What is the best treatment for adults with acute cough with and without wheezing?

Evidence-based answer

*Pelargonium sidoides* may be slightly effective for the cough of acute bronchitis, and the evidence is mixed for antibiotics, dextromethorphan, guaifenesin, and antihistamine–decongestant combinations. Antihistamines alone and beta2-agonists do not work. Evidence is limited that beta2-agonists may be effective for acute cough with wheezing (SOR: C, meta-analysis with heterogeneous data).

Evidence summary

A Cochrane review of 3 RCTs with 746 adults with acute bronchitis evaluated the effectiveness of *Pelargonium sidoides*, an herbal remedy, on respiratory symptoms compared with placebo. Patients in the treatment group took a 10-, 20-, or 30-mg tablet or 30 to 60 drops of an alcohol root extract. All of the included trials were funded by the manufacturer, used nonvalidated outcome measures, and showed significant heterogeneity. Adverse effects were not reported. Results are shown in the TABLE.

A Cochrane review with 7 RCTs of 969 patients evaluated the effectiveness of either erythromycin or doxycycline compared with placebo in adults for the treatment of acute bronchitis (TABLE). Antibiotic use was associated with no significant increase in adverse events of nausea, vomiting, diarrhea, headaches, skin rash, and vaginitis and no significant reduction in mean days of illness. The authors concluded the small benefits seen by antibiotics were offset by the nature of treating a self-limiting illness, increased cost, and increased resistance patterns.

Another Cochrane review that included 18 studies and almost 4,000 patients evaluated codeine, dextromethorphan, guaifenesin, antihistamines, and antihistamine–decongestant combinations compared with placebo for the treatment of acute cough in adults resulting from an acute upper respiratory infection (TABLE). The included studies showed significant variability and were of low quality.

A 2011 Cochrane review included 7 RCTs of 552 patients evaluated the effectiveness of beta2-agonists compared with placebo for the treatment of acute cough or acute bronchitis in adults without underlying pulmonary disease (TABLE). For patients with acute cough and wheezing, subgroup analysis of 15 patients from 1 RCT showed that inhaled beta2-agonists significantly reduced cough symptom scores starting on day 2 of treatment.

Continued...
<table>
<thead>
<tr>
<th>Medication</th>
<th>Trial details</th>
<th>Outcome</th>
<th>Strength (vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelargonium sidoides extract</td>
<td>3 RCT, 746 adults, liquid or tablets 2 RCT, 341 adults, liquid 3 RCT, 405 adults, tablets</td>
<td>Improved sputum resolution Improved cough at day 7 Improved cough at day 7</td>
<td>RR 0.70 (95% CI, 0.60–0.82) RR 0.63 (95% CI, 0.47–0.85) RR 0.94 (95% CI, 0.90–0.98)</td>
</tr>
<tr>
<td>Antibiotics (erythromycin or doxycycline)</td>
<td>4 RCT, 275 adults 4 RCT, 538 adults 6 RCT, 969 adults 7 RCT, 713 adults</td>
<td>Decreased number of patients with cough at days 7–14 Decreased number of patients with night cough at days 7–14 No significant reduction of cough duration No significant reduction of cough production</td>
<td>RR 0.64 (95% CI, 0.49–0.85) RR 0.67 (95% CI, 0.54–0.83) Mean difference (in days) –0.44 (95% CI, –0.95 to 0.07) RR 0.97 (95% CI, 0.82–1.16)</td>
</tr>
<tr>
<td>Codeine</td>
<td>1 RCT, 82 adults, 30 mg QID 1 RCT, 82 adults, 50 mg one time</td>
<td>No significant reduction of cough or severity No significant reduction of cough frequency &amp; subjective score at 90 min</td>
<td>$P &gt; .2$ $P = .8$ $P$ not reported</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>3 RCT, 451 adults, 30 mg once 1 RCT, 44 adults, 30 mg once 5 RCT, 710 adults, 30 mg once</td>
<td>Decrease in cough count No significant decrease in cough frequency and score Decrease in cough bouts, components, and effort</td>
<td>Treatment group 36% reduction, placebo 19% reduction ($P &lt; .05$) Frequency ($P = .38$) Score $P = .08$ Average of 17% reduction for active vs 12% for placebo (all outcomes $P &lt; .05$)</td>
</tr>
<tr>
<td>Guaifenesin</td>
<td>RCT 239 adults, 200 mg/10 mL QID for 3 days RCT 65 adults, 480 mg/30 mL q6h x 30 h</td>
<td>Reduced cough frequency at 72 h No significant Improvement in cough frequency No significant improvement in cough severity Reduced sputum thickness</td>
<td>75% for active vs 31% placebo ($P &lt; .01$) $P = .5$ $P = .2$ $P = .001$</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>RCT 100 adults, terfenadine 120 mg BID x 4–5 d RCT 250 adults, terfenadine 60 mg BID x 3.5 d RCT 1,500 adults, thonzylamine 50 mg TID x 3 d</td>
<td>No significant difference in cough score No significant difference in cough scores No significant improvement in cough</td>
<td>$P &gt; .35$ Not reported $P = .5$</td>
</tr>
<tr>
<td>Antihistamine-decongestant combinations</td>
<td>RCT 283 adults, loratadine + pseudoephedrine 5/120 mg BID x 4 d RCT 73 adults, dexbrompheniramine + pseudoephedrine 6/120 mg BID x 7 d</td>
<td>No significant reduction in cough score Reduced cough severity after treatment on days 3–5</td>
<td>$P &gt; .5$ Severity score 1.4 in active vs 2.0 in placebo group ($P &lt; .05$)</td>
</tr>
<tr>
<td>Beta2-agonist</td>
<td>3 RCTs 220 adults, albuterol inhaler, fenoterol aerosol, or albuterol pills vs placebo 2 RCTs 119 adults, albuterol inhaler or fenoterol aerosol vs placebo 2 RCTs 210 adults, albuterol inhaler or fenoterol aerosol vs placebo</td>
<td>No significant reduction of cough after 7 days No significant reduction of productive cough at 7 days No significant reduction of night cough at 7 days</td>
<td>RR 0.86 (95% CI, 0.63–1.18) RR 0.76 (95% CI, 0.32–1.84) RR 0.84 (95% CI, 0.54–1.33)</td>
</tr>
</tbody>
</table>

