Evidence-based answer

Nothing dramatically improves viral upper respiratory tract infection (URI) symptoms in children, but honey and vapor rubs appear to produce some benefits. 

- Honey modestly improves cough and child sleep, but may be associated with hyperactivity. (SOR: B, based on 1 blinded and 1 nonblinded RCT.)
- Vapor rubs modestly improve cough, congestion, and child sleep, but may be associated with local irritation. (SOR: B, based on 1 partially double-blind RCT.)
- Adjunctive nasal saline results in statistically but not clinically significant lower symptom scores. (SOR: B, based on 1 nonblinded RCT.)
- Neither zinc gluconate nor zinc sulfate decrease symptom severity or duration. (SOR: B, based on 2 double-blind RCTs.)
- Echinacea does not provide significant improvement in common cold symptoms in children. (SOR: B, based on 1 double-blind RCT.)

Evidence summary

Honey

A Cochrane review included 1 RCT (n=105) that compared one-time treatment with honey, dextromethorphan (DMF), or no treatment in children 2–18 years old with URIs. Honey was dosed like DMP syrup (1/2–2 tsp depending on age). Family-reported symptom scores were obtained before and 24 hours after intervention using 7-point Likert scales.1,2

Honey modestly decreased cough frequency (mean difference [MD] −0.97; 95% CI, −1.63 to −0.35), and child sleep quality (MD −0.92; 95% CI, −1.77 to −0.07) versus no treatment. There were no significant differences in illness severity or duration. Five of 35 children in the honey group had hyperactivity, nervousness, or insomnia.

One nonblinded RCT (n=139) published after the Cochrane compared 2.5 mL honey, DMP, diphenhydramine, or supportive care in children 2–5 years of age with a URI using similar 7-point Likert symptom scales.3 All groups received supportive care (saline nose drops, water vapor, and acetaminophen). At 24 hours compared with supportive care alone, honey improved cough frequency (MD
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Clinical Inquiries

-1.2; P<.001), cough severity (MD -1.2; P<.001), and cough impact on child sleep (MD -1.1; P<.001). Nervousness was reported in 2 of 33 patients in the honey group.

Vapor rub
One RCT (n=138) compared 1 dose of vapor rub, petrolatum jelly, or no treatment in children 2–11 years old with viral URI symptoms using a parent-rated 7-point Likert scale. Compared with no treatment, vapor rub modestly improved cough frequency (MD -1.5; P<.001), severity (MD -0.9; P=.006), congestion severity (MD -1.0; P=.01), and child sleep quality (MD -1.3; P<.001). Adverse effects were more common in the vapor rub group, most commonly a burning sensation of the skin (12/44).

Saline nasal spray
One nonblinded RCT (n=390) compared nasal saline spray (6x per day) plus standard treatment (antipyretics, nasal decongestants, mucolytics, or systemic antibiotics) with standard treatment alone in children ages 6–10 years with uncomplicated cold or flu. The nasal saline group experienced statistically significant lower parent and physician-rated scores on 4-point Likert scales for sore throat, nasal secretion, nasal secretion type, and nasal breathing score, but the differences were not considered to be clinically significant (MD 0.14, 0.31, 0.34, and 0.33, respectively; P<.05 for all).

Zinc compounds
One double-blind RCT (n=249) compared daily 10 mg zinc gluconate lozenges with placebo in grade school children with cold symptoms. Time to symptom resolution and days of school lost did not differ between the groups. Adverse events with zinc and placebo were similar (86% vs 79%, respectively; P=.06) and included bad taste, nausea, oropharyngeal irritation, and diarrhea.

One double-blind RCT (n=120) compared daily 15 mg zinc sulfate syrup with placebo in children 1–10 years old with URIs using parent-rated 4-point Likert scales for symptom severity. There was no difference in time to resolution between zinc and placebo (median 6 days each). Some symptom scores were statistically but not clinically significantly lower with zinc on days 2–5.

Echinacea
One double-blind RCT (n=407) compared twice-daily *Echinacea purpurea* syrup with placebo for URI in children ages 2–11 years. The syrup was dosed by manufacturer’s recommendations: children 2–5 received 50% of the adult dose (3.75 mL twice daily) and children 6–10 received 67% of the adult dose (5 mL twice daily). Parents scored peak severity, number of days at peak, number of days of fever, concurrent medication use, and overall severity daily with 4-point Likert scales.

There was no statistical difference in any of the above measures between *Echinacea* and placebo. Two of 200 children in the *Echinacea* group had allergic reactions requiring emergency department visits.

Recommendations from others
The Food and Drug Administration (FDA) recommends against the use of OTC cough and cold medications in children <2 years of age for safety reasons. A review by the FDA is currently underway evaluating the safety and efficacy in children 2–11 years of age. The American Academy of Pediatrics (AAP) recommends against OTC cold medications in children <6 due to lack of efficacy and potential side effects. The AAP recommends hand washing, saline nasal spray, humidifiers, chest physical therapy, honey, cough drops, ibuprofen, or acetaminophen for the common cold.

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REFERENCES
Dear EBP Readers,

Several years ago, my family and I went on a wonderful summer vacation trip to Alaska. On the final leg of our journey, we boarded the Alaska State Ferry and headed south through the Inland Passage. We set up our tents on the back of the boat and in the daytime we admired the mountains and glaciers as they majestically slid past our deck chairs. At night we slept to the sound of the engines rumbling up through our pillows.

I remember being impressed by the seemingly endless forests. These were temperate rain forests, dark and rich, blanketing an entire landscape. Huge trees marched from the waterline, across the low lands, and up over range after range of craggy peaks.

