any time, or in pain with activity after the first week postinjury.\textsuperscript{2}

Recommendations
A recently published evidence-based clinical guideline on the diagnosis, treatment, and prevention of ankle sprains developed under the auspices of the Royal Dutch Society of Physical Therapy cautions that “there are no indications that the use of ice only is effective to reduce swelling, increase function and reduce pain at rest in the event of an acute ankle injury,” yet also states that “ice and compression in combination with rest and elevation is an important aspect of treatment in the acute phase of lateral ankle injury.”\textsuperscript{3}

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\begin{table}
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\begin{tabular}{|l|l|l|l|l|}
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N in trial & Cryotherapy & Comparison & Outcome: effect size (95\% CI) & PEDro \\
\hline
30 & Ice bath + exercise & Heat + exercise & Swelling: \textbf{1.4} (0.35 to 2.3) & 5 \\
30 & Ice bath + exercise & Contrast bath + exercise & Swelling: \textbf{2.4} (1.13 to 3.4) & 5 \\
30 & Ice & Ice + E stim frequency 28 pps & Pain: \textbf{−0.64} (−1.5 to 0.28) \\
& & & Swelling: \textbf{−0.47} (−1.3 to 0.44) \\
& & & ROM: \textbf{−0.69} (−1.6 to 0.24) & 4 \\
30 & Ice & Ice + E stim frequency 80 pps & Pain: \textbf{−0.62} (−1.5 to 0.3) \\
& & & Swelling: \textbf{−1.4} (−2.3 to 0.36) \\
& & & ROM: \textbf{−1.4} (−2.3 to −0.3) & 4 \\
30 & Ice + compression & No Rx & Pain: \textbf{1.5} (1.2 to 1.8) & 3 \\
34 & Ice + compression & Compression (same mode) & Function: \textbf{−0.14} (−0.97 to 0.7) & 3 \\
34 & Ice + compression & Compression (different mode) & Function: \textbf{0.55} (0.32 to 1.4) & 3 \\
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\end{tabular}
\caption{Randomized controlled trials of cryotherapy for acute ankle sprain\textsuperscript{1}}
\end{table}

Positive numerical outcomes favor cryotherapy. Outcomes in boldface type are statistically significant.
E stim=electrical stimulation; PEDro=Physiotherapy Evidence Database Scoring Scale; pps=pulses per second; ROM=range of motion.


\begin{tabular}{|l|l|l|}
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ARR=absolute risk reduction & HR=hazard ratio & OR=odds ratio \\
CDC=Centers for Disease Control and Prevention & LOE=level of evidence & RCT=randomized controlled trial \\
CI=confidence interval & MRI=magnetic resonance imaging & RR=relative risk \\
CT=computed tomography & NNH=number needed to harm & SOR=strength of recommendation \\
FDA=US Food and Drug Administration & NNT=number needed to treat & SSRI=selective serotonin reuptake inhibitor \\
NSAID=nonsteroidal anti-inflammatory drug & & \\
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PB&J versus BLT

When I was younger, I really had a thing for peanut butter and jelly sandwiches. I probably ate 5 per week for 7 years straight. But when I got to medical school, PB&J and I had something of a falling out.

I was eating my usual chunky style with strawberry jam when an epidemiologist at the podium began discussing aflatoxins. She told us that aflatoxins were formed in moldy peanuts, caused cancer in animals, and were epidemiologically linked to liver cancer in humans. I slowly put down my sandwich and swallowed what I thought would be my last mouthful of peanut butter—ever.

But as I went along in medicine, I began hearing the drumbeat of epidemiological links between food and cancer over and over again. One year the culprit was coffee. The next year coffee was rehabilitated, and saccharin was the problem. For both physicians and the public, this sort of thing is crazy-making.

So I was fascinated to see a recent study in which authors randomly selected 50 ingredients from a cookbook and surveyed the literature for evidence of cancer links.1 While it was unfortunate that peanuts were not randomly selected, some of my other favorite foods were. As expected from random chance, about half the ingredients had a slightly positive association with cancer and the other half had a slightly negative association with cancer. When researchers lumped all the food ingredients together, the relative risk of getting cancer from PB&J versus BLT

uh, eating ... was about 1 (average RR 0.96).

The authors did not mention any individual foods in the text as being healthy or unhealthy. However, in 1 graph, there appeared to be only positive associations between cancer and bacon. So maybe BLTs are a poor substitute for PB&J. Foods with only healthy correlations included onions and olives, indicating perhaps muffuletta is the way to go (hold the salami, hold the cheese).

But there's one take home message that's clear: enjoy a varied diet and don’t be afraid of your food. I’m going for a PB&J right now. Bon appetit!
Diving for PURLs

PURLs Criteria

**Relevant:** Is the topic relevant to family medicine?
**Valid:** Are the findings scientifically valid?
**Change in practice:** Would this change practice?
**Medical care setting:** Is this implementable in clinic, etc?
**Implementable:** Can we implement this immediately?
**Clinically meaningful:** Are results clinically meaningful?