CI=confidence interval; NNT=number needed to treat; RCT=randomized controlled trial; RR=relative risk ratio.

REFERENCES
From the Editor

Blockbusters

Dear EBP Readers,

I always enjoy learning about the origins of words.

For example, I recently learned about the evolution of the term “blockbuster” on Wikipedia. The anonymous authors noted that the meaning changed through usage in the military, film, and stage, and more recently the pharmaceutical industry. The term probably started during World War II to describe the largest bombs the allies were lobbing at the axis powers. But it seems the term was quickly adopted on Broadway to describe a play so successful that other plays being produced nearby went out of business. Soon thereafter, the word came to describe a major success on the silver screen.

Currently, a film making more than $100 million in US ticket sales is described by Hollywood as a “blockbuster.” Examples include such memorable movies as Jaws, Star Wars, Titanic, and Avatar.

That brings us to the use of the word “blockbuster” in the pharmaceutical industry. Here the term applies to any intervention with sales that exceed a whopping $1 billion per year. In 2011, 60 different drug products on sale in the United States met this definition; 24 of them actually brought in $2 billion dollars in sales. That really puts Hollywood to shame. Compared to that, Jaws is just another rubber bathtub toy.

This is a lot of money sloshing around. It is so much money, in fact, that it has been suggested that a fraction of it could be used to fund some really good research. This opportunity is made all the more important because many blockbuster drugs are supported by trials with only modest numbers, intermediate endpoints, short follow-up, and poor toxicity reporting. If we consumers are all paying a collective $1 billion/year for the patent-life of a blockbuster drug, manufacturers could probably spend $40 million or even $400 million proving it’s really safe and effective for huge audiences... er, I mean patient numbers.

That would make “the price of fame” something tangible and assure that blockbuster drugs are safe and effective for everyone on the block.

Regards,

Jon O. Neher, MD


Do you need to provide VTE prophylaxis for patients with end-stage liver disease and an elevated INR?

A 56-year-old man with end-stage liver disease secondary to chronic alcohol abuse presents to the emergency department with progressive abdominal fullness and “flapping hands” for the past 3 days. The patient is admitted with a diagnosis of hepatic encephalopathy. He has no history of gastrointestinal bleed and has an elevated international normalized ratio (INR) of 2.3 in the absence of anticoagulation therapy. Should this patient be placed on pharmacologic prophylaxis for venous thromboembolism (VTE) on admission?

Review of the evidence

A 2009 nationwide Danish case-control study evaluated the risk of VTE in more than 99,000 patients discharged with a diagnosis of liver disease compared with nearly 500,000 population controls over 26 years.\(^1\) Compared with general population controls, the risk of VTE (pulmonary embolism or deep vein thrombosis [DVT]) was increased in patients with liver cirrhosis (risk ratio [RR] 1.7; 95% CI, 1.5–2.0) and in those with noncirrhotic liver disease (RR 1.9; 95% CI, 1.7–2.0).

In a subgroup analysis of unprovoked VTE, which excluded patients with a diagnosis of cancer, fractures, trauma, surgery, or pregnancy within 90 days of hospitalization, the risk of unprovoked VTE was increased compared with controls in patients with cirrhosis (RR 2.1; 95% CI, 1.8–2.4) and in patients with noncirrhotic liver disease (RR 2.1; 95% CI, 1.9–2.3).\(^1\)

A 2010 retrospective cohort trial evaluated the incidence of VTE in 193 hospitalized patients with a primary diagnosis of chronic liver disease.\(^2\) Patients were divided into 4 quartiles according to highest recorded INR. A calculated risk factor score (based on malignancy, prior VTE, and hypercoagulability) was similar and there was no statistical difference in DVT prophylaxis use (mechanical or pharmacologic) across quartiles. No significant difference was noted in the incidence of in-hospital VTE with increasing INR (3% in patients with INR <1.4; 3% with INR 1.4–1.7; 4% with INR 1.7–2.2; 2% with INR >2.2; ANOVA \(P=.665\)).

A 2013 retrospective cohort study evaluated the incidence of VTE and bleeding in 392 hospitalized patients with chronic liver disease who received pharmacologic prophylaxis compared with 1,189 patients who did not.\(^3\) No statistical difference was noted in INR between groups. Incidence of VTE was lower in those who received prophylaxis versus those who did not (0.5% vs 1.8%; \(P=.05\)). Pharmacologic prophylaxis was protective against VTE (OR 0.34; 95% CI, 0.04–0.88). Bleeding rates were significantly lower in patients who received prophylaxis compared with patients who did not (2.0% vs 10%; \(P<.001\)). A subanalysis of patients with a history of bleed (N=299) revealed there was no difference in bleeding in the group that received prophylaxis compared with patients who did not receive prophylaxis (0.3% vs 1.1%; \(P=.13\)).

