POEMs

Patient-Oriented Evidence that Matters

Each month, the POEMs editorial team reviews more than 80 journals of interest to primary care physicians, identifying articles you need to know about to stay up to date. We call these articles POEMs (Patient-Oriented Evidence that Matters) because they address common primary care problems, report outcomes that matter to patients, and, if valid, require us to change the way we practice. The 8 most important articles are critically appraised here each month. Occasionally, we include articles that confirm an important practice for which there had been only weak evidence previously (POEs – Patient-Oriented Evidence) or research that is focused on intermediate outcomes (DOEs – Disease-Oriented Evidence). We call attention to the latter so improper changes in currently valid practices are prevented. The collected reviews are available online. Additional POEMs and other important evidence-based material are published in a monthly newsletter called *Evidence-Based Practice* (available through subscription—phone: 1-201-782-5726; fax: 1-201-391-2778; Internet: www.infopoems.com).

Ipratropium in Adults with Acute Bronchospasm

Weber EJ, Levitt MA, Covington JK, Gambrioli E. Effect of continuously nebulized ipratropium bromide plus albuterol on emergency department length of stay and hospital admission rates in patients with acute bronchospasm. Chest 1999; 115:937-44.

Clinical question **Does the addition of ipratropium bromide to continuously nebulized albuterol improve pulmonary function, hasten discharge from the emergency department, or decrease hospitalization rates in adult patients with acute bronchospasm?**

Background Emergency department visits and hospitalizations for acute bronchospasm are largely preventable. Despite this, there are approximately 470,000 hospitalizations per year related to asthma.[1] Primary prevention of asthma exacerbations and acute bronchospasm should remain the management focus for these patients, but advances in the treatment of acute exacerbations need to be pursued as well.

Population studied Patients aged 18 years and older presenting to an urban emergency department with acute bronchospasm were eligible for inclusion. Exclusion criteria included pregnancy, pneumonia, congestive heart failure, and need for immediate intubation. The 67 patients studied were similar in most demographic measures; those in the control group, however, were more likely to have a smoking history (74% vs 48%) and had lower baseline peak expiratory flow rates (39.9% vs 49.9% of predicted). These differences were statistically significant, and analyses were adjusted for both characteristics. Other differences noted in baseline characteristics (ie, prior hospitalization or intubation, current theophylline use, and heart rate) were not statistically significant.

Study design and validity A prospective randomized double-blind placebo-controlled design was used. All emergency department patients presenting with acute bronchospasm were given an immediate 2.5 mg nebulized albuterol treatment. Those with peak expiratory flow rates (PEFR) less than 70% of predicted following treatment were eligible for inclusion. All patients received 60 mg oral prednisone at the time of entry into the study. Patients then received either 10 mg per hour of continuous nebulized albuterol plus 1 mg per hour of ipratropium bromide, or albuterol plus saline (control group). Treatment continued for a maximum of 3 hours or until admission or discharge. Reassessment occurred at least hourly, and disposition was determined by the treating emergency department physician. The methodology was impressive, but the statistical significance of the study findings were limited by the small sample size (n = 67).

Outcomes measured The primary outcomes were improvement in PEFR, hospital admission rate, and length of stay in the emergency department. Long-term outcomes, such as length of stay for those hospitalized and rate of return to the emergency department for those discharged, were not evaluated.

Results After adjusting for initial differences in PEFR, combination therapy yielded an overall 6.3% greater improvement over baseline PEFR when compared with controls. Although median length of stay in the emergency department was longer in the control group (245 vs 210 minutes), adjusting for initial PEFR resulted in a nonsignificant difference (P = .26). Combination therapy was no better than albuterol alone in preventing hospitalization (odds ratio = 0.88; 95% confidence interval, 0.28 - 2.8). A nonsignificant trend favoring combination therapy was demonstrated in all 3 primary outcomes. The small sample size, however, reduced the statistical power to detect small but significant differences between the 2 groups. No complications or significant side effects were observed in either group.

Recommendations for clinical practice **Recent guidelines advocating combined use of ipratropium and albuterol in the management of acute bronchospasm[1] are not supported by the results of this study. When added to standard therapy with**

nebulized albuterol, ipratropium did not have a significant impact on PEFR, length of stay in the emergency department, or hospitalization rate. However, an insufficient number of patients were enrolled in this study to demonstrate small differences in outcomes, if they existed. Larger clinical trials are needed to further investigate this widely used therapy.

