

Nebulized salbutamol with and without ipratropium bromide in the treatment of acute asthma

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Background: Routine addition of ipratropium bromide to β -agonist therapy in acute asthma is of uncertain benefit. **Objective:** This study was carried out to evaluate: (1) whether nebulized ipratropium (0.5 mg) plus salbutamol (2.5 mg) (Combivent) confers additional bronchodilation over nebulized salbutamol (2.5 mg) alone in patients with acute asthma and (2) whether adjustment for prognostic indicators of outcome influences any benefit seen with ipratropium.

Methods: A double-blind, two-center, randomized, single-dose study was performed in 338 patients with asthma, aged 18 to 55 years, who attended the emergency department for treatment of acute asthma. The primary end point was FEV₁ at 90 minutes.

Results: The mean absolute difference in FEV₁ at 90 minutes for Combivent compared with salbutamol was 113 ml (SEM \pm 48 ml, $p < 0.05$). Independent of the study drug received, a poor response to treatment was predicted by frequent use of inhaled β -agonist before presentation ($p < 0.0001$), severity of the attack ($p < 0.05$), and longer duration of attack ($p < 0.05$). Subjects who had taken more than 10 puffs of inhaled β -agonist through a metered-dose inhaler or who had serum salbutamol levels of greater than 2 mmol/L on presentation demonstrated no benefit from the addition of ipratropium. Patients with an FEV₁ less than 1 L on presentation also responded less well to Combivent, which was explained by the association between severity of attack and greater use of inhaled β -agonist therapy.

Conclusion: A single dose of nebulized Combivent confers additional bronchodilation over salbutamol alone ($p < 0.05$) in acute asthma. Patients who exhibited most benefit from the addition of ipratropium were those who had consumed the least inhaled β -agonist before presentation, not those with the most severe asthma. (*J Allergy Clin Immunol* 1997; 100:165-70.)

Key words: Ipratropium bromide, salbutamol, acute severe asthma

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Abbreviations used

ANCOVA:	Analysis of covariance
Δ FEV ₁ 90:	Change in FEV ₁ at 90 minutes
ED:	Emergency department
PEF:	Peak expiratory flow

International guidelines recommend nebulized β -agonist therapy and corticosteroids in the management of acute severe asthma.^{1,2} Anticholinergic drugs can be added to β -agonists as initial therapy, particularly for patients with a severe episode,² or later if the therapy fails. Several studies indicate that additional bronchodilation can be achieved by adding ipratropium bromide to salbutamol (albuterol) or fenoterol,³⁻¹¹ though in only four studies was this found to be statistically significant.¹² Three studies have shown that patients with more severe asthma (FEV₁ < 1 L,^{6,13} peak expiratory flow [PEF] < 140 L/min⁴) benefit most from the addition of ipratropium to β -agonist therapy.

The aim of this study was to evaluate the effects of nebulized ipratropium bromide solution in combination with salbutamol sulfate (Combivent) in patients with acute asthma, first seen in the emergency department (ED), to determine whether ipratropium augments the bronchodilator effect of a single dose of salbutamol. Those factors that best predicted extra benefit from the addition of ipratropium were determined, specifically to assess whether the greatest improvement occurred in patients with the most severe asthma at presentation.

METHODS

Two New Zealand EDs participated in a double-blind, randomized, active-controlled, parallel-group study comparing the bronchodilating effect of a fixed combination of nebulized ipratropium (0.5 mg) and salbutamol (2.5 mg) (Combivent) with nebulized salbutamol (2.5 mg) alone in patients with acute severe asthma.

Patients

Study participants were recruited from among patients with asthma who attended the two participating EDs. Inclusion criteria were: age between 18 and 55 years, provision of witnessed informed consent, ability to perform an adequate forced expiratory maneuver, and an FEV₁ of less than 70% of predicted value. Exclusion criteria were: smoking history of more than 10 pack-years, complicating medical illnesses such as chronic obstructive pulmonary disease (American Thoracic

