Are beta-blockers safe to use in patients with asthma or COPD?

Evidence-based answer
Beta-blockers (cardioselective and nonselective) appear safe in patients with mild to moderate asthma or chronic obstructive pulmonary disease (COPD) and do not produce significant adverse respiratory effects (SOR: A, systematic review of RCTs). Beta-blockers are not associated with increased hospital admissions or length of stay and are, in fact, associated with fewer outpatient clinic visits. Avoiding beta-blockers in patients with asthma or COPD who present with acute coronary syndrome is associated with increased mortality (SOR: B, cohort studies).

Evidence summary
A Cochrane meta-analysis of 29 RCTs examined the effects of cardioselective beta-blockers in adults with mild to moderate asthma or COPD. The age range of participants was 20 to 65 years (mean age 40 years). Single-dosed cardioselective beta-blockers reduced forced expiratory volume in 1 second (FEV1) by 7.5% compared with placebo (19 trials, n=240; mean difference [MD] –7.5%; 95% CI, –9.3 to –5.6), without clinically significant adverse respiratory effects (specifically wheezing, dyspnea, or asthma exacerbation).

The change in FEV1 with use of a beta2-agonist after a beta-blocker was larger than the change with the use of a beta2-agonist after placebo (15 trials, n=444; MD 4.6%; 95% CI, 2.5–6.8). Continuous beta-blocker treatment that lasted 2 to 28 days produced no change in FEV1 (10 trials, n=136; MD –0.42%; 95% CI, –3.74 to 2.91), respiratory symptoms, or inhaler use compared with placebo. Most of the participants were relatively young, had only mild to moderate airway obstruction, and no recent asthma exacerbations. Many of the studies were of short duration.

A retrospective cohort study using Veteran’s Administration inpatient and outpatient records in Iowa and Nebraska examined possible associations between healthcare resources used (clinic
visits and hospital admissions) and beta-blocker therapy among patients with asthma or COPD. Patients with a diagnosis of asthma or COPD receiving treatment with beta-blockers or another cardiovascular agent were included (N=8,390, 97% male, mean age 67 years).

Adjusted for comorbidity and demographics, patients receiving selective beta-blockers had similar odds for hospital admission as those receiving other agents (OR for cardioselective beta-blockers 1.2; 95% CI, 0.98–1.4; OR for nonselective beta-blockers 1.1; 95% CI, 0.73–1.7, relative to the non–beta-blocker group). There was also no difference in length of stay. After adjusting outpatient visits related to asthma or COPD for comorbidity and other factors, patients receiving beta-blockers averaged approximately half as many outpatient clinic visits/year as those receiving other cardiovascular drugs (selective beta-blockers –0.47 visits; 95% CI, –0.61 to –0.33; nonselective beta-blockers –0.54 visits; 95% CI, –0.91 to –0.18).

A large retrospective cohort study evaluated current use of beta-blockers in patients with reactive airway disease (RAD, primarily asthma or COPD) who were hospitalized with acute coronary syndrome (ACS). The Get with the Guidelines database was used to evaluate use of a beta-blocker within 24 hours of admission and at discharge in patients with ACS who had (n=12,967) and did not have (n=81,140) a history of RAD. Data were collected in 435 hospitals between January 2000 and September 2006.

Compared with patients with no history of RAD, patients with a history of RAD were 42% less likely to receive beta-blockers upon admission (OR 0.58; 95% CI, 0.54–0.62) and 55% less likely to receive beta-blockers at discharge (OR 0.45; 95% CI, 0.41–0.48). However, receiving beta-blockers within 24 hours after admission was associated with a lower in-hospital mortality rate compared with patients not receiving beta-blockers, for patients both with RAD (OR 0.52; 95% CI, 0.45–0.60) and without RAD (OR 0.38; 95% CI, 0.34–0.42).

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REFERENCES
Showdown at the O.B. corral

Long long ago (in 2011), there was something of a showdown at the journal Obstetrics & Gynecology. It started innocently enough, when a group of cowpokes published a paper about health outcomes under obstetric policies that restricted elective inductions before 39 weeks. The group reported that the policies were associated with an alarming increase in macrosomia and stillbirth. While it was a cohort study and not randomized, the sheer size of the trial (>24,000 pregnancies) lent the findings considerable weight.

A few months later, however, a letter to the editor appeared in the same journal from another group of cowpokes who had also been tracking the effect of the policies. This group had a dataset that was nearly 4 times larger than the one just published. Analysis of these data revealed absolutely no change in the rates of macrosomia or still birth.

This created something of a western-style stand-off (cue the whistling and guitar music). The original group had clearly demonstrated that they were faster to the draw, and they now held the high ground of first publication. But the Johnny-come-latelies had significantly more firepower. In reading the literary back and forth, you could almost sense the Clint Eastwood-like clinched jaws, tough posturing, and squinting stares. But both sides ultimately backed away from the brink, agreeing that elective inductions before 39 weeks should be discouraged and that the outcomes of such policies should be watched closely … very closely.

Struggles like this one—over little corners of truth—are going on all the time, all around us. This is how a professional community like ours comes to understand its own science. We all need this sort of give and take (even if it can be a little uncomfortable at times) to keep us academically alert and aware of our intellectual blind spots.

So while we think we’re pretty sharp shooters here at EBP, we’re not afraid to be tested. Want to challenge something we’ve said? Write to us. C’mon. Give us your best shot.

Jon O. Neher, MD

REFERENCES
Diving for PURLs

PEG in place of lactulose for treatment of acute hepatic encephalopathy

This RCT of 50 patients 18 to 80 years old admitted to the hospital with acute hepatic encephalopathy compared treatment with lactulose (n=25) to polyethylene glycol (PEG, n=25).

The primary outcome was improvement of ≥1 point in the HESA (Hepatic Encephalopathy Scoring Algorithm) score at 24 hours, where 0 is normal and 4 is comatose.

Fifty-two percent of patients in the lactulose group (13 of 25) met the primary outcome compared with 91% (21 of 23 evaluated) in the PEG group \((P<.01; \text{NNT}=3)\). The median time for resolution of hepatic encephalopathy was 1 day for the PEG group versus 2 days in the lactulose group \((P=.01)\). There were no adverse events related to use of PEG, although 2 patients in the PEG group relapsed after 24 hours of treatment.

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**Bottom line:** In this small study PEG was superior to lactulose at resolving symptoms of acute hepatic encephalopathy. Further studies are needed to confirm the generalizability of this finding and further evaluate the relapse rate for PEG.

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

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Skip the drip when prescribing PPIs for high-risk bleeding ulcers

This systematic review and meta-analysis compared intermittent oral or intravenous (IV) proton pump inhibitor (PPI) therapy with standard continuous PPI infusion (80 mg IV bolus followed by 8 mg/h for 72 hours) in patients who had received endoscopic therapy for active upper gastrointestinal bleeding from a gastric or duodenal ulcer, a nonbleeding visible vessel, or an adherent clot. Thirteen RCTs were included with 1,691 patients.

Ten studies with 1,346 patients addressed the primary outcome of recurrent bleeding within 7 days. Secondary outcomes included recurrent bleeding within 3 and 30 days, need for red blood cell transfusion, length of stay, need for surgery of radiologic intervention, and mortality. The authors established that a 3% absolute risk difference (ARD) in recurrent bleeding within 7 days was necessary for intermittent therapy to be determined inferior to the standard.

Results of this noninferiority trial yielded a risk ratio of 0.72 (upper bound 95% CI, 0.97) for rebleeding within 7 days and an ARD of −2.64% (upper bound 95% CI, −0.28%), which was within the noninferiority margin. Noninferiority was also demonstrated for all secondary outcomes.

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**Bottom line:** Intermittent PPI therapy is equivalent to the standard continuous IV PPI infusion for high-risk bleeding ulcers, although the optimal dose and route of administration require further study. The American College of Gastroenterology currently recommends IV PPI infusion for 72 hours.\(^1\)


Review and Summary Author: Lauren Oshman, MD, MPH, Northshore University Health System–University of Chicago, Chicago IL
Diving for PURLs

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

Evidence-Based Practice / Vol. 18, No. 6

Allopurinol: An old drug revitalized for CKD?

This post hoc analysis of a prior RCT evaluated patients (N=107) with stable chronic kidney disease (CKD) randomized to receive allopurinol 100 mg daily or placebo. The original study followed patients for 2 years and this follow-up study followed them for an additional 5 years (median follow-up 84 months).