About half-way through the trip, the boat rounded a corner in a narrow channel and, without explanation, we passed a gigantic cedar festooned with dozens of pink plastic flamingos. It was strange indeed, the first time I had ever seen lawn ornaments in the wilderness.

I thought about the Alaskan flamingo tree again recently when I came across an article in a major scientific journal that claimed to find evidence of precognition (a form of ESP).1 That, too, was strange indeed. In fact, it was so strange that others felt compelled to point out certain statistical problems in the report.2 The evidence of ESP, they stated rather emphatically, would go away using appropriate Bayesian analysis, which uses cumulative rather than static probabilities.

But rather than get bogged down in Bayesian details, I just happily contemplated the example of the flamingo tree. On our trip, we had already seen maybe half a billion trees without flamingoes. Then suddenly we saw a one full of flamingoes. What would a reasonable person conclude about the odds of seeing more flamingos in more trees?

Well, as our intrepid little boat sailed on down to Bellingham, we probably watched another half a billion trees go by and—no surprise—there were no flamingoes in any of them.

Regards,

Jon O. Neher, MD


From the Editor:

Alaskan flamingos
Azithromycin may prevent minor COPD exacerbations


This RCT compared the effect of using daily azithromycin 250 mg or placebo (along with usual care) in 1,142 patients with chronic obstructive pulmonary disease (COPD) on the frequency of COPD exacerbations. A Kaplan-Meier survival analysis showed that after 1 year, 43% of patients in the azithromycin group remained exacerbation-free compared with 32% in the placebo group ($P<.001$).

There were no differences between groups in the incidence of all-cause, cardiac, or respiratory mortality, or hospitalizations. A small degree of temporary hearing loss was more common in the azithromycin group (25% vs 20%; $P=.04$; NNH=20).

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**Bottom line:** Although azithromycin does not influence the rate of hospitalization, it is a potential adjunct therapy in COPD patients to decrease the frequency of exacerbations. The benefits of this medication are similar in magnitude to inhaled corticosteroids or anticholinergic medications for COPD. Patients should be educated about the potential risk of hearing loss.

**Article Reviewer:** Dionna Brown, MD  
**Summary Authors:** Dionna Brown, MD, and Kate Rowland, MD  
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Tai chi for chronic low-back pain


This RCT compared tai chi with usual care for chronic low-back pain lasting 3 months or more. Participants with moderate nonspecific low-back pain and no serious spinal pathology were recruited. One hundred sixty participants were randomized to receive either usual care (as defined by their physician) or tai chi, which consisted of a 10-week tai chi course including 18 standardized sessions taught by a trained instructor. Participants were evaluated before and immediately after the 10 weeks for pain, bothersomeness of pain, and disability.

Compared with usual care, the participants in the tai chi group reported that their pain was less bothersome (1.7-point difference on a 10-point scale; $P=.000$) and less intense (1.3-point difference on a 10-point scale; $P=.000$). The tai chi participants also reported less pain-related disability. In order for 1 person to experience 30% less pain, 4 people would need to be treated with tai chi instead of usual care. Interviews of the participants revealed that they felt a 10-week tai chi course was worth the improvement in symptoms that were observed in this study.

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**Bottom line:** Tai chi was effective at improving chronic low-back pain and disability in this trial. However, the participants and investigators were not blinded to their treatment, and the participants in the control group received dramatically less attention than those in the tai chi group. It is not clear if the benefits observed in the treatment group are a function of tai chi, the social interaction among participants, the attention participants received from instructors and study personnel, or other factors. It is also unclear if this specific tai chi protocol is widely available.

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Additional information can be found at:
www.fpin.org/purlsoverview
Diving for PURLs

LMW heparin and mortality

This placebo-controlled RCT studied the effect of low-molecular-weight heparin (enoxaparin) on the rate of death from any cause and risk of major bleeding on acutely ill, hospitalized medical patients. Participants were recruited from 193 sites in Asia, Latin America, and Africa.

The inclusion criteria were men and women, ages 40 and over, hospitalized within 48 hours before randomization for acute congestive heart failure or active cancer diagnosed within 6 months. Patients were also included if they had severe systemic infection with at least 1 of the following risk factors for deep vein thrombosis: chronic pulmonary disease, history of venous thromboembolism, obesity, or age >60. Patients also needed to have an American Society of Anesthesiologists health status score of ≤3 (scale of 1 to 6, with 6=worst status) or an Eastern Cooperative Oncology Group performance status score of ≤2 (scale of 0 to 5, with 5=worst status).

About 8,300 patients received either subcutaneous enoxaparin 40 mg daily or subcutaneous 0.9% saline daily (both with graduated compression stockings) for 6 to 14 days.

The primary efficacy outcome was rate of death from any cause at 30 days. The primary safety outcome was rate of “major bleed” within 48 hours after treatment period.

The rate of death was 4.9% In the enoxaparin group, compared with 4.8% in the placebo group (RR 1.0; 95% CI, 0.8–1.2; P=.83). The rate of major bleed in the enoxaparin group was 0.4%, compared with 0.3% in the placebo group (RR 1.4; 95% CI, 0.7–3.1; P=.35). Rates of minor bleed were higher in the enoxaparin group (RR 1.5; 95% CI, 1.1–2.1; P=.01).

Bottom line: While the study demonstrated that enoxaparin was associated with an increase in rates of total bleeding, it did not detect a difference in rates of death from any cause with enoxaparin versus placebo or a difference in major bleeding rates. However, based on the study design and results, there was a 23% chance of missing a statistically significant difference in mortality if such a difference exists (23% chance of type 2 error).