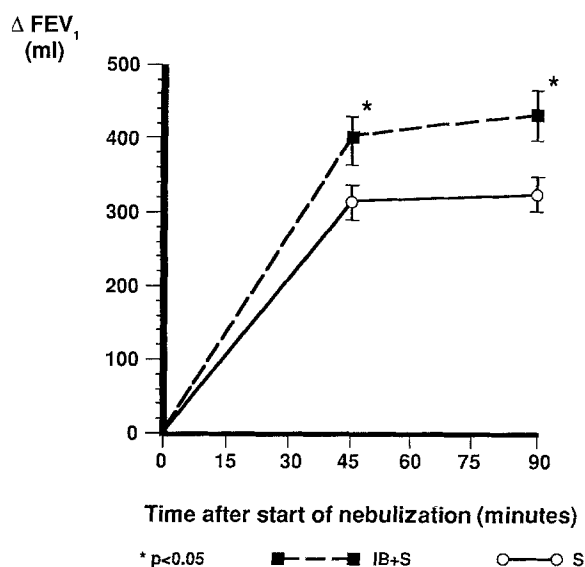


FIG. 1. Change in FEV₁ from baseline at 45 minutes and 90 minutes when comparing Combivent with salbutamol.

Society criteria),¹⁴ pneumonia, pneumothorax, myocardial infarction, congestive heart failure, glaucoma, or hepatic or renal impairment. Pregnant women and nursing mothers were excluded, as were patients requiring medications other than the study drugs to treat the acute attack of asthma. Patients who had been previously recruited into the study were also excluded. Patients were not excluded if they had received nebulized bronchodilator in the 6 hours before presentation. The study was approved by the human ethics committee at each center and conducted according to the Declaration of Helsinki, Hong Kong 1989.

Treatment regimens

Indistinguishable unit dose vials of 2.5 ml were developed for the Combivent and salbutamol solutions. Salbutamol sulfate (3.0 mg, equivalent to 2.5 mg of salbutamol base) solutions were used. The solutions were given through a Hudson nebulizer/mask (Type Baxter Airlife 001206, Baxter Healthcare), driven by oxygen at a flow rate of 6 L/min until completely nebulized. All patients received intravenous hydrocortisone, 200 mg, within 15 minutes of the start of treatment. No other medication was given during the study period, unless the ED doctor deemed it essential, at which stage patients ended their participation in the study after an additional FEV₁ value was determined. Isotonic intravenous fluid was given if needed.

Measurements

Demographic data collected on entry into the study were age, gender, height, and race. Clinical data including smoking history, asthma history, history of first attack, usual medications used by the patient and those taken within the 6 hours before presentation were also recorded. Blood was drawn for measurement of baseline serum theophylline, salbutamol, and potassium and for a complete blood count. Theophylline levels were determined by using a high-pressure liquid chromatographic method, and salbutamol levels were determined by using a gas chromatographic mass spectrometric method with deuterated salbutamol as an internal standard. Immediately before and 45 and 90 minutes after the start of nebulizer treatment, spiromet-

TABLE I. Demographic and clinical characteristics of study populations

Characteristics*	Ipratropium bromide + salbutamol (n = 171)	Salbutamol (n = 167)
Age (yr)	29.5 (0.7)	29.6 (0.8)
Duration of asthma (yr)	17.0 (0.7)	17.7 (0.7)
No. ED visits asthma past year	0.9 (0.1)	1.2 (0.2)
Saw doctor earlier in attack (%)	31%	33%
Concurrent nights awoken with asthma before presentation	1.5 (0.3)	1.4 (0.2)
Time from onset of attack until ED attendance (hr)	26.2 (2.9)	32.2 (4.3)
Baseline FEV ₁ (L)	1.41 (0.04)	1.37 (0.04)
Predicted FEV ₁ (%)	39.7 (1.0)	39.6 (1.0)
Current smokers (%)†	31.6	32.9

*Defined as mean ± SEM or as percentage.

†Patients with smoking history of more than 10 pack-years were excluded.

ric measurements were obtained with a rolling-seal spirometer linked with an IBM XT microcomputer (Spirotech Model A5155). Quality control of lung function testing was achieved by using a program similar to that used in the North American Lung Health Study.¹⁵ The best FEV₁ of three consecutive efforts was used. Patients were coached to achieve a PEF time of less than 85 msec and were only accepted into the study if two FEV₁ values were within 5% or 100 ml of each other. Predicted normal spirometric values¹⁶ with an adjustment made for Maori and Pacific Island patients (based on the study by Macfie et al.¹⁷) were used. Respiratory rate, heart rate, and blood pressure were recorded. Oxygen saturation was recorded by Miniox pulse oximeter with finger probe. Any side effects of therapy were elicited.