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**Capsaicin 8% patch: hurts so good?**


This meta-analysis of 7 RCTs (N=2,114) identified in the Qutenza Clinical Trials Database compared the onset and duration of response to Qutenza (8% capsaicin patch) with that of a low-dose concentration capsaicin patch (0.04%) in patients with postherpetic neuralgia (PHN; N=1,313) and HIV-associated neuropathy (HIV-AN; N=801).

At 2 to 12 weeks after patch application, 43% of participants in the intervention group (44% of PHN patients and 41% of HIV-AN patients) reported at least a 30% decrease in pain intensity score from baseline versus 34% in the control group (35% of PHN patients and 31% of HIV-AN patients) (RR 1.3; 95% CI, 1.1–1.4; NNT=11). Complete pain relief for all participants at 12 weeks was higher in the intervention group than among controls (9% vs 6%; labeled as statistically significant but no *P* value given).

Three of the studies allowed participants in either group to receive treatment with open-label high-dose patches after the initial 12 weeks (N=389, median time of follow-up 336 days). In these participants followed up to 1 year, 40% (79/196) of PHN patients and 36% (69/193) of HIV-AN patients maintained a 30% reduction in pain score, while 9% (18/196) and 10% (19/193), respectively, reported complete pain relief.

**Bottom line:** The literature review was limited only to a single clinical trials database. The research was funded by the company that distributes the brand name patch. There was no control group in the patients with long-term follow-up. These limitations are all important potential sources of bias.

**Review Author and Summary Author:** Jennifer K. Bello, MD, NorthShore University Health System, Evanston, IL

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**Short-term steroids appropriate for COPD exacerbations**


This noninferiority trial included 314 patients older than 40 years with chronic obstructive pulmonary disease (COPD) who presented to the emergency department with an exacerbation. Patients were randomized to either 5 (short-term) or 10 days (conventional) of 40 mg prednisolone.

Among patients treated with short-term steroids, 37% (95% CI, 0.3–0.45) of patients treated with short-term steroids experienced an exacerbation within 180 days compared with 38% (95% CI, 31%–46%) of patients who received the conventional 10-day treatment (difference of −1.2%; 95% CI, −12% to 9.8%) There were also no differences between groups in the secondary outcomes of symptom scores for dyspnea and bronchitis.

**Bottom line:** Treating COPD exacerbation with 5 days of steroids is associated with no worse outcomes than treating for 10 days.

**Reviewer and Summary Author:** Anne Mounsey, MD, University of North Carolina, Department of Family Medicine, Chapel Hill, NC

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**Additional information can be found at:**

www.fpin.org/purlsoverview
Penicillin for prevention of recurrent cellulitis


This double-blind RCT of 274 patients compared penicillin with placebo for prevention of recurrent leg cellulitis. Patients with a history of recurrent cellulitis within the preceding 6 months and a minimum of 2 episodes within the past 3 years received either penicillin 250 mg PO BID or placebo for 12 months (prophylaxis phase). Adverse events, use of health services, and recurrence of cellulitis were assessed by telephone calls at 3-month intervals during the prophylaxis phase and every 6 months during the follow-up phase (13–36 months).

The primary outcome was time from randomization to recurrence of cellulitis. Secondary outcome measures included proportions of participants with recurrent cellulitis, new edema or ulceration, and adverse events.

Median times to recurrent cellulitis were 626 days with penicillin and 532 days with placebo. During the prophylaxis phase, there was a 45% lower incidence of recurrent cellulitis in patients who received penicillin (HR 0.55; 95% CI, 0.35–0.86, P=.01). There was no difference in incidence in the follow-up phase, nor was there a significant difference in adverse events between the 2 groups.

**Bottom line:** Low-dose penicillin can be used to prolong time to recurrence and decrease the frequency of repeat episodes of cellulitis. However, it is unclear if treatment longer than a year results in continued benefit.

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Superficial thrombophlebitis: treatment and prevention of complications


This systematic review of topical, systemic, and surgical treatments for patients with superficial thrombophlebitis included 30 RCTs with 6,507 patients. Both inpatients and outpatients with a clinical or objective diagnosis of superficial thrombophlebitis were included. The primary outcomes were complications (VTE, PE, DVT, or extension or recurrence of superficial thrombophlebitis), pain, signs of superficial thrombophlebitis, and quality of life. The secondary outcomes were mortality, adverse effects of treatment, allergy to treatments, and arterial thromboembolic events.

Because of generally poor study quality, no conclusions could be drawn about the efficacy of low-molecular-weight heparins, NSAIDS, topical treatments, surgery, or other medications. One large study of fondaparinux versus placebo found a reduction in recurrence of superficial thrombophlebitis (RR 0.21; 95% CI, 0.08–0.54), extension of superficial thrombophlebitis to the saphenofemoral junction (RR 0.09; 95% CI, 0.03–0.22), and incidence of DVT (RR 0.17; 95% CI, 0.05–0.56).

**Bottom line:** This review contributes little to the literature, as the authors were only able to restate findings from a single previous fondaparinux study.

