Combined Ipratropium and β_2–Adrenergic Receptor Agonist in Acute Asthma

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Editors' Note: *This month we continue the new feature - STEPped Care: An Evidence-Based Approach to Drug Therapy. These articles are designed to provide concise answers to the drug therapy questions that family physicians encounter in their daily practice. The format of the feature will follow the mnemonic STEP: safety (an analysis of adverse effects that patients and providers care about), tolerability (pooled drop-out rates from large clinical trials), effectiveness (how well the drugs work and in what patient population[s]), and price (costs of drug, but also cost effectiveness of therapy).*[1] *Hence, the name STEPped Care.*

Since the informatics pioneers at McMaster University introduced evidence-based medicine,[2] *Slawson and colleagues*[3,4] *have brought it to mainstream family medicine education and practice. This feature is designed to further the mission of searching for the truth in medical practice. Authors will provide information in a structured format that allows the readers to get to the meat of a therapeutic issue in a way that can help physicians (and patients) make informed decisions. The articles will discourage the use of disease-oriented evidence (DOE) to make treatment decisions. Examples of DOEs include blood pressure lowering, decreases in hemoglobin* A_{1c}*, and so on. We will include studies that are POEMs - patient-oriented evidence that matters (myocardial infarctions, pain, strokes, mortality, etc) - with the goal of offering our patients the most practical, appropriate, and scientifically substantiated therapies. Number needed to treat to observe benefit in a single patient will also be included as a way of defining advantages in terms that are relatively easy to understand.* [5,6]

At times this effort will be frustrating. Even as vast as the biomedical literature is, it does not always support what clinicians do. We will avoid making conclusions that are not supported by POEMs. Nevertheless, POEMs should be incorporated into clinical practice. The rest is up to the reader. Blending POEMs with rational thought, clinical experience, and importantly, patient preferences can be the essence of the art of medicine.

We hope you will find these new articles useful and easy to read. Your comments and suggestions are welcome. You may contact the editors through the editorial office of JABFP or on the Internet (http://clinic.isu.edu/drugsteps/intro.html). We hope the articles provide you with useful information that can be applied in everyday practice, and we look forward to your feedback.

Rex W. Force, PharmD, STEPped Care Feature Editor
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Asthma is a chronic inflammatory disease of the lungs that afflicts an estimated 13.7 million people in the United States.[1] Approximately 30% of patients with asthma are children.[1] From 1980 to 1994, the prevalence of self-reported asthma more than doubled.[1] The mainstay of asthma management involves prevention of chronic airway inflammation with antiinflammatory drugs, including inhaled corticosteroids, mast cell stabilizers, and leukotriene modifiers. Unfortunately, patients can experience exacerbations of asthma that require acute therapy in either an emergency department or an outpatient clinic. In 1995 there were more

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than 1.8 million emergency department visits for asthma. The estimated number of asthma-related hospitalizations in America increased from 386,000 during 1979 to 1980 to 466,000 during 1993 to 1994.[1]

In the most recently published *Guidelines for the Diagnosis and Management of Asthma*,[2] an expert panel recommended adding nebulized ipratropium to inhaled β_2–adrenergic receptor agonist (β-agonist) therapy for severe asthma exacerbations (forced expiratory volume in 1 second [FEV_1] or peak expiratory flow rate [PEFR] < 50% of predicted). The role of ipratropium in the treatment of acute asthma remains controversial despite numerous studies evaluating the risks and benefits. Because their mechanisms of action are different, combining nebulized β-agonist and anticholinergic therapy theoretically can produce more bronchodilation compared with β-agonist monotherapy.

Some trials have concluded that combined use of ipratropium with β-agonist for acute asthma is beneficial,[3–20] while others have suggested that no further bronchodilation is produced by the combination.[21–27] In addition, the population of patients who might benefit most from combined therapy has not been conclusively determined. Allergens and nonimmunologic stimuli, including cold air, exercise, emotion, and irritants, can activate the vagal reflex arc in airways. Increased cholinergic activity can contribute to the bronchial hyperresponsiveness that develops during viral respiratory illnesses.[28] Seasonal variations in the presence of cholinergic stimuli, such as respiratory viruses, can occur. Most published trials have assessed pulmonary function test results as the primary outcome measure. Only a limited number of studies have provided data that serve as patient-oriented evidence that matters (POEMs), such as reduction in hospital admission rates.[10–12,16,17,19,20,23–27] This article will review the role of the combined use of ipratropium and β-agonist in the treatment of acute asthma by using the STEP approach, focusing on *safety*, *tolerability*, *effectiveness*, and *price*. It will summarize the data obtained from the trials measuring hospital admission rates, as either a primary or secondary endpoint.