Statistical analysis

The primary efficacy analysis used absolute change in FEV₁ at 90 minutes (Δ FEV₁ 90) after commencement of nebulization between the two treatment groups. According to protocol, the method of last observation carried forward was used to impute Δ FEV₁ 90 in those patients who were withdrawn from the study. It was calculated that a study size of at least 326 assessable patients was necessary to achieve 90% statistical power to detect a 150 ml difference in FEV₁ from baseline between the two treatment groups, assuming a standard deviation of 0.4175 L (based on overall response in FEV₁ in patients with asthma from a previous study).⁶

A formal analysis of covariance (ANCOVA) was used to separate the treatment effect (i.e., the addition of ipratropium) from other factors that might influence outcome (Δ FEV₁ at 90 minutes). Covariates used in the statistical model included baseline FEV₁, age, use of medications 6 hours before ED presentation, and time between onset of attack and ED attendance as incorporated in the objective of the study. ANCOVA models examined the statistical significance of the covariates when all are included in the model, when included separately

TABLE II. ANCOVA results

ANCOVA model no.	IB + S vs S	Baseline FEV ₁	Age	Duration of attack	Covariates				
					Asthma medications in previous 6 hours				
					Inhaled β-agonist	Inhaled IB	Oral theophylline	Inhaled steroid	Oral steroid
1	0.02	0.0007	—	—	—	—	—	—	—
2	0.02	—	0.05	—	—	—	—	—	—
3	0.04	—	—	0.02	—	—	—	—	—
4	0.08	—	—	—	0.0001	—	—	—	—
5	0.03	—	—	—	—	0.01	—	—	—
6	0.03	—	—	—	—	—	0.2	—	—
7	0.02	—	—	—	—	—	—	0.8	—
8	0.03	—	—	—	—	—	—	—	0.13
9	0.21	0.01	0.08	0.02	0.0001	0.12	0.52	0.12	0.9
10	0.16	0.01	0.07	0.02	0.0001	—	—	—	—

Probability (*p*) values are adjusted for prior asthma medication and baseline measurements on ΔFEV₁ 90 from adding ipratropium to 2.5 mg of salbutamol. The analysis identified baseline FEV₁, age, β-agonist use within 6 hours, and duration of attack as having a significant impact on response to therapy. Of these, only β-agonist use within 6 hours had any effect on the benefit of adding IB to S (reduced to *p* = 0.08).

IB, Ipratropium bromide; S, salbutamol.

on outcome (ΔFEV₁), and on the differential effect of Combivent versus salbutamol on ΔFEV₁ 90.

Further analyses were then undertaken to assess the effects of: (1) serum theophylline and serum salbutamol levels in patients taking these medications; (2) an FEV₁ < 1 L and FEV₁ ≥ 1 L on attendance; and (3) inhaled β-agonist use in the previous 6 hours defined as 0, 1 to 9 puffs, and 10 puffs or more (1 nebulized β-agonist was considered equivalent to 20 puffs through a metered-dose inhaler) on the differential effect of Combivent and salbutamol on ΔFEV₁ 90.

Paired Student's *t* tests were used when appropriate to compare differences between means. Data were analyzed by using SAS software (version 6.08, SAS Institute).

RESULTS

A total of 338 of 442 patients screened entered the study over a 542-day period. One center enrolled 231 patients, and the other enrolled 107 patients. The most common reasons for exclusion of the 104 patients were an FEV₁ greater than 70% of predicted value (73%) and inability to satisfactorily perform spirometry (19%).