Review Author and Summary Author: Sonia Oyola, MD, The University of Chicago, Department of Family Medicine, Chicago, IL

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Behavioral Health Matters

What simple behavioral techniques are effective for childhood enuresis?

Bottom line
Simple behavioral treatments (rewards, rewards plus lifting, and bladder training) are more effective than placebo for childhood enuresis. They are probably less effective than enuresis alarms. Behavioral treatments can be recommended to parents as initial interventions that are safe and relatively inexpensive, although they can be difficult to sustain.

The evidence
Simple behavioral treatments for nocturnal enuresis can include fluid restriction, lifting, scheduled wakening, reward systems, and retention control training. Lifting refers to the practice of a parent carrying the child to the bathroom on a schedule or randomly. This practice can be done with or without a password used to awaken and cue the child to urinate in the proper place. In lifting without a password, the child may still be sleeping when taken to the bathroom.1

A 2013 Cochrane review examined behavioral therapies for nocturnal enuresis.1 Sixteen trials (N=1,643 children) were included. Rewards for dry nights, with or without lifting, and waking appeared to be effective but each finding was based on single small trial. Rewards led to fewer wet nights than control (mean 1.1 vs. 5.7, respectively; 95% CI for difference, –6.4 to –2.9). Rewards plus lifting resulted in 2 of 10 children failing to achieve 14 dry nights at the end of treatment versus 9 of 10 controls (RR 0.22; 95% CI, 0.06–0.78), and 2 of 10 children failed or relapsed after treatment stopped compared with 9 of 10 controls (RR 0.22; 95% CI, 0.06–0.78). Bladder training (compared with controls) was associated with fewer mean wet nights at the end of treatment (3.3 vs. 5.2; 95% CI for difference, –3.7 to –0.13) in 1 analysis but there was no difference in number not achieving 14 dry nights at the end of treatment.

Overall, the review found behavioral interventions to be more effective than placebo, although no single behavioral intervention was clearly best. The most common reason for discontinuation was that training was too demanding on the child or the family; otherwise, interventions did not appear to be harmful.1

One RCT used in the above Cochrane compared bladder training, with or without oxybutynin, to enuresis alarms.2 One hundred forty-nine children, median age 7.5 years, were randomized to 5 groups: holding exercises with placebo, holding exercises with oxybutynin, placebo alone, oxybutynin alone, and enuresis alarm. The holding exercise consisted of an oral water load of 20 mL/kg body weight over 30 minutes with voiding postponed for as long as possible. “Maximum voided volume” was the greatest voided volume from a 48-hour bladder diary, and “holding exercise volume” was the greatest volume produced with postponement of voiding after a fluid load, once daily for 4 days.

Holding exercises combined with placebo or oxybutynin increased holding exercise volume (by 25%; P<.001) and maximum voided volume (21%; P<.01) in the group randomized to exercises+placebo. Holding exercise volume and maximum voided volume increased 43% (P<.001) and 41% (P<.001), respectively, in the group randomized to exercises+oxybutynin. Medication (placebo or oxybutynin) without holding exercises did not increase holding exercise volume or maximum voided volume. However, alarm therapy improved nocturnal enuresis more often than all 4 holding exercise/volume modulating study arms (73% vs 7%, respectively; P<.001).2

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REFERENCES
Is use of an oral hormonal contraceptive during pregnancy harmful to a fetus?

**Evidence-Based Answer**

Oral contraceptive (OC) use during pregnancy does not appear to increase the risk of fetal death or birth defects (SOR: B, meta-analysis of cohort studies and consistent cohort studies).

Unintended pregnancy occurs to 2% to 5% of OC users.¹

A meta-analysis included 12 prospective cohort studies comparing congenital malformation rates in infants born to women who had used OCs during pregnancy (N=6,100) versus women who had not (N=83,000).² OC use was defined as use anytime during pregnancy or within 1 month of conception. Nonusers were women who either had never used OCs or had used OCs but stopped well before conception. Overall, no difference was seen between the 2 groups in all malformations (RR 0.99; 95% CI, 0.83–1.2), congenital heart defects (RR 1.1; 95% CI, 0.72–1.6), or limb reduction defects (RR 1.0; 95% CI, 0.30–3.6).

The Danish National Birth Cohort was a prospective cohort trial comprising nearly 93,000 women that examined whether the use of OCs during pregnancy was associated with an increased risk of fetal death.¹ Of participants, 22% (20,000) had used an OC at some time during the 4 months prior to becoming pregnant and 1.2% (1,100) had actually become pregnant while taking an OC. Of the women who had experienced an OC failure, most stopped taking the medication prior to the 10th gestational week; however, 4.8% ceased use after week 10 and 5.6% were unsure when they stopped.