Methods

A MEDLINE search was performed for January 1966 to August 1999 using the search terms "ipratropium," "acute asthma," and "acute severe asthma." This search was further limited to human clinical trials published in the English language. Reference lists from studies and review articles were also reviewed for additional primary literature. Studies were selected if they had POEMs as primary or secondary outcomes resulting from the combined use of nebulized ipratropium and β-agonist for the treatment of acute asthma in pediatric and adult patients. Because children often respond differently from adults to some medical treatments, trials conducted in adults are addressed separately from those in children. The number needed to treat (NNT) to prevent one negative outcome was calculated for trials that found a statistically significant difference between treatment groups with regard to hospitalization rates.

Safety and Tolerability

The manufacturer reports adverse effects for ipratropium bromide inhalation solution from 12-week active-controlled clinical trials.[29] The most common adverse effects reported are minor. Many of the reported adverse effects occurred during administration of ipratropium for more than 12 weeks, which might not correlate with side effects observed during acute administration. Temporary blurring of vision, worsening or precipitation of narrow-angle glaucoma, and eye pain have been reported when the solution has come in contact with eyes. Ipratropium solution for inhalation is rated as pregnancy category B, but none of the medications used to treat acute asthma exacerbations has a better safety rating in pregnancy. Safety and efficacy in children younger than 12 years of age have not been established.

In the trials being reviewed for this article, the frequency of adverse effects and subject dropout resulting from side effects from combined therapy generally did not differ from the control group, which received only β-agonist therapy.[10–12,16,17,19,23,24,26,27] The most commonly reported adverse effects occurring in patients receiving combined ipratropium and β-agonist therapy include tremor, agitation, vomiting, increase in pulse, dry mouth, palpitations, headache, dizziness, nausea, chest pain, back pain, and nervousness.[11,12,17,23] Most trials did not report adverse effect rates. In a pooled analysis including 10 trials investigating ipratropium as adjunctive therapy with β-agonist in adults with acute

asthma, no serious adverse effects were associated with any therapy, and ipratropium did not cause more side effects compared with placebo.[30] In a meta-analysis that pooled results of randomized controlled trials of children with acute asthma treated with β-agonist with or without single or multiple doses of inhaled anticholinergic therapy, there was no apparent increase in the incidence of side effects compared with β-agonist alone.[31] In the studies investigating the effects of single or multiple doses of combination therapy and reporting adverse effect frequency, only one or two nebulizer treatments were administered. In clinical practice, inhalation therapy is commonly administered in multiple doses every 20 to 30 minutes, and the incidence of side effects might be higher if ipratropium is given in that manner. When a continuously nebulized albuterol and ipratropium bromide combination was compared with albuterol alone, however, the incidence of tremor was the same for both groups.[27] No arrhythmias or tachycardia was reported. Adverse effects that were noted include emesis, dry mouth, and headache, and they all occurred in the control group.

Effectiveness

Adults

Karpel and colleagues[23] conducted a trial to clarify the role of combination therapy with nebulized ipratropium and albuterol for acute asthma ($FEV_1 \leq 60\%$ of predicted) by measuring FEV_1 as the primary endpoint. Hospital admission rates were reported as a secondary endpoint. Patients (n = 384) were randomized to receive nebulized treatments of albuterol-placebo or albuterol-ipratropium administered 45 minutes apart, and spirometry was performed at baseline and 45 minutes after each treatment. To be included in the study, patients could not have a smoking history of 10 or more pack-years. There was no difference between groups with respect to length of asthma exacerbation before emergency department visit or precipitating factors reported by patients, including allergy, weather, upper respiratory tract infection, and exercise. Following the study treatment period, therapeutic decisions were made by emergency department providers at their own discretion. There was no significant difference between groups with regard to FEV_1 at 45 or 90 minutes of the study.

From subgroup analysis of those patients who had more severe bronchoconstriction ($FEV_1 \leq 1.0$ L), the authors concluded that no advantage resulted from combination therapy. A significant improvement in FEV_1 was defined as a 15% increase above baseline. The number of patients experiencing improved airflow at 45 minutes was significantly higher in the combination group (85%) vs the albuterol monotherapy group (78%) (P = .045). At 90 minutes, a difference between groups was no longer evident. Admission rates to the general hospital ward for the combination therapy and albuterol only groups were 12% and 13% (P = .629), respectively, and the admission rate to the intensive care unit was 1% for both treatment groups (P = .558). Importantly, because specific criteria for admission were not defined, it is difficult to determine whether admission rates were truly affected by the addition of ipratropium.