Nonalcoholic fatty liver disease may not increase mortality

This prospective cohort study of more than 11,300 adults aged 20–74 used data from the Third National Health and Nutrition Examination Survey (NHANES). Mortality was compared between patients with and without nonalcoholic fatty liver disease (NAFLD), based on ultrasound-diagnosed hepatic steatosis. Patients with elevated liver enzymes were excluded if they had evidence of hepatitis B or C antibodies or iron overload. Death certificates were reviewed 12 to 18 years later.

No difference in all-cause mortality was found between those with and without NAFLD (multivariate adjusted hazard ratio 0.75; 95% CI, 0.45–1.24). Further, no difference was observed when the steatosis group was divided into those with normal hepatic enzymes (HR 0.92; 95% CI, 0.78–1.09) or elevated enzymes (HR 0.80; 95% CI, 0.52–1.22). Rates of death from specific causes, including cardiovascular disease, liver disease, and cancer, were similar in both groups.

Bottom line: This study shows that there appears to be no increase in mortality from NAFLD. We do not know, however, if steatosis persisted throughout the study period. Patients with NAFLD were told their diagnosis, and may have changed their behavior in ways that reduced mortality. We also do not believe that concerns about mortality currently influence the way physician diagnose, treat, and provide counseling to patients about NAFLD.

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

Bottom line: This study shows that there appears to be no increase in mortality from NAFLD. We do not know, however, if steatosis persisted throughout the study period. Patients with NAFLD were told their diagnosis, and may have changed their behavior in ways that reduced mortality. We also do not believe that concerns about mortality currently influence the way physician diagnose, treat, and provide counseling to patients about NAFLD.

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What is the value of a follow-up chest x-ray in a patient who has been hospitalized for community-acquired pneumonia?

**Bottom line**
In hospitalized patients with community-acquired pneumonia (CAP), the resolution of radiographic abnormalities does not appear to correlate with clinical cure as assessed by physicians. Monitoring patients at 1 and 4 weeks after initial diagnosis does not appear to offer additional value beyond clinical judgment. Follow-up chest radiographs may have some value in patients older than 50 years to assess for lung cancer.

**Review of the evidence**
Despite a wide array of antimicrobials at our disposal to treat infections, pneumonia (along with influenza) remains the 8th leading cause of death and the most prevalent cause of mortality due to infectious causes in the United States. Radiographic evaluation has established value in confirming the diagnosis of pneumonia in patients with a suspected pulmonary infection. But repeating studies to assist in documenting resolution of the infection has been a cause for some debate and, to this point, only a paucity of evidence exists on the topic.

**Rates of radiographic resolution do not match those of clinical cure**
A small, prospective cohort study carried out in the Netherlands enrolled 195 immunocompetent adults admitted with CAP and looked at the value of follow-up chest x-ray (CXR) at day 7 and day 28 after diagnosis.1 All patients had pneumonia severity index scores of more than 90, a score consistent with a 30-day all-cause mortality of 9% or more.

At day 7, approximately 25% of patients had resolution of radiographic abnormalities and 56% had clinical cure (mean difference 31%; 95% CI, 0.25–0.37). At day 28, 53% of patients had resolution of CXR abnormalities and 78% had clinical cure (mean difference 25%; 95% CI, 0.19–0.31). Mortality was 6.1% in patients whose follow-up CXR revealed evidence of deterioration, as opposed to 7.4% in patients whose CXR did not reveal deterioration (risk difference 1.5%; 95% CI, 0.40–1.89, P=.71). Of note, patients with pneumococcal pneumonia had both slower clinical cure rates as well as delayed resolution of radiographic abnormalities compared with the overall study population.1

Another smaller prospective cohort study enrolled 119 patients with mild to moderately severe CAP and compared CXR and clinical cure rates on days 10 and 28.2 At day 10, clinical cure was documented in 93% of patients, whereas radiographic resolution was found in only 32%. At day 28, clinical cure was observed in 89% of patients, whereas radiographic resolution was 68% (no statistical comparison data available).

**CXR to screen for lung cancer**
A recent population-based cohort study of 3,398 patients, designed to assess the incidence of cancer diagnoses in follow-up CXRs, showed the incidence of lung cancer diagnoses to be 1.1% within 90 days and 1.7% at 1 year. Age >50 years had the greatest association with lung cancer (adjusted hazard ratio [aHR] 19; 95% CI, 5.7–64).3 Men and smokers also had an increased incidence (although the aHR was <2 for each). This finding suggests that follow-up CXRs might reasonably be considered in patients older than 50 years to screen for lung cancer.

**Recommendations**
Older American Thoracic Society guidelines for the management of CAP (released in 2001) had recommended a follow-up office visit, 4 to 6 weeks after hospital discharge, with radiographs to provide new baseline radiography and rule out malignancy in older smokers.4 These guidelines were updated in 2007 by a joint committee of the Infectious Disease Society and American Thoracic Society. In the updated version, there was no recommendation on posttreatment radiography.5

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What are the long-term health consequences of childhood sexual abuse?

Summary

A history of childhood sexual abuse (CSA) is common among primary care patients. Any type of CSA is associated with subsequent psychiatric morbidity, eg, depression, anxiety disorders, and substance dependence, and severity of abuse increases psychopathology. CSA is also related to increases in nonspecific physical symptoms, with poorer gynecological, musculoskeletal, and cardiopulmonary health.

The evidence

Prevalence rates of CSA are estimated at about 30% in women and 15% in men, with rates of 50% or more among patients seen in primary care. Screening for childhood abuse is not a common practice among primary care physicians, and they often report a lack of knowledge about abuse prevalence, conditions related to abuse, and signs and symptoms of abuse.