Use of OC during the 4 months prior to pregnancy was not associated with an increased risk of fetal death compared with nonusers, whether the woman used a combined OC (HR 1.0; 95% CI, 0.94–1.1) or a progesterone-only OC (HR 0.96; 95% CI, 0.71–1.3). Use of a combined OC during pregnancy did not increase risk of fetal death (HR 1.0; 95% CI, 0.71–1.5) compared with nonusers. Use of a progesterone-only OC during pregnancy also was not associated with an increased risk of fetal death (HR 1.4; 95% CI, 0.65–2.9) compared with nonusers.¹

A Chinese prospective cohort trial compared outcomes for 332 pregnant women who had used levonorgestrel emergency contraception during their current pregnancy and 332 pregnant nonusers.³ No difference was seen in the rate of birth defects (RR 1.1; 95% CI, 0.28–4.4). There was no increase in first trimester spontaneous abortions in users compared with the nonuser group (RR 1.2; 95% CI, 0.74–1.9).

A multistate case-control study compared nearly 10,000 infants with birth defects with 4,000 infants without birth defects as part of the National Birth Defects Prevention Study to assess for a relationship between first trimester maternal OC use and risk of 32 structural birth defects.⁴ Maternal OC use during the first 3 months of pregnancy was associated with an increased risk of 2 defects: hypoplastic left heart syndrome (OR 2.3; 95% CI, 1.3–4.3) and gastroschisis (OR 1.8; 95% CI, 1.3–2.7). The authors noted that when analyzing 32 categories, an elevated OR in 2 categories could simply be due to chance and the increased risk of these 2 categories should be considered hypothetical until evaluated further.

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What is the best test to diagnose urinary tract stones?

**Evidence-Based Answer**

For the identification of urinary tract stones, helical noncontrast computed tomography (NCCT) is more sensitive and more specific than either intravenous urogram (IVU) or renal ultrasonography (RUS) (SOR: A, systematic reviews of RCTs and cohort trials).

A recent meta-analysis of 10 RCTs and prospective cohort trials including 914 patients suspected of having urolithiasis examined the accuracy, appropriateness, and radiation dosage of helical NCCT versus IVU.¹ The gold standard for confirmation of urolithiasis was recovery, removal, or direct visualization.

NCCT had superior sensitivity in every trial, ranging from 66% to 99%, versus 41% to 87% for
IVU. Specificity was found to be similar with NCCT (94%-100%) and IVU (91%-100%). Modeling based on population cohort data looking at radiation exposure indicated that NCCT would result in an estimated lifetime cancer risk of 1 in 2,869 to 8,130 versus 1 in 6,969 to 18,762 for IVU.\textsuperscript{1}

Another meta-analysis of 7 prospective cohort trials with 1,061 patients with renal colic evaluated the performance characteristics of newer low-dose (<3 mSv) helical NCCT.\textsuperscript{2} Patients received low-dose or full-dose NCCT. The combination of other radiologic tests, surgical results, and follow-up was used as the gold standard. The pooled sensitivity was 96% and specificity was 95% for low-dose NCCT (positive likelihood ratio [LR+] 19 and negative likelihood ratio [LR–] 0.04).

A prospective cohort study of 112 patients with symptoms of renal colic evaluated the accuracy of helical NCCT and RUS.\textsuperscript{3} In this study, all participants had NCCT, IVU, and RUS and documentation of stone passage or recovery was the gold standard. RUS was 19% sensitive and 97% specific (LR+ 6.3; LR– 0.84), while NCCT was 94% sensitive and 97% specific (LR+ 31; LR– 0.06).

The American College of Radiology (ACR) rates the appropriate use of different diagnostic imaging modalities by an ongoing systematic literature review on a scale of 1 to 9; ratings of 7 to 9 are considered appropriate diagnostic tools, ratings of 4 to 6 may be, and ratings of 1 to 3 are usually not appropriate.\textsuperscript{4} The ACR recommends helical NCCT, low dose preferred, as the usually appropriate (rating: 8) first-line test for suspected urolithiasis. However, the ACR guidelines state that in certain populations of patients, including pediatric and obstetric populations, the risks of ionizing radiation may still make other tests more appropriate. For example, the ACR notes that US plus abdominal radiography is the preferred testing modality in pregnancy (rating: 6), offering a compromise in accuracy and radiation risk.

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A 2010 RCT investigated the efficacy of an allergen-specific immunotherapy with a high-dose hypoallergenic house dust mite preparation in 65 children (aged 6–17 years) with allergic asthma. After reaching asthma control during a 5-month period, patients were assigned to either immunotherapy plus fluticasone propionate or fluticasone propionate alone by block randomization. After 2 years, the mean daily dose of fluticasone propionate in the immunotherapy group decreased more than in the control group (–179 vs –84 mcg; \( P < .05 \)). Adverse events were similar in both groups (97% in immunotherapy group vs 97% in control group, no \( P \) value). In the immunotherapy group, 12 of 33 events had a possible relationship to the study medication. Events included reaction at administration site (pain, pruritus, and swelling), rhinitis, conjunctivitis, and urticaria. No adverse events were thought to be serious.

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What is the value of measuring cervical length in pregnant patients with prior preterm labor?

Evidence-Based Answer
Cervical length is a good predictor of preterm delivery in women with a singleton gestation who have a history of preterm delivery (SOR: \( B \), retrospective cohort trial). Early cervical length measurements potentially identify women who may benefit from cerclage placement, which has been shown to reduce previable birth (SOR: \( B \), single RCT).