Another investigation enrolling 254 adults with acute asthma assessed the influence of combination therapy on the primary endpoints of PEFR, admission-discharge ratios, and length of stay in the emergency department.[25] The study was designed in sequential fashion with patients being given three doses of albuterol for the first 3 months of the study. For the final 3 months, patients were given ipratropium with the first albuterol treatment followed by two additional albuterol doses, and one additional ipratropium dose was administered if discharge criteria were not met following initial therapy. Patients met discharge criteria if they were asymptomatic, showed no accessory muscle use, had absent or diminished wheezing, and a PEFR ≥ 60% of predicted. If discharge criteria were not met following nebulizer treatment, patients received parenteral methylprednisolone and aminophylline to avoid admitting the patient to the hospital. The administration of ipratropium did not reduce hospital admissions (28% vs 25%), lengths of stay in the emergency department, or PEFR. The sequential design of the study might have affected the results of the trial because of seasonal variations of precipitating factors. The trigger of asthma exacerbations could have differed among the treatment groups because combination therapy was given during fall and winter months, when cholinergic stimuli, such as respiratory viruses and cold air, are more likely to irritate airways.[28]

FitzGerald and colleagues[24] conducted a trial in 342 adult patients with acute asthma ($FEV_1 \leq 70\%$ of predicted) to evaluate the efficacy of a single treatment of ipratropium-albuterol compared with

albuterol alone. All patients also received intravenous methylprednisolone within 15 minutes of starting nebulizer treatment. Primary endpoints were FEV_1, necessity of supplemental medications at emergency department discharge, and hospital admission. Hospital admission criteria were not defined, and physicians were allowed to treat patients at their discretion after the 90-minute study period. Hospitalization rates and asthma exacerbations between the groups 2 weeks after study completion were similar, but there was a trend toward fewer hospitalizations in the group receiving both ipratropium and albuterol (5.9% vs 11.2%, NS). Both groups experienced a significant improvement in mean change in FEV_1 from baseline, but there was no statistical difference between the groups. When the authors conducted a subanalysis of the patients with more severe bronchoconstriction (data not provided), even less difference between groups was shown, which differs from conclusions from the previous trial by Rebuck et al.[8]

A subsequent study evaluated the use of ipratropium with β-agonist for acute asthma using a very similar study design. Garrett and colleagues[10] enrolled 338 adult patients with acute asthma ($FEV_1 \leq 70\%$ of predicted) to evaluate the efficacy of a single nebulizer treatment of ipratropium and albuterol compared with albuterol alone. All patients also received intravenous hydrocortisone within 15 minutes of starting treatment, but no other medications were allowed during the study. The primary endpoint for this trial was change in FEV_1 at 90 minutes, and secondary endpoints were admission rates and adverse effects. There was a trend toward fewer hospitalizations in the ipratropium-albuterol group (15% vs 23%), but the difference was not statistically significant.

Combination therapy with ipratropium and albuterol produced a greater effect on FEV_1 than albuterol alone. The mean absolute difference plus or minus the standard error of the mean in change in FEV_1 between groups favored the combination therapy group by 93 ± 24 mL ($P = .03$) at 45 minutes and 113 ± 18 mL ($P = .02$) at 90 minutes. Based on these data, it appears that most of the airflow improvement was evident by 45 minutes following the single ipratropium dose. The authors also performed a subgroup analysis by separating patients into two groups, initial $FEV_1 < 1$L vs $FEV_1 \geq 1$L. Interestingly, in the group with less severe airflow obstruction, patients receiving combination therapy had a greater increase in FEV_1 from baseline at 90 minutes of 522 ± 44 mL compared with 346 ± 38 mL ($P < .005$) for patients receiving albuterol only. In the subgroup with more severe airflow obstruction, there was no difference between groups in the change in FEV_1 at 90 minutes. The authors of this study also found that patients who consumed more inhaled β-agonist before coming to the emergency department had an unexplainable smaller increase in FEV_1 after administration of ipratropium-albuterol compared with albuterol alone.

In a trial evaluating the use of nebulized ipratropium in combination with nebulized albuterol, 55 adult patients with asthma who came to the emergency department with an acute exacerbation (PEFR<200 L/min) were enrolled.[11] Primary endpoints were changes in PEFR and in percentage of predicted PEFR; admission rate was assessed as a secondary endpoint. The results from this trial suggest that administering a single dose of ipratropium with the first nebulizer treatment of albuterol, followed by two additional doses of albuterol, reduced the need for hospital admission compared with three doses of albuterol alone (11% vs 36%; 95% CI, 3%–46%, $P = .03$). Criteria for hospital admission included any of the following after treatment: accessory muscle use, respiratory rate >24/min, arterial blood Pco_2 >44 mm Hg, arterial blood Po_2 (on room air) <70 mm Hg, associated diseases such as pneumonia or febrile illness >38.8°C (102°F), and failure to show improvement after 5 to 6 hours of observation with associated fatigue and shortness of breath with exertion. One limitation of this study is that the treatment groups were different with respect to duration of acute symptoms before coming to the emergency department. The albuterol group had a mean (±SD) duration of symptoms of 4.1 (±4.6) days and the combination group 1.7 (±2.3) days, but after adjustments were made for multiple comparisons, the difference does not appear to be statistically significant.

