Cochrane for Clinicians

Putting Evidence into Practice

GERD Treatment for Chronic Nonspecific Cough in Children and Adults

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The Cochrane Abstract on the next page is a summary of a review from the Cochrane Library. It is accompanied by an interpretation that will help clinicians put evidence into practice. Dr. Fogleman presents a clinical scenario and question based on the Cochrane Abstract, followed by an evidence-based answer and a critique of the review. The practice recommendations in this activity are available at http://www.cochrane.org/reviews/en/ab004823.html.

EB CME

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Clinical Scenario

A 24-year-old man presents with a cough of six months' duration. He has a history of gastroesophageal reflux disease (GERD) but denies recent symptoms. A physical examination, pulmonary function tests, and chest radiography reveal no cause for his chronic cough.

Clinical Question

Should acid suppressants or prokinetic agents be used to treat patients with chronic nonspecific cough?

Evidence-Based Answer

Acid suppressants or prokinetic agents should not be used to treat chronic nonspecific cough in infants or children. There is insufficient evidence to support or discourage use of these agents to treat chronic nonspecific cough in adults, even in those with a history of GERD. (Strength of Recommendation = B, based on inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

Cough is a presenting symptom in as many as 30 million outpatient visits per year.[1] Fifty percent of adults with cough lasting three to eight weeks have postinfectious symptoms that resolve spontaneously; the term chronic cough refers to persons with symptoms lasting more than eight weeks.[2] The most common etiology of chronic cough in adults is upper airway cough syndrome secondary to postnasal drip, asthma, or GERD. This etiology represents the diagnosis in 99 percent of symptomatic persons who do not smoke, who do not use angiotensin-converting enzyme inhibitors, and who have unremarkable findings on chest radiography.[2]

In children, the differential diagnosis of chronic cough (i.e., lasting longer than four weeks) is much broader, including congenital anomalies and tracheomalacia.[3] GERD is not among the leading causes included in the American College of Chest Physicians' (ACCP) guidelines for the evaluation of chronic cough in children.[3]

In this update of a Cochrane review first published in 2005, six studies of children were examined, five of which involved infants.[4] In four trials examining thickened feeds, GERD symptoms improved but cough was increased. Only one study used a proton pump inhibitor (PPI; lansoprazole [Prevacid]) to treat infants, and the results showed an increase in cough.[5] Adverse outcomes, including lower respiratory tract infections, were more common with use of the PPI (number needed to harm = 11 over four weeks).[4] The lone study including older children compared cisapride and domperidone (neither drug available in the United States) with placebo and found no benefit to treatment. The authors concluded that the data do not support using GERD-related agents to treat nonspecific cough in children. This conclusion is consistent with the ACCP guidelines on the management of nonspecific chronic cough in children.[3]

Most of the 13 studies of adults were small, with only two studies involving more than 100 patients.[4] The mean age range was 46 to 58 years. In all but one study, reflux was confirmed objectively, most often with pH probe. Nine studies compared PPI use with placebo, although the medications and dosages varied. Omeprazole (Prilosec) was used most often, and higher PPI dosages (maximum therapy and/or twice-daily dosing) were used in seven studies. Measures of

Cochrane Abstract

Background: Gastroesophageal reflux disease (GERD) is said to be the causative factor in up to 41 percent of adults with chronic cough. Treatment for GERD includes conservative measures (diet manipulation), pharmaceutical therapy (e.g., motility or prokinetic agents, histamine H_2 antagonists, proton pump inhibitors [PPIs]), and fundoplication.

Objectives: To evaluate the effectiveness of GERD treatment on chronic cough in children and adults with GERD and prolonged cough that is not related to an underlying respiratory disease (i.e., nonspecific chronic cough).

Search Strategy: The authors searched the Cochrane Airways Group Specialized Register, the Cochrane Register of Controlled Trials (CENTRAL), Medline, EMBASE, review articles, and reference lists of relevant articles. The date of last search was April 8, 2010.

Selection Criteria: All randomized controlled trials (RCTs) on GERD treatment for cough in children and adults without primary lung disease.

Data Collection and Analysis: Two review authors independently assessed trial quality and extracted data. They contacted study authors for further information.