The Preterm Prediction Study was a prospective trial that tried to determine the probability of spontaneous preterm birth at less than 35 weeks of gestation in women who had previous spontaneous preterm deliveries. Women were excluded if they had a history of medically indicated preterm deliveries. Three hundred seventy-eight women with a prior preterm delivery were compared with a control group of 904 parous women with previous term pregnancies. Controls were matched for maternal age, ethnicity, education, and tobacco use. Cervical length was measured between 22 weeks and 24 weeks 6 days of gestation using real-time ultrasonography.

The risk of preterm delivery was higher in patients with cervical length <25 mm and a history of preterm birth than in women in the control group with a cervical length of <25 mm (30% vs 8%; \( P < .001 \)). The risk decreased for cervical length >35 mm, but was still higher compared with the control group with a cervical length of >35 mm (8% vs 2%; \( P < .001 \)).

A blinded observational study of 183 women with singleton gestations who had a previous spontaneous delivery before 32 weeks of gestation examined the relationship between cervical length and preterm delivery before 35 weeks’ gestation. Women with chronic or obstetric conditions that are associated with preterm delivery were excluded. Cervical length was initially measured between 16 weeks and 18 weeks 6 days of gestation, then biweekly up to 23 weeks 6 days gestation. Forty-eight women delivered before 35 weeks; 35 before 32 weeks; 29 before 28 weeks; and 20 before 24 weeks.

Women with shorter cervical lengths at initial sonographic examination had higher rates of spontaneous preterm delivery than women who had normal cervical length and minimal to no change in cervical length during serial ultrasonography (15 mm relative risk [RR] 4.1; 95% CI, 3.2–5.4; 25 mm RR 3.3; 95% CI 2.1–5.0; 30 mm RR 2.5; 95% CI, 1.6–3.9). The median rate of cervical length shortening was 1.1 mm per week.

A multicenter RCT of 301 pregnant women who had a prior spontaneous preterm birth at less than 34 weeks of gestation and cervical length <25 mm examined the efficacy of cerclage. Compared with the control group (no cerclage), no significant reduction was noted in preterm delivery at less than 35 weeks’ gestation for the cerclage group (RR 0.78; 95% CI, 0.58–1.0). However, cerclage placement was associated with a significant decrease in previable birth (RR 0.4; 95% CI, 0.2–0.9).

The American College of Obstetricians and Gynecologists (ACOG) does not make specific recommendations on cervical length measurements for prevention of preterm delivery. ACOG, however, proposes an algorithm for physicians that identifies patients with a short cervix on ultrasonography. ACOG
A 2007 systematic review of 13 RCTs with 1,557 COPD patients also analyzed the clinical benefit of antibiotics for COPD exacerbations. Five trials with 593 patients showed no statistically significant effect on treatment failure rate in mild to moderate exacerbations, defined as 1 or 2 of the Winnipeg symptoms of dyspnea, increased sputum volume, and sputum purulence (OR 1.1; 95% CI, 0.75–1.6). Antibiotic use was associated with a lower likelihood of treatment failure in severe exacerbations (defined as all 3 Winnipeg criteria) compared with placebo (4 trials, N=472; OR 0.25; 95% CI, 0.16–0.3; NNT=4). Antibiotics also reduced mortality in patients hospitalized with severe exacerbations compared with placebo (4 trials, NNT=401; OR 0.20; 95% CI, 0.06–0.62; NNT=14).

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What are the most effective nonpharmacologic treatments for urinary incontinence in women?

Evidence-Based Answer
Pelvic floor muscle training (PFMT) decreases symptoms in women with all types of urinary incontinence (UI) and appears particularly helpful in patients with urge incontinence (SOR: B, small but consistent RCTs). Pessaries may decrease stress incontinence, but do not appear to work better than a tampon (SOR: B, small RCTs).

A Cochrane review of 14 RCTs (N=672) evaluated the effectiveness of PFMT in women with stress, urge, or mixed UI. The type of UI in 3 studies was based on signs and symptoms, and 11 trials reported a urodynamic diagnosis. Most studies performed multiple PFMT (30–200 contractions/relaxation in sets of 10) ranging from 8 weeks to 6 months in duration (most used 12 weeks).

PFMT in nonpoored data increased perception of cure or improvement in stress UI compared with sham or no treatment (1 trial, N=55; risk ratio [RR] 14; 95%
CI, 2.0–103; and in a second trial, N=66; RR 20; 95% CI, 2.9–140). PFMT used in all types of UI combined compared with sham or no treatment also improved perception of cure (1 trial, N=125; RR 2.3; 95% CI, 1.5–3.4).¹

PFMT in nonpooled data significantly decreased daily leakage episodes in stress UI compared with the control group, with a mean difference ranging from –0.8 to –2.9 episodes/day in 4 trials with less than 100 patients each. PFMT decreased daily leakage episodes in all types of UI combined (1 trial, N=125; MD –0.77; 95% CI, –1.2 to –0.32).¹