The primary outcome of both studies was progression of renal disease (defined as the initiation of dialysis therapy, doubling of serum creatinine level, or ≥50% decrease in estimated glomerular filtration rate). Secondary outcomes included cardiovascular complications of myocardial infarction, coronary revascularization, angina pectoris, congestive heart failure, cerebrovascular disease, and peripheral vascular disease. In the 5-year follow-up, 10 patients from the control group (n=51) received allopurinol and 12 patients from the allopurinol group (n=56) discontinued allopurinol.

After 5 years, 9 patients in the allopurinol group had a renal event versus 24 patients in the control group (HR 0.32; 95% CI, 0.15–0.69; P=.004; NNT=4). There were 16 cardiovascular events in the allopurinol group versus 23 in the control groups (HR 0.43; 95% CI, 0.21–0.88; P=.02; NNT=8). No serious adverse effects of allopurinol were reported in either the initial or follow-up study.

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Bottom line: While this study demonstrated a lower risk of kidney disease progression in patients with CKD treated with allopurinol with minor adverse effects, the crossover of many patients and small sample size limit the generalizability of this information.

Review Author: Jennie Broders Jarrett, PharmD, BCPS, UPMC St. Margaret FMRP, Pittsburgh, PA

Summary Authors: Jennie Broders Jarrett, PharmD, BCPS, and Marianne Koenig, PharmD, BCPS, UPMC St. Margaret FMRP, Pittsburgh, PA

The best way to discontinue PPIs is still in (re)flux

This systematic review included 3 RCTs and 3 non-RCTs evaluating the safest and most effective method for discontinuing chronic PPI use. The primary outcomes varied, but most evaluated the proportion of patients who either reduced or discontinued PPI use.

The populations selected varied across studies in their indication for and duration of use of PPIs. The interventions used to reduce PPI use were dissimilar and included patient education on lifestyle change and medication use, and the use of medications for breakthrough symptoms, such as H2 blockers, alginates, pro-kinetics, and antacids. The follow-up times ranged from 12 weeks to 12 months.

Success in discontinuing or decreasing the dose of chronic PPI use ranged from 14% to 64%. No study found a worsening of symptoms. Each of the 3 RCTs reviewed either found no significant differences in PPI use at their maximum follow-up times or did not provide statistical analysis. One RCT found a nonsignificant increase in discontinuation rates for patients who were tapered compared with abrupt cessation. Overall study quality was poor.

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Bottom line: Due to the variability in study quality, design and heterogeneity of the study populations, this diligent systematic review does not recommend a best evidence-based method to discontinue PPIs.

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

Additional information regarding the PURLs and Diving for PURLs series can be found at: http://www.fpin.org/purls-faqs/
When should subcutaneous versus oral vitamin K be used to treat elevated INR?

**Case**

A 63-year-old man with a history of atrial fibrillation (on warfarin), hypertension, and diabetes was admitted to the hospital for community-acquired pneumonia treatment. On hospital day 2 the patient developed antibiotic associated diarrhea. His international normalized ratio (INR) was checked daily and on hospital day 3 it increased to 11. Without any signs of bleeding, should oral or subcutaneous (SC) vitamin K be used to treat this elevated INR?

**Review of the evidence**

A 2006 meta-analysis of 10 RCTs and 11 prospective cohort trials (N=993) examined the change in INR at 24 hours in patients without major bleeding and an INR of more than 4 who were treated with IV, oral, SC, or placebo vitamin K. Eight trials compared either 1 route of vitamin K administration with another or various doses of 1 route of vitamin K for patients taking warfarin with an INR between 4 and 10.

Target INR (1.8–4) was achieved at 24 hours in the oral group 82% of the time (4 trials, n=75; 95% CI, 70%–93%), in the IV group 77% (6 trials, n=69; 95% CI, 60%–95%), in the SC group 33% (3 trials, n=58; 95% CI, 7%–55%), and in the placebo group 20% (2 trials, n=27; 95% CI, 0%–47%). Oral and IV vitamin K were more effective at returning INR to target range than SC, which was similar in effectiveness to placebo (no P values provided).

A 2002, multicenter, open RCT discussed in the meta-analysis above is reviewed here as it directly compared the effectiveness of oral versus SC vitamin K at lowering supratherapeutic INR levels.

The trial included 51 patients who presented with INR 4.5–10, were asymptomatic, and randomized to receive a one-time 1-mg dose of either oral or SC vitamin K. The primary outcome was the percent of patients who achieved INRs between 1.8 and 3.2 on the day after vitamin K administration. More patients in the oral vitamin K group achieved the target range INR than in the SC group (58% vs 24%; OR 4.3; 95% CI, 1.1–17).

**Recommendations**

A 2012 evidence-based clinical practice guideline on anticoagulation-related management problems recommends against administration of vitamin K for an INR of 4.5–10 in the absence of bleeding (2B, weak recommendation, and moderate quality of evidence).

When the INR is elevated above 10 in the absence of bleeding, the guideline recommends administration of oral vitamin K (2C, weak recommendation, low quality of evidence). Nowhere in these guidelines is SC vitamin K recommended for the treatment of elevated INR.

**Case Wrap-Up**

Oral vitamin K should be preferentially chosen over SC vitamin K in any scenario in which either route is indicated. In the hospitalized patient discussed in the above case, oral vitamin K administration would be the appropriate next step in management.

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**REFERENCES**


Do you need to use heparin when initiating Coumadin therapy in a patient with atrial fibrillation?

Evidence-Based Answer
While the evidence is limited, current guidelines and biochemical studies suggest that it is probably not necessary to use heparin when initiating warfarin therapy in a patient with chronic stable atrial fibrillation (SOR: C, expert opinion and disease-oriented evidence).

A nonblinded RCT compared 40 patients with atrial fibrillation who were being initiated on anticoagulation, with 17 patients randomized to warfarin and 20 patients randomized to low-molecular-weight heparin (LMWH). Multiple biochemical markers of the hypercoagulable state (prothrombin fragment 1+2, fibrin d-dimer, and soluble fibrin) were measured at baseline and at 12, 36, and 60 hours.

No significant difference was noted in the biochemical markers of the hypercoagulable state at each time period—not in prothrombin fragment 1+2 (1.4 nmol/L with warfarin vs 1.2 nmol/L with LMWH; P=.70), fibrin D-dimer (68 ng/dL with warfarin vs 86 ng/dL with LMWH; P=.26), or soluble fibrin (35 ng/mL with warfarin vs 35 ng/mL with LMWH; P=.403).

The evidence-based American College of Chest Physicians (ACCP) guidelines for oral anticoagulant therapy from 2012 recommended initiating oral vitamin K antagonist (VKA) alone in patients with stable atrial fibrillation (grade 2 C, weak limited or no evidence)—10 mg warfarin daily for the first 2 days, followed by oral VKA dose adjustments based on the international normalized ratio (INR), in patients who are “sufficiently healthy to be treated as outpatients.”

Other ACCP guidelines from 2012 recommended the use of a rapidly acting parenteral anticoagulant at the same time as an oral VKA (eg, “bridging”) when rapid anticoagulation is necessary (eg, acute deep venous thrombosis or pulmonary embolus).

What antihypertensive agents are least likely to cause erectile dysfunction?

Evidence-Based Answer
Certain β-blockers and chlorthalidone, when prescribed for hypertension, are associated with an increased incidence of erectile dysfunction (ED), while other classes of antihypertensive agents are not (SOR: B, meta-analysis, RCTs).

A double-blind, placebo-controlled, randomized trial from 1997 included 557 men (age range 45–69 years) with stage 1 hypertension and no evidence of cardiovascular disease. Patients were randomized to placebo or 1 of the following hypertension therapies: acebutolol 400 mg/d, amlodipine 4 mg/d, chlorthalidone 15 mg/d, doxazosin 2 mg/d, or enalapril 5 mg/d.

In a report on sexual side effects in this trial, after 2 years, men receiving chlorthalidone had a significantly higher incidence with problems obtaining an erection compared with placebo (16% vs 4.9%; P<.01). Compared with placebo (8.1%) at 2 years, men receiving treatment with acebutolol (9.2%; P=.57), amlodipine (8.3%; P=.99), or enalapril (9.7%; P=.88) did not experience a significant difference in ED incidence. This trial was limited by the fact that it was only powered to detect moderate to large differences between groups.