In a study using the Virginia Twin Registry, 1,411 female twin pairs completed a mailed questionnaire and interviews about CSA and major depression, generalized anxiety, panic disorder, bulimia, alcohol dependence, drug dependence, and reporting ≥2 disorders. Thirty percent reported 1 or more episodes of any CSA (nongenital contact, genital contact, or intercourse). Any type of CSA doubled the rates of major depression, generalized anxiety, panic disorder, and alcohol/drug dependence. Greater pathology was associated with greater reported severity of abuse. Nongenital contact was associated with alcohol and drug dependence (OR 2.42 and 2.93, respectively; 95% CI, 1.27–4.61 and 1.39–6.16, respectively) and ≥2 disorders (OR 1.61; 95% CI, 1.02–2.56), while intercourse was significantly associated with all 7 adverse psychiatric outcomes (OR 2.55–5.70). Controlling for familial factors such as parenting behavior, financial status, and parental psychopathology did not change the ORs. Twin pairs discordant for sexual abuse (1 twin without abuse) showed an OR of 2.83 (P < .05) for alcohol dependence.

In a study of childhood physical and sexual abuse and self-reported health, 3,568 women aged 18–64 randomly selected from a health insurance plan completed a telephone interview. Of those surveyed, 19.4% (n=693) reported sexual abuse only before age 18, with 76% reporting the abuse occurring at age 12 or younger. The women reporting sexual abuse had significantly higher prevalence rates of 9 of the 14 common physical symptoms compared with women who had no types of abuse. The prevalence ratios (adjusted for age and income) ranged from 1.17 (95% CI, 1.06–1.28) for joint pain to 1.55 (95% CI, 1.22–1.98) for facial ache. The study did not take into account severity or chronicity of abuse and the generalizability is limited by the study participants: employed, highly educated insured women.

A meta-analysis looking at 31 studies (with >11,000 patients who reported CSA) connecting CSA and physical health consequences included subjects reporting at least 1 health outcome in 6 categories: general health, gastrointestinal health, gynecological health, musculoskeletal/general pain, cardiopulmonary symptoms, or obesity. Separate analyses were done for studies tracking continuous versus dichotomous health outcomes. There were higher rates of physical health complaints with CSA, with a significant small-to-moderate effect size (ESs ranging from 0.15 to 0.75) for all categories, except continuous measures of gastrointestinal symptoms and obesity. For example, combined data for studies looking at gynecological health outcomes showed an effect size of 0.64 when comparing history of sexual abuse with control (95% CI, 0.48–0.80). The analysis was limited by the small number of studies meeting inclusion criteria.

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REFERENCES


We invite your questions and feedback. Email us at EBP@fpin.org.
What is the optimal number of prenatal visits for low-risk women in the United States?

Evidence-Based Answer
In high-income countries, low-risk women can be managed with 8 to 9 prenatal visits (PNVs) without an increased risk in perinatal or maternal morbidity or mortality. In low- to middle-income countries, women having fewer than 5 PNVs are at risk for increased perinatal mortality compared with standard care. (SOR: A, based on a large meta-analysis.) Overall, patient satisfaction is lower with reduced-visit care models. (SOR: A, based on a large meta-analysis.)

A Cochrane review of 7 studies including 60,000 low-risk pregnant women from high- and low- to middle-income countries was recently published. It evaluated perinatal outcomes in women attending a reduced schedule of antenatal visits versus standard care. In high-income country trials, the number of visits was reduced to approximately 8. In low-income country trials, the numbers of visits was reduced to approximately 4.

In both low- and high-income countries, there were no differences in rates of preterm deliveries, low birth weight, induction rates, caesarean section rates, or maternal mortality. There was a borderline significant increase in perinatal mortality in subjects randomized to reduced visits versus standard care (RR 1.14; 95% CI, 1.00–1.31). When high-income countries were evaluated in a subgroup analysis, there was no difference in perinatal mortality. When low- to middle-income country trials were evaluated separately, the difference in perinatal mortality became statistically significant (RR 1.15; 95% CI, 1.01–1.32). In both lower and higher income countries, satisfaction with care was higher in women randomized to standard care. In the United States, 84% of women in standard care groups were satisfied with the number of visits compared with 71% in the reduced visit group (P<.001).1 These findings are consistent with a 2001 Cochrane review.2

An RCT from the United States of 2,328 18- to 39-year-old low-risk women compared 9 PNVs versus 14.3 There was no difference in percent of low-birth-weight infants, preterm labor, or C-section. There was no difference in the percentage of women who had screenings for antenatal neural tube defect, gestational diabetes, or anemia. There was an increase in 15- to 24-week ultrasounds ordered in the traditional visit group. Notably, there was no increased utilization of other departments by the women undergoing fewer visits. Between the 2 groups, both had the same number of visits to antenatal testing, the emergency department, and other nonobstetrical providers, as well as the same number of telephone calls to their OB provider.

A retrospective study from the United States compared outcomes of 1,647 pregnancies before a 9-visit pathway implementation and 1,710 pregnancies after guideline implementation.4 The mean number of visits decreased from 10.9 to 9.2, while showing no difference in maternal outcomes or satisfaction. Fewer PNVs was associated with an increase in the number of antenatal visits to labor and delivery by 0.4. There was a decrease in postterm deliveries after 42 weeks and a decrease in large-for-gestational-age infants in the reduced visits group. There was no significant change in preterm deliveries, mode of deliveries, level 2 nursery admissions, or patient satisfaction.

An RCT from the United Kingdom of 2,794 low-risk women compared a traditional 13-visit pathway with a 6- to 7-visit pathway.5 However, the actual number of visits was 10.8 versus 8.6. There were no differences in the hypertensive disorders, small-for-gestational-age infants, C-section rates, or maternal morbidity. The rates of dissatisfaction increased from 16.2% to 32.5% in the reduced-visit pathway.