Physicians were permitted to administer parenteral methylprednisolone to patients if they believed the patients were not adequately responding to nebulizer therapy. In the albuterol group, 32% received methylprednisolone, whereas 15% in the albuterol-ipratropium group received corticosteroid therapy (95% CI, 5%–39%, $P = .13$). The difference in corticosteroid administration might

also be a confounding variable when interpreting the results. It is possible that the albuterol-only group included patients with more severe exacerbations because more patients required parenteral corticosteroids during the exacerbation. When patients receiving parenteral corticosteroids before or at 40 minutes into the protocol were excluded from analysis, however, greater improvement was still seen in the combination therapy group. No patients had pneumonia or fever (temperature >38.8°C), which were both criteria for admission. Recent oral prednisone therapy was reported by 5 of 28 patients in the albuterol-alone group and 7 of 27 in the combination therapy group. In addition, approximately 46% and 40% of patients receiving albuterol alone and combination therapy, respectively, reported steroid inhaler use. Patients receiving combination treatment experienced greater increases in PEFR and percentage of predicted PEFR during the study period ($P \leq .001$) compared with the monotherapy group. The NNT to prevent one hospital admission was calculated to be 4 for this trial.

A randomized, controlled trial comparing continuously nebulized albuterol and ipratropium bromide with albuterol alone investigated the effect of treatment on pulmonary function (PEFR, percentage of predicted), length of stay in the emergency department, and hospital admission rates in 67 adults.[27] Patients were enrolled if they came to the emergency department with acute bronchospasm with a PEFR < 70% of predicted following an initial nebulized dose of albuterol. Exclusion criteria included pregnancy, pneumonia, congestive heart failure, or the need for immediate intubation. All patients received prednisone 60 mg orally. Patients were randomized to receive continuous nebulizer treatment with either the combination of ipratropium bromide 1 mg/h and albuterol 10 mg/h or albuterol 10 mg/h alone for a maximum of 3 hours.

Of the 67 patients included in analysis, 85% had asthma and 15% had chronic obstructive pulmonary disease. At baseline, the albuterol-alone group had more patients with a history of smoking (74% vs 48%, $P = .05$) and a lower baseline PEFR percentage of predicted (39.9 ± 10.3% vs 49.9 ± 12.7%, $P = .001$). Statistical analysis was adjusted only for the difference in PEFR because smoking history did not affect the results. The combination therapy group experienced a 6.3% (95% CI, 15%–27%) greater improvement in PEFR from baseline compared with the albuterol-alone group. Improvement in PEFR was not statistically significant between the treatment groups at any time during the study. Length of stay in the emergency department was shorter for the combination group (210 vs 245 minutes, $P = .03$), but the difference was not statistically significant when adjusted for baseline PEFR differences. Hospital admission rate for the combination therapy group was 23% and for the albuterol-alone group was 39%. The odds ratio for admission for the combination therapy group was 0.88 (95% CI, 0.28–2.8) after adjustment for baseline PEFR. In addition, there were no differences detected between treatment groups with regard to secondary endpoints, including improvements in respiratory rate, heart rate, and Borg dyspnea score. When analysis was performed separately on the subset of patients (n = 57) with the diagnosis of asthma, no difference was found in the primary outcomes compared with the entire group.

Investigators of trials previously reviewed in this article conducted a pooled analysis of randomized, double-blind trials[10,23,24] studying the efficacy of combined ipratropium and albuterol for the treatment of acute asthma in adults.[32] The studies collectively randomized 1064 patients from the United States, Canada, and New Zealand to receive either albuterol plus ipratropium or albuterol alone. The combination therapy group showed greater improvement in FEV_1 of 43 mL (CI, 20–107) at 45 minutes and 47 mL (CI, 28–122) at 90 minutes, but the differences were not statistically significant. Among patients reporting upper respiratory tract symptoms, those receiving combination therapy experienced a greater increase in FEV_1 of 83 mL (95% CI, 10–156) at 45 minutes and 105 mL (95% CI, 17–194) at 90 minutes compared with the control group. POEM data, including risk of hospitalization and asthma exacerbation within 48 hours and need for additional treatment in the emergency department after completion of the study protocol, were analyzed. Individually, none of the trials showed a statistically significant difference in the hospitalization rate between the two treatment groups. In the pooled analysis, combination therapy lowered the risk of hospitalization by 20% (risk ratio [RR]=0.80, 95% CI, 0.61–1.06), risk of asthma exacerbation by 16% (RR = 0.84, 95% CI, 0.67–1.04), and need for further asthma therapy by 8% (RR = 0.92, 95% CI, 0.84–1.00).