PFMT in nonpooled data resulted in lower volume of leaked urine compared with sham or no treatment in stress UI (1 trial, N=61; MD –30 g; 95% CI, –48 to –12; and in a second trial, N=50; MD –12 g; 95% CI, –22 to –3.0). There was no difference with PFMT regarding volume of leaked urine compared with sham or no treatment in all types of UI, although the confidence interval was wide (1 trial, N=29; MD –5.1 mL; 95% CI, –11 to 1.1).¹

A Cochrane review of 21 RCTs of 1,490 women with stress, urge, or mixed UI involved comparison of 11 different PFMT interventions.² The average age of participants was 50 and most had only stress UI. Ten of the trials excluded elderly participants. The authors found confounding factors and/or poor study design in many of the trials and concluded that evidence was insufficient to recommend 1 type of PFMT over another. The data were both pooled and not pooled (due to heterogeneity of the study design and chosen outcomes). This review was limited by blinding issues, selection bias, and lack of intention-to-treat analysis.

Another Cochrane review examined the efficacy of mechanical devices, such as pessaries, to treat incontinence in 7 randomized parallel and crossover studies that included 732 women.³ Two small trials (N=6 and 18) compared mechanical devices with no treatment during exercise and found pessaries were better than no treatment (MD of pad weight –6.6 g; 95% CI; –11 to –1.9); but no difference with a tampon versus no treatment (MD of pad weight –14 g; 95% CI, –38 to 9.8). Four trials compared different devices against each other and found no evidence of superiority of 1 device over another. One trial compared mechanical devices with behavioral interventions and found no lasting difference between the groups. The authors concluded that the evidence is insufficient to recommend mechanical devices for the treatment of incontinence in women.

Evidence-Based Answer

Does long-term use of metformin cause vitamin B₁₂ deficiency?

 Probably. Long-term treatment with metformin is associated with an increased risk of vitamin B₁₂ deficiency (SOR: C, RCT and cohort studies using disease-oriented outcomes).

A RCT in 390 patients with type 2 diabetes examined the effects of long-term metformin on vitamin B₁₂ levels.¹ Compared with placebo, metformin 850 mg TID for a mean period of 4.3 years was associated with a mean decrease in vitamin B₁₂ concentration of 19% (95% CI, 0.24–0.14; P<.001) and a nonsignificant increase in homocysteine concentration of 5% (95% CI, –0.01 to 0.11; P=.091). The absolute risk of vitamin B₁₂ deficiency (<150 pmol/L) at the end of the study was 9.9% in the metformin group compared with 2.7% in the placebo group (mean difference [MD] 7.7%; 95% CI, 0.023–0.12; P=.004; NNH=14 over 4.3 years). The absolute risk of low vitamin B₁₂ concentration (150–220 pmol/L) was higher in in the metformin group (18%) compared with the placebo group (7%) (MD 11%; 95% CI, 0.046–0.18; P=.001; NNH=9 over 4.3 years).

In a nested case-control study 155 patients with diabetes taking metformin and with vitamin B₁₂ deficiency were compared with 310 matched controls, selected from the cohort who did not have vitamin B₁₂ deficiency while taking metformin.² After adjusting for confounders, each 1-g/d increment in metformin dose increased the risk of developing a vitamin B₁₂ level less than 150 pmol/L (OR 2.9; 95% CI, 2.2–3.9) compared with matched controls. Using metformin for more than

3 years increased the risk of vitamin B₁₂ deficiency compared with patients taking metformin for less than 3 years (OR 2.4; 95% CI, 1.5–3.9).

The analysis of data on US adults older than 50 years of age with (N=1,621) or without (N=6,867) type 2 diabetes from the National Health and Nutrition Examination Survey 1999–2006 demonstrated that biochemical B₁₂ deficiency was present in 5.8% of patients using metformin and 2.4% of patients not using metformin (adjusted OR 2.9; 95% CI, 1.3–6.8; \( P_{=.0026} \)). B₁₂ deficiency was seen 3.3% of those without diabetes.

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Should breast reconstruction be done at the time of mastectomy or should it be delayed?

Evidence-Based Answer
The answer is unclear. Patients who choose immediate breast reconstruction (IBR) have reduced psychiatric morbidity at 3 months postoperatively, but report no difference in psychosocial function at 1 year postoperatively, compared with women who choose delayed breast reconstruction (DBR) (SOR: B, small RCT). However, if postoperative chemotherapy and/or radiation are necessary, IBR carries a higher risk of surgical site infections and capsular contracture (SOR: B, cohort studies).

Women who undergo mastectomy for breast cancer have 3 reconstructive options: IBR, DBR, or no reconstruction. A 2011 Cochrane review evaluating immediate versus delayed reconstruction after mastectomy found only 1 older RCT involving 64 women that addressed psychosocial outcomes. Two IBR patients as opposed to 10 DBR patients were diagnosed with psychiatric illness, as assessed by questionnaire, 3 months postoperatively (\( P_{<.05} \)). Psychiatric illness rates decreased for both groups 12 months after mastectomy, with no statistically significant difference between the 2 groups. However, usefulness of this RCT may be limited by the outdated surgical technique used and weakened by incomplete follow-up of 1 study arm.