Bottom line

Even though this patient with end-stage liver disease has an elevated INR, he is at an increased risk of VTE. Specific VTE prophylaxis will lower the incidence of VTE without an increase in bleeding risk.

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REFERENCES

**Diving for PURLs**

### Evidence-Based Practice learning objectives

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

### Can’t tolerate CPAP? Get MAD


In this randomized crossover trial, 108 patients with mild to severe obstructive sleep apnea received either 1 month of optimal continuous positive airway pressure treatment (CPAP) or 1 month of a custom-fitted 2-piece oral appliance called a mandibular advancement device (MAD).

The primary outcome was mean arterial blood pressure. Secondary outcomes included sleepiness, driver simulator performance, and other quality-of-life indicators.

The mean arterial blood pressure was not significantly different in patients who used the MAD compared with when they were using the CPAP. Blood pressure did not decrease on either treatment (CPAP − MAD difference = 0.2 mmHg (95% CI, −0.7 to 1.1)).

CPAP was better than MAD in improving apnea/hypopnea and mean oxygenations, but patients self-reported higher compliance with the MAD device. Both treatments showed similar improvements in sleepiness, driving simulator performance, and other quality-of-life indicators.

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

**Bottom line:** MAD should be considered in patients who do not tolerate CPAP, but the long-term effectiveness of MAD is not known.

**Review Author and Summary Author:** Janice Benson, MD, NorthShore University Family Medicine, The University of Chicago, Chicago, IL

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**Diving for PURLs**

### Daily colchicine promising for secondary prevention of CAD


This randomized trial of 532 patients with stable coronary artery disease (CAD) compared the effect of low-dose colchicine (0.5 mg daily) plus usual care with usual care alone on the risk of new cardiovascular (CV) events. Usual care included aspirin or other platelet inhibitors, statins, and beta-blockers plus angiotensin-converting enzyme inhibitors or angiotensin receptor blockers as indicated.

The primary outcome was the combined number of new acute coronary syndrome events, out-of-hospital cardiac arrests, and noncardioembolic ischemic strokes. Median follow-up was 36 months (range, 24–44 months).

A new CV event occurred in 5.3% of patients in the colchicine group and 16.0% of the usual care group (HR 0.33; 95% CI, 0.18–0.59; NNT=11). Medication was withdrawn in 62 patients in the colchicine group (22%); 39 patients (14%) quit because of gastrointestinal intolerance.

**Bottom line:** Colchicine may reduce the risk of new CV events in patients with known CAD. The long-term side effects and safety in this high-risk population, however, remain unknown.

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**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?
Is transdermal nitroglycerin an effective treatment for tendon injury?

**Evidence-Based Answer**
Yes, transdermal nitroglycerine reduces pain with activities of daily living in patients with chronic tendon injuries (SOR: A, systematic review of consistent RCTs).

A 2010 meta-analysis examined the effectiveness of topical nitroglycerine (NTG) in 7 RCTs involving 446 adult patients with tendinopathy pain. The tendinopathy involved the rotator cuff in 3 studies, elbow in 2, and Achilles tendon in 2. Duration of symptoms varied from acute (<2 weeks of symptoms), to subacute (2–6 weeks of symptoms), to chronic (>6 weeks of symptoms). The primary outcome was pain, measured both with subjective pain scales and local tenderness scales. NTG was given in varying formulations including patches and ointments.

NTG reduced pain during activities of daily living in chronic tendinopathies (3 trials; N=220; OR 4.4; 95% CI, 2.3–8.4) when compared with placebo. There was no reduction in pain with NTG during the acute phase when compared with placebo (1 trial; N=20; OR 21; 95% CI, 0.97–453), but the trial was underpowered.

One of the trials included above (with a longer follow-up period) was a RCT that examined the effects of a daily NTG patch (1.25 mg every 24 hours) on 41 tendons compared with placebo patch on 43 tendons for 24 weeks in patients with chronic Achilles tendinopathy. All patients also underwent a tendon rehab program. Pain at 0, 2, 6, 12, and 24 weeks was assessed using a 4-point pain scale (no pain to very severe pain).

The NTG group experienced a significant decrease in pain with activity compared with the placebo group at 12 weeks (mean score 0.9 vs 1.6, respectively; P=.02) and 24 weeks (0.4 vs 1.0; P=.03). At 24 weeks, complete relief of symptoms during activities of daily living was also more common in the NTG group than the placebo group (78% vs 49%; P=.001).

In 2007, a long-term follow-up study of the above RCT demonstrated the efficacy of NTG treatment 3 years after discontinuation of therapy. Assessment of 52 patients (68 tendons) included VISA-A score (8 questions that measure the domains of pain, function in daily living, and sporting activity; no symptoms = 100). There were 32 tendons in the treatment group and 36 tendons in the placebo group. Of the patients who were previously treated with topical NTG, more patients had a VISA-A score of 100 than patients treated with rehabilitation alone (88% vs 67%, respectively; P=.03).

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What are the sensitivity and specificity of head CT for subarachnoid hemorrhage?

**Evidence-Based Answer**
Using contemporary multidetector CT scanners, the sensitivity of noncontrast CT scanning for subarachnoid hemorrhage (SAH) is 93% to 100%, and the specificity is 100%. The sensitivity and specificity are the highest within the first 5 days from onset of symptoms (SOR: B, prospective and retrospective cohort studies).

