

POEMs

PATIENT ORIENTED EVIDENCE THAT MATTERS

Practice Recommendations from Key Studies

Neuraminidase inhibitors slightly beneficial for shortening flu symptoms

Cooper NJ, Sutton AJ, Abrams KR, Wailoo A, Turner DA, Nicholson KG. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2003; 326:1235-1240.

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■ PRACTICE RECOMMENDATIONS

Oseltamivir (Tamiflu) and zanamivir (Relenza) are effective for reducing the duration of symptoms of influenza by about 1 day when given to healthy individuals aged <65 years, and if given early in the course of the disease. Benefit to individuals aged >65 years and those with chronic medical conditions were not established.

Important outcomes, such as prevention of death and hospitalization due to influenza, were not discussed. No head-to-head trials were included, and these drugs could be considered interchangeable. Patients in the studies had laboratory confirmation of influenza, something that is not always done in general practice.

Given that these drugs are expensive (about \$60 for a typical course), routine use for all flu patients may not be cost-effective. Rather, balancing the cost of treatment against risks and benefits need to be individualized. Use of these drugs should not replace primary prevention strategies.

■ BACKGROUND

Influenza epidemics cause considerable morbidity and mortality, and account for substantial time

lost from work. In general, the elderly and the very young are at greatest risk from serious complications of the flu. Treatment of relatively healthy populations is usually aimed at symptom alleviation and return to work and normal activities.

■ POPULATION STUDIED

The patients in the 24 studies included in this meta-analysis represent a heterogeneous population, and results would be applicable to the patient profile of the typical family practice.

■ STUDY DESIGN AND VALIDITY

The authors selected 17 treatment studies and 7 prevention studies using strict criteria. For inclusion, the study had to be a double-blind, randomized controlled trial in English, studying treatment or prevention of naturally occurring influenza with zanamivir or oseltamivir at standard dosing.

The researchers looked for studies in PubMed and requested unpublished studies from pharmaceutical companies. They also reviewed cited literature in all reviewed articles, as well as previous systematic reviews and meta-analyses.

The analysis considered 3 groups: children

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What is a POEM?

Each month, the POEMs (Patient-Oriented Evidence that Matters) editorial team reviews 105 research journals in many specialties, and selects and evaluates studies that investigate important primary care problems, measure meaningful outcomes, and have the potential to change the way medicine is practiced. Each POEM offers a Practice Recommendation and summarizes the study's objective, patient population, study design and validity, and results. The collected POEMs are available online at www.jfponline.com.

aged <12 years, generally healthy individuals aged 12 to 64 years, and a “high-risk” group aged 65 years or older or with chronic medical conditions.

The methodology was generally good, but a few weaknesses make application of this study to the general population open to question. Its strengths were inclusion of only randomized controlled trials and inclusion of unpublished data. The authors described adequate search, selection, abstraction, and meta-analytic techniques. Weaknesses were inclusion of only English-language publications, and selection of studies in which varying proportions of patients were vaccinated prior to entry into the trial.

No analysis of side-effect profiles was done. Additionally, given the considerable variation as to what constitutes appropriate uses of antibiotics, the outcome of complications requiring use of antibiotics would be extremely variable across studies and difficult to analyze.

■ OUTCOMES MEASURED

The primary outcomes were subjective time to alleviation of symptoms and complications requiring antibiotics. Other outcomes were self-reported return to normal activity or admission to the hospital. Cost-effectiveness was not directly analyzed.

■ RESULTS

Zanamivir reduced symptom duration by an average 0.8 days in healthy individuals (95% confidence interval [CI], 0.26–1.31), 0.9 days (95% CI, 0.05–1.9) in high-risk individuals, and 1.0 days in children (95% CI, 0.48–1.52). Oseltamivir reduced symptom duration by 0.8 days (95% CI, 0.3–1.4 days) in healthy individuals and 0.9 days (95% CI, 0.25–1.5 days) in children, but was not shown to decrease symptom duration in high-risk individuals.

Studies of prophylaxis were small and too heterogeneous for meta-analysis. Because of study heterogeneity, outcomes of admission to the hospital and complications treated by antibiotics could not be evaluated.

Tapering inhaled steroids effective for chronic asthma

Hawkins G, McMahon A, Twaddle S, Wood S, Ford I, Thompson N. *Stepping down inhaled corticosteroids in asthma: randomised controlled trial. BMJ 2003; 326:1115–1118.*

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■ PRACTICE RECOMMENDATIONS

Chronic stable asthma patients who use at least 1000 µg beclomethasone or its equivalent daily may reduce their dose of inhaled corticosteroids by as much as 50% without compromising control of symptoms.

■ BACKGROUND

Asthma management guidelines recommend a reduction in steroid use once control is obtained. While some evidence shows that this approach is effective in mild disease, the approach had not been tested long-term in people with moderate to severe disease.