A 2004–2007 prospective longitudinal survey of 190 Canadian women examined psychosocial impact after mastectomy for breast cancer in patients undergoing IBR, DBR, or no reconstruction. Using a psychosocial questionnaire, women undergoing DBR had higher levels of body stigma (average score of 33 on a 9–84 point Likert adverse body image scale vs 26 for IBR, \( P_{=.01} \)), body concerns (21 on a 7–36 point scale vs 16 for IBR, \( P_{=.002} \)), and worry about the obviousness of their appearance (12 on a 0–23 point scale vs 9.5 for IBR, \( P_{=.002} \)) than women undergoing IBR. No posttreatment differences were noted in quality of life, psychological symptoms, or sexual function, although psychological distress was common regardless of timing of reconstruction. All women had improved quality of life 1 year postoperatively.

A prospective observational cohort study of 163 women undergoing mastectomy with IBR and presurgical, postsurgical, or no chemotherapy (chemo) examined the effect of chemo and its timing on IBR outcomes. Postsurgical chemo patients had a higher rate of surgical site infections (44%) than presurgical (23%) and no chemo patients (25%; ANOVA \( P_{=.05} \)). There were no differences with respect to return to the operating room (32% vs 33% and 28%, respectively; ANOVA \( P_{=.70} \)) or complications with implant or autologous donor site (22% vs 26% and 18%, respectively; ANOVA \( P_{=.70} \)).

A prospective, observational cohort study of 107 women undergoing IBR with saline-filled implants compared outcomes in irradiated versus nonirradiated breasts. The rate of implant capsular contracture over 5 years was significantly higher for irradiated than for nonirradiated breasts (42% vs 15%, respectively; \( P_{=.01} \)). Patients receiving DBR were not examined in either study.

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How should a DEXA scan be used to evaluate the effectiveness of osteoporosis therapy in postmenopausal women?

Evidence-Based Answer
After starting therapy for osteoporosis, dual energy x-ray absorptiometry (DEXA) scan results do not directly correlate with fracture risk (SOR: A, meta-analysis). In asymptomatic postmenopausal women on therapy for osteoporosis, a repeat DEXA scan is probably not helpful for at least 3 years (SOR: C, disease-oriented evidence).

A 2002 meta-analysis of 12 RCTs with more than 21,000 patients compared the pre- and posttreatment bone mineral density (BMD) and vertebral fracture risk in postmenopausal women treated with antiresorptive drugs (1–3 years of estrogens, bisphosphonates, raloxifene, or calcitonin) or placebo. Compared with placebo, for every 1% improvement in spine BMD there was a 3% decrease (95% CI, 0.02–0.05; P=.002) in the relative risk of a vertebral fracture.

The review authors then attempted to predict the “normal” risk of vertebral fracture according to bone density using data from the placebo group in an RCT of 2,027 postmenopausal women. Taken together, the calculated relative risk of vertebral fracture based on the observed differences of BMDs was 20%, but the actual reduction in vertebral fracture with treatment was 45%.

A 2009 secondary analysis of an RCT (N=6,459, postmenopausal women with low baseline BMD defined as <0.68 g/cm²) examined whether routine monitoring of BMD was needed after starting alendronate therapy. Patients were randomized to receive either alendronate 10 mg daily or placebo over 3 years and had BMD evaluated yearly. Compared with placebo, alendronate was associated with a BMD increase of 0.0085 g/cm² per year (P<.001). The between-person effect of 1 year of treatment on hip bone density ranged from an increase of 0.002 g/cm² (2.5 percentile) to 0.024 g/cm² (97.5 percentile). At 3 years, the increase in BMD ranged from 0.019 g/cm² (2.5 percentile) to 0.041 g/cm² (97.5 percentile) and the mean cumulative treatment effect of alendronate therapy was 0.030 g/cm². The authors concluded that checking BMD in the first 3 years is unnecessary.

A 2010 US Preventive Services Task Force osteoporosis screening update found insufficient evidence to directly evaluate screening effectiveness, harms, and intervals.

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

What is the most effective treatment for hirsutism in a patient with polycystic ovarian syndrome (PCOS)?

**Bottom line**

Effective single treatments for hirsutism in patients with PCOS include metformin, oral contraceptives (OCs), finasteride, flutamide, spironolactone, and thiazolidinediones. Thinner patients and those with more hirsutism at baseline tend to have better responses. Combination therapy with metformin and OCs or with eflorentine cream and laser treatment may be more effective than single therapy (SOR: **A**, systematic reviews of RCTs and evidence-based guideline). Weight reduction in obese patients is associated with decreased hirsutism (SOR: **B**, evidence-based guideline).