In a retrospective trial conducted from 2000 to 2005 to determine the sensitivity of CT scanners in detecting subarachnoid hemorrhage (SAH), 499 patients were included who were referred to the neurosurgical unit with a diagnosis of SAH or suspicion of SAH. Investigators recorded clinical history, examination findings, and time from onset of symptoms (days) to CT scan. All patients had a noncontrast head CT performed using contemporary, industry-standard multidetector scanners. Patients with a positive CT scan underwent angiography. All patients with a negative CT scan underwent lumbar puncture. In 203 patients, the diagnosis of SAH was excluded by negative head CT and negative lumbar puncture.

SAH was diagnosed in 296 patients based on a positive CT scan and confirmed by angiography. From day 1 of symptom onset to day 5, noncontrast CT scanning had a sensitivity of 100% and a specificity of 100%. One patient was diagnosed with SAH on day 6 by lumbar puncture, yielding an overall sensitivity of 99.7% and the specificity of 100%.

A 2011 prospective cohort trial involving 11 tertiary care emergency departments enrolled
3,132 neurologically intact adults with nontraumatic headache to determine the sensitivity of current-generation CT scanners for detecting SAH. The time of onset of headache was recorded and all patients underwent noncontrast head CT using contemporary, industry-standard multidetector scanners. Lumbar puncture was performed at the discretion of the attending physician according to usual practice. The diagnostic “gold standards” for SAH included bleeding identified on the CT scan, xanthochromia of the cerebrospinal fluid, or spinal fluid showing red blood cells >5×10^6/L in the final tube plus aneurysm identified on cerebral angiography. To identify any missed SAH, investigators followed up patients with negative CT scans by phone call and records review at 1 and 6 months.

Of 953 patients scanned within 6 hours of headache onset, 121 were diagnosed with SAH. All were identified by CT, so the sensitivity of CT scan in this group was 100% and the specificity was 100%. When the CT scan was performed between 8 hours and 8 days after headache onset, 17 of 119 patients with SAH were not identified on CT (sensitivity 86%). For all study patients, the sensitivity of noncontrast CT overall was 93% and the specificity was 100%.

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Will increasing the dose of methylphenidate control symptoms better in refractory ADHD?

Evidence-Based Answer

The evidence is conflicting as to whether increasing the dose of methylphenidate (Ritalin) will control symptoms better in refractory attention deficit hyperactivity disorder (ADHD). There is no clear agreement regarding titration or optimal dosing (SOR: C, consensus, clinical practice guidelines, and opinion).

A RCT of 579 children (7–9 years old) with ADHD evaluated the effectiveness of ADHD treatment over 14 months. Diagnosis of ADHD was established per DSM-IV criteria. Of the initial 579 children enrolled, 546 completed the study. Participants were randomly assigned to 1 of 4 groups: medical management (MedMgt) (n=144) with primarily methylphenidate (MP) at a variety of doses; behavioral therapy (n=144); combined (Comb) (n=145), which was medical management and behavioral therapy; or routine community care (n=146) as the control.

Symptom control (defined as absence of clinically significant ADHD symptoms and medication side effects) was achieved with MP in 77% (198) of patients (MedMgt and Comb groups). A wide range of MP dosing produced a response: low dose ≤15 mg/d (n=57), intermediate dose 16 to 34 mg/d (n=65), and high dose ≥34 mg/d (n=76). Average MP dosing was 30.5 mg/d. In the placebo group, 13% (n=32) were responders (defined as absence of clinically significant ADHD symptoms without medication).

In the MP group, 10% (n=26) were nonresponders (no MP dose significantly reduced ADHD symptoms; however, other medications were employed).

A retrospective analysis of the above database noted a significant difference in end-of-trial MP dose in the MedMgt versus the Comb groups (38 vs 31 mg/d; P<.001). Changes in dosing occurred on average 1 month sooner in the MedMgt compared with the Comb group (4.1 vs 5.1 months; P<.05). Most MP dose changes (430 changes) were increases versus decreases (62% and 31%, respectively), or a change in the type of medication (7%). Decreases in MP were due to medication side effects.

The direction of dosing change was related to the initial MP dose. For example, from the 198 MP responders, low-dose MP initiators tended to have dose increases: 25% had no change, 3% had the dose lowered, and 61% had the dose raised. High-dose MP initiators were more likely to have decreases: 33% had no change, 37% had the dose lowered, and 21% had the dose raised.

A 6-center RCT evaluated the efficacy and safety of MP-immediate release (MP-IR) in preschoolers (3–5.5 years old) diagnosed with ADHD. Initially 303 patients enrolled, 165 patients participated, and 147 of the 165 patients completed the trial. Subjects were randomized into 1 of 5 groups (a placebo group, and 1 of 4 MP-IR dosing groups: 1.25, 2.5, 5, or 7.5 mg) given 3 times a day. Outcomes were given as effect size (0.2–0.3 is a small effect, 0.5 a medium effect, and 0.8+ a large effect).

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CONTINUED
ADHD symptoms decreased significantly with MP-IR at tid dosing versus placebo with 2.5 mg (n=165; effect size 0.48; P<.01), 5 mg (n=165; effect size 0.52; P<.001), and 7.5 mg (n=142; effect size 0.87; P<.001). Dosing of 1.25 mg tid was not statistically significant (n=165; effect size 0.22; P<.06) in decreasing ADHD symptoms compared with control. The mean optimal treatment dose was 14 mg/d (or 0.7 mg/kg per day).

The American Academy of Pediatrics clinical practice evidence-based guidelines state that titrating MP for patients with ADHD is appropriate management. No optimal titration table or dosing was defined in regard to controlling symptoms for refractory ADHD.

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1. The MTA Cooperative Group. Arch Gen Psychiatry. 1999; 56(12):1073–1086. [LOE 1b]

Are oral steroids effective in the treatment of acute low back pain?