Fifty-nine of 338 patients recruited into the study were withdrawn before the primary outcome measurement of FEV₁ at 90 minutes (ΔFEV₁ 90) was obtained; 13 requested early withdrawal, (9 receiving Combivent and 4 receiving salbutamol), 45 were withdrawn early by the ED doctor because of a lack of satisfactory improvement (18 receiving Combivent and 27 receiving salbutamol), and one was withdrawn before treatment was administered because he was unable to provide blood samples. The mean age (± SEM) of the 338 patients was 29.5 ± 0.7 years; 60.7% were female, 55.9% European, 17.2% Maori, 24.3% Pacific Island, and 2.6% Asian. There was no significant difference between the treatment groups for any of the demographic or clinical variables measured (Table I). FEV₁ at baseline revealed a difference of 40 ± 57 ml in favor of Combivent (*p* = 0.4485). Analysis of change in FEV₁ from baseline, as well as

incorporation of baseline FEV₁ as a covariate in the statistical model, ensured that there was no effect on the primary efficacy end point from this small difference.

The mean absolute difference in change in FEV₁ at 45 minutes was 93 ± 24 ml (*p* = 0.03) and at 90 minutes 113 ± 18 ml (*p* = 0.02) in favor of the Combivent group when compared with the salbutamol group (Fig. 1). Most of the improvement in either treatment group occurred by 45 minutes with minimal additional bronchodilation observed at 90 minutes (37 ml Combivent, 17 ml salbutamol).

Eighty percent of patients reported using medications within 6 hours of presentation to the ED. Thirteen percent reported taking oral corticosteroids, 31.7% inhaled corticosteroids (± cromolyn ± ketotifen), 79.9% inhaled β-agonist, 10.1% oral theophylline, and 7.4% inhaled anticholinergics.

Independent of the study drug received, a poor response to treatment was predicted by frequent use of inhaled β-agonist in the 6 hours before presentation (*p* < 0.0001), severity of the attack (i.e., low baseline FEV₁) (*p* < 0.007), longer duration of attack (*p* < 0.05), and older age (*p* < 0.05) (Table II). Inclusion of covariates in the statistical model incorporating prior asthma medication reduced the importance of baseline FEV₁ as a covariate from a *p* value of 0.007 to a *p* value of 0.01 (model 9), even when oral theophylline, inhaled corticosteroids, oral corticosteroids, and inhaled anticholinergics were removed from analysis (model 10).

Patients with more severe asthma on presentation, as defined by a lower FEV₁, were less likely to show improvement after either of the treatment regimens. Nevertheless, when adjustment was made for baseline FEV₁ in the ANCOVA model and when FEV₁ was treated as a continuous variable, the advantage of Combivent over salbutamol remained significant (*p* = 0.02) (model 1, Table I). Baseline FEV₁ was then treated

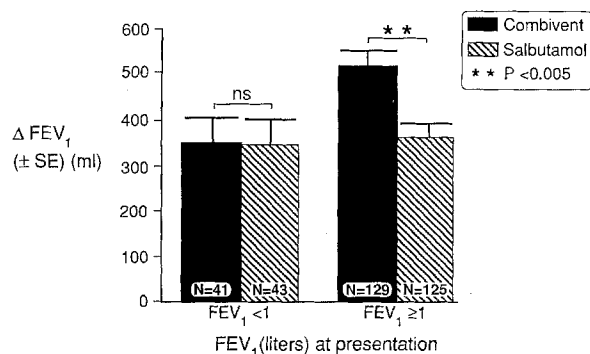


FIG. 2. Effect of severity on response to Combivent compared with salbutamol at 90 minutes.

categorically in the manner used by Rebeck et al.⁶ and Rossing et al.¹³ (i.e., $FEV_1 < 1$ L [84 patients; 23% Combivent, 26% salbutamol] or $FEV_1 \geq 1$ L [254 patients; 77% Combivent, 74% salbutamol]). Patients with an FEV_1 of less than 1 L exhibited only a small benefit from Combivent (359 ± 56 ml) compared with salbutamol alone (337 ± 66 ml; difference = 22 ml [not significant]), whereas those with an $FEV_1 \geq 1$ L exhibited a significant benefit from Combivent (522 ± 44 ml) compared with salbutamol alone (346 ± 38 ml; difference = 176 ml) ($p < 0.005$) (Fig. 2).