Although the authors concluded that the combination therapy group had lower risk for each of the clinical outcomes, the difference is not statistically significant for risk of hospitalization and asthma exacerbation.

Ten randomized, double-blind, placebo-controlled trials were included in a meta-analysis of adults with acute asthma exacerbations treated with ipratropium as adjunctive therapy with β-agonists.[30] Only 3 of the studies, the same trials included in the meta-analysis reviewed above,[32] reported hospitalization rates.[10,23,24] The 1064 patients receiving ipratropium added to β-agonist therapy in those 3 trials had a relative risk of hospital admission of 0.73 (95% CI, 0.53–0.99), which differs from the findings of the other meta-analysis.[32]

Children

The earliest study that reported hospital admission rate data, as a secondary endpoint, in children with acute asthma receiving ipratropium plus albuterol or albuterol alone was published by Beck and colleagues.[12] Twenty-eight children 6 years of age or older with $FEV_1 < 50\%$ of predicted were enrolled in this trial. One treatment group received nebulized albuterol as a loading dose followed by doses given every 20 minutes for six additional doses. The other group received the same regimen with the addition of nebulized ipratropium 0.25 mg administered with the albuterol at 60 minutes (the albuterol-only group received 1 mL normal saline). During the first 60 minutes of the study, both groups had similar changes in FEV_1. After 1 hour, FEV_1 rose an additional 21% in the combination group, while it rose only 4% in albuterol-only group ($P < .05$). Despite the apparent improvement in airflow with combined nebulizer treatment, there was no difference between groups with regard to hospital admission or relapse rates (stated by authors).

Schuh and colleagues[16] published a three-arm, placebo-controlled trial that included 120 children aged 5 to 17 years who came to the emergency department with acute severe asthma evidenced by baseline $FEV_1 < 50\%$ of predicted. All patients received three doses of albuterol nebulized every 20 minutes. One group received three doses of nebulized ipratropium 0.25 mg in combination with albuterol (group 1). Another group received only one ipratropium dose (group 2), and the final group received none (group 3). To avoid confounding factors, corticosteroids and other bronchodilators were not given during the study period. The primary outcome measure was the percentage of change in predicted FEV_1. Secondary outcome measures included changes in accessory muscle score, wheeze score, dyspnea score, respiratory rate, heart rate, oxygen saturation, and overall score. POEM data in the form of hospitalization rates were also reported even though these data were not described as primary or secondary outcome measures. At 120 minutes, the mean percentage of improvement in FEV_1 from baseline was 33% to 57% in group 1, from 34% to 52% in group 2, and from 35% to 48% in group 3 ($P = .0001$ for all groups). The authors also analyzed a subgroup of those patients with baseline $FEV_1 < 30\%$ predicted, and more dramatic responses to intervention were detected. The mean percentage of improvement in FEV_1 from baseline was 25% to 51% in group 1, from 25% to 40% in group 2, and from 26% to 37% in group 3 ($P = .0001$ for all groups). Overall, there was no difference in admission rates among groups. In contrast, for the subgroup with baseline $FEV_1 < 30\%$ of predicted, admission rates were 27% in group 1, 56% in group 2, and 83% in group 3 ($P = .027$ for all groups).

From this trial in children, it appears that ipratropium in combination with albuterol in repeated doses can improve airflow more than albuterol alone when baseline FEV_1 is less than 50% predicted. In addition, children with very severe airflow obstruction ($FEV_1 < 30\%$) might be admitted less frequently when given multiple doses of combined nebulized ipratropium and albuterol. The NNT to prevent one hospital admission for the subgroup with baseline $FEV_1 < 30\%$ was calculated to be 2 for the patients receiving three doses of ipratropium-albuterol and 4 for the group receiving a single dose of ipratropium with multiple doses of albuterol compared with standard albuterol only.

Another published trial investigating the effect of adding ipratropium to albuterol in children enrolled 90 patients who were 6 to 18 years of age with acute asthma (PEFR < 50% of predicted).[11] The primary outcomes were change in percentage of predicted PEFR, change in percentage of predicted FEV_1, hospitalization rate, and adverse effects. One treatment group received only albuterol 0.15 mg/kg nebulized every 30 minutes for three

doses. The other group received ipratropium 0.5 mg nebulized every 60 minutes for two doses in addition to the previously described albuterol regimen. All patients were given oral corticosteroids. At baseline, the two treatment groups were different with regard to PEFR and FEV_1, but the authors adjusted for this difference in their statistical analysis. When examining PEFR response, there was a difference between groups, favoring the combination therapy, beginning at 60 minutes, which lasted through the end of the study period (120 minutes). With respect to FEV_1, the two groups were similar until the 120-minute assessment. The lack of correlation between FEV_1 and PEFR response was not explained by the authors. The percentage of patients admitted in the combination therapy group was 20%, whereas 31% of patients in the albuterol-alone group were admitted ($P = .33$).