Evidence-Based Answer
No. Oral and intravenous (IV) steroids are likely no different than placebo for the treatment of low back pain (SOR: B, multiple small RCTs).

A small 2008 RCT compared the effects of a 9-day oral prednisone taper (60 mg × 3 days, 40 mg × 3 days, 20 mg × 3 days) with placebo in 27 patients with acute sciatica (1 week of symptoms) in the primary care setting. All participants had regular follow-up through 6 months. Pain, as measured on the Roland-Morris Pain Rating Scale, did not differ significantly between treatment and placebo groups at any time during the study (data shown on graph only). Similarly, no difference was noted in mental and physical well-being and disability scores between the groups. No differences between groups were seen for physical findings, use of narcotics or nonsteroidal anti-inflammatory drugs, or rates at which patients returned to work.

A 2006 RCT examined the effectiveness of a 1-time dose of 160 mg IV long-acting methylprednisolone compared with placebo for the treatment of back pain in 87 adult patients presenting to the emergency department (ED) with acute nonradicular back pain. All patients were also provided with a “back pack,” which included 14 naproxen 500 mg and 12 oxycodone tablets with discharge instructions. Patient follow-up was by phone at 1 week and 1 month.

No difference was noted on an 11-point numerical pain score between the treatment and placebo groups in improvement from baseline at 1 week (mean difference [MD] 0.6; 95% CI, –0.9 to 2.2) and 1 month (MD 0.6; 95% CI, –1.0 to 2.2). There was also no difference between groups for time to return to daily activities, scores on disability scales, and ratings of “back pain free.”

A 2006 RCT studied the efficacy of a single IV bolus of methylprednisolone 500 mg in 60 patients hospitalized with acute back pain and sciatic leg pain lasting longer than 1 week but less than 6 weeks. On a validated 10-cm visual analog pain scale (VAS), the glucocorticoid treatment group had a small but significantly greater improvement in pain during the first day (MD 0.57 cm; 95% CI, 0.03–1.1) compared with placebo, but this benefit was no longer present after 3 days.

A 2008 randomized, double-blind, placebo-controlled trial examined the effects of a single-dose of 160 mg intramuscular methylprednisolone compared with placebo in 82 patients presenting to the ED with acute (<7 days) radicular back pain and a positive straight leg raise sign. Pain intensity on a validated 11-point numerical scale at 1 week posttreatment was not significantly different between the treatment and placebo groups (MD 1.1; 95% CI, –0.5 to 2.8). There was also no difference between groups in pain scores 1 month after treatment (MD 1.3; 95% CI, –0.2 to 2.7).

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What is the appropriate diagnostic evaluation of uterine fibroids?

**Evidence-Based Answer**

Both saline-infusion sonohysterography (SHG) and transvaginal sonography (TVS) are effective imaging modalities for diagnosing uterine pathology (SOR: B, based on cohort studies). Magnetic resonance imaging (MRI) evaluation appears to have a higher sensitivity compared with TVS (SOR: B, based on a cohort study). However, due to its noninvasive nature and relative cost efficiency, TVS is the preferred primary imaging modality to evaluate for fibroid disease (SOR: C, guideline based on opinion).

A prospective cohort study compared the accuracy of TVS and SHG for detecting uterine abnormalities in 346 women undergoing an infertility workup.¹ Using hysteroscopy as the gold standard, all participants underwent all 3 examinations and results were interpreted by gynecologists who were blinded to the other examinations. Saline-infusion SHG had a sensitivity of 99% and a specificity of 98% (positive likelihood ratio [LR+] 50 and negative likelihood ratio [LR–] 0.01), whereas TVS had a sensitivity of 95% and specificity of 96% (LR+ 24; LR– 0.05). There was no statistical comparison between the 2 imaging modalities.

Another prospective cohort study evaluated saline-infusion SHG and TVS diagnostic tools in 104 women of reproductive age with irregular uterine bleeding. Histopathologic evaluation of tissue obtained from hysteroscopy was the gold standard.² All women underwent TVS, SHG, and hysteroscopy. Saline-infusion SHG had a sensitivity of 88% and specificity of 99% (LR+ 88; LR– 0.12), and TVS had a sensitivity of 75% and specificity of 92% (LR+ 9.4; LR– 0.27). There was no statistical comparison between the imaging modalities.

A cohort study, in which all women underwent both MRI and TVS within 2 weeks of having a hysterectomy (n=18 women with 151 fibroids detected), compared MRI versus TVS for determining fibroid burden with pathologic evaluation of hysterectomy specimens serving as the gold standard.³ MRI identified 121 surgically confirmed fibroids (sensitivity 80%) while TVS identified 60 surgically confirmed fibroids (sensitivity 40%). TVS most often missed intramural fibroids. When small fibroids (diameter ≤1 cm) were excluded from the analysis, the sensitivity of TVS increased to 47%, and the sensitivity of MRI increased to 84%. No statistical comparison between the imaging modalities was performed.

The American College of Obstetrics and Gynecology evidence-based practice guideline recommends TVS as the primary imaging study for evaluation of abnormal uterine bleeding, citing the advantages of reasonable sensitivity and cost effectiveness (based on expert opinion).⁴ SHG or hysteroscopy are recommended if further evaluation was necessary. MRI is not recommended as a primary imaging modality.

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Are there safe and effective medications for insomnia in children?

**Evidence-Based Answer**

Melatonin was found to increase sleep onset and duration (SOR: A, consistent RCTs). Diphenhydramine is not effective in improving sleep in infants (SOR: B, RCT). Zolpidem is well tolerated in children, but sleep efficacy studies are lacking (SOR: B, limited open-label study).