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The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the US Government.

We are military service members or employees of the US Government. This work was prepared as part of our official duties. Title 17 U.S.C. 105 provides that “Copyright protection under this title is not available for any work of the United States Government.” Title 17 U.S.C. 101 defines a US Government work as a work prepared by a military service member or employee of the US Government as part of that person’s official duties.

Breathing nebulized hypertonic (4.5%) saline (HS) is considered an indirect test of bronchial hyperresponsiveness, requiring the presence of inflammatory cells. Breathing nebulized histamine and methacholine are direct tests that may stimulate bronchoconstriction even without inflammatory cells being present.

HS nebulization, isocapnic hyperventilation (ICH), and histamine challenge (HC) tests were administered to 12 children with mild asthma according to American Thoracic Society criteria and 12 without asthma. HS was administered by successively doubling the inhalation durations (0.5, 1, 2, 4, and 8 minutes) until FEV1 measured at 0.5, 1.5, and 3 minutes after each dose fell by 20%. Seven subjects with asthma had a positive response to ICH, 7 to HS, and 11 to HC (statistics not given). One subject without asthma had a positive response to HC; there were no false-positive tests with ICH or HS. ICH and HS were equally specific (100%) and sensitive (58%).

HS, methacholine, and exercise were studied in 10 adults without asthma and 50 adults and 18 children with clinical asthma. HS doses were doubled until a 20% drop in FEV1 was observed or a predetermined maximum dose was reached. HS produced a 6% drop in FEV1 in 10 adults without asthma. In 44 of 50 adults with asthma and 13 of 18 children with asthma, HS nebulization was associated with a drop in FEV1 of at least 20%. HS was 88% sensitive and 100% specific.

In a third trial, children (n=721) aged 13 to 14 from 6 schools responding positively to a survey for wheezing or whistling were divided into 2 groups: 83 in the “more than 12 months ago” group and 238 in the “within the previous 12 months” group. A control group of 237 children responded “no wheezing or whistling ever.” An HS challenge was completed by 382 (162, 59, 161 for the respective groups) and an exercise challenge (EC) was completed by 357 children (151, 54, and 152, respectively). Of these children, 348 completed both tests. A fall of 15% in the FEV1 was considered diagnostic. For the diagnosis of asthma, specificity was 92% for HS and 88% for EC. Sensitivity was 47% and 46%, respectively.

The American Pain Society and American Academy of Pain Medicine convened a multidisciplinary panel of 21 pain experts in 2006 to develop a practice guideline on the use of chronic opioid therapy for chronic noncancer pain. The panel formulated their recommendations based on an evidence review that searched multiple databases for studies pertinent to their identified key questions, one of which was, “What are the benefits and harms of continuing opioids versus switching to alternative analgesics in women with chronic noncancer pain who become pregnant or are planning to become pregnant?”

The evidence review noted that nearly all studies of opioid use during pregnancy involve women receiving methadone maintenance for narcotic addiction, a distinctly different population from women receiving opioids for chronic pain. These studies did identify an association between opioid use and adverse neonatal outcomes, including neonatal withdrawal syndrome, lower birth weight, and breastfeeding difficulties.
There were no studies identified, however, comparing outcomes of continuing versus discontinuing opioids during pregnancy.

Despite the insufficient evidence, the panel strongly recommends clinicians counsel women on the risks and benefits of chronic opioid therapy during pregnancy and encourage minimal or no use of chronic opioids in pregnancy unless the benefits outweigh the risks.¹

In the absence of experimental data, observational studies provide further information about neonatal outcomes of infants exposed to chronic opioids in utero and assist the clinician in defining the risks of opioid therapy during pregnancy. A large case-control study compared more than 17,000 infants who had major structural birth defects with 6,700 control infants without birth defects.² Therapeutic opioid use during pregnancy was reported in 2.6% of mothers of cases and 2.0% of mothers of controls. Congenital heart disease (OR 1.4; 95% CI, 1.1–1.7), spina bifida (OR 2.0; 95% CI, 1.3–3.2), hydrocephaly (OR 2.0; 95% CI, 1.0–3.7), and gastroschisis (OR 1.8; 95% CI, 1.1–2.9) were associated with maternal opioid use.

A retrospective cohort study compared neonatal outcomes of infants born to mothers using methadone for pain control versus for maintenance of opiate addiction.³ At a single institution, the 19 infants in the pain control group were less likely to require treatment for neonatal abstinence syndrome than were the 24 infants in the opiate addiction group (11% vs 58%; P=.0016) but were more likely to be born before 37 weeks (58% vs 13%; P value not given), mainly because of induction for uncontrolled pain.

A pair of case series studies reported neonatal outcomes of infants exposed in utero to chronic opioids used for pain control. Neonatal abstinence syndrome occurred in 6% of the 167 infants in 1 study⁴ and 38% of the 13 infants in the second study,⁵ while admission to the neonatal intensive care unit occurred in 41% and 38% of infants, respectively.

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What interventions are effective for the prevention of suicide?

Evidence-Based Answer
School-implemented suicide prevention programs decrease self-reported suicide attempts. (SOR: A, based on consistent RCTs.) Cognitive therapy after a suicide attempt decreases rates of subsequent attempts. (SOR: B, based on a single RCT.) Treatment with selective serotonin reuptake inhibitors (SSRIs) has not been shown to alter the rates of suicide. (SOR: A, based on meta-analysis of RCTs.)