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REFERENCE

1. National Asthma Education and Prevention Program. Expert panel report II: guidelines for the diagnosis and management of asthma. Bethesda, Md: National Heart, Lung, and Blood Institute and the National Institutes of Health, 1997.

Continuous Terbinafine Versus Intermittent Itraconazole for Toenail Onychomycosis

Evans EG, Sigurgeirsson B. Double-blind, randomised study of continuous terbinafine compared with intermittent itraconazole in treatment of toenail onychomycosis. BMJ 1999; 318:1031-5.

Clinical question **How do continuous terbinafine and intermittent itraconazole compare in efficacy and safety for the treatment of toenail onychomycosis?**

Background Onychomycosis is one of the most common nail diseases, and one of the few that is treatable. Commonly used systemic therapies include terbinafine, which is primarily fungicidal, and itraconazole, which is primarily fungistatic. Because itraconazole persists in therapeutic concentrations after discontinuation of treatment, it is commonly prescribed in a pulse-like manner. This study is the first large-scale double-blind comparison of continuous terbinafine and intermittent itraconazole.

Population studied The study included men and women aged 18 to 75 years from 35 centers in 6 European countries with the clinical diagnosis of onychomycosis. All had involvement of the great toe confirmed by a positive mycologic culture and positive KOH microscopy. Patients were excluded for use of systemic antifungals in the previous 12 months or topical antifungals in the previous 4 weeks, and for drugs or conditions known to interact with the effectiveness or safety of the study drugs.

Study design and validity This was a prospective randomized double-blind multicenter parallel group study lasting 72 weeks that was funded by Novartis, the manufacturer of terbinafine. Patients were randomly allocated to 1 of 4 groups: T_{12}, terbinafine 250 mg (1 tablet) once a day for 12 weeks; T_{16}, terbinafine 250 mg (1 tablet) once a day for 16 weeks; I_3, itraconazole 400 mg (4 capsules) each day for 1 week in every 4 weeks for a 12-week period; and I_4, itraconazole 400 mg (4 capsules) each day for 1 week in every 4 weeks for a 16-week period. Placebo tablets and capsules were used "double dummy" to ensure that all patients took 1 tablet a day for 16 weeks plus 4 capsules a day during the 1st, 5th, 9th, and 13th weeks. The 4 groups were similar regarding mean age, percentage of women, race, number of infected toenails, species of dermatophyte causing infection, proportion of target nail involved, and duration of current episode of infection. Compliance criteria were appropriate and well defined. Results were analyzed on an intention-to-treat basis.

The lack of a control group was a primary limitation, and the reported results contained minimal statistical data. Incomplete explanation was provided for discrepancies between the number of patients used in the tabulation of the final results and the number of patients who completed the study. And treatment other than experimental medication was not delineated. For example, did patients file nails, receive any other confounding medications once the study began, or change hygiene habits? Finally, the evaluation of drug safety did not describe the methods used to collect complaints of side effects and lacked laboratory data to further support safety, such as follow-up monitoring of the initially gathered liver function tests and creatinine levels.

Outcomes measured The primary disease-oriented outcome was mycologic cure at 72 weeks, defined as negative culture and KOH microscopy. The primary patient-oriented outcomes were clinical cure (100% toenail clearing) at 72 weeks, complete cure (mycologic and clinical cure), and clinical effectiveness (mycologic cure and at least 5 mm of new clear toenail growth). Patients and physicians made global assessments of the perceived condition of all affected at weeks 12 and 72; the amount of improvement was rated on a scale from poor to excellent.

Results Of the 496 patients randomized to 1 of 4 treatment groups, 409 completed the study. The authors accounted for all withdrawals. Mycologic cure rates were: T_{12} = 76% (81 of 107); T_{16} = 81% (80 of 99); I_3 = 38% (41 of 107); and I_4 = 49% (53 of 108); $P < .001$. In all other outcomes measured, terbinafine was also shown to be significantly superior (range = $P < .001$ to $P \leq .004$). However, the clinical cure rate was much lower than the mycologic cure rate in all treatment groups: T_{12}, 54% (59 of 110); T_{16}, 60% (59 of 98); I_3, 32% (34 of 107); and I_4, 32% (35 of 109). Therefore,