In 2002, a systematic review analyzed 6 randomized placebo-controlled trials with 14,897 male and female patients treated for hypertension, heart failure, or post-myocardial infarction with β-blockers. The review found that reported impotence was significantly increased in men treated with β-blockers compared with placebo (risk ratio [RR] 1.2; 95% CI, 1.1–1.4).

A 2005, multicenter randomized trial evaluated the effects of sexual function in 131 male patients (age range 35–55 years) with hypertension and no ED. Patients completed a 4-week single-blind placebo run-in and a 12-week double-blind treatment period with nebivolol (5 mg/d), atenolol (50 mg/d), or atenolol (50 mg/d) + chlorthalidone (12.5 mg/d).

Patients taking nebivolol reported a similar number of episodes of satisfactory sexual intercourse compared with baseline (6.0 vs 6.4; P=NS). Patients receiving atenolol reported fewer episodes of satisfactory sexual intercourse compared with baseline (3.7 vs 7.0;
Evidence-Based Answer

Low-albumin, seasonal trivalent influenza vaccine (TIV) appears safe for patients with egg allergies (SOR: B, RCT and case series). It also appears safe for patients with a history of Guillain-Barré syndrome (GBS) (SOR: C, retrospective cohort trial). Immunocompromised patients also benefit from influenza vaccination and generally the vaccination is well tolerated (SOR: A, systemic review of RCTs).

A multicenter RCT involving 143 patients evaluated the safety of the seasonal TIV among severely allergic children. Inclusion criteria for this 2-phase study required both a history of a severe reaction, including anaphylaxis, to ingestion of egg and a positive skin test result. Phase 1 consisted of a randomized, prospective, double-blind placebo-controlled trial of TIV administration to 31 egg-allergic children using a 2-step approach. Group A (n=14) received 0.1 mL influenza vaccine followed, if no reaction, by the remainder of an age-appropriate dose. Group B (n=17) received a sham challenge of normal saline followed by a full age-appropriate TIV. Phase 2 was a retrospective analysis of a single dose (n=87) versus split-dose administration (n=25) of TIV in eligible study participants who declined participation in the RCT.

No patients in either phase developed an allergic reaction. The authors concluded that low-albumin TIV administration is safe, even in children with history of severe egg allergy, and that the 2-step split-dosing appears unnecessary because a single dose was well tolerated. A case series assessed whether systemic reactions occur in egg-sensitized pediatric patients with risk-stratified administration of the low-albumin H1N1 influenza vaccine. Egg allergy was confirmed with skin testing and the H1N1 influenza vaccine was administered. Patients with a mild egg allergy received 1 dose and patients with a severe egg allergy received 2 split doses. Patients with severe egg allergy or significant comorbidities were tested with the vaccine and had a 5-step desensitization if positive or age-appropriate dosing administration if negative. Seventy-seven of the 79 available patients were vaccinated.

No patient had a systemic reaction or required treatment. These results suggest that most egg-allergic tertiary care pediatric patients can be vaccinated with a low-ovalbumin–content influenza vaccine without prior vaccine testing.

A retrospective study identified GBS cases from Kaiser Permanente databases from 1995 to 2006. Of the 453 individuals with a single episode of GBS, 107 were noted to have had 405 post-GBS TIV vaccinations. It was unclear if these vaccinations were low-albumin vaccines. No cases of recurring GBS were noted within 1 year after TIV vaccination. Among 6 individuals with recurrent GBS, none had TIV exposure in the prior 12 months.

A systematic review and meta-analysis of 209 RCTs assessed evidence of efficacy and complications after influenza vaccination in immunocompromised patients. Various classes of immunocompromised patients who received TIV were observed to have fewer influenza-like illnesses when compared with patients receiving placebo or no vaccine: patients with HIV (13 trials, n=not reported; OR 0.20; 95% CI, 0.05–0.88), patients with cancer (12 trials, n=not reported; OR 0.26; 95% CI, 0.15–0.46), and transplant recipients
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(15 trials, n=not reported; OR 0.27; 95% CI, 0.11–0.66). No study reported adverse events that differed statistically from controls. A transient increase in viremia and a decrease in percentage of CD4+ cells in some HIV-positive patients were noted, but these changes were not accompanied by worsening of clinical symptoms.

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Does osteopathic manipulative treatment (OMT) improve length of hospital stay and feeding dysfunction in preterm infants?

Evidence-Based Answer

OMT may reduce length of hospital stay and reduce gastrointestinal symptoms, such as regurgitation and vomiting, in hospitalized preterm infants (SOR: B, RCT and cohort trial).

Criteria for discharge of sick and preterm infants include competent breast- or bottle feeding without cardiorespiratory compromise, which directly affects hospital length of stay (LOS).¹

An RCT of 110 preterm newborns between 28 and 38 weeks compared osteopathic evaluation and OMT techniques with routine pediatric care without OMT on hospital LOS.² Compared with routine care, OMT was associated with a significantly shorter LOS (mean difference [MD] –5.9 days; 95% CI, –7.9 to –3.9). However, the OMT group did not demonstrate a significant difference in weight gain (MD 3.7 g; 95% CI, –0.065 to 7.5). No complications associated with OMT were identified.

A prospective cohort trial of 350 preterm infants in a NICU compared a control group that received routine care with a nonrandomly assigned treatment group that received routine care with OMT.³ OMT reduced average daily gastrointestinal symptoms by 55% (OR 0.45; 95% CI, 0.26–0.74) and resulted in a more than 75% reduction in “excessive” LOS, defined as ≥28 days (OR 0.22; 95% CI, 0.09–0.51). The gastrointestinal symptoms were recorded as average daily occurrences of regurgitation, vomiting, presence of gastric residual in infants with orogastric or nasogastric tubes, and enema administrations, each per patient-care encounter. Study weaknesses included lack of blinding, inadequate sample size, lack of randomization, and lack of sham OMT procedures for the control group. No complications associated with OMT were identified.

A case report directly measuring feeding of newborn twins born at 26 weeks with failure to adequately nipple-feed reported that after the OMT began, the twins’ nipple-feeding volume steadily improved.⁴ No complications associated with OMT were identified.

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Are there any topical alternatives to long-acting topical antihistamines for allergic conjunctivitis?

Evidence-Based Answer

Tacrolimus suspension is an effective treatment for severe allergic conjunctivitis that is refractory to common first-line agents (SOR: B, small RCT). Topical cyclosporine (SOR: A, meta-analysis), topical alcaftadine, and topical cromolyn (SOR: B, single RCTs) also reduce symptoms of allergic conjunctivitis.

A multicenter, doubled-blind, paralleled RCT involving 56 patients with severe allergic conjunctivitis examined the effectiveness of tacrolimus ophthalmic suspension 0.1% compared with placebo suspension.¹ Patients were at least 6 years old and had failed prior treatment with topical antiallergic agents and corticosteroids. Treatment was given twice daily for 4 weeks and outcomes were analyzed at 1, 2, and 4 weeks. The primary outcome was change from baseline on a 10-item questionnaire (3-point scales, maximum 30) of objective signs such as bulbar hyperemia and edema, and follicle size and number. The secondary outcome was change in subjective symptoms using a visual analog scale (0–80 mm).
There was significant improvement in the objective score in the tacrolimus group compared with placebo (mean difference [MD] −5.5; 95% CI, −8.1 to −2.9). Subjective symptoms improved more with tacrolimus than placebo for itching (from 39 to 14 vs 30 to 26; P=.003), discharge (from 47 to 12 vs 39 to 33; P=.001), lacrimation (from 50 to 14 vs 42 to 35; P=.018), and foreign body sensation (from 41 to 11 vs 31 to 29; P=.008). There was actually an increase in subjective hyperemia with placebo (from 31 to 46; P=.011).

A 2013 meta-analysis of 7 RCTs (N=153 patients; N=306 eyes) compared cyclosporine eye drops with placebo in patients of all ages to evaluate improvement in symptoms of allergic conjunctivitis. The concentration of cyclosporine ranged from 0.05% to 2% and the dose between 4 and 6 times per day. Follow-up was between 2 and 16 weeks.

Compared with placebo, cyclosporine drops led to a decrease in symptoms (standard mean difference [SMD] −0.84; 95% CI, −1.5 to −0.16; symptom scale not described). Symptoms were defined as redness, tearing, burning, discomfort, foreign body sensation, discharge, and photophobia. Statistically significant heterogeneity of outcomes was noted.