Main Results: The authors included 19 studies (six pediatric studies, 13 adult studies). None of the pediatric studies could be combined for meta-analysis. A single RCT in infants found that PPI use (compared with placebo) was not effective for cough outcomes (favoring placebo odds ratio [OR] = 1.61; 95% confidence interval [CI], 0.57 to 4.55), but those taking a PPI had significantly increased adverse events (OR = 5.56; 95% CI, 1.18 to 26.25; number needed to harm in four weeks = 11; 95% CI, 3 to 232). In adults, analysis of H_2 antagonists, motility agents, and conservative treatment for GERD was not possible (lack of data), and there were no controlled studies of fundoplication. The authors analyzed nine adult studies comparing PPI (two to three months) with placebo for various outcomes in the meta-analysis. Using intention-to-treat, pooled data from studies resulted in no significant difference between treatment and placebo in total resolution of cough (OR = 0.46; 95% CI, 0.19 to 1.15). Pooled data revealed no overall significant improvement in cough outcomes (end of trial or change in cough scores). They only found significant differences in sensitivity analyses. The authors found a significant improvement in change of cough scores at the end of intervention (two to three months) in those receiving PPI (standardized mean difference = −0.41; 95% CI, −0.75 to −0.07) using generic inverse variance analysis on crossover trials. Two studies reported improvement in cough after five days to two weeks of treatment.

Authors' Conclusions: PPI is not effective for cough associated with GERD symptoms in very young children (including infants) and should not be used for cough outcomes. There are insufficient data in older children to draw any valid conclusions. In adults, there is insufficient evidence to conclude definitely that GERD treatment with PPI is universally beneficial for cough associated with GERD. Clinicians should be cognizant of the period (natural resolution with time) and placebo effect in studies that utilize cough as an outcome measure. Future pediatric and adult studies should be double-blind, randomized controlled, and parallel-design, using treatments for at least two months, with validated subjective and objective cough outcomes, and include ascertainment of time to respond as well as assessment of acid and/or nonacid reflux.

treatment effects included complete cure, improvement of cough during treatment, and improvement of cough by the end of the trial. The differences in cure rates between the interventions and placebo were not statistically significant.

Risks of GERD treatment in adults are small but include community-acquired pneumonia and hip fracture.[6,7] Physicians should allow patients to make informed decisions and explain that PPIs are unlikely to benefit most patients with chronic nonspecific cough. If a trial of therapy is offered, a PPI such as omeprazole is the most reasonable option, and patients should be given the opportunity to discontinue therapy after eight weeks. These recommendations are similar to those from the ACCP, which suggest an empiric trial of a PPI only in patients whose history and physical examination suggest GERD as a cause of chronic nonspecific cough.[1]

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Cochrane Briefs

Acellular Vaccines for Preventing Pertussis in Children

Clinical Question

Are acellular vaccines as safe and effective as whole-cell vaccines for preventing pertussis (whooping cough) in children?

Evidence-Based Answer

Multicomponent (i.e., three or more) acellular vaccines are as effective as whole-cell vaccines at preventing pertussis and mild pertussis disease (e.g., cold symptoms, cough without classic whoop or cough paroxysms) in children. Adverse effects are similar to those from placebo and less severe than those from whole-cell vaccines. (Strength of Recommendation = A , based on consistent, good-quality patient-oriented evidence.)

Practice Pointers

Worldwide, there are approximately 50 million cases of pertussis each year, leading to about 400,000 deaths. In recent years, high-income countries have seen large increases in adolescent pertussis rates; the incidence of pertussis in U.S. adolescents has risen 19-fold since 1996. Whole-cell vaccines have been available for 70 years. Concerns about adverse effects (e.g., convulsions, encephalopathy, hypotonic episodes, fever, vomiting) led to the development of acellular recombinant vaccines in the 1970s and 1980s; however, it was not definitively known whether acellular vaccines were as effective as whole-cell vaccines.

This Cochrane review included 52 safety trials and six effectiveness trials. The effectiveness of multicomponent vaccines was 84 to 85 percent in preventing pertussis, and 71 to 78 percent in preventing mild pertussis disease. In contrast, single-component (one to two) vaccines were 59 to 79 percent effective in preventing pertussis and 41 to 54 percent effective in preventing mild disease. The authors were unable to directly compare acellular with whole-cell vaccines because of the wide range of effectiveness of different whole-cell vaccines (36 to 95 percent), but both were found to be effective.

Acellular and whole-cell vaccines had a low incidence of adverse effects; however, in the acellular vaccine studies, more patients completed the series, fewer patients had febrile convulsions, and fewer patients experienced hypotonic-hyporesponsive episodes. Although not statistically significant compared with whole-cell vaccines, adverse effects from acellular vaccines increased as the series progressed, including fever (60 to 162 per 1,000 persons), local redness (96 to 162 per 1,000 persons), and swelling (117 to 275 per 1,000 persons). Deaths from infections and all causes were rare, and no difference was seen between vaccines.

Guidelines from the Centers for Disease Control and Prevention recommend acellular vaccines in all age groups. Recommendations include the diphtheria and tetanus toxoids and acellular pertussis (DTaP) combination vaccine at two, four, six, and 15 to 18 months of age, with a booster of the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine between 11 and 18 years of age, and a one-time Tdap booster as an adult. Clinicians should strongly recommend Tdap vaccination in adults who are in contact with infants younger than 12 months.[1]

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