■ POPULATION STUDIED

A total of 259 adult participants were recruited from rural and urban general medical practices in Scotland. They had an asthma diagnosis for 1 year or more, and daily treatment with at least 800 µg beclomethasone dipropionate, fluticasone, or budesonide equivalent. Eighty-two percent of patients completed the study.

Patients were excluded if they had used oral corticosteroids within the previous 2 months, had a visit to a general practitioner or hospital for asthma in the previous 2 months, or were unable to use a peak flow meter.

■ STUDY DESIGN AND VALIDITY

In this long-term, randomized, double-blind trial, patients received either beclomethasone or fluticasone at the dose used before the study began.

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After this run-in period, they were randomized to receive either a reduction in their dose of inhaled steroids (step-down) or a sham reduction.

Investigators assessed patients at 3, 6, and 12 months; they reduced the steroid dose if patients demonstrated good control. If patients were deemed to have poor control, they were kept on the same usual dose. About half (49%) of patients in the step-down group actually received a reduced dosage; the rest, presumably, did not achieve a level of control suitable for the physician to initiate the taper.

Overall, this appears to be a well-designed study. Allocation to randomization was concealed from the enrolling investigators. Patients were randomized using a computer-generated allocation sequence, and the code was kept by the pharmacy. Investigators performed an intention-to-treat analysis. Given that only half of the patients actually received the intervention, an on-treatment analysis would be helpful in determining whether or not step-down therapy would result in deterioration of asthma control, though this type of analysis was not performed.

All data collection tools were validated. Many patients in both groups were on long-acting beta-2 agonists, which could have altered the outcome. However, subgroup analysis, excluding these patients, found similar results.

■ OUTCOMES MEASURED

The primary objective was to compare the rates of asthma exacerbation over 1 year. Other outcomes included the number of general practice visits, hospital admissions, and the proportion of patients receiving a 50% reduction in the dose and health status.

■ RESULTS

At various points during the study, 84% of the step-down group met adequate control criteria and they were given a reduction in the inhaled steroids. Of that group, 49% of the patients achieved a 50% reduction in their dose while maintaining good asthma control. No significant difference was found in the rate of asthma exacerbation or events

between the 2 groups. Thirty-one percent (40 people) in the step-down group and 26% (33 people) in the control group had an exacerbation requiring oral steroids (odds ratio [OR]=1.29; 95% confidence interval [CI], 0.75–2.23; $P=.354$). Overall, the results showed no significant difference in the annual dose of oral steroids between the groups.

The most common asthma-related event was a visit to a general practitioner, with a (statistically insignificant) greater number of people in the step-down group making a visit (OR=1.14; 95% CI, 0.68–1.91; $P=0.629$). Other markers of asthma-related events were rare in both groups, and the health status of both groups was similar.

Antioxidant vitamins do not prevent cardiovascular disease

Vivekananthan DP, Penn MS, Sapp SK, Hsu A, Topol EJ. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. Lancet 2003; 361:2017–2023.

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■ PRACTICE RECOMMENDATIONS

This meta-analysis of randomized controlled trials showed that neither beta-carotene nor vitamin E appears to prevent all-cause or cardiovascular mortality in patients with known heart disease or those at risk for heart disease. Similarly, use of these antioxidant vitamins did not affect number of stroke events. The use of beta-carotene and vitamin E should not be recommended for primary and secondary prevention of cardiovascular disease.

■ BACKGROUND

Oxidized low-density lipoprotein is thought to play an important role in the development of

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Beta-carotene and vitamin E should not be recommended for prevention of cardiovascular disease

atherosclerosis. Animal studies and studies of various human populations have suggested that dietary supplementation with the antioxidants vitamin E and beta-carotene may reduce cardiovascular disease by inhibiting the atherogenic process.

■ POPULATION STUDIED

In this meta-analysis, 138,113 and 81,788 persons took beta-carotene or vitamin E, respectively, alone or in combination with other antioxidants. The daily dose range for vitamin E was 50–800 IU; for beta-carotene it was 15–50 mg.

Four of the beta-carotene studies were secondary prevention studies of populations with either cardiovascular disease or risk factors for lung cancer (smoking or asbestos exposure) and skin cancer (previous skin cancer). The other 4 beta-carotene studies were primary prevention studies with low-risk participants, such as male and female health professionals without history of vascular and malignant events.

Five of the 7 vitamin E trials were secondary prevention studies that included patients with known cardiovascular disease or smokers. The remaining 2 vitamin E studies included patients with 1 or more cardiovascular risk factors or those at risk of cataracts or macular degeneration.

The age range of participants was generally between 40 and 80 years, although 1 of the smaller studies included participants as young as 20 years. Ten of the 15 studies had between 4.5 and 6.3 years of follow-up.