In a 2001 RCT, the Signs of Suicide (SOS) prevention program was incorporated into the curriculum of 5 high schools in Hartford, CT and Columbus, GA.¹ The study assigned 1,027 students to the treatment group and 1,073 to the control group. The treatment group participated in didactic sessions aimed at teaching students to recognize the signs of depression and suicidality in themselves and others and to take appropriate action to respond to those signs. Three months after implementation of the program, students in both the treatment and control group completed a questionnaire regarding self-reported suicide attempts, suicidal ideation, knowledge and attitudes about depression and suicide, and help-seeking behavior.

Individuals in the treatment group reported fewer suicide attempts in the previous 3 months versus the control group (3.6% vs 5.4%, respectively; P<.05) yielding a NNT of 55. There was no statistically significant effect on help-seeking behavior or suicidal ideation.¹

The SOS program was implemented the following year and expanded to include not only the Hartford and Columbus schools, but also 4 schools in Massachusetts (n=4,133).² Similar results were obtained in the subsequent 3-month evaluation in self-reported suicide attempts (3% in the treatment group vs 4.6% in the control group; P<.05). An important limitation to these studies was a short follow-up period. A potential bias was that subjects in the treatment group might have felt compelled to answer in a certain manner after their sessions.

In an RCT evaluating the effects of cognitive therapy on suicide attempts, 120 patients who had recently attempted suicide were randomized into either a treatment group or control group.³ Patients in both

groups received usual care including referral services and follow-up with a case manager. Patients in the treatment group also received outpatient cognitive therapy focusing on identifying thoughts, images, and core beliefs present before the suicide attempt, and were assisted in developing methods of coping with stressors. After 18 months of follow-up, 13 participants (24.1%) in the cognitive therapy group and 23 participants (41.6%) in the usual care group had at least 1 reattempt at suicide ($P=.05$; NNT=6).

A meta-analysis of more than 40,000 patients in 477 randomized placebo-controlled trials was performed to investigate whether adults treated with SSRIs have an increased risk of suicide-related outcomes. Most (but not all) patients were being treated for depression; the mean study length was 8 to 10 weeks. There were 16 suicides, 172 episodes of nonfatal self-harm, and 177 episodes of suicidal thoughts reported. The data failed to show either a decrease or an increase in the rate of suicide in patients taking an SSRI (OR 0.85; 95% CI, 0.20–3.4).

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**Does St. John’s wort treat depression in adult patients?**

**Evidence-Based Answer**

In treating patients with major depressive disorder (MDD), St. John’s wort (*Hypericum perforatum*) is as effective as standard antidepressants and often better tolerated. (SOR: A, based on a meta-analysis.) Clinically, St. John’s wort may be considered for use in treating mild to moderate MDD. (SOR: B, based on an evidence-based guideline.)

In 2008, Cochrane authors reviewed all RCTs comparing St. John’s wort with placebo or prescription antidepressants, identifying 29 high-quality trials with 5,489 patients meeting the inclusion criteria: 18 comparisons with placebo and 17 comparisons with synthetic standard antidepressants. In the 18 placebo-controlled trials, 16 trials used reductions in the Hamilton Depression Scale (HAMD scale) to assess response on treatment. A significant response was defined as a final HAMD score <10 or a reduction to <50% of the baseline score.

Compared with placebo, more patients taking St. John’s wort were significant responders, with a response rate ratio (RR) of 1.48 (95% CI, 1.23–1.77). The dropout rate was the same for St. John’s wort and placebo.

In the 17 trials with standard antidepressants, St. John’s wort had an equivalent response rate (RR of significant response 1.01; 95% CI, 0.93–1.09). There was no difference in response rate for St. John’s wort compared with older antidepressants (tricyclic, tetracyclic, and related antidepressants) (RR 1.02; 95% CI, 0.90–1.15), or compared with selective serotonin reuptake inhibitors (SSRIs) (RR 1.00; 95% CI, 0.90–1.12). Patients taking St. John’s wort were significantly less likely to drop out due to adverse effects than patients taking either older antidepressants (OR 0.24; 95% CI, 0.13–0.46) or SSRIs (OR 0.53; 95% CI, 0.34–0.83).

The American Psychiatric Association Task Force for complementary and alternative medicine in MDD issued guidelines based on their literature review from 1965 to January 2010 that included 7 articles (1 meta-analysis, 4 RCTs, and 2 non-RCTs). The guideline authors stated that placebo-controlled studies showed mixed results but larger studies demonstrated significant improvement in mild to moderate depression. The task force concluded that St. John’s wort is a reasonable treatment for mild to moderate MDD.

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**Evidence-Based Practice learning objectives**

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

Evidence-Based Answer
A combination of osteopathic manipulative treatments (OMT) may reduce the length of hospital stay for hospitalized patients with pneumonia compared with conventional treatment only or conventional treatment with light touch. (SOR: C, based on a small systematic review and a larger, inconsistent RCT).

A 2010 Cochrane review of chest physiotherapy for pneumonia in adults identified 2 RCTs (79 patients, mean age 78 years old) comparing OMT with control for the treatment of community-acquired or nursing home-acquired pneumonia.1 The OMT techniques used were bilateral paraspinal inhibition, bilateral rib raising, diaphragmatic myofascial release, condylar decompression, soft tissue technique to the cervical muscles, myofascial release to the anterior thoracic inlet, and thoracic lymphatic pump. Treatments lasted 10 to 15 minutes twice a day until hospital discharge, respiratory failure, or death. Control subjects received a light touch sham treatment without movement of myofascial structures or articulation of joints. Treated areas and duration were similar to the OMT group.