A 2011 randomized, double-blind, placebo-controlled trial assessed the efficacy and safety of alcaftadine 0.25% ophthalmic solution versus a placebo vehicle in preventing itching associated with allergic conjunctivitis. Fifty-eight Caucasian patients older than 10 years (average age 36 years) with allergic conjunctivitis were included. After initial screening visits, patients were assigned to treatment or placebo and received conjunctival allergen challenges at various intervals after medication administration (measuring itching, episcleral redness, chemosis, and lid swelling on a 0- to 4-point scale).

Itching, episcleral redness, chemosis, and lid swelling were reduced by more than 1 conjunctival allergen challenge point between groups (MD −1.7, −1.7, −1.6 at 3, 5, and 7 minutes, respectively; P<.001 at each interval) at 16 hours after medication administration.

A 2011, randomized, double-blind parallel study compared the efficacy and safety of cromolyn sodium 2% ophthalmic solution with and without 0.01% benzalkonium chloride preservative. Thirty-four patients with allergic conjunctivitis were followed for 2 weeks. Mean patient symptom diary scores (10-point scale) improved from baseline in both the cromolyn group (−4.1; P<.001) and the cromolyn plus preservative group (−4.7; P<.001). No statistical difference (P=.840) was noted between groups.

When is the best time to clamp the umbilical cord after a routine term vaginal delivery?

Evidence-Based Answer

Delayed cord clamping (after 1–5 minutes) is associated with increased infant birth weight and hemoglobin concentration (Hgb), but it is also associated with an increased risk of jaundice and need for phototherapy (SOR: B, systematic review of RCTs with moderate risk of bias). Early cord clamping (before 1 minute) is associated with decreased iron stores at 3 to 6 months, but not at 12 months (SOR: C, disease-oriented outcome). Evidence remains insufficient for or against delayed cord clamping in term infants (SOR: C, committee opinion).

A 2013 Cochrane review included 15 RCTs comparing the effect of timing of umbilical cord clamping on maternal and neonatal outcomes in 3,911 women and term infant pairs. Comparing early (<1 min) and delayed (1–5 min) cord clamping, no differences were noted in the primary outcomes of maternal severe postpartum hemorrhage (ie, ≥1,000 mL) (5 trials, n=2,066; risk ratio [RR] 1.0; 95% CI, 0.65–1.7) or neonatal death (2 trials, n=381; RR 0.37; 95% CI, 0.04–3.4). Among secondary outcomes, infants in the late clamping group had an increased birth weight (12 trials, n=3,139; mean difference [MD] 101 g; 95% CI, 45–158) and Hgb at 24 to 48 hours (4 trials, n=884; MD 1.5 g/dL; 95% CI, 1.2–1.8). Infants with early cord clamping were more than twice as likely to...
be iron deficient at 3 to 6 months (5 trials, n=1,152; RR 2.7; 95% CI, 1.0–6.7; NNH=16), but had a decreased need for phototherapy (7 trials, n=2,324; RR 0.63; 95% CI, 0.41–0.96; NNT=62).

Secondary outcomes with no significant differences between groups included maternal postpartum Hgb, need for manual placenta removal, 5-min Apgar score <7, and newborn admission to a special or intensive care unit. Threats to validity in this review included the variability in timing of late clamping (1–5 min, or when the cord stopped pulsing) and inconsistent definition of iron deficiency. Overall, the authors judged the trials to have a moderate risk of bias.

A follow-up report of 1 RCT in the Cochrane review provided infant outcome data at 1 year. This study randomized infants born to nonsmoking, healthy women who were carrying a low-risk singleton pregnancy with an expected term vaginal delivery (N=347) to cord clamping at either <10 seconds or 180 seconds. At 12 months, researchers measured Hgb, mean corpuscular volume, ferritin, transferrin saturation, soluble transferrin receptor, iron level, and administered the Ages and Stages Questionnaire (a validated parent-completed survey of infant development). No differences were found in measured outcomes between the 2 groups.

The American College of Obstetrics and Gynecology (ACOG) noted in 2012 that, based on the 2008 Cochrane review, there was insufficient evidence for or against delayed cord clamping in term infants born in resource-rich areas. A delay of 60 seconds was thought reasonable in infants at risk for iron deficiency anemia. However, ACOG acknowledged that more research was needed to determine optimal time to cord clamping. The American Academy of Pediatrics endorsed these guidelines.

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How effective are probiotics in the prevention of C difficile diarrhea in immunocompetent adults who are prescribed antibiotics?

Evidence-Based Answer

Although as a group, probiotics prevent 1 episode of Clostridium difficile–associated diarrhea (CDAD) for every 29 immunocompetent adults who are treated with antibiotics in an inpatient setting, evidence is insufficient to recommend a specific dose or species of probiotics (SOR: B, systematic review of heterogeneous RCTs). The combination of Lactobacillus acidophilus, Bifidobacterium bifidum, and Bifidobacterium lactis is likely not effective in elderly patients (SOR: B, small RCT).

A recent Cochrane meta-analysis of 31 RCTs (N=4,492) examined the effectiveness of probiotics in preventing CDAD in immunocompetent patients (age range 15–93 years) receiving antibiotics, most of whom were hospitalized. CDAD is defined as diarrhea and a positive stool cytotoxin/culture for C difficile. Despite a variety of probiotic species and dosing regimens in the trials, most studies used Saccharomyces boulardii species. Duration of probiotics administration was typically the duration of the antibiotic course plus 2 to 14 additional days, or a total of 12 to 20 days, or until hospital discharge. Reevaluation occurred at 1 to 12 weeks after antibiotic discontinuation.

Based on pooled results from 19 trials (N=3,551), the incidence of CDAD decreased in the group receiving probiotics compared with the placebo group (RR 0.36; 95% CI, 0.24–0.52; NNT=29), although the incidence of C difficile infection (defined as a positive stool test without diarrhea) did not differ between groups. The incidence of adverse effects, such as abdominal cramping, nausea, fever, soft stools, flatulence, and taste disturbance, was lower in the probiotic group than in the placebo or no treatment group (14% vs 19%; RR 0.80; 95% CI, 0.68–0.95). Four studies reported serious adverse events, but none were attributable to the probiotic intervention. Across studies, not all patients who developed antibiotic-associated diarrhea were tested for C difficile and 6 of the studies were industry sponsored. The meta-analysis was limited by heterogeneity in species and strains of probiotics.

A subsequent RCT (N=2,941) studied immunocompetent, hospitalized adults older than
65 years who were treated with antibiotics and received a daily capsule containing $6 \times 10^{10}$ live bacteria, in a combination of *L. acidophilus*, *B. bifidum*, and *B. lactis*, or placebo for 21 days. Most patients in the treatment (71.6%) and placebo (72.1%) groups were exposed to penicillins; about half in the treatment group (51.2%) and placebo group (51.9%) were exposed to 3 or more antibiotic classes. Follow-up was scheduled 8 to 12 weeks after stopping antibiotics.

The probiotics did not prevent CDAD related to antibiotic use compared with placebo (RR 0.71; 95% CI, 0.34–1.5). However, CDAD was uncommon (1% of patients) and the study was underpowered to detect a small difference due to the lower than expected incidence of CDAD. No serious adverse effects were associated with the use of the probiotics. The major limitation of this study included incomplete data, as only 40% of patients who developed diarrhea had stool samples obtained.

The 2010 Infectious Diseases Society of America (IDSA) guidelines recommend against use of probiotics to prevent primary *C. difficile* infection because of limited data to support this strategy and a theoretical risk for bloodstream infection. This recommendation has a strength of recommendation of C, based on expert opinion and lack of high-quality evidence given the heterogeneity among the existing evidence.

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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 groundbreaking 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 children with cryptorchidism, at what age does the risk of malignancy outweigh the benefits of waiting for spontaneous descent?**

**Evidence-Based Answer**

Cryptorchidism should be corrected before age 10 to 13 years to reduce the risk of testicular cancer, but what the actual cutoff age should be is unclear (SOR: B, cohort study and meta-analysis of cohort and case-control studies). Spontaneous descent is uncommon beyond 12 months of age (SOR: B, cohort studies).