■ STUDY DESIGN AND VALIDITY

The authors performed a meta-analysis of antioxidant trials, using studies of 1000 or more patients performed in developed coun-

tries without known vitamin deficiencies in their populations.

The authors searched MEDLINE using the terms “randomized controlled trials,” “vitamin E,” and “beta-carotene” and found publications of antioxidant vitamins used in primary and secondary prevention of cardiovascular disease, malignancy, and eye disease. Only large trials with 1000 or more patients were included. The bibliographies of identified papers were searched to identify additional studies.

Two investigators worked independently to determine eligibility of studies. Inclusion criteria included randomized controlled trials, randomization scheme, trial size, and use of intention-to-treat analysis.

No description was available on methods of data extraction or conflict resolution, or on the rate of concordance between reviewers. The results were consistent across the trials, with the exception of cardiovascular death or nonfatal myocardial infarction. In the 4 studies of vitamin E that evaluated this combined endpoint, a small suggestion of heterogeneity was seen ($P=.053$).

■ OUTCOMES MEASURED

Four outcomes were measured: all-cause mortality, cardiovascular mortality, cerebrovascular accidents, and combined outcome of cardiovascular death or nonfatal myocardial infarction.

■ RESULTS

For beta-carotene, all-cause mortality and cardiovascular mortality were slightly higher in the actively treated group than in the control group—odds ratio (OR)=1.07 (95% confidence interval [CI], 1.02–1.11) for all-cause mortality (number needed to harm [NNH]=250; 95% CI, 129–714), and OR=1.1 (95% CI, 1.03–1.17) for cardiovascular mortality (NNH=333; 95% CI, 192–1111). Beta-carotene had no effect on the rate of cerebrovascular events. Vitamin E had no effect on any of the measured outcomes.

Hawthorn extract improves chronic heart failure

Pittler MH, Schmidt K, Ernst E. Hawthorn extract for treating chronic heart failure: meta-analysis of randomized trials. *Am J Med* 2003; 114:665–674.

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■ PRACTICE RECOMMENDATIONS

Based on the findings of this meta-analysis, hawthorn extract can be recommended as an adjunctive therapy to improve the physical performance and ameliorate heart failure–related symptoms of patients with chronic heart failure. It should not replace standard therapy.

The most effective dose is unknown, but these studies used 160–1800 mg/d. Long-term data on hawthorn extract's impact upon prognosis is still lacking.

■ BACKGROUND

In most herbal reference texts, hawthorn extract (*Crataegus monogyna* or *Crataegus laevigata*) is recommended as an oral treatment option for chronic heart failure. In Germany, its use has been approved for use in patients with New York Heart Association (NYHA) class II symptoms, and the extract is marketed as a prescription medicine. The extract is believed to possess positive inotropic and negative chronotropic cardiac properties, and increase coronary blood flow. Unlike most other inotropic agents, it exhibits antiarrhythmic properties.

■ POPULATION STUDIED

Eight clinical trials enrolling 632 patients with chronic heart failure (NYHA classes I–III) were included in the meta-analysis. No standard demographic comparisons were reported with respect to gender, age, race, or socioeconomic status.

■ STUDY DESIGN AND VALIDITY

The authors extensively searched databases, subject experts, and manufacturers for published and unpublished studies. To be included, a trial had to be randomized, double-blinded, and placebo-controlled; use preparations containing only hawthorn extract with leaf and flowers; include patients with chronic heart failure; and report data in a form appropriate for statistical pooling. All articles not in English were translated. Two reviewers independently selected and assessed the methodological quality of the trials. It was not disclosed whether these reviewers were blinded to the source of the studies.

The 8 studies were small and varied considerably in size (30–139 subjects), duration of therapy (3–16 weeks), dropout rate (0%–33.5%), severity of illness (NYHA I–III), type of hawthorn extract preparation (WS 1442, LI 132), daily dose (160–1800 mg), and use and type of concomitant therapy.

The investigators used strong methodology to control for many biases typically found in meta-analyses. The study's strengths included use of weighted mean differences of outcome measures, 2 independent reviewers, homogeneity testing, sensitivity analyses, and funnel plots.

The small sample size of the included studies could have introduced bias that limits the internal and external validity of the results. For example, the use of other medications for the treatment of heart failure might not have been equally distributed between treatment and control groups, or the patients may not be representative of typical patients with heart failure. Publication bias, whereby studies that did not show a benefit to hawthorn were not published, is also a risk.

Only a few, small studies were used in the analysis. Additionally, across the studies patients varied on numerous characteristics that could be related to outcome, such as level of risk and treatment regimens. Not much information was given concerning patients within each study, except their disease severity. One study had a large dropout rate.