OMT reduced the duration of hospital stay by 2.0 days (95% CI, 3.5–0.58) compared with placebo. OMT also decreased the duration of IV antibiotic treatment (by 2.1 days; 95% CI, 3.4–0.87) and total antibiotic treatment (by 1.9 days; 95% CI, 3.1–0.74), compared with placebo. Mortality rates were not significantly different between groups (RR 0.27; 95% CI, 0.05–1.57). Some nonosteopathic techniques, such as positive expiratory pressure, were also found to reduce the mean duration of hospital stay, while conventional chest physiotherapy and active cycle breathing did not.

A 2010 double-blind RCT studied 406 hospitalized patients ≥50 years old with pneumonia.2 Patients were randomized into conventional care only, conventional care and OMT, and conventional care with light touch sham treatment. There were no significant differences in outcomes between groups in the intention-to-treat (ITT) analysis. However, in the per-protocol (PP) analysis (where 18% of subjects in the ITT analysis were removed due to missed treatments, delayed initiation of treatment, treatment differing from protocol, and study withdrawal) there were significant differences in the length of hospital stay, duration of IV antibiotics, and incidence of respiratory failure/death (TABLE).

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### TABLE

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Analysis</th>
<th>Conventional care plus OMT</th>
<th>Conventional care only</th>
<th>Conventional care with light touch sham treatment</th>
<th>P value (for comparison across all 3 groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median length of hospital stay (primary outcome)</td>
<td>ITT</td>
<td>3.9 days 95% CI, 3.4–4.7 n=130</td>
<td>4.3 days 95% CI 3.9–4.9 n=133</td>
<td>4.5 days 95% CI 3.8–4.9 n=124</td>
<td>.53</td>
</tr>
<tr>
<td></td>
<td>PP</td>
<td>3.5 days 95% CI, 3.2–4.0 n=96</td>
<td>4.5 days 95% CI 3.9–4.9 n=127</td>
<td>3.9 days 95% CI 3.5–4.8 n=95</td>
<td>.01</td>
</tr>
<tr>
<td>Duration of IV antibiotics</td>
<td>ITT</td>
<td>3.3 days 95% CI, 2.9–3.7 n=130</td>
<td>3.5 days 95% CI 3.1–3.9 n=133</td>
<td>3.7 days 95% CI 2.9–3.9 n=124</td>
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</tr>
<tr>
<td></td>
<td>PP</td>
<td>3.0 days 95% CI, 2.7–3.5 n=96</td>
<td>3.5 days 95% CI 3.2–3.9 n=127</td>
<td>3.3 days 95% CI 2.7–3.8 n=95</td>
<td>.05</td>
</tr>
<tr>
<td>Incidence of respiratory failure</td>
<td>ITT</td>
<td>3% n=124</td>
<td>8% n=132</td>
<td>3% n=124</td>
<td>.08</td>
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<tr>
<td></td>
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<td>7% n=127</td>
<td>2% n=95</td>
<td>.006</td>
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<tr>
<td>Incidence of death</td>
<td>ITT</td>
<td>2% n=124</td>
<td>6% n=127</td>
<td>3% n=124</td>
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<td>0% n=96</td>
<td>6% n=127</td>
<td>3% n=95</td>
<td>.006</td>
</tr>
</tbody>
</table>

CI=confidence interval; ITT=intention-to-treat; IV=intravenous; OMT=osteopathic manipulative treatment; PP=per protocol.
## Adhesive capsulitis (frozen shoulder)

Syndrome of pain with restricted active and passive glenohumeral joint range of motion.

**Four-stage process**
- **Painful stage**
  - 0–3 months
  - Pain with active and passive range of motion
  - Full range of motion (ROM) early in phase, then loss of ROM toward end of phase
- **Freezing stage**
  - 3–9 months
  - Worsening pain and progressive loss of active and passive ROM
- **Frozen stage**
  - 9–15 months
  - Significant shoulder stiffness with relatively less pain
- **Thawing stage**
  - 15–24 months
  - Decreasing pain and increasing ROM
- Some describe only 3 stages by combining painful and freezing stages

**Incidence/prevalence**
- 2%–3% in the general population
- Patients usually over age 40, with peak incidence at ages 60–70
- 70% of cases are in women
- Patients can later develop syndrome in opposite shoulder

**Therapeutics**
- Almost always self-limited
  - Initial treatment should be conservative—a combination of pain medication, activity modification, and ROM exercises

**Prognosis**
- Variable recovery time, with total duration of symptoms ranging from 1 to 3 years
- After 5–10 years, many patients have clinically limited ROM without functional significance
- A small percentage of patients have long-term functional limitation

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## Exercise-induced asthma

Defined as exercise-induced symptoms of asthma in patients who have asthma. Exercise-induced bronchoconstriction (EIB), in contrast, is airway obstruction with exercise in patients without asthma.

- Between 60% and 90% of people with asthma consider exercise a major trigger of asthma symptoms
- About 10% of patients without asthma will have EIB

**Risk factors**
- High ventilation sports (eg, football, basketball)
- Endurance sports (eg, cross country skiing, swimming, long-distance running)
- Winter sports
- Participation in a location with environmental pollutants (eg, automobile exhaust, sulfur dioxide, nitrogen dioxide, smoke, ozone, chlorine)
- Cold temperatures
- Dry air
- Allergens, molds, dust, irritants
- Respiratory tract infections
- Sinusitis
- Rhinitis
- Concurrent medications (eg, salicylates, NSAIDs, beta-blockers)
- Pre-exercise food allergens: peanuts, celery, shrimp, grain, carrots, bananas

**Long-term care**
- Any underlying asthma should be diagnosed and controlled first (SOR: C)
- Additional measures may include (if not already being used)
  - Inhaled bronchodilators
  - Inhaled corticosteroids
  - Intranasal steroids
  - Antihistamines
- Dietary salt restriction may improve lung function after exercise and possibly baseline lung function
  - Difficult to maintain due to need for severe sodium restriction (<165 mmol/d)

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**Editor:** Robert Marshall, MD, MPH, MISM, CMIO, Madigan Army Medical Center, Tacoma, WA
What is the best pharmaceutical treatment for adults with exercise-induced asthma?