A systematic review and meta-analysis of 2 cohort and 3 case-control trials (N=4,531 cases, 32,967 controls) evaluated the relationship between orchiopexy and testicular cancer. Initial analysis showed no difference in cancer risk when cryptorchidism was corrected after age 10 to 11 years (OR 3.4; 95% CI, 0.7–18). However, 1 cohort study focused on testicular descent via hormonal manipulation instead of surgical treatment, (N=583 cases, 822 controls). Reanalysis after this study was removed yielded a statistically significant 6-fold increased risk of testicular cancer in men whose surgical orchiopexy occurred after the age of 10 to 11 years compared with men who had had orchiopexy at a younger age (OR 5.8; 95% CI, 1.8–19).

A large, prospective cohort trial identified 16,983 Swedish men surgically treated for cryptorchidism and followed them for 209,984 person-years. Testicular cancer developed in 56. Men who underwent orchiopexy before 13 years of age (range 0–13 years) had a higher risk of cancer (RR 2.2; 95% CI, 1.6–3.1) than the Swedish general population. This risk more than doubled when cryptorchidism was corrected after age 13 (RR 5.4; 95% CI, 3.2–8.5).

A prospective cohort trial examined spontaneous testicular descent in 84 boys with cryptorchidism (total of 126 testes). With serial exams at 2, 4, and 6 months, and 1 year, testicular descent was noted in 38% of term infants and 63% of preterm infants. However, none descended after 6 months of age.

Another cohort trial evaluated the prevalence of congenital cryptorchidism in Denmark and Finland (N=2,562) and examined spontaneous descent. Boys were examined at birth, 3 months, and 18 months, and spontaneous descent was calculated as the probability of descent per person per month. There was a dramatic difference in the probability of descent between boys...
younger than 3 months (Denmark 0.26 per person/month, Finland 0.18 per person/month) and those older than 3 months (Denmark 0.03 per person/month, Finland 0.01 per person/month).

A cohort trial evaluated the prevalence of cryptorchidism at birth, 3 months, and 1 year of age in 6,935 infants, 255 of whom were cryptorchid. Spontaneous descent occurred in 68% of infants by 3 months of age. Only 11% of the remaining infants with cryptorchidism at 3 months had testicular descent by 1 year (7 of 63).

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1. Walsh TJ, et al.  
3. Hamza AF, et al.  
Pediatrics. 1993; 92(1):44–49. [STEP 3]

What bacterial pathogens are responsible for nursing home–acquired pneumonia?

Evidence-Based Answer

**Streptococcus pneumoniae** is the most common bacteria isolated from nursing home patients hospitalized with pneumonia (36%–58%). Less common organisms include *Enterobacteria, Legionella, Staphylococcus aureus*, and *Pseudomonas* species (SOR: B, observational studies).

A 2011, multicenter, prospective, observational trial examined the pathogens causing pneumonia in 518 nursing home patients (median age 83 years) in Germany. Inclusion criteria included nursing home patients hospitalized over a 90-month period with a pulmonary infiltrate on chest radiograph and clinical symptoms of fever, cough, purulent sputum, or positive auscultation. Microbial etiology was determined by lower respiratory tract cultures, blood cultures, urinary antigen testing for *S. pneumoniae* and *Legionella pneumophila* serogroup 1, serology, and nasal and pharyngeal swabs. Positive results indicating the etiology of the pneumonia was determined in 117 patients (23%) (TABLE).

A 2009 observational trial evaluated 150 consecutive cases of patients hospitalized with a nursing home–acquired pneumonia (median age 82 years) over a 10-year period. Fifty-seven positive cultures were obtained, of which 58% were *S pneumoniae* followed by methicillin-resistant *S aureus* (5%), *L pneumophila* (5%), *Haemophilus influenzae*, *Pseudomonas aeruginosa*, Klebsiella pneumoniae, Mycoplasma pneumoniae (all at 3.5%), and any other bacterial causes (1%).

A 2013, retrospective, observational trial reviewed a database collection of patients with community-acquired pneumonias admitted to 43 hospitals over 3 continents. A pathogen was detected in 68 (23%) of 287 patients with nursing home–acquired pneumonia. *S pneumoniae* was the most common agent, accounting for 32% of the pathogens detected. *S aureus* was found in 28%: methicillin-resistant in 17% and methicillin-sensitive in 11% of patients. Gram-negative bacilli accounted for 20% of the pathogens and *L pneumophila* for 3.7%.

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2. Polverino E, et al.  
Respir Care. 2014; 59(7):1078–1085. [STEP 3]
Are alpha-blockers effective therapy for ureteral stones?

**Bottom line**

Yes. Alpha-blockers improve the expulsion rate of ureteral calculi by 50% and reduce expulsion time by more than 3 days compared with no treatment or other treatments such as analgesics and anti-inflammatories (SOR: A, meta-analysis of RCTs and consistent RCTs).

**Evidence summary**

A 2013 meta-analysis of 20 RCTs (N=1,345) examined the use of tamsulosin to facilitate expulsion of ureteral stones compared with anti-inflammatory, antispasmodic, or analgesic treatments. Tamsulosin 0.4 mg daily resulted in a significantly higher rate of ureteral stone expulsion (risk ratio [RR] 1.5; 95% CI, 1.4–1.6) compared with the control group over 10–42 days. Expulsion time was also shorter in the tamsulosin group (7 trials, n=555; mean difference [MD] –3.6 days; 95% CI, –4.1 to –3.1) compared with controls.

A 2010 RCT (n=112) examined the effectiveness of ureteral stone expulsion using the selective alpha 1A-adrenoceptor antagonist silodosin with symptomatic unilateral distal ureteral calculi of less than 10 mm. The control group (n=56) received 2 L water and the intervention group (n=56) received 2 L water plus silodosin 8 mg/d. During the 4-week follow-up, expulsion rate, time to expulsion, and analgesic use were measured.

Expulsion rate, regardless of calculus size, was higher in the silodosin group than in the control group (72% vs 55%; P=.106). The expulsion rate was higher for calculi <5 mm (92% vs 69%; P=.05) and >5 mm (76% vs 18%; P=.01). Expulsion time was faster in the silodosin group compared with controls (9.3 vs 13 days; P=.012).

A 2011 RCT (N=103) assessed the effectiveness of combined tamsulosin and tolterodine therapy for facilitating the spontaneous expulsion of intramural ureteral stones between 4 and 9 mm. Stone size was measured by KUB. Patients were randomized into 3 treatment groups and followed for 14 days. Treatment group 1 (n=37) received tamsulosin 0.4 mg/d, group 2 (n=34) received tamsulosin 0.4 mg/d plus tolterodine 2 mg (twice a day), and group 3 (n=32) received tolterodine 2 mg (twice a day). Each group was instructed to drink 2 L water daily.

Stone expulsion was observed in 81% of group 1, 85% of group 2, and in 56% of group 3. A significant difference was found between the groups 1 and 3 and 2 and 3 (P=.000 and P=.000, respectively).

A 2010 RCT (N=67) examined spontaneous passage rate in patients with acute ureteral stones (5–10 mm) taking alfuzosin. The treatment group received alfuzosin SR 10 mg daily for 4 weeks plus an analgesic while the control group received the analgesic only. Patients were followed for 5 weeks. Overall, 66% (44/67) of patients passed the stone spontaneously. More patients in the treatment group than in the control group passed the stone (82% vs 50%; P=.006).