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Treatment with hawthorn extract increased maximal cardiac workload compared with placebo

■ OUTCOMES MEASURED

The primary outcome was mean change in maximal workload as compared with baseline. Maximal workload was assessed using bicycle ergometry, with an increase of 25 Watts every 2 minutes until patients had to stop. Secondary outcomes included changes in blood pressure–heart rate product, which was defined as systolic blood pressure in mm Hg × heart rate per minute/100, exercise tolerance, and other heart failure–related symptoms such as dyspnea and fatigue.

■ RESULTS

For the physiological outcome of maximal workload, treatment with hawthorn extract significantly increased maximal workload compared with placebo (weighted mean difference, 7 Watts; 95% confidence interval [CI], 3–11; $P < .01$; $n = 310$ patients from 4 studies).

Hawthorn also reduced blood pressure–heart rate product (weighted mean difference, -20 ; 95% CI, -32 to -8 ; $n = 264$ patients from 5 studies) and had a marginally nonsignificant effect on exercise tolerance (weighted mean difference, 117 Watt min; 95% CI, -1 to 235 Watt min; $n = 98$ patients from 2 studies). Patients receiving extract reported improvement on a standard heart failure symptom score (weighted mean difference, -6 out of a possible 72; 95% CI, -9 to -2 ; $n = 169$ patients from 2 studies).



Estrogen plus progestin may increase incidence of dementia

Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. *The Women's Health Initiative Memory Study: a randomized controlled trial.* JAMA 2003; 289:2651–2662.

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■ PRACTICE RECOMMENDATIONS

Estrogen plus progestin does not decrease—and may actually increase—the incidence of dementia, mild cognitive impairment, and cognitive dysfunction in elderly postmenopausal women. The effect of unopposed estrogen on these outcomes is still unknown. With these new findings and the recently reported results of the Women's Health Initiative, for most women the benefits of estrogen plus progestin do not outweigh the risks.

■ BACKGROUND

Lower endogenous estrogen levels in postmenopausal women is a potential reason why women have a higher risk of developing Alzheimer disease than men. However, the results of previous trials evaluating the effects of estrogen on Alzheimer disease have been inconsistent. In addition, the role of progestin in Alzheimer disease is unclear. To date, the Women's Health Initiative Memory Study is the largest randomized controlled trial evaluating the effects of estrogen plus progestin on dementia.

■ POPULATION STUDIED

The Women's Health Initiative Memory Study, a substudy of the Women's Health Initiative, included 4532 of the 4894 postmenopausal women in the Women's Health Initiative aged 65 years or older without probable dementia.

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For most women the benefits of estrogen plus progestin do not outweigh the risks

Participants of the study were subject to the same exclusion criteria published in the Women's Health Initiative.

■ STUDY DESIGN AND VALIDITY

This randomized, double-blind, placebo-controlled study evaluated the effects of estrogen plus progestin (n=2229) compared with placebo (n=2303) on the incidence of dementia and mild cognitive impairment. Participants were randomly assigned to estrogen 0.625 mg/d plus medroxyprogesterone acetate 2.5 mg/d or matching placebo. They were followed for a mean duration of 4 years.

The study was divided into 4 phases. In phase 1, all participants completed a baseline and annual Modified Mini-Mental State Examination, which was used to screen for and track changes in global cognitive impairment. Participants were only referred to phase 2 and 3 for neuropsychological battery testing and physician examination if their scores on the exam were lower than the cutoff points, determined by the number of years of education completed by each participant. Participants were referred to phase 4 if the physician suspected probable dementia, and they were tested for reversible causes of dementia. Less than 1% of the study participants in both groups were referred to phases 2 to 4.

This study used concealed allocation, and results were analyzed by intention-to-treat. Baseline characteristics did not significantly differ between groups, with the exception of a lower percentage of stroke and a higher percentage of participants using statin therapy in the hormone group. Adherence to therapy in both groups significantly decreased over time, with only 50% and 61% of participants adhering to hormone therapy and placebo, respec-

tively, for 4 years ($P<.001$). Other estrogen and progestin formulations, doses, or routes of administration were not evaluated. The estrogen-only arm of this study is ongoing and will, we hope, clarify the effect of estrogen alone without a progestin on the incidence of dementia in the elderly.

■ OUTCOMES MEASURED

The outcomes of this study were to determine the effect of estrogen plus progestin on all-cause dementia (primary outcome), mild cognitive impairment (secondary outcome), and global cognitive functioning¹ in elderly postmenopausal women.

■ RESULTS

Sixty-one participants were diagnosed with probable dementia: 40 (66%) in the estrogen plus progestin group and 21 (34%) in the placebo group (hazard ratio [HR]=2.05; 95% confidence interval [CI], 1.21–3.48; $P=0.01$). This risk translates into an additional 23 cases of dementia per 10,000 women per year taking estrogen plus progestin compared with placebo. After excluding participants at higher risk of developing dementia at baseline, a higher rate of probable dementia in the estrogen plus progestin group was still seen when compared with placebo (HR=2.64; 95% CI, 1.26–5.53).