Bottom line
Inhaled short-acting beta₂-agonists (SABAs) taken 10 to 15 minutes before exercise prevent exercise-induced bronchospasm in more than 80% of patients. (SOR: A, based on a systematic review.) In patients with frequent and severe exercise-induced asthma (EIA), daily use of an inhaled corticosteroid significantly reduces the frequency and severity of bronchoconstriction and improves spirometry results. (SOR: C, based on a systematic review with disease-oriented outcomes.) Long-acting beta₂-agonists (LABAs), leukotriene receptor antagonists, and mast-cell stabilizing agents (MCSAs) are also beneficial but are not recommended as first-line therapy. (SOR: C, based on evidence-based guidelines.)

Evidence summary
In 2009, a Cochrane review compared the use of SABAs and MCSAs for treating EIA.¹ The review found that in patients with stable asthma (n=271, 91 of whom were children), the mean maximum reduction in postexercise FEV1 using an MCSA was 11.2% compared with 4.3% using a SABA (WMD 6.8%; 95% CI, 4.5%–9.2%). Participants were prevented from developing bronchospasm significantly more often using SABAs compared with MCSA (85% vs 66%, respectively; OR 0.3; 95% CI, 0.2–0.5). Outcomes were similar in separate subanalyses of adults and children.

A 2007 Cochrane review examined the effectiveness of inhaled corticosteroids for treating EIA.² The combined results of 3 parallel studies (n=101, 67 of whom were children) found that ICS used for 4 weeks or more before exercise testing significantly improved spirometry results when compared with placebo, by demonstrating an attenuated fall in FEV1 of 12% (95% CI, 10%–13%). Outcomes were similar in separate subanalyses of adults and children.

Current National Heart, Lung, and Blood Institute evidence-based guidelines strongly recommend that SABAs be the treatment of choice, as LABAs may disguise poorly controlled persistent asthma and, in any case, are not recommended to be used alone.³ The guidelines state that leukotriene receptor antagonists taken before exercise have modest benefit in EIA, as do nedocromil and cromolyn; however, the evidence is weaker and benefit is less than with SABAs and therefore these agents are not recommended as first-line therapy.⁴

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REFERENCES

Pitfalls in diagnosing exercise-induced bronchospasm
A detailed history and provocative testing (for older children and adults) are complementary approaches for making the diagnosis of exercise-induced bronchospasm. But the following conditions can complicate one or both approaches to diagnosis:

False positives
- Deconditioning
- Nonasthmatic airway obstruction
- Tracheal stenosis
- Glottic dysfunction
- Occult cardiac disease
- Muscular dystrophies

False negatives
- Poor technique in bronchospasm challenge tests
- H1 blockers
- Calcium channel blockers
- Leukotriene agents
- Caffeine

1. In developed countries, decreasing the number of prenatal visits has been associated with which one of the following outcomes?
   a. Increased neonatal intensive care unit admissions
   b. Decreased patient satisfaction
   c. Decreased rates of antenatal screening for neural tube defects
   d. Increased utilization of the emergency department or labor deck

2. When might you consider follow-up chest x-ray after patients are discharged from a hospitalization for community-acquired pneumonia?
   a. At 2–4 weeks in men only
   b. At 1 and 6 weeks in patients who do not smoke
   c. Weekly, until complete radiographic resolution
   d. At 3 months in patients >50 years of age

3. Which of the following statements is true of health outcomes related to childhood sexual abuse (CSA)?
   a. Greater psychopathology is unrelated to severity of abuse
   b. Affected patients have higher rates of physical health complaints, including low general health, pain, and gynecological problems
   c. Controlling for familial factors significantly reduces the association between psychopathology and CSA
   d. Screening for CSA is a common practice in primary care

4. The most appropriate first-line pharmaceutical agent for exercise-induced asthma treatment is:
   a. Salmeterol
   b. Nedocromil sodium
   c. Albuterol
   d. Zafirlukast

5. Which of the following statements is correct about St. John’s wort for the treatment of major depression?
   a. It is as effective as placebo
   b. It is more effective than standard antidepressant treatment
   c. It is as effective as standard antidepressant treatment
   d. It increases anxiety and is commonly discontinued

6. All of the following interventions for the prevention of suicide have been shown to be effective EXCEPT
   a. SSRI antidepressants
   b. Cognitive therapy
   c. School-implemented suicide prevention programs
   d. None of the above

7. Which of the following statements is true regarding osteopathic manipulative treatment (OMT) for patients with pneumonia?
   a. OMT has no effect on pneumonia
   b. OMT does not improve mortality in patients with pneumonia
   c. OMT may help decrease the duration of hospital stay
   d. All the above

8. A 16-year-old patient presents to your office with shortness of breath and wheezing. Her FEV1 falls by 25% after 2 minutes of a 4.5% saline aerosol nebulization. Your interpretation is:
   a. The patient needs a confirmatory test for asthma with a histamine challenge
   b. The patient has asthma. Initiate appropriate therapy
   c. The patient has a viral bronchitis. Start prednisone 40 mg daily for 5 days
   d. Order a chest x-ray to rule out pneumonia

Answer key: 1. b; 2. d; 3. b; 4. c; 5. c; 6. a; 7. c; 8. b
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