Sixty-six patients indicated no prior use of an inhaled β -agonist. The 41 patients in the Combivent group had a mean ΔFEV_1 90 of 853 ± 125 ml, which translated to a treatment difference of 315 ± 135 ml in favor of Combivent over salbutamol (Fig. 3, A). Patients were then grouped according to inhaled β -agonist intake in the previous 6 hours or serum salbutamol levels (patients taking bricanyl or fenoterol were excluded from this analysis [$n = 50$] at baseline before nebulization of the study drugs (Fig. 3, B). Patients who had consumed the most β -agonist before ED attendance exhibited a smaller increase in FEV_1 after administration of nebulized bronchodilator and were least likely to show any benefit from the addition of Combivent (Fig. 3, A and B).

Although inhaled ipratropium (7.4% of subjects) taken in the 6 hours before ED attendance appeared to influence ΔFEV_1 90 in the ANCOVA (Table I, model 5) ($p = 0.01$), the effect was nonsignificant ($p = 0.12$) when it was included in the saturated model (model 9). This was explained by the strong association between frequent inhaled β -agonist use and any inhaled ipratropium use before ED attendance. Oral theophylline use, serum theophylline at baseline (for those taking theophylline), and steroid use (inhaled or oral) did not influence ΔFEV_1 90.

There was no difference in mean heart rate, blood pressure, oxygen saturation, and respiratory rate between the treatment groups over the 90-minute study period; and there were no differences in frequency of adverse events, apart from a somewhat greater need for

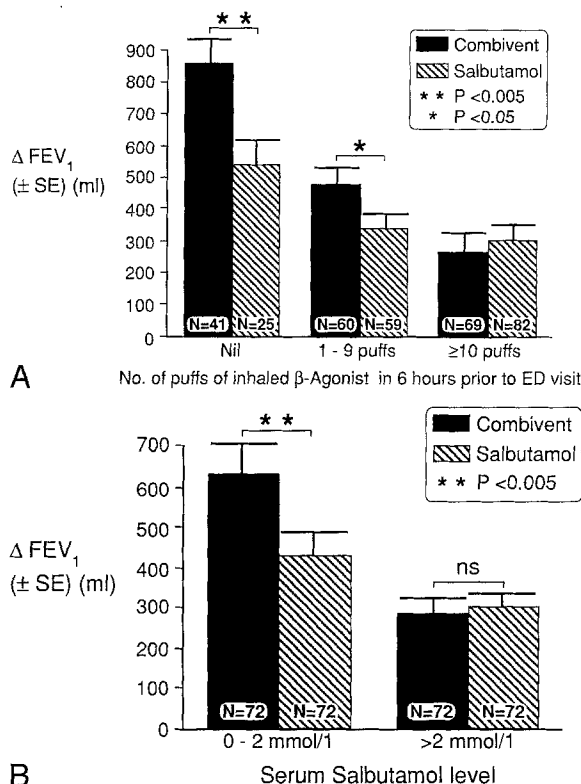


FIG. 3. A, Effect of inhaled β -agonist in previous 6 hours on response to Combivent compared with salbutamol at 90 minutes (a nebulizer of β -agonist was defined as 20 puffs through a metered-dose inhaler). B, Effect of serum salbutamol level on presentation at ED on ΔFEV_1 90 (Combivent vs salbutamol) analyzed in patients who were taking inhaled salbutamol or no β -agonist ($n = 271$, 80%).

hospitalization in the salbutamol treatment group (22.3%) compared with the Combivent group (15.3%, not significant).

DISCUSSION

Our data show that a significant improvement in lung function is associated with the addition of ipratropium to salbutamol (2.5 mg) in the initial management of acute severe asthma. Further, the improvement was achieved without additional side effects or cardiovascular changes, including changes in pulse and blood pressure.

The majority of previous studies had the potential for a large type II error and had wide confidence intervals for pulmonary function outcome variables.¹² To avoid this, we estimated a study size of at least 326 patients to detect at the $\alpha = 0.05$ significance level a 150 ml difference in FEV_1 with 90% probability. The improvement in FEV_1 of 113 ml with the addition of ipratropium to salbutamol was less than anticipated but nevertheless attained significance ($p < 0.05$), mainly as a result of the improved accuracy of spirometry, which resulted in less variability in the measurement of FEV_1 . Performance of high-quality lung function testing in patients with acute asthma is notoriously difficult and was achieved by

training of research nurses and performance monitoring by use of a spirometry quality control program.¹⁵ When possible, patients attained a PEF time of less than 85 msec (in 68% of instances) and performed two measurements of FEV₁, which were within 5% or 100 ml of each other. As such, the spirometry quality control procedures were considerably more stringent than the American Thoracic Society and Epidemiology Standardization Project recommendations that were available at the time of the study.¹⁸