**Evidence summary**

A 2010 Cochrane review analyzed 4 RCTs for the effects of different therapies, over a median of 6 months, on hirsutism in 109 women with PCOS. Hirsutism was measured by the Ferriman-Gallwey (F-G) scale (based on 9 hormone-sensitive body sites with scoring from 0=no terminal hair to 4=complete hair cover; maximum score=36). In 3 studies, 69 patients received metformin 500 mg TID or an OC (ethinyl estradiol 35 mcg/cyproterone acetate 2 mg [EE35-CPA2]) daily. In the fourth study, 40 patients received metformin 500 mg TID and EE35-CPA2 daily or EE35-CPA2 daily alone.

No difference in hirsutism was found with metformin compared with OCs (standardized mean difference –0.18; 95% CI, –0.67 to 0.32). Combination therapy resulted in significant reduction in F-G hirsutism scores compared with OCs alone (weighted mean difference –2.8; 95% CI, –5.5 to –0.17).

A 2008 systematic review of 28 RCTs including 1,226 hirsute women examined F-G scores after 6 months of treatment with common pharmaceutical therapies. Decreases from pretreatment F-G scores were seen for metformin (19%), finasteride (20%), ethinyl estradiol OCs (27%), thiazolidinediones (31%), combined cyproterone acetate and ethinyl estradiol OCs (36%), spironolactone (38%), and flutamide (41%) (no P values provided for changes from baseline). No assessment of relative efficacy between treatment methods could be made. Body mass index was inversely related to improvement in F-G score. The greatest reduction in F-G scores occurred in trials with the most severe hirsutism at pretreatment.

**Recommendations**

The American College of Obstetrics and Gynecology Practice Bulletin for PCOS stated that the addition of eflorentine cream to laser treatment improved hirsutism over laser alone (based on “good and consistent scientific evidence”). The bulletin also noted that weight reduction was associated with decreased hirsutism (based on “limited and inconsistent scientific evidence”). There was no preferred primary treatment for hirsutism in PCOS.

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You have our word on it.
1. All of the following statements are true regarding the risks and benefits of immediate breast reconstruction (IBR) after mastectomy compared with delayed breast reconstruction (DBR) or no reconstruction, except:
   a. Compared with DBR, IBR was found to confer less psychological distress at 1-year postoperatively
   b. IBR patients receiving postsurgical chemotherapy have a higher rate of surgical site infections than IBR patients not requiring chemotherapy
   c. IBR patients requiring postsurgical radiation therapy have a higher risk of capsular contracture than patients not requiring postsurgical radiation
   d. Psychological distress after mastectomy is common regardless of timing of reconstruction
2. For a 62-year-old man with suspected nephrolithiasis, which diagnostic test is most sensitive and specific?
   a. Helical noncontrast computed tomography
   b. Intravenous urogram
   c. Renal ultrasound
   d. Renal ultrasound plus abdominal radiography
3. What should you tell an 80-year-old woman with known osteoporosis (documented on dual energy x-ray absorptiometry [DEXA] scan 1 year ago), currently taking bisphosphonate, calcium, and vitamin D, regarding further DEXA scan screening?
   a. Bone mineral density (BMD) measurement via DEXA scan is a good predictor of vertebral fracture risk
   b. BMD measurement via DEXA scan is a good predictor of hip fracture risk
   c. Current evidence argues against further DEXA scan evaluation at this time
   d. The US Preventive Services Task Force recommends annual screening
4. Which of the following statements is true about urinary incontinence treatment?
   a. Pelvic floor muscle training (PFMT) increases the number of leakage episodes
   b. PFMT decreases the volume of leaked urine
   c. PFMT is associated with a decreased perception of cure or improvement
   d. Mechanical devices are more effective than behavioral interventions
5. A patient with an acute ankle sprain presents to your office. You can let the patient know that:
   a. There will likely be less swelling with a program of ice and exercise than with heat and exercise
   b. Application of an ice bag for 20 minutes every 2 hours is the best icing schedule to eliminate pain with activity
   c. Icing is known to consistently improve ankle function
   d. Ice and compression result in more pain than no treatment
6. Regarding the treatment of hirsutism in women with polycystic ovarian syndrome, which of the following statements is true?
   a. Addition of efomorphine cream to laser treatment improves hirsutism over laser alone
   b. Body mass index is unrelated to hirsutism severity or medication response
   c. Oral contraceptives are superior to other methods of treatment for hirsutism
   d. Spironolactone is not effective in the treatment of hirsutism
7. Which of the following statements is true about simple behavioral intervention for nocturnal enuresis?
   a. Simple behavioral interventions provide no benefit over waiting for the enuresis to resolve on its own
   b. Simple behavioral interventions achieve dry nights for children more effectively than enuresis alarms
   c. Reward systems are statistically superior to other behavioral interventions
   d. Simple behavioral interventions are inexpensive and better than no intervention
8. Which of the following statements is true regarding vitamin B12 deficiency in a diabetic patient and metformin use?
   a. There is no clear relationship between vitamin B12 deficiency and metformin use
   b. B12 deficiency is less common in patients with diabetes; metformin use equalizes rates between diabetic and nondiabetic populations
   c. Metformin increases the risk of vitamin B12 deficiency in a dose- and exposure-dependent fashion
   d. Metformin has been shown to significantly increase homocysteine levels, but not alter B12 levels
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