Despite the differences at baseline among women with a prior history of stroke and prior use of statin therapy, no difference was found in the diagnosis of probable dementia in these subgroups. No difference was found in the diagnosis of mild cognitive impairment between the groups (HR=1.07; 95% CI, 0.74–1.55; $P=0.72$). More women in the estrogen plus progestin group had a significant decrease in global cognitive functioning.¹

REFERENCE

1. Rapp SR, Espeland MA, Shumaker SA, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women. The Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003; 289:2663–2672.

Thrombolytic therapy for acute ischemic stroke: risks vs benefits

Wardlaw JM, Sandercock PAG, Berge E. Thrombolytic therapy with recombinant tissue plasminogen activator for acute ischemic stroke: Where do we go from here? A cumulative meta-analysis. *Stroke* 2003; 34:1437-1442.

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■ PRACTICE RECOMMENDATIONS

The evidence is not strong enough to recommend routine use of recombinant tissue plasminogen activator (rtPA) in the setting of acute ischemic stroke.

Although independence in activities of daily living 3 to 6 months later is better in those who receive rtPA, acute adverse events (including fatal intracranial hemorrhage) also significantly increase. Given the potentially fatal risks and heterogeneity of results among trials, thrombolytic therapy in the setting of acute ischemic stroke needs more investigation. In the future, we may be able to define a more specific group of patients for whom the potential benefits clearly outweigh the risks.

■ BACKGROUND

The research on the use of rtPA for victims of acute ischemic stroke has shown a mixed effect. Initially optimistic results demonstrated in highly controlled clinical settings have not been replicated in studies of more typical use. This meta-analysis reviewed and incorporated the accumulated new evidence evaluating the outcomes of rtPA use.

■ POPULATION STUDIED

The authors included randomized controlled trials of thrombolytic agents administered within 6 hours of the onset of image-confirmed nonhemorrhagic stroke. Although this article focuses on

More research may define a group of patients for whom the benefits of rtPA outweigh the risks

rtPA, studies of other thrombolytics (such as streptokinase and prourokinase) were also reviewed. Published and unpublished studies were eligible, but no unpublished studies were found. Publications not in English were translated and included.

■ STUDY DESIGN AND VALIDITY

As part of the Cochrane Database of Systematic Reviews, this was a thorough meta-analysis with clear search criteria as outlined in the Cochrane Library. The authors considered 1992 to be the first year with a modern thrombolytic trial in the setting of acute hemorrhagic stroke, and they performed a separate analysis in each year with new data.

They pooled results despite evidence of significant heterogeneity between trials, perhaps explaining why some of the confidence intervals do not narrow as markedly as one may expect over time. All but 1 trial used intention-to-treat analysis, and discussion of interobserver agreement was not readily apparent. The increasing number of study subjects over time allowed for some subgroup analysis, but very few adults aged >80 years were included in any of the trials.

■ OUTCOMES MEASURED

The primary outcomes were death or dependence on others for performance of activities of daily living (dependency) within 3 to 6 months of treatment, and symptomatic intracranial hemorrhage within 10 days of treatment. Dependency was measured with 1 of 2 previously validated instruments, the modified Rankin Scale and the Barthel Index. Symptomatic intracranial hemorrhage included any neurological deterioration or death temporally associated with a new intracranial hemorrhage seen on computed tomography scan or autopsy.

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■ RESULTS

A total of 6 rtPA trials enrolling 2830 patients were included in this analysis. The combined endpoint of death or dependency favored rtPA (odds ratio [OR]=0.80; 95% confidence interval [CI], 0.69–0.93). In terms of absolute risk reduction, 55 fewer patients out of 1000 treated would be dead or dependent within 3 to 6 months of treatment (number needed to treat [NNT]=19). However, it appears likely that this benefit was due only to the reduction in long-term disability.

When all-cause mortality was examined alone, a statistically insignificant trend was seen toward more deaths in the rtPA group (OR=1.16; 95% CI, 0.95–1.43). A markedly higher incidence of symptomatic intracranial hemorrhage was seen in the rtPA group (OR=3.13; 95% CI, 2.34–4.19), including a quadrupling of the fatal hemorrhage rate.

In terms of absolute risk increase, 62 more patients out of 1000 treated would have a symptomatic hemorrhage, including 25 more patients who would die from this (number needed to harm [NNH]=17 for all symptomatic intracranial hemorrhage, NNH=40 for fatal symptomatic intracranial hemorrhage). Unlike the death or disability outcomes, symptomatic intracranial hemorrhage had no heterogeneity between trials, giving us more confidence in the point estimate.