A randomized, double-blind, placebo-controlled trial examined the effect of nebulized ipratropium added to albuterol therapy in 434 pediatric patients 2 to 18 years of age with acute asthma exacerbations.[19] The primary outcome of this investigation was hospitalization rate. Secondary outcomes were time to disposition, number of nebulizer treatments, PEFR, oxygen saturation, number of patients seeking medical care within 72 hours after discharge, disposition location, and change in severity according to asthma score. The asthma score uses respiratory rate, oxygen saturation, auscultation findings, extent of retractions, and severity of dyspnea to rate asthma severity in young children unwilling or unable to perform PEFR measurement accurately. A higher asthma score (15-point scale) indicates a more severe asthma exacerbation. Moderate asthma was defined as PEFR 50% to 70% of predicted or an asthma score of 8 to 11. Severe asthma was defined as PEFR < 50% of predicted or an asthma score of 12 to 15. Patients were enrolled in the study if their exacerbations were moderate or severe. All patients received nebulized albuterol every 20 minutes for three doses and were administered a corticosteroid (prednisone or prednisolone) orally with the second dose of albuterol. The treatment group was given nebulized ipratropium bromide 0.5 mg with the second and third doses of albuterol, and the control group received normal saline. The attending physician decided to admit patients based on objective changes in clinical measurements, PEFR, and oxygen saturation.

There were more female patients in the treatment group compared with the control group (48% vs 38%, $P = .04$). The rate of hospitalization was lower in the treatment group compared with the control group (27.4% vs 36.5%, $P = .05$). The NNT to prevent one hospital admission was calculated to be 11 for the patients receiving the combination of ipratropium-albuterol compared with placebo-albuterol. When analyzing only patients who had moderate asthma exacerbations, no difference in hospitalization rates was detected. In contrast, for the subset of patients with severe asthma, the treatment group had a lower admission rate compared with the control group (37.5% vs 52.6%, $P = .02$). The NNT to prevent one hospitalization was reported as 6.6 (95% CI, 3.7 to 29.4) for children with severe asthma treated with the combination of nebulized ipratropium and albuterol compared with the control group. Regarding secondary outcomes that serve as POEMs (number of patients seeking medical care within 72 hours after discharge and disposition location), there was no difference found between treatment groups.

The hospital admission rate results of this trial differed from the findings of the previous study conducted by Qureshi and colleagues.[17] Both trials were designed similarly, but the most prominent difference is that the more recent trial enrolled patients with all levels of asthma severity while the previous study included patients with acute severe asthma (PEFR<50% of predicted). It was postulated that a type II error resulted in not finding a reduction in hospital admission rates. The follow-up trial did enroll a larger number of patients (434 vs 90), and 271 of the patients were considered to have acute severe asthma. The larger number of patients enrolled in this trial might have reduced the likelihood of a type II error.

A randomized, controlled trial in 275 pediatric patients, 3 to 17 years of age, with mild to moderate asthma exacerbations investigated the safety and efficacy of nebulized albuterol and ipratropium bromide in a 2 × 2 factorial design.[26] Children were excluded if they had severe asthma requiring continuous nebulized albuterol or immediate therapy before baseline lung function could be documented. Patients were randomized to receive one of four different treatment regimens. Patients were administered either high-dose albuterol (0.15 mg/kg every hour) or frequent low doses of albu-

terol (0.075 mg/kg every 30 minutes). Patients were also randomized to receive one dose of ipratropium bromide 0.25 mg or placebo at 30 minutes. Regardless of treatment arm, patients received a nebulized treatment every 30 minutes for a minimum of 60 minutes. The protocol continued until a disposition decision was made, but no additional ipratropium was administered. Corticosteroid and theophylline therapy was allowed and recorded. The primary outcome was change in pulmonary function, measured as respiratory resistance by forced oscillation at 8 Hz (Rfo_8). Secondary endpoints included hospital admission, relapse (second unscheduled visit for asthma exacerbation) within 10 days, oxygen saturation, and corticosteroid use. Overall, no group differences were detected in primary or secondary outcomes. The investigators examined the subset of patients with rhonchi and cough, which were considered to be signs and symptoms of a prominent cholinergic component to airway obstruction. This subgroup did not show a greater response to ipratropium therapy compared with those patients without rhonchi or cough. It was previously shown that adding ipratropium to albuterol might produce more benefit in children with more severe asthma exacerbations.[16] In this trial, no improvement was seen in any of the outcomes, but only patients with mild to moderate asthma were enrolled.