Three previous studies^{4,6,13} have shown that patients with the most severe asthma (PEF < 140 L/min⁴, FEV₁ < 1 L^{6,13}) benefit more from the addition of ipratropium bromide. Conversely, Roeseler et al.³ found that patients with a PEF of less than 60 L/min did not benefit as much. Our study shows that patients with the most severe asthma (FEV₁ < 1 L) derive less benefit from the addition of ipratropium bromide to salbutamol (Fig. 2). This discrepancy is best explained by differences in study design. Two of the earlier studies^{4,6} excluded patients who had received prior nebulized β -agonist therapy. Twenty-eight percent of our patients had been administered a β -agonist through a nebulizer before ED attendance, and their inclusion reflected a more pragmatic study design. Those who had used a nebulized β -agonist within 6 hours of an ED visit not only had the most severe asthma on presentation¹⁹ but were also less likely to benefit from the addition of any further nebulized bronchodilator (Combivent or salbutamol) (Fig. 3, A and B).

The majority of our patients had received asthma therapy at home. This would be expected to influence the results of treatment received in the ED. Although plasma levels of theophylline^{13,20,21} and β -agonist^{20,22,23} have been estimated at the time of arrival in the ED in previous studies, little is known about the way the medication taken before arrival affects the outcome of acute asthma treatment. Although one study²² indicated no difference in the emergency treatment between patients who had or had not taken β -agonists before hospitalization, another suggested that patients with the highest plasma levels of β -agonist on arrival do less well with nebulized β -agonist therapy than those with lower levels.²³ Patients who were taking oral theophylline had the most severe asthma at presentation to the ED in our study.¹⁹ The majority of patients who were taking theophylline had subtherapeutic levels and theophylline use did not affect response to treatment (Table II). Conversely, those who had consumed the most inhaled β -agonist and who had the highest serum β -agonist levels not only had more severe asthma on arrival in the ED¹⁹ as Janson et al.²⁴ have shown but were also less likely to experience improvement with nebulized bronchodilator (either Combivent or salbutamol) (Fig. 3, A and B, Table II). Further, patients who had consumed more inhaled β -agonist before an ED visit derived less additional benefit from ipratropium, and this suggests that there is a dose-response curve to inhaled bronchodilators, whether ipratropium or salbutamol. This remains

the most logical explanation for the smaller improvement in FEV₁ with the addition of ipratropium to salbutamol (113 ml) in our study than was predicted (150 ml) from the study by Rebeck et al.⁶ from which patients were excluded if they had received nebulized β -agonist before attendance. Presumably, those patients who still exhibit airway obstruction despite consuming large doses of β -agonist have an element of fixed airway obstruction or moderate to severe bronchial wall edema and airway mucus plugging and therefore gain little extra benefit from the addition of ipratropium. One would have expected a muscarinic receptor antagonist such as ipratropium to confer additional benefit to those patients who had gained maximum benefit from frequent administration of inhaled β -agonists. However, this was not observed, and therefore our results do not support the theory that cholinergic mechanisms are of greater importance in acute exacerbations of asthma.²⁵

Conclusion

Ipratropium augments the bronchodilator effect of a single dose of salbutamol (2.5 mg). Patients who are first seen with severe acute asthma (low baseline FEV₁) and who have consumed the greatest amount of inhaled β -agonist are least likely to derive benefit from the addition of ipratropium, which does not support the use of ipratropium as second-line treatment if patients fail to respond adequately to treatment with high-dose inhaled β -agonist. More studies examining multiple dosing of ipratropium in addition to salbutamol need to be performed to assess whether the improvement in lung function from a single dose translates into clinically important differences in outcome such as hospitalization.