Results were similar for other thrombolytics, and subgroup analysis suggested some variation in risks and benefits depending on the clinical scenario. Thrombolytic therapy was associated with a trend toward more deaths among patients with more severe stroke symptoms at presentation, as well as among those with more aspirin and heparin use. When considering time to randomization, those treated within 3 hours had more favorable results for the combined death or disability outcome (OR=0.66; 95% CI, 0.52–0.82), although mortality itself did not vary between those treated within 3 hours and within 6 hours.

Negative antigen test misses <5% of strep pharyngitis

Giesecker KE, Roe MH, MacKenzie T, Todd JK. Evaluating the American Academy of Pediatric diagnostic standard for Streptococcus pyogenes pharyngitis: Backup culture versus repeat rapid antigen testing. Pediatrics 2003; 111:e666–e670.

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■ PRACTICE RECOMMENDATIONS

For patients with an average risk of having streptococcal pharyngitis, a number of testing strategies can rule out infection, including a single negative rapid strep antigen test, which has a negative predictive value of more than 95%. In patients at higher risk of having strep, based on clinical criteria, all the test strategies being studied are more likely to be falsely negative.

While it is reasonable to rely on a variety of strategies to exclude strep throat in average-risk patients, high-risk patients with a negative rapid antigen test should have an additional rapid strep test or a throat culture to exclude strep with a certainty of greater than 95%.

■ BACKGROUND

Thirty percent of pharyngitis in children is caused by *Streptococcus pyogenes*. Since it is the practice in the US to treat this cause of pharyngitis, current recommendations for diagnosis state that a confirmatory culture should be obtained in patients with a negative rapid strep antigen test. This strategy can be cumbersome in clinical practice, may delay treatment, and result in unnecessary use of antibiotics while awaiting culture results.

■ STUDY DESIGN

The authors performed a prospective cohort study. They enrolled 891 children presenting to a

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High-risk patients with a negative rapid antigen test require another test or throat culture to exclude strep

large pediatric practice who were suspected of having *S pyogenes* pharyngitis. Although the authors did not explicitly state inclusion and exclusion criteria, the spectrum of patients is likely representative of children presenting with a sore throat to a family practice.

Office staff swabbed patients' throats with 2 swabs simultaneously. They used 1 swab to inoculate a culture plate and for performance of an immediate rapid strep antigen test in the office, and sent the second to a central laboratory where a microbiologist, unaware of the results of the office antigen test, inoculated a culture plate and performed a rapid strep antigen test. Microbiologists blinded to results of the rapid antigen tests read both sets of culture plates.

The researchers used as the gold standard for a positive case the isolation and confirmation of *S pyogenes* on either culture plate. They determined the sensitivity and specificity of 4 testing strategies: single rapid antigen test (Genzyme OSOM Ultra Strep A Test[®]) performed in office; single rapid antigen test performed in laboratory (using the same rapid antigen test); result of either rapid antigen test; and single rapid antigen test in office plus culture. The researchers compared these strategies for the entire cohort, and for a subgroup with a higher risk of having strep throat, as defined by the presence of a scarlatina rash, tonsillar exudate or anterior cervical adenitis, without cough or runny nose.

■ OUTCOMES MEASURED

Sensitivity and specificity of different testing strategies.

■ RESULTS

Four patients did not have paired cultures, leaving 887 patients for analysis. The prevalence of strep throat in the entire sample was 23.7%; among the high-risk patients the prevalence

was 40%. The combination of rapid test and culture was statistically more sensitive than other strategies ($P=.01$), but the negative predictive value for all strategies was $>95\%$.

Sensitivity was 86.2% for the single rapid antigen test, 91.4% for the combination of both antigen tests, and 95.7% for the combination of rapid antigen test and culture. More importantly, at low prevalence (27%) the negative predictive values were 96%, 97%, and 98.6%, respectively; similarly, the negative likelihood ratios were 0.14, 0.09, and 0.04.

No significant difference in sensitivity was found among the various strategies in the high-risk subgroup, although this group was likely too small to find a small difference. In this group the sensitivity, negative predictive values, and negative likelihood ratios were, respectively, 90.5%, 94%, and 0.10 for a single rapid antigen test; 93.7%, 95.8%, and 0.07 for both rapid antigen tests, and 96.8%, 97.9%, and 0.03 for a negative rapid antigen test and negative culture.

Oral prednisone prevents relapse in COPD exacerbations

Aaron SD, Vandemheen KL, Hebert P, et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. *N Engl J Med* 2003; 348:2618–2625.

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■ PRACTICE RECOMMENDATIONS

A short course of oral prednisone in the outpatient setting prevents relapse and decreases dyspnea in patients with an exacerbation of chronic obstructive pulmonary disease (COPD). However, physicians should be aware of the potential for weight gain, increased appetite, and insomnia in patients taking this medication.