In a 2001 double-blind placebo-controlled study evaluating treatment for insomnia, 40 elementary school age children, aged 6 to 12 years, were randomized to melatonin 5 mg or placebo.¹ There was a 1-week baseline period and a 4-week treatment period. Follow-up was performed after 18 months.

Children given melatonin experienced a greater increase in total sleep time compared with placebo (41 vs 4 minutes; P=.026). Lights-off time (defined as when parents put children to bed) advanced 34 min from baseline in the melatonin group compared with 8 min in the placebo group (P=.035).¹
A 2006 randomized, double-blind, placebo-controlled crossover trial evaluated sleep onset latency between melatonin 5 mg and placebo in children ages 6 to 14 years with a diagnosis of attention deficit hyperactivity disorder who failed a sleep hygiene intervention (n=19). Medication was administered 20 minutes prior to scheduled bedtime. Mean sleep onset latency was 46 minutes in the melatonin group versus 62 minutes in the placebo group (P<.01).

A 2006 randomized, double-blind clinical trial examined the effectiveness of diphenhydramine (1 mg/kg) on sleep of infants aged 6 to 15 months (n=44). Diphenhydramine was administered 30 minutes prior to bedtime. There was no difference between groups for parental report of improved nighttime awakening at week 2 (mean difference [MD] –9%; 95% CI, –26 to 8). At week 4, a significant difference was observed with greater improvement in the placebo group compared with the diphenhydramine group (MD –23%; 95% CI, –40 to –5). Parental overall happiness with their child’s sleep on a scale of 1 to 10 was not different between the 2 arms of the study at either 2 or 4 weeks.

A 2008 multicenter, open-label, age- and dose-stratified dose-escalation study evaluated the pharmacokinetics of zolpidem in children aged 2 to 18 years. Patients were assigned to 1 of 3 age-stratified dose groups—ages 2–6 y: 0.125 mg/kg (n=21); 6–12 y: 0.25 mg/kg (n=22); and 12–18 y: 0.5 mg/kg (n=22). The maximum dose for all groups was 20 mg. Zolpidem was well tolerated, with only 1 adverse event related to the study (abnormal eye movement). Effect on sleep was a secondary outcome.

There was a decrease in sleep latency (5 min) and an increase in total sleep time (30 min) (P values not reported). All results were without considering dose and age.

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Evidence-Based Answer

A combination of B12, folate, and vitamin B6 may slow the decline of cognitive function in elderly patients with elevated homocysteine levels (>11–13 micromol/L), and a combination of B12 and folate may improve cognitive function in elderly patients with depression (SOR: B, single RCTs). However, the National Institutes of Health (NIH) does not recommend vitamins as a treatment for cognitive decline (SOR: C, expert opinion).

A 2010 RCT involving 266 patients with mild cognitive impairment aged 70 years or older compared vitamins with placebo in slowing cognitive and clinical decline. Participants were randomly assigned to receive 0.8 mg folic acid + 0.5 mg vitamin B12 + 20 mg vitamin B6 daily, or placebo for 2 years. Of the 266 participants, 223 completed the 24-month study. Multiple cognitive testing tools were used including but not limited to HVLT (Hopkins verbal learning test), CDR (clinical dementia rating), and IQCODE (The Informant Questionnaire on Cognitive Decline in the Elderly).

In the whole intention-to-treat cohort, B vitamins had no significant effect on CDR or IQCODE. However, patients with high homocysteine levels (>11 micromol/L) who were given vitamins were 69% more likely to show improvement on the HVLT (OR 1.7; P=.00; no CI provided) compared with placebo. Also in the vitamin group, clinical benefit occurred for those in the upper quartile of homocysteine levels (>13 micromol/L) in global CDR score (0=no dementia to 3=severe dementia). A CDR score of 0 was seen in 25% of patients with elevated homocysteine at baseline and 58% at follow-up (P=.02), whereas there was no change in the placebo group (24% at baseline vs 28% at follow-up; P=1.0).¹

A 2006 RCT involving 909 depressed patients aged 60 to 74 years evaluated the effectiveness of folic acid and vitamin B12 for preventing cognitive decline.² Patients who had no history of dementia or other psychiatric diagnoses, had competent literacy skills, and were medically stable were given either a tablet consisting of 400 mcg folic acid + 100 mcg vitamin B12 or placebo daily. In 2007 the dose was adjusted to 200 mcg folic acid + 50 mcg vitamin B12 dosed twice daily for the remainder of the 24-month intervention.

The vitamin group had a significantly greater increase in TICSM (Interview of Cognitive Status-modified) scores from baseline to 24 months than the placebo group (effect size 0.17; P=.032). An effect size ≤0.2 is usually considered “small.”²

The NIH Consensus Development Conference Statement on Preventing Alzheimer Disease and Cognitive Decline notes that, after literature review, no role was found for vitamins, nutrients, and dietary supplements in preventing cognitive decline.³ The authors remarked that identified trials used varying doses of nutrients, did not uniformly measure and monitor patients’ cognitive function and nutritional status, and may have been underpowered.

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Is therapy based on endoscopy (results) better than empiric therapy for dyspepsia?

**Evidence-Based Answer**

Prompt endoscopy for dyspepsia leads to a small decrease in the proportion of patients who are symptomatic at 1 year, but it is not cost-effective (SOR: A, meta-analysis of RCTs). A test-and-treat strategy is less expensive, results in fewer patients receiving endoscopy, and results in similar long-term symptom control (SOR: B, RCTs.)