**References**


**Glossary**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ARR</td>
<td>Absolute risk reduction</td>
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<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>CT</td>
<td>Computed tomography</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<td>LOE</td>
<td>Level of evidence</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NNH</td>
<td>Number needed to harm</td>
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<tr>
<td>NNT</td>
<td>Number needed to treat</td>
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<tr>
<td>NSAID</td>
<td>Nonsteroidal anti-inflammatory drug</td>
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<td>OR</td>
<td>Odds ratio</td>
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<td>RCT</td>
<td>Randomized controlled trial</td>
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<td>RR</td>
<td>Relative risk</td>
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<td>SOR</td>
<td>Strength of recommendation</td>
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<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitor</td>
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<td>WHO</td>
<td>World Health Organization</td>
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</table>
1. When provided to preterm newborns with feeding problems, osteopathic manipulative treatments have been shown to significantly:
   a. Accelerate weight gain
   b. Shorten duration of hospitalization
   c. Increase daily gastrointestinal symptoms
   d. None of the above

2. A 55-year-old man is admitted with acute chest pain suggestive of cardiac ischemia. The patient has a 20 pack-year history of smoking and hyperinflation on the admission chest x-ray consistent with chronic obstructive pulmonary disease (COPD). What is your best course of action regarding the use of beta-blockers?
   a. The use of beta-blockers is contraindicated because they might worsen COPD
   b. Beta-blockers should be prescribed due to a lower risk of death
   c. The risk-to-benefit ratio of beta-blocker use is balanced and the decision to use these agents depends entirely on patient preference
   d. Tell the patient that beta-blockers do not have any benefit in this situation

3. Delayed cord clamping has been shown to:
   a. Decrease risk of severe postpartum hemorrhage
   b. Improve the 5-minute Apgar score
   c. Increase infant hemoglobin at 24–48 hours
   d. Decrease need for phototherapy

4. Which of the following organisms is least likely to be isolated from a patient with nursing home–acquired pneumonia?
   a. Enterobacteria
   b. Methicillin-resistant Staphylococcus aureus
   c. Mycoplasma pneumoniae
   d. Streptococcus pneumoniae

5. You would like to give a diabetic patient the low-albumin trivalent influenza vaccine. An absolute contraindication would be:
   a. Egg allergy
   b. History of Guillain-Barré syndrome
   c. Immunocompromised state
   d. None of the above

6. How should you initiate anticoagulation therapy in a healthy 55-year-old man with newly diagnosed atrial fibrillation?
   a. Start with low-molecular weight heparin (LMWH) for at least 5 days before starting oral warfarin
   b. Start with oral warfarin and adjust to therapeutic international normalized ratio (INR)
   c. Start with inpatient intravenous heparin and oral warfarin together and adjust warfarin dose to therapeutic INR
   d. Start with outpatient subcutaneous heparin followed by oral warfarin

7. Which of the following medications is associated with the highest incidence of erectile dysfunction?
   a. Enalapril
   b. Irbesartan
   c. Amlodipine
   d. Chlorthalidone

8. Which one of the following treatments is most likely effective for reducing the signs and symptoms of severe, refractory allergic conjunctivitis?
   a. Cyclosporine
   b. Cromolyn sodium
   c. Tacrolimus
   d. Alcaftadine
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Can breathing exercises lower blood pressure?

Evidence-Based Answer
Device-guided breathing may lower blood pressure slightly in the short term (SOR: C, meta-analysis of RCTs at high risk of bias). Qigong meditation and breathing practice may lower blood pressure to the same extent as drug treatment or exercise (SOR: C, meta-analysis of lower quality RCTs). Yoga that includes breathing exercises decreases nighttime diastolic blood pressure (SOR: C, small RCT).

A 2012 meta-analysis of 8 RCTs (N=494) studied the effect of device-guided breathing on blood pressure in hypertensive adult patients compared with music, music with blood pressure monitoring, blood pressure monitoring alone, or routine care. All RCTs studied the RESPeRATE® device, a device that trains users to breathe at fewer than 10 breaths per minute for 15 minutes per day. The studies lasted from 4 to 9 weeks. Device-guided breathing decreased systolic blood pressure by 3.1 mmHg (95% CI, 1.4–4.7; P=.0002) and diastolic blood pressure by 2.4 mmHg (95% CI, 1.2–3.5; P=.0001). Limits of the meta-analysis included varying control groups in the studies. Also, 5 of the studies were sponsored by or involved the manufacturers of RESPeRATE. A meta-analysis of the 3 non–device-sponsored studies did not show an overall reduction in blood pressure.

A 2008 meta-analysis of 9 RCTs (N=908) studied the effect of qigong, a type of traditional Chinese medicine that uses breathing and meditation, on blood pressure in patients with essential hypertension. The meta-analysis included RCTs of qigong alone or qigong combined with an antihypertensive agent compared to different controls (no treatment, drug, exercise, no intervention, or muscle relaxation). A subanalysis of 3 studies (N=130) comparing qigong with no intervention controls found a mean decrease of systolic and diastolic blood pressure in the qigong intervention group of 17 mmHg (95% CI, 12–23; P<.001) and 10 mmHg (95% CI, 2.6–17; P<.001), respectively. Qigong was not superior to antihypertensive agents, muscle relaxation, or exercise. Key weaknesses included studies with variation in length, lack of standardization in type of qigong practice, and RCTs with small sample sizes.

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rehabilitation with option of delayed operative ACL reconstruction.\(^1\) Five-year follow-up was then reported in a second RCT.\(^2\) Baseline, 2-, and 5-year follow-up testing included osteoarthritis outcome score, function and knee activity, Tegner activity scale (a rating scale to quantify activity levels in patients with ACL injury), SF-36 (a subject health quality-of-life rating scale), and radiographic evidence of osteoarthritis. Of the patients with initial nonoperative treatment, 51% eventually underwent surgery. At 2- and 5-year follow-up, the groups were compared based on their original group, regardless of whether delayed ACL reconstruction was performed. At 2 and 5 years, no significant difference was noted between the 2 groups in any outcomes measured.

A case-control trial matched 69 nonoperatively treated patients with ACL injuries with operatively managed patients, based on sex, pre-injury sport, and age.\(^3\) Baseline testing and 1-year follow-up testing included sport participation level, KT-1000 arthrometer measurements, 4 hop test, and patient-reported outcomes. No statistical difference was noted in return to sport (nonoperative 68% vs operative 68%; \(P=1.0\)) or in return to level I sport, which involve significant jumping, cutting, and pivoting (nonoperative 55% vs operative 62%; \(P=.66\)). However, nonoperatively treated patients who participated in level I sport prior to injury had lower return to previous level of sport than nonoperatively treated patients who participated in level II sports, which involve minimal cutting and pivoting, prior to injury (nonoperative level I 55% vs nonoperative level II 89%; \(P=.03\)). Nonoperative patients had higher knee joint laxity based on KT-1000 measurement (5.6 vs 2.7 mm; \(P<.001\)). But nonoperative patients had better hop test limb symmetry (an aggregate of single hop, crossover hop, timed distance hop, and triple hop for distance performance) (96.3% of normal side vs 90.5% of normal side for operative patients; \(P=.009\)) and better subjective knee function (95% of normal vs 91% of normal for operative patients; \(P<.001\)).\(^3\)

A cohort study of 125 patients (mean age 27 years) compared operative versus nonoperative management of ACL tears.\(^4\) Follow-up measures at 1 year included single-leg hop test, knee arthrometer, and Knee Outcome Survey – Activities of Daily Living Survey measures as well as subjective giving way and activity level. Half of the patients underwent nonoperative treatment.

No difference was noted in performance on the single leg hop test when compared as a percentage to the uninjured knee (88% vs 82%; \(P=.07\)). No other differences were observed, including general rating of knee function (VAS 0–100; 92 vs 85; \(P=.07\)), daily function, patient satisfaction, or return to previous level of sport.\(^4\)

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### Does long-term proton pump inhibitor (PPI) therapy increase the risk of fractures?

**Evidence-Based Answer**

It appears that any use of a PPI is associated with an increased risk of vertebral fractures (SOR: C, systematic review of case-control and cohort studies). It is unclear if long-term PPI use increases the risk of hip fractures (no SOR given because of conflicting results from a systematic review of observational studies and a large cohort study).

A 2011 meta-analysis of 6 case-control and 4 cohort studies with approximately 1 million patients evaluated the risk of PPI use versus non- or past-PPI use and hip, spine, and arm fracture events.\(^1\) Fracture outcomes were obtained from diagnosis coding or from patient-reported history later confirmed by a radiology report. PPI use was obtained from prescription claims data or patient-reported history.

A subanalysis of long-term PPI use (2.5–10 years, 5 case control and 2 cohort trials), found no statistically significant increased risk of hip fractures (OR 1.3; 95% CI, 0.98–1.7). Short-term PPI use (<1 year) and any PPI use had a statistically significant increase in hip fracture risk (OR 1.2; 95% CI, 1.2–1.3 and OR 1.3; 95% CI, 1.1–1.4, respectively). For any PPI use there was a statistically significant increased risk of vertebral fracture risk (4 trials, OR 1.5; 95% CI, 0.98–1.7). Limitations of this meta-analysis were...
substantial heterogeneity between many included trials, inclusion of low-quality observational studies, and that most patients were women. 

In 2012, a prospective cohort trial evaluated PPI use and hip fractures from low or moderate trauma in 79,899 postmenopausal women (age range 30–55 years) who were previously a part of the Nurses’ Health Study. Patients who reported on a questionnaire regular use of a PPI in the past 2 years were placed into the PPI user group.