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Cumulative rate of relapse after 30 days and dyspnea were both improved in the prednisone group

■ BACKGROUND

The management of a COPD exacerbation is generally directed at relieving symptoms and restoring functional capacity. Steroids, along with bronchodilators and antibiotics, have been a mainstay of treatment for exacerbations, though evidence of benefit is scarce.

■ POPULATION STUDIED

Investigators enrolled 147 patients presenting to an emergency department with a COPD exacerbation. Patients were excluded for excessive reversibility with bronchodilators (implying a component of asthma), recent use of systemic steroids, evidence of pneumonia or congestive heart failure on x-ray, or if they required admission.

■ STUDY DESIGN AND VALIDITY

Patients were randomized, using concealed allocation, to receive either oral prednisone 40 mg or matching placebo once daily for 10 days. All patients received inhaled albuterol 4 times daily, oral trimethoprim sulfa or doxycycline for 10 days, and inhaled ipratropium bromide for 30 days.

The investigators performed a double-blind, randomized controlled trial with intention-to-treat analysis. The study groups were balanced at the beginning (mean age=69 years, 58% male, mean forced expiratory volume in 1 second [FEV₁] 38%). Dropout rates were similar in both groups (4 from prednisone group, 3 from placebo group). Although the ethnic makeup of the group was homogeneous (96% were white), results should be similar in other populations.

■ OUTCOMES MEASURED

Patients were monitored for relapse requiring

a visit to a physician or the emergency department because of worsening dyspnea during the first 30 days after discharge.

■ RESULTS

The cumulative rate of relapse after 30 days of initiation of treatment was lower in the prednisone group than in the placebo group (27% vs 43%; number needed to treat=6). Patients also had improved dyspnea in the prednisone group, as measured by greater improvement on a dyspnea index scale (3.95 vs 2.07; *P*=.04). Improvement in COPD-specific measures of quality of life was only minimal in the prednisone group compared with the placebo group. Common side effects in the prednisone group were increased appetite, weight gain, and insomnia.

Educational interventions improve outcomes for children with asthma

Guevara JP, Wolf FM, Grum CM, Clark NM. Effects of educational interventions for self management of asthma in children and adolescents: systematic review and meta-analysis. BMJ 2003; 326:1308-1312.

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■ PRACTICE RECOMMENDATIONS

Asthma education interventions for children may result in modest improvement in a wide range of clinical outcomes. Interventions should target children with more severe asthma and teach them to use objective measures of lung function, such as peak flow for self-monitoring instead of symptom-based self-monitoring.

■ BACKGROUND

A previously published meta-analysis suggested

that asthma education programs for children do not affect asthma-related morbidity or use of health care resources. However, a number of new studies do show improved clinical outcomes resulting from such programs. This meta-analysis incorporates these more recent studies.

■ POPULATION STUDIED

This meta-analysis pooled results from 32 controlled clinical trials of asthma education interventions for children. Eligible trials enrolled a total of 3706 children with mild, moderate, or severe asthma who were aged 2 to 18 years.

The interventions studied focused on teaching self-management skills for asthma, including prevention of asthma exacerbations, management of asthma attacks, and development of social skills. Details of the recruitment settings (ie, emergency room, inpatient) were not provided in the meta-analysis manuscript or on the journal Web site containing details describing the included studies.

■ STUDY DESIGN AND VALIDITY

For this quantitative meta-analysis, the authors conducted a systematic search for eligible controlled trials of asthma education interventions targeting children, employing both electronic and hand searches. While the interventions studied varied widely in intensity and focus, trials of simple information-only educational interventions were excluded.

All of the interventions taught some form of self-monitoring based on either symptom tracking or peak flow diaries. The number of sessions ranged from 1 to 26 sessions per participant. Studies published in other languages were included. However, the researchers made no attempt to include results from unpublished studies.

The researchers used appropriate statistical methods, including stratification and weighting, to account for quality differences and het-

erogeneity of the included studies. Because they used different units and scales to measure outcomes in different studies, they converted all outcomes to effect size.

While the overall construction of this meta-analysis was excellent, I have 2 concerns with the study design. First, asthma education programs for 2- to 5-year-olds would be very different than asthma education programs for adolescents. No mention of these important differences or attempts to stratify results by age are reported in the manuscript. Secondly, a large number of outcomes were evaluated with relatively few studies pooled for each of the outcomes. This small number of studies contributing evidence for each of the outcomes makes the results more susceptible to the effects of biases, including publication bias.

■ OUTCOMES MEASURED

Eight different asthma-related outcomes were considered: lung function as measured by forced expiratory volume in 1 second (FEV_1) or peak expiratory flow rate, number of days absent from school, number of days of restricted activity, number of disturbed nights, self-efficacy scales, symptom scores, number of visits to an emergency department, and hospitalizations.