A 2005 meta-analysis of 5 RCTs with 1,924 patients with dyspepsia (mean ages 34–44 years) compared prompt endoscopy with a *Helicobacter pylori* test-and-treat approach. Compared with the test-and-treat strategy, prompt endoscopy was associated with a lower risk of symptoms at 1 year (RR 0.95; 95% CI, 0.92–0.99). However, a cost analysis showed that prompt endoscopy was more expensive (4 trials; N=1,771; weighted mean difference at 12 months $389/case; 95% CI, 276–502). The authors concluded that early endoscopy was not a cost-effective strategy.

A 2009 RCT (N=762) conducted in a primary care setting assigned patients with dyspepsia to 4 groups: prompt endoscopy, *H pylori* test and endoscopy for positive cases, *H pylori* test-and-treat, or empirical therapy. At 2 months, patients receiving prompt endoscopy were significantly more likely to report having no or minimal symptoms (TABLE). However, this difference disappeared at 12 months. Similarly, at 2 months, those receiving empiric therapy were most likely among the 4 treatment groups to report being dissatisfied with therapy, but no significant differences were noted between groups at 12 months. Patients randomized to the endoscopy group incurred the highest health services costs over 12 months, and the test-and-treat group had the lowest costs (no statistical analysis provided).

A 2004 follow-up survey was completed by 363 patients after participation in a RCT for the treatment of dyspepsia. Patients were initially randomized to an *H pylori* test-and-eradicate strategy or to prompt endoscopy. At a mean of 6.7 years, the proportion of symptom-free days was similar in both groups (0.52 in the test-and-eradicate group vs 0.64 in the prompt endoscopy group; mean difference 0.05; 95% CI, −0.03 to 0.14; P=.27.) However, the test-and-eradicate group received 0.88 endoscopies per patient, compared with 1.5 endoscopies per patient in the endoscopy group (P<.0001). The authors concluded that, on a long-term basis, a test-and-eradicate strategy is as effective as prompt endoscopy for symptom control of dyspepsia, and reduces healthcare resource use.

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### TABLE

<table>
<thead>
<tr>
<th></th>
<th>Endoscopy</th>
<th><em>H pylori</em> test and endoscopy</th>
<th><em>H pylori</em> test and treat</th>
<th>Empiric therapy</th>
<th><em>P</em> value (4-way comparison)</th>
</tr>
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<tbody>
<tr>
<td>No symptoms or minimal symptoms at time = 2 months</td>
<td>74%</td>
<td>65%</td>
<td>68%</td>
<td>55%</td>
<td>.009</td>
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<tr>
<td>No symptoms or minimal symptoms at time = 12 months</td>
<td>55%</td>
<td>53%</td>
<td>52%</td>
<td>50%</td>
<td>NS</td>
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<tr>
<td>Dissatisfied with treatment at time = 2 months</td>
<td>14%</td>
<td>13%</td>
<td>16%</td>
<td>29%</td>
<td>.007</td>
</tr>
<tr>
<td>Dissatisfied with treatment at time = 12 months</td>
<td>20%</td>
<td>18%</td>
<td>22%</td>
<td>20%</td>
<td>NS</td>
</tr>
<tr>
<td>Cost per patient over 12 months (endoscopy cost £200)</td>
<td>£265</td>
<td>£199</td>
<td>£159</td>
<td>£174</td>
<td>Not given</td>
</tr>
</tbody>
</table>
Does screening overweight children for hyperlipidemia lead to improved outcomes?

Evidence-Based Answer

Obese children are more likely to have abnormal low-density lipoprotein (LDL) values than normal weight children (SOR: C, cohort study with disease-oriented outcomes). Statin therapy has been shown to reduce intima-medial thickness (IMT) (SOR: C, RCT with disease-oriented outcome), but there is currently little evidence that screening overweight children for hyperlipidemia will lead to better clinical outcomes.

An observational study of 2,011 children in Taiwan examined the association of body weight and lipid levels. In this study, an abnormal high-density lipoprotein (HDL) level was defined ≤35 mg/dL and an abnormal LDL level was ≥110 mg/dL. Overweight children (body mass index [BMI] >85%) were more likely to have abnormal HDL values than normal weight children (OR 3.4; 95% CI, 1.1–9.2). Obese children (BMI >95%) were more likely to have abnormal LDL values levels (OR 1.6; 95% CI, 1.2–2.0) and abnormal HDL values (OR 3.4; 95% CI, 1.2–9.4).

A double-blinded RCT of 214 children with familial hypercholesterolemia examined the efficacy and safety of pravastatin therapy. All children were initiated on a fat-restricted diet and exercise was encouraged before randomization to pravastatin or placebo. After 2 years of therapy, there was significant regression in carotid atherosclerosis (IMT via carotid ultrasound) with pravastatin (change in IMT from baseline –0.010 mm; P=0.049), but not with placebo (+0.005 mm; P=0.44). No adverse effects were noted in regards to sexual maturity, growth, hormone levels, or liver and muscle tissue between the 2 groups.

In 2011, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children & Adolescents recommended universal screening in all children for lipid levels between the ages of 9 and 11 years of age and again at 17 to 21 years of age.3

This endorsement is in contrast to the USPSTF recommendations from 2007, in which they concluded the evidence was insufficient (grade I) to recommend for or against routine screening for lipid disorders in infants, children, adolescents, or young adults (up to age 20).4 The USPSTF stated there are potential harms of screening: labeling children whose dyslipidemia may not persist into adulthood and possible long-term adverse effects from lipid-lowering medications and low-fat diets.

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.

What are the long-term effects of the sport supplement creatine monohydrate?