After 565,786 person-years of follow-up and 893 new hip fractures, PPI users had a statistically significant increase in the absolute risk of hip fracture compared with non-PPI users (2.0 vs 1.5 hip fractures per 1,000 person-years, age adjusted; HR 1.4; 95% CI, 1.1–1.6). The risk of hip fracture increased with duration of PPI use (HR 1.4; 95% CI, 1.1–1.7 after 2 years’ use; HR 1.4; 95% CI, 1.1–1.9 after 4 years’ use; HR 1.6; 95% CI, 1.0–2.3 after 6–8 years’ use). Adjusting for confounding variables of body mass index, dietary or supplemental intake of calcium, smoking, physical activity, history of osteoporosis, or medications that can affect the risk of fracture did not substantially change the risk of fracture in PPI users. Follow-up responses to the health questionnaire were >90%; however, due to the observational study design the results are limited by residual confounding.

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Is benign breast disease a risk factor for breast cancer?

Evidence-Based Answer

There appears to be an increased risk of breast cancer associated with proliferative and atypical lesions on breast biopsy histology. The increased risk persists for 15 to 25 years after biopsy (SOR: B, prospective cohort studies).

A prospective cohort study (N=9,087, median follow-up 15 years) compared the incidence of breast cancer in women originally diagnosed via histology with benign breast disease (nonproliferative lesions, proliferative lesions without atypia, and atypical hyperplasia). The reference population used to estimate the risk of developing breast cancer was the Iowa Surveillance, Epidemiology, and End Results registry, which was demographically similar to the study population.

Women with benign breast disease had an increased risk of developing breast cancer compared with the reference population (risk ratio [RR] 1.6; 95% CI, 1.5–1.7). When separated by histology findings, there was an increased risk in patients with nonproliferative lesions (n=6,061; RR 1.3; 95% CI, 1.2–1.4), proliferative lesions without atypia (n=2,690; RR 1.9; 95% CI, 1.7–2.1), and atypical hyperplasia (n=336; RR 4.2; 95% CI, 3.3–5.4). This increased risk of breast cancer persisted for 25 years after biopsy.

In a multicenter, prospective cohort trial, 1,145 women with biopsy-confirmed benign breast disease were followed over a mean of 15 years to examine the association between the different histologic types of benign breast disease and breast cancer. The cohort was composed of women who had biopsy-confirmed benign breast disease and went on to develop breast cancer within the next 15 years. The controls were women with a positive biopsy for benign breast disease, but did not develop breast malignancy during this time frame. As above, benign breast disease included nonproliferative disease, proliferative disease without atypia, and atypical hyperplasia.

As compared to nonproliferative benign breast disease or normal pathology, there was an increased risk for developing breast cancer after being diagnosed with proliferative disease without atypia (OR 1.5; 95% CI, 1.1–1.9) and atypical hyperplasia (OR 5.3; 95% CI, 2.3–12).

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**Is humidified air helpful in the management of croup in children?**

**Evidence-Based Answer**

No, the use of humidified air does not improve symptoms or decrease hospitalizations in children with croup compared with room air (SOR: A, meta-analysis of RCTs). Mode of delivery, relative humidity, and water droplet size does not decrease croup symptoms (SOR: B, single RCT).

A 2007 meta-analysis of 3 RCTs (N=135) evaluated the effectiveness of humidified air compared with room air in the treatment of children 6 months to 3 years old with mild to moderate croup. Humidified air was administered by “blow-by” technique in 2 studies and infused into a Plexiglas-covered crib in the other.

The studies assessed response to therapy using the Westley Croup score, which assesses 5 clinical categories (stridor, retractions, air entry into lungs, cyanosis, and level of consciousness) with scores from 0 (no symptoms) to maximums of 2, 3, or 5. Because 1 study used a modified version of the Westley score (maximum score of 14) and 2 studies used the original Westley score (maximum score of 17), pooled results were reported as a standardized mean difference (SMD) instead of mean difference. Patients in 1 emergency department (ED) study received oral dexamethasone while the other studies (1 in the ED and 1 in the hospital) did not.

The pooled croup scores from 20 minutes after treatment in 1 study and 60 minutes after treatment in 2 studies did not show improvement with the use of humidified air compared with room air (SMD –0.14; 95% CI, –0.75 to 0.47). Pooled data from the 2 trials (N=119) in ED patients showed no significant difference in the risk of hospitalization using humidified air compared with room air (OR 3.1; 95% CI, 0.71–13).

A single-blinded RCT (N=140) examined the effectiveness of humidified oxygen containing various-sized water droplets delivered by tubing or face mask in children 3 months to 10 years old presenting to the ED with moderate croup. This RCT was not included in the above meta-analysis because there was not a “no treatment” group.

Children received 30 to 60 minutes of one of the following therapies: humidified oxygen with uncontrolled water particle sizes using blow-by technique through tubing (likely around 40% humidity), 40% humidity of uncontrolled particle size by face mask, or 100% humidity containing water particles between 5 and 10 µm (the size believed to optimally reach the larynx) by face mask.

Mean Westley scores at baseline for groups 1, 2, and 3 were 3.17, 2.95, and 3.00, respectively, and each group improved by a nonsignificant difference of about 1 point at 60 minutes. Limitations of the study included the nonblinding of the assistants who set up and administered the treatments and the wide age range of children, thereby including older children whose disease likely had a different mechanism or etiology.

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**Do any dietary interventions improve migraine symptoms?**

**Evidence-Based Answer**

In patients with migraines, elimination diets based on food-related IgG response may reduce the number of headache days and migraine attacks (SOR: B, RCT). Low-fat diets may also decrease migraine headache frequency (SOR: C, small cohort study). Increasing omega-3 and reducing omega-6 fatty acids in the diet may reduce headache days per month (SOR: C, extrapolated from RCT in patients with chronic daily headache).

In 2010, a randomized, double-blinded, crossover trial compared baseline diets with elimination diets and provocation diets in 30 patients (age range 18–55 years; 28 of 30 were females) with migraine without aura to examine the effect of IgG-based elimination on migraines. The patients had a 6-week pretreatment period consuming their baseline diet. IgG antibodies to food antigens were then assessed with ELISA. Top positive IgG foods were spices, seed and nuts, seafood, starch, food additives, and vegetables. The patients were next randomized into 2 groups: an elimination diet group versus a provocation diet based on the
food antigens. The patients were subsequently placed back on their baseline diets for 2 weeks then followed through 6 weeks of crossover diets.

Compared with baseline, the elimination diet period had a reduced number of headache days (from 11 to 7.5; \( P < .001 \)) and number of migraine attacks (from 9.0 to 6.2; \( P < .001 \)).

In 1994, a cohort study of 54 patients with migraine headaches examined the effect of dietary fat on headache frequency and medication intake. Patients had a 28-day baseline period, a 28-day intervention period with a goal of fat intake less than 20 g/d, and a 28-day postintervention period. Compared with baseline on usual diet, the decreased dietary fat intervention was associated with a decrease in headache days (~5 days over 4 weeks; \( P < .0001 \)) and fewer medications (~6.5 doses over 4 weeks; \( P < .0001 \)).

In 2013, a randomized, single-blinded trial of 67 patients with chronic daily headaches examined the role of omega fatty acids in headache patients. Patients were randomized into 1 of 2 intensive, food-based 12-week interventions groups: high omega-3 plus low omega-6 (H3-L6) intervention versus low omega-6 (L6) intervention group. The Headache Impact Test-6 (HIT-6), a questionnaire with a score range of 36 to 78, measured headache-related disability based on self-reported pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress. Headache hours per day, severe headache days, and medication use were derived from headache diaries.

In an intention-to-treat analysis, the H3-L6 diet produced significantly greater improvement in the HIT-6 score (~7.5 vs ~2.1; \( P < .001 \)) and number of headache days per month (~8.8 vs ~4.0; \( P = .02 \)), compared with the L6 group. The H3-L6 intervention also reduced headache hours per day (~4.6 vs ~1.2; \( P = .01 \)) and the probability of experiencing a severe headache day (~28% vs ~8%; \( P = .02 \)) compared with the L6 group.

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Are routine skin exams effective in reducing morbidity and mortality in patients at average risk?