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REFERENCES

1. British Thoracic Society. Guidelines for management of asthma. *Thorax* 1993;48:S1-24.
2. Asthma Management Handbook 1996. National Asthma Campaign Ltd. Australia. p. 32-5.
3. Roeseler J, Reynaert MS. A comparison of fenoterol and fenoterol-ipratropium nebulisation treatment in acute asthma. *Acta Therapeutica* 1987;13:571-6.
4. O'Driscoll BR, Taylor RJ, Horsley MG, Chambers DK, Bernstein A. Nebulised salbutamol with and without ipratropium bromide in acute airflow obstruction. *Lancet* 1989;1:1418-20.
5. Watson WTA, Becker AB, Simons FER. Comparison of ipratropium solution, fenoterol solution and their combination administered by nebulizer and free mask to children with acute asthma. *J Allergy Clin Immunol* 1988;82:1012-8.
6. Rebeck AS, Chapman KR, Aboud R, Pare PD, Kreisman H, Wolkove N, Vickerson F. Nebulised anticholinergic and sympathomimetic treatment of asthma and chronic obstructive airways disease in the emergency room. *Am J Med* 1987;82:59-64.

7. Leahy B, Gomm SA, Cullen SC. Comparison of nebulised salbutamol with nebulised ipratropium bromide in acute asthma. *Br J Dis Chest* 1983;77:159-63.
8. Higgins RM, Stradling JR, Lane DM. Should ipratropium bromide be added to beta-agonists in the treatment of acute severe asthma? *Chest* 1988;94:718-22.
9. Summers QA, Tarala R. Nebulised ipratropium in the treatment of acute asthma. *Chest* 1990;97:430-4.
10. Ward MJ, Fentem PH, Smith WHR, Davies D. Ipratropium bromide in acute asthma. *Br Med J* 1981;282:598-600.
11. Bryant D. Nebulised ipratropium bromide in the treatment of acute asthma. *Chest* 1988;88:24-8.
12. Ward MJ. The role of anticholinergic drugs in acute asthma. In: Cross NJ, editor. *Anticholinergic therapy in obstructive airways disease*. London: Franklin Scientific Publications; 1993. p. 155-62.
13. Rossing TH, Fanta CH, McFadden ER. A controlled trial of the use of single versus combined drug therapy in the treatment of acute episodes of asthma. *Am Rev Respir Dis* 1981;123:190-4.
14. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987;136:225-44.
15. Enright PL, Johnson LR, Connett JE, Voelker H, Buist AS. Spirometry in the Lung Health Study. 1. Methods and quality control. *Am Rev Respir Dis* 1991;143:1215-23.
16. Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis* 1981;123:659-64.
17. Macfie AE, Harris EA, Whitlock RML. The maximal expiratory flow/volume curve in 197 healthy New Zealanders: a comparison with recent American standards. *Aust N Z J Med* 1981;11:517-21.
18. Gardner RM, Hunkinson JL, Clausen JE, Crapo RO, Epler GR. Standardization of spirometry: 1987 update. Official statement of the American Thoracic Society. *Am Rev Respir Dis* 1987;136:1285-98.
19. Garrett J, Frankel A, Lanes S, Rodwell P, Kelly AM, Town GI. Factors predicting severity and response to therapy in acute asthma [abstract]. *Am J Respir Crit Care Med* 1995;151:A380.
20. Boe J, Ljungholm K. Drug intake and plasma concentrations in acute asthma. *Respiration* 1984;45:430-7.
21. Fanta CH, Rossing TH, McFadden ER. Emergency treatment of asthma. *Am Med J* 1982;72:416-22.
22. Rossing TH, Fanta CH, McFadden ER. The effect of outpatient treatment of asthma with beta-agonists on the response to sympathomimetics in an emergency room. *Am J Med* 1983;75:781-4.
23. Boe J, Carlsson LG, Hetta L, Karlson B, Ljungholm K. Acute asthma-plasma levels and effect of terbutaline IV injections. *Eur J Respir Dis* 1985;67:261-8.
24. Janson C, Boe J, Boman G, Mossberg B, Svedmyr N. Bronchodilator intake and plasma levels on admission for severe acute asthma. *Eur Respir J* 1992;5:80-5.
25. Barns P, Belvisi MG, Mak JCW, Haddad EB, O'Connor B. Tiotropium bromide, a novel long-acting muscarinic antagonist for the treatment of obstructive airways disease. *Life Sci* 1995;56:853-9.

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