**Bottom line**

When used with a training program, creatine monohydrate (CM) supplementation is associated with greater increases of fat-free mass (FFM), muscle strength, and endurance than placebo, and has no serious effects on kidney function with long-term use (SOR: B, a systematic review of heterogeneous RCTs and individual RCTs).

**Evidence summary**

A systematic review of 22 RCTs evaluated the effect of resistance training and concurrent CM supplementation on muscle strength and weightlifting performance.¹ The studies ranged from 7 to 91 days with 483 healthy athletes (88% men) taking CM 5 g/d for the entire supplementation period.

Sixteen trials (N=369) reported an average of an 8% greater increase in muscle strength (P<.05) and a 14% difference in weightlifting performance (P<.05) for CM compared with placebo. The authors noted considerable interindividual variability in these outcomes.

A RCT examined the effect of CM and conjugated linoleic acid (CLA) on enhancing muscle strength and improving body composition after resistance training in 39 adults aged 65 to 85 years (49% men).² Patients were randomized to a combination of CM 5 g/d + CLA 6 g/d (n=21) or placebo (n=18) for 24 weeks. The participants were not enrolled in any sports in the year prior to the study, and were otherwise healthy. The strength training was conducted twice weekly for 6 months.

Exercise increased FFM from baseline and this effect was significantly higher in men taking supplementation (+2.1 kg; P=.02) compared with placebo (+0.9 kg; P=.06). Every measure of muscle strength increased after training. Women taking CM + CLA showed the greatest increase in knee extension 1RM (repetition maximum) strength after training compared with placebo (75% increase vs 34%, respectively; P=.0001). The only difference in blood biochemistry due to supplementation was an increase in serum creatinine (SCr) level. In men SCr increased from 1.0 to 1.3 mg/dL (P=.0001), and in women SCr increased from 0.8 to 0.9 mg/dL (P=.0001) pre- and posttraining, respectively.²

Another small RCT studied potential adverse effects of long-term CM supplementation in patients with Parkinson disease older than 60 years of age.³ Patients (70% men) had no known kidney disease and Parkinson disease severity less than 2.5 on the Unified Parkinson Disease Rating Scale (0=no signs of disease; 5.0=wheelchair-bound/bedridden unless aided). They were given 4 g/d of CM for 2 years.

At 1 year, SCr levels were higher in the CM group compared with placebo (1.4 vs 1.2 mg/dL; P<.05), but the difference disappeared between 12 and 24 months (1.3 mg/dL in both groups).³

**Recommendations**

International Society of Sports Nutrition consensus-based recommendations from 2007 state that CM supplementation is safe and possibly beneficial in regard to preventing injury or management of select medical conditions when taken within recommended guidelines.⁴ To increase muscle creatine stores, the authors recommended consuming 0.3 g/kg per day of CM for at least 3 days followed by 3 to 5 g/d thereafter.

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1. Which of the following statements is true about treating acute cough in adult patients?
   - a. Beta2-agonists significantly decrease cough symptoms in all patients
   - b. Codeine is more effective than dextromethorphan for reducing cough frequency
   - c. Antihistamines are more effective than antibiotics for reducing cough severity
   - d. Evidence is limited that any medication effectively treats cough

2. Which of the following statements is true regarding venous thromboembolism (VTE) prophylaxis in patients hospitalized with a history of end-stage liver disease?
   - a. VTE prophylaxis increases the risk of bleeding
   - b. VTE prophylaxis does not decrease the risk of VTE
   - c. VTE prophylaxis decreases the risk of VTE
   - d. VTE prophylaxis increases the risk of bleeding in patients with a history of bleeding

3. The initial imaging study recommended by the American College of Obstetrics and Gynecology for assessment of abnormal uterine bleeding is
   - a. Magnetic resonance imaging
   - b. Hysteroscopy
   - c. Transvaginal ultrasound
   - d. No specific imaging recommendation

4. What medication and dose has been shown in several clinical trials to statistically decrease sleep latency and aid in the treatment of childhood insomnia?
   - a. Diphenhydramine 1 mg/kg
   - b. Zolpidem 0.125 mg/kg
   - c. Melatonin 5 mg
   - d. Diphenhydramine 0.5 mg/kg per dose

5. Consumption of creatine monohydrate in doses of 5 g/d for 1 year leads to:
   - a. A decrease in fat-free body mass
   - b. An increase in serum creatinine level
   - c. Lower muscle endurance
   - d. None of the above

6. For the initial treatment of dyspepsia without alarm symptoms, which statement is true regarding patient outcomes and cost effectiveness?
   - a. Early endoscopy is less expensive because it confirms the clinical diagnosis and reduces downstream healthcare costs
   - b. Early endoscopy results in significantly better outcomes as long as 5 years after presentation
   - c. Test-and-treat protocols are more expensive due to missed diagnoses and need for later endoscopy
   - d. Early endoscopy may result in better symptom control early on, but test-and-treat protocols have similar long-term outcomes

7. Which of the following statements is true about computed tomography (CT) for subarachnoid hemorrhage (SAH)?
   - a. Sensitivity of modern multidetector CT scan for SAH is very low
   - b. CT scan is only appropriate for detecting SAH when performed at the onset of headache
   - c. Sensitivity of modern multidetector CT scan for SAH is 93% to 100%
   - d. CT scan is appropriate for detecting SAH only when performed 2 weeks after onset of headache

8. In the treatment of adults with low back pain:
   - a. Systemic steroids do not help with long-term pain or sciatica
   - b. Parenteral (but not oral) steroids help with long-term pain and sciatica
   - c. Systemic steroids are effective for long-term control of sciatica but not back pain
   - d. Oral steroids are effective for back pain but not sciatica

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