Evidence-Based Answer

A skin cancer screening exam is effective for skin cancer recognition, including melanomas, and there does not appear to be a difference in accuracy between primary care physicians (PCPs) and dermatologists (SOR: A, systematic review). Performing a total body skin exam for atypical nevi can identify a small group of higher risk patients for more thorough evaluation (SOR: C, observational trials). The optimal frequency of screening is unclear.

A systematic review of 32 prospective, retrospective and screening trials (total N not provided) compared the biopsy/referral accuracy of PCPs and dermatologists with regard to melanoma. The biopsy/referral accuracy was defined as the clinician’s ability to correctly determine that a lesion may be malignant and to either biopsy or refer to a melanoma specialist. The gold standard was either biopsy or the opinion of a reviewing expert panel.

Dermatologists had a sensitivity of 82% to 100% and a specificity of 70% to 89%. PCPs had a sensitivity of 70% to 88% and a specificity of 70% to 87%. Receiver operating characteristic curves for biopsy/referral ability were similar and indicated no statistically significant difference between dermatologists and PCPs in accurately identifying suspicious lesions.

A systematic review examined 500 skin cancer screening articles. One prospective trial of 3,889 patients validated the use of an initial count of atypical moles in predicting the incidence of melanoma over 5 years. Atypical moles were diagnosed clinically by a dermatology fellow based on a total body skin exam and patients were then followed for 5 years. Seven percent of the patients fell into the highest risk group, and accounted for 56% of the melanomas that developed. Sixty-four percent of the patients were in the lowest risk group and accounted for 11% of patients who developed melanoma. By this method, a relatively small (<10%) group of patients could be selected for a more thorough evaluation.

Five mass screening trials reported on the sensitivity and specificity of a screening skin exam, although the gold standard varied by study and included skin cancer,
suspected melanoma, and rule out melanoma. Overall the sensitivity of the screening exam was 94% and specificity was 98% (positive likelihood ratio [LR+] 47, negative likelihood ratio [LR−] 0.06). Only 1 of mass screening trials, of 1,961 patients, followed up patients with negative screens to determine the false-negative rate of screening skin examination. In this study the sensitivity of screening was 94% and the specificity was 98%.  

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Does daily meditation decrease blood pressure in patients with prehypertension?

Evidence-Based Answer  
Meditation relaxation techniques reduce systolic blood pressure (SBP) by 3.1 to 7.0 mmHg and diastolic blood pressure (DBP) by 1.9 to 3.9 mmHg in prehypertensive patients. The type of meditation, duration of practice required, and whether these practices need to be continued to maintain significant reduction in blood pressures (BPs) is unclear. There is no evidence as to whether this reduction in blood pressure leads to any patient-oriented outcomes (SOR: C, disease-oriented outcome).

A 2013 RCT examined the effect of mindfulness-based stress reduction (MBSR) on 56 patients 30 to 60 years old with BPs in the prehypertensive range (SBP 120–139 mmHg or DBP 80–89 mmHg). Patients were all nonsmokers, taking no medications, and had no experience with meditation or relaxation techniques. Patients were randomized to receive either MBSR or control.

The active intervention included 8, 2.5-hour sessions of MBSR, which included a relaxation exercise, mediation practice, yoga, and a home program 45 min/d for 6 days/week. The control included 8, 2.5-hour sessions of progressive muscle relaxation (PMR) and a home program recommendation of 45 min/d for 6 days/week. Patients were followed for 8 weeks. Primary outcomes were change in clinic BPs and change in 24-hour ambulatory BPs.

The clinic BPs measured after 8 weeks of therapy were reduced 4.9 mmHg SBP in the MBSR group, compared with 0.7 mmHg (P=.016) in the PMR group. The MBSR group DBP reduced 1.9 mmHg compared with 1.2 mmHg in the PMR group (P=.008). Ambulatory BPs were also significantly different between groups (SBP decrease of 3.1 mmHg in MBSR vs 1.5 mmHg decrease in the PMR group; P=.043).

A 2001 RCT investigated the effectiveness of transcendental meditation (TM) on 35 adolescent patients 15 to 18 years old with BPs in the prehypertensive range (85th–95th percentile for age and sex) for at least 3 consecutive readings. Patients were otherwise healthy and did not receive medications for BP during the study.

The intervention group (n=17, average baseline SBP=125 mmHg) were instructed to do 2, 15-minute TM sessions daily for 2 months. One session occurred at school and 1 was instructed to take place at home. The control group (n=18, average SBP=119 mmHg) received 7, 1-hour education sessions on decreasing dietary salt, dietary fat, and other hypertension-related health behaviors. Patients were followed for 2 months.

After 2 months, patients in the TM group had a lower average resting SBP of 120 mmHg (P<.05 for change from baseline) and patients in the control group had a higher average of 121 mmHg (P<.05 for change from baseline). The difference in change from baseline between the control and intervention group was also statistically significant (−4.8 mmHg in the intervention group vs +2.6 mmHg in the controls; P<.03).

A 1974 cohort study included 22 adult volunteers with at least 3 BPs above the normotensive range (average BP 147/95 mmHg), who were not taking any antihypertensive medication. The patients all received twice-daily, 20-minute TM sessions before breakfast and dinner for 25 weeks. BP was measured at nonmeditation times every 11 days. The researchers found average decreases of 7.0 mmHg in SBP and 3.9 mmHg in DBP compared with baseline (P<.001).
What dietary interventions are effective in the treatment of fatty liver disease?

Evidence-Based Answer
Reducing caloric intake combined with exercise and reducing fructose consumption are both associated with histologic and biochemical improvements in fatty liver disease (SOR: C, small RCTs and observational trials of disease-oriented outcomes).

A 2013 RCT enrolled 41 patients with biopsy-proven nonalcoholic fatty liver disease (NAFLD) to 1 of 4 lifestyle modification subgroups for 6 months: standard care, low-fat diet and moderate exercise (LFDE), moderate-fat/low-processed-carbohydrate diet and moderate exercise (MFDE), and moderate exercise only (ME).

Pooled data from all intervention groups showed a decrease from baseline of –0.9 in nonalcoholic fatty liver disease activity score (NAS) (scores assessed steatosis, lobular inflammation, and ballooning, from 0–8) over the 6-month period ($P<$ .001). Analysis of each intervention group showed a decrease in NAS of the LFDE (–1.3; $P<$ .05), MFDE (–1.2; $P<$ .05), standard care (–0.4; $P>$ .05), and ME (–0.7; $P>$ .05) from baseline. However, no significant difference was observed between subgroups ($P=$ .31).

In secondary health outcomes, pooled data from all groups also revealed a significant decrease from baseline in the Brunt grade (scale graded on steatosis, hepatocyte ballooning, portal inflammation, and lobular inflammation with a score between 0 and 12, with 12 indicating more severity) (–0.3; $P=$ .022), alanine transaminase (ALT) (–18 IU/L; $P=$ .004), and aspartate aminotransferase (AST) (–12 IU/L; $P=$ .012).

A 2010 retrospective observational trial analyzed data from 341 patients within 3 months of liver biopsy for NAFLD to assess fructose consumption (thought to be metabolically hepatotoxic) and disease severity. Food questionnaires assessed frequency and number of fructose-containing beverages and separated participants into 3 categories: nonconsumers (NC) (0 servings per week), minimum to moderate consumers (MMC) (1–6 servings per week), and daily consumers (DC) (≥7 servings per week).

Compared with the NC group, the MMC group did not have an increase in high-grade steatosis (OR 0.7; 95% CI, 0.4–1.1), but the DC group had significantly more (OR 2.6; 95% CI, 1.4–5).

A prospective observational trial with the aim to investigate long-term effects of weight loss enrolled 31 patients including 27 patients with chronic hepatitis C (HCV), to a 15-month study. The program included regular meetings with a dietician to reduce caloric intake and recommend aerobic exercise of 150 minutes per week.

After 3 months, patients had significant decreases in ALT with weight reduction (non-HCV ALT levels from 133 to 100 U/L; $P=$ .02; HCV ALT levels from 77 to 48 U/L; $P=$ .02). Patients who maintained weight loss at 15 months maintained these reductions in ALT (approximately 100 U/L at baseline and approximately 80 U/L at month 15; $P=$ .004). Patients who regained their weight at 15 months showed no difference in ALT levels. Fourteen patients consented to liver biopsy, and there was a significant improvement in steatosis (graded by the percent of hepatocytes affected) associated with an average weight reduction.

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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 US Army at large, or the Department of Defense.