■ RESULTS

This meta-analysis provides some evidence for a modest effect of asthma education interventions for children in particular. Lung function increased, with FEV_1 increasing an average of 0.24 L and peak flow measures increasing an average of 9.5, though it did not consistently affect symptom scores. The number of days of restricted activity were moderately decreased (effect size, -0.29 ; 95% CI, -0.49 to -0.08).

Absence from school decreased modestly (effect size, -0.14 ; 95% CI, -0.23 to -0.04). Measures of self-efficacy were moderately improved (effect size, 0.36 ; 95% CI, 0.15 – 0.57).

Interventions that taught objective measures of lung function seemed to have the largest effects

The number of days of restricted activity were moderately decreased (effect size, -0.29 ; 95% CI, -0.49 to 0.08). Emergency room visits decreased a small amount (effect size, -0.21 ; 95% CI, -0.33 to -0.09).

The education interventions did not appear to have an effect on either hospitalizations or symptom scores. Interventions that targeted children with more severe asthma and interventions that taught children to use objective measures of lung function for self-monitoring as opposed to symptom based self-monitoring seemed to have the largest effects.

Ginkgo ineffective for tinnitus

Ernst E, Stevinson C. *Ginkgo biloba for tinnitus: a review. Clin Otolaryngol* 1999; 24:164-167.

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■ PRACTICE RECOMMENDATIONS

Although the results of published trials are inconsistent, *Ginkgo biloba* is probably not effective for the treatment of tinnitus. Positive results of earlier small studies with serious methodological limitations are not supported by larger, more rigorous trials. However, the lack of any established pharmacological treatment for chronic tinnitus, combined with ginkgo's excellent safety profile, make it an option for patients who desire to try it.

■ BACKGROUND

There is no definitive pharmacological treat-

ment for tinnitus. A wide variety of drugs—including alprazolam, antiarrhythmics, antihistamines, baclofen, tricyclic antidepressants, lamotrigine, melatonin, misoprostol, niacin, and zinc—have been investigated, mostly in small trials, but none has established itself as particularly effective. Because of its effects on cognition, memory, and cerebral blood flow, *Ginkgo biloba* has been repeatedly investigated for this condition.

■ POPULATION STUDIED

This meta-analysis included a total of 541 patients in 5 different studies with chronic or severe persistent tinnitus. No other information about the patients is available.

■ STUDY DESIGN AND VALIDITY

The authors conducted a comprehensive literature search on the topic; they also asked ginkgo manufacturers for any unpublished data. Included trials were controlled (comparator or placebo), performed with *Ginkgo biloba* as a single therapy, and used subjects with a primary complaint of tinnitus or sudden hearing loss.

Each trial was assigned a Jadad score, which measures methodological quality by assessing a study's description of randomization, blinding, and patient withdrawals. Due to the heterogeneity of the study designs of the trials, results were reported qualitatively.

■ OUTCOMES MEASURED

Measured outcomes were different among the 5 studies in the meta-analysis. Outcomes included severity score, specialist evaluation, patient preference, and audiometry. Adverse effects were not reported.

■ RESULTS

Of the 5 studies, 4 showed a beneficial effect of ginkgo extract, 120-160 mg/d, on their outcome measures of chronic tinnitus. The 1 negative study used a subtherapeutic dose of ginkgo. Methodological quality varied—

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Differences between preparations
is a possible reason for inconsistent
results among ginkgo studies

2 of the positive studies had low Jadad scores (0 and 2 on a scale of 1 to 5, with 5 being best), 2 studies had high scores (4 and 5), and 1 study was not evaluable since it was published in abstract form only.

The methodological limitations of the 2 low-scoring studies included unclear criteria for evaluation, improper randomization, and incomplete information on dropouts, blinding, and duration of therapy. The authors cautiously concluded that ginkgo had favorable effects on tinnitus.

A large double-blind, placebo-controlled trial¹ of ginkgo in treating tinnitus was published after the meta-analysis. The investigators randomized 978 patients (with a mean duration of tinnitus of 10 years) in a matched-pair fashion to 50 mg 3 times daily of a standardized extract of ginkgo or placebo for 12 weeks. Primary outcomes, which included loudness and the patient's perception of the trouble caused by the disorder, were measured by a mailed, validated questionnaire.

The results did not show a difference in outcomes between ginkgo extract and placebo. Adverse effects were similar. This was a well-designed and well-performed trial with nearly twice as many patients as the entire meta-analysis. The authors note that possible reasons for the inconsistent results between this study and previous positive studies include the difference in ginkgo preparations and the method of assessing tinnitus.

REFERENCE

1. Drew S, Davies E. Effectiveness of Ginkgo biloba in treating tinnitus: double-blind, placebo-controlled trial. *BMJ* 2001; 322:1-6.

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