Zorc and colleagues[20] conducted a double-blind, randomized, controlled trial of ipratropium added to nebulized albuterol and oral corticosteroid in 427 pediatric patients older than 12 months with acute asthma. All patients received nebulized albuterol every 20 minutes for 3 doses and a single oral dose of corticosteroid within 1 hour. Patients randomly received either placebo or ipratropium 0.25 mg added to the first nebulized dose of albuterol. Outcomes included time to discharge, number of nebulizer treatments required before discharge, and hospital admission rate. Patients were excluded if they were pretreated with corticosteroids (within 3 days) or ipratropium (within 24 hours), exhibited signs of respiratory failure, or required therapy with continuous albuterol or subcutaneous epinephrine or terbutaline. Patients with a history of glaucoma, cystic fibrosis, or sickle cell disease were also excluded. Clinical severity scores for accessory muscle use, wheezing, and dyspnea were determined by the enrolling physician for each child. The severity groups were mild (1–3), moderate (4–6), and severe (7–9). The hospital admission rate of 18% for the combination therapy group was not different from the rate of 22% for the control group ($P = .3$). Patients were discharged from the emergency department 28 minutes faster in the combination therapy group compared with control ($P = .001$). The median number of albuterol doses given before emergency department discharge was four for the control group compared with three for the ipratropium treated group ($P < .01$). There was no difference between groups with regard to number of patients returning to the emergency department within 72 hours (2 control vs 4 ipratropium; $P = .38$). The hospitalization rate was not significantly different between treatments when grouped by severity. When combining patients whose severity score was moderate or severe, the hospitalization rate was 8% lower in the combination therapy group (odds ratio = 0.64, 95% CI, 0.36–1.15), which is not statistically significant. Patients receiving ipratropium who were discharged from the emergency department were more likely to be assigned to a lower level of care ($P < .05$) compared with the control group, which corresponded to a $36 lower mean hospital charge per patient.

Ten randomized controlled trials were included in a meta-analysis of children with acute asthma treated with a β-agonist with or without single or multiple doses of an inhaled anticholinergic agent.[31] It was concluded that the addition of a single dose of inhaled anticholinergic agent to β-agonist therapy did not reduce hospital admission rates (relative risk 0.93, 95% CI, 0.65–1.32). The results differed when pooled data from studies adding multiple anticholinergic doses to inhaled β-agonist therapy were analyzed. It appears that adding multiple doses of an inhaled anticholinergic to therapy for pediatric patients, particularly those with severe exacerbations, reduces hospital admission rates by 30% (relative risk 0.72, 95% CI, 0.53–0.99). According to this meta-analysis, treating 11 pediatric patients with severe asthma with combination therapy (multiple anticholinergic doses) prevents 1 hospitalization (95% CI = 5–250).

Table 1 displays the selected outcomes for adults and children from the clinical trials of combined ipratropium and β-agonist compared with β-agonist alone.

Table 1. Selected Outcomes from Clinical Trials of Combined Ipratropium and β-Adrenergic Receptor Agonist Compared With β-Agonist Alone.

Study (year)	Outcome	Significance	NNT
Adults			
Karpel (1996)[23]	HAR (general ward) 12% (IP + A) vs 13% (control)	$P = .629$	
	HAR (ICU): 1% for both IP + A and control	$P = .558$	
McFadden (1997)[25]	HAR 28% (IP + A) vs 25% (control)	$P = .3$	
	ED LOS	$P = .37$	
Fitzgerald (1997)[24]	HAR 6% (IP + A) vs 11% (control)	NS	
Garrett (1997)[10]	HAR 15% (IP + A) vs 23% (control)	NS	
Lin (1998)[11]	HAR 11% (IP + A) vs 36% (control)	95% CI for difference, 3%, 46% $P = .03$	4
Weber (1999)[27]	HAR 23% (IP + A) vs 39% (control)	OR = 0.88, 95% CI, 0.28, 2.8 (NS)	
	ED LOS 210 min (IP + A) vs 245 min (control)	$P = .03$	
	ED LOS adjusted for initial PEFR	NS	
Children			
Beck (1985)[12]	HAR	NS	
	Relapse rates	NS	
Schuh (1995)[16]	HAR (overall)	NS	
	HAR ($FEV_1 \leq 30\%$): 27% (IP × 3 doses + A)	$P = .027$ for all groups	2
	56% (IP × 1 dose + A)		4
	83% (control)		
Qureshi (1997)[17]	HAR 20% (IP + A) vs 31% (control)	$P = .33$	
Qureshi (1998)[19]	HAR (overall) 27% (IP + A) vs 36.5% (control)	$P = .05$	11
	HAR (severe) 38% (IP + A) vs 53% (control)	$P = .02$	6.6
	Number seeking medical care within 72 h	NS	
	Disposition location	NS	
Ducharme (1998)[26]	HAR	NS	
	Relapse within 10 days	NS	
Zorc (1999)[20]	HAR 18% (IP + A) vs 22% (A)	$P = .33$	
	ED LOS 185 ± 69 min (IP + A) vs 213 ± 82 min (control)	$P = .001$	
	Relapse within 72 hours 4% (IP + A) vs 2% (control)	$P = .38$	

NNT = number needed to treat, HAR = hospital admission rate, IP + A = combination therapy with ipratropium and albuterol, ICU = intensive care unit, ED LOS = length of stay in emergency department, PEFR = peak expiratory flow rate, FEV_1 = forced expiratory volume in 1 sec, CI = confidence interval, OR = odds ratio.

Price

The cost of several doses of ipratropium administered by nebulizer is small when compared with the cost of a hospital admission. The cost of a single adult dose of ipratropium 0.02% inhalation solution (2.5 mL) is approximately $1.75 (AWP).[33] Because ipratropium solution for inhalation can be mixed with albuterol solution for inhalation, using the combination of agents does not contribute to an increase in cost of administration secondary to personnel required to give the treatments.

Summary

Table 2 displays the drug STEPs overview. For the treatment of acute episodes of bronchoconstriction associated with asthma, ipratropium should not be used as monotherapy because it has a slower onset of action than β-agonists and only reverses cholinergically mediated bronchoconstriction.[2] Despite the relatively large number of studies that have been published evaluating the use of inhaled ipratropium in combination with β-agonist for acute asthma, its role continues to remain unclear. Current expert panel guidelines, however, recommend adding nebulized ipratropium to inhaled β-agonist therapy for severe asthma exacerbations.[2] Ipratropium appears to be a safe and well-tolerated agent as an adjunct to treating acute asthma exacerbations. In conclusion, based on clinical trials, the benefit of adding nebulized ipratropium to β-ago-

Table 2. Drug STEPs Overview.

Safety and tolerability	Ipratropium is well tolerated and safe. In clinical trials, adverse effect frequency and dropout rate are essentially no greater than for albuterol alone
Effectiveness	Benefit of adding nebulized ipratropium to albuterol for acute asthma is unclear. Trial in adults with the best design showed improvement in airflow and reduction in admission rates. Combination therapy reduced hospitalizations in children with very severe (FEV_1<30%) exacerbations of asthma. Trials enrolling children consistently show improvement in airflow measurements
Price	Ipratropium inhalation solution for nebulization costs approximately $1.75 per dose. No studies on cost-effectiveness have been conducted
Summary	Administering combined nebulized ipratropium and β-agonist in asthmatics with PEFR or FEV_1 <50% of predicted might result in increased airflow and fewer admissions, but further well-designed studies investigating impact on hospitalization rates and subjective parameters, such as symptom improvement and a patient's perception of whether ipratropium is beneficial, need to be conducted

FEV_1 = forced expiratory volume in 1 sec, PEFR = peak expiratory flow rate.

nist for acute asthma in adults remains uncertain. Administration of combination therapy might improve airflow and reduce admissions without increasing the risk of adverse events. Combination therapy with ipratropium and β-agonist might be of particular benefit in pediatric patients given that it showed reduced hospital admission rates in children with acute asthma in two trials.[16,19]

The Guidelines for the Diagnosis and Management of Asthma state that ipratropium should be administered to adults or children experiencing acute severe asthma exacerbations ($PEFR/FEV_1 < 50\%$ predicted) coming to the emergency department or outpatient clinic.[2] If ipratropium is used, it should be given in combination with albuterol by nebulizer. Adults should be administered ipratropium 0.5 mg with albuterol 2.5 to 5 mg every 20 minutes for three doses followed by ipratropium 0.5 mg every 2 to 4 hours and albuterol 2.5 to 10 mg every 1 to 4 hours as needed. Children should be administered ipratropium 0.25 mg with albuterol 0.15 mg/kg every 20 minutes for three doses then ipratropium 0.25 mg every 2 to 4 hours and albuterol 0.15 to 0.3 mg/kg every 1 to 4 hours. After the patient attains ≥ 70% of the predicted $PEFR/FEV_1$, ipratropium should be discontinued. It might take up to 2 hours for ipratropium to reach its maximal effect on $PEFR/FEV_1$. In addition, systemic corticosteroid therapy should also be started when a patient comes to the emergency department or clinic with acute severe asthma.

The desired outcome of this approach is to avoid admitting the patient to the hospital, to improve the patient's quality of life, and to improve patient's satisfaction with health care. Issues that have not sufficiently been addressed in clinical trials are subjective parameters, such as symptom improvement and a patient's perception of whether ipratropium is beneficial. Further trials enrolling patients with $PEFR/FEV_1 < 50\%$ need to be conducted because most cases of adult asthma studied in clinical trials to date were not defined as severe. Ideally, it would be best to determine which patients show a response to ipratropium administration, and continue to use this adjunctive drug in those selected patients.

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