Randomized, double-blind, placebo-controlled trial of intravenous salbutamol and nebulized ipratropium bromide in early management of severe acute asthma in children presenting to an emergency department

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**Background:** In acute severe asthma, treatment must be initiated early to reverse the pathophysiology that may render airways less responsive to bronchodilatation. The addition of nebulized ipratropium bromide to initial emergency department therapy improves pulmonary function, but it is unclear whether this approach results in earlier hospital discharge. The early use of bolus intravenous salbutamol has also been shown to improve outcome, including earlier discharge. We therefore assessed the relative benefits of intravenous salbutamol and nebulized ipratropium bromide in the early management of acute severe asthma in children by a double-blind, randomized, controlled trial.

**Methods:** This study was undertaken at a tertiary children’s hospital, The Children’s Hospital at Westmead, The Royal Alexandra Hospital for Children, Westmead, Sydney, Australia. Only children with severe acute asthma as determined by the National Asthma Campaign guidelines criteria and pulmonary index were included. All children received initial nebulized salbutamol therapy (2.5–5 mg salbutamol in 4 mL of normal saline depending on age) at initial emergency department presentation. If asthma remained severe 20 mins later, an intravenous cannula was inserted and intravenous methylprednisolone (1 mg/kg) was administered to all children receiving nebulized salbutamol every 20 mins. Children were then randomized to one of three groups: intravenous salbutamol (15 μg/kg as a single bolus over 10 mins), ipratropium bromide (250 μg), or intravenous salbutamol plus ipratropium bromide. All observers were blinded to treatment groups. Children were randomly assigned to receive a single-dose intravenous bolus of either saline or salbutamol and either nebulized saline or ipratropium bromide determined by a number generated randomly in the hospital pharmacy.

The primary outcomes were recovery time and discharge time of each group. Respiratory and hemodynamic monitoring were continuous during the first 2 hrs of the study and then children were monitored clinically for 24 hrs.

**Results:** A total of 55 children with acute severe asthma were entered into the study over an 18-month period. The three groups were similar demographically, with a mean age of 5.9 yrs, and mean duration of attack of 19.6 hrs. No side effects or treatment intolerance were reported. Children in the groups that received intravenous salbutamol had a significant reduction in recovery time to achieving second hourly inhaled salbutamol (p = .008) compared with those administered intrahal bronchodilator alone. The addition of ipratropium bromide to intravenous salbutamol provided no significant further benefit in terms of nebulizer therapy (intravenous salbutamol compared with intravenous salbutamol plus ipratropium bromide). Children administered intravenous salbutamol ceased supplemental oxygen therapy earlier than those administered ipratropium bromide alone at 12 hrs postrandomization (p = .0003). Children administered intravenous salbutamol could be discharged from the hospital 28 hrs earlier than those administered ipratropium bromide (p = .013).

**Conclusion:** Children administered intravenous salbutamol for severe acute asthma showed a more rapid recovery time, which resulted in earlier discharge from the hospital than those administered inhaled ipratropium bromide. There was no additional benefit obtained by combining ipratropium bromide and intravenous salbutamol administration. (Crit Care Med 2002; 30:448–453)

**Key Words:** asthma; acute; intravenous salbutamol; ipratropium bromide
and decreased hospitalization rates and amount and duration of ongoing treatment in children with severe asthma (9–13). In children with severe asthma, early management with intravenous bronchodilators, in particular salbutamol, has also been shown to improve patient outcome (14). We have reported the benefit of using intravenous salbutamol (15 μg/kg as a single bolus dose over 10 mins) in addition to conventional inhaled salbutamol as initial treatment in the emergency department. In Australia, a specific intravenous preparation of salbutamol is available. In a preliminary report, we found that a single-dose intravenous bolus of salbutamol reduced recovery time, need for supplemental oxygen therapy, and duration and frequency of maintenance salbutamol, and resulted in early discharge from the hospital (14).

These findings suggest that both frequent inhaled ipratropium bromide and a single-dose intravenous bolus of salbutamol, when combined with frequent-dose inhaled salbutamol and corticosteroids as initial emergency department therapy, have clinical benefits for children with acute severe asthma. However, it is not known which of these two treatments is most effective and whether there is any additional benefit in combining them.

In this study, we evaluated the two asthma therapies, namely intravenous salbutamol (15 μg/kg single dose bolus over 10 mins) and frequent inhaled ipratropium bromide (250 μg every 20 mins), both alone and in combination, to determine which was the best mode of initial therapy for children with severe acute asthma presenting to the emergency department.

PATIENTS AND METHODS

All children presenting to the Emergency Department of The Children’s Hospital at Westmead, The Royal Alexandra Hospital for Children, Sydney, NSW, Australia, with severe acute asthma were eligible for entry to the study, with recruitment taking place between May 1997 and November 1998. Initial assessment took place at the emergency department triage desk. The severity of asthma was assessed on a standard clinical assessment scale (National Asthma Campaign Guidelines) (15).

Children were classified as having severe asthma if they had all four features of respiratory distress (wheeze, external retraction, accessory muscle use, and dyspnea) or had any of the absolute criteria (cyanosis, pulsus paradoxus, altered consciousness, or a silent chest on auscultation). These children were immediately referred to an acute treatment area and assessed by a physician. All children were given salbutamol nebulizer therapy consisting of 4 mL saline with 2.5 mg salbutamol for children ≤2 yrs, or 5 mg of salbutamol for children >2 yrs. As all children in this study had severe asthma, they were admitted to an inpatient bed.

The following exclusion criteria were used: any child with life-threatening asthma (risk of respiratory arrest), age <12 months, presence of heart disease, family history of Wolff-Parkinson-White syndrome or past supraventricular tachycardia, respiratory disease other than asthma, clinical or radiologic pneumonia, known hypersensitivity to the study drugs, weight <10 kg or >60 kg, and those who had already received inhaled ipratropium bromide that day.

The parents or guardians of children who met the eligibility criteria of the study were approached, and, once written informed consent was obtained, the child was enrolled into the study. Parents were free to withdraw their child from the study at any time. If on repeat clinical assessment a child had not improved from the first baseline assessment 30 mins after initial nebulization, the study protocol, which had been approved by the ethics committee of the hospital, was instituted. Trained research assistants undertook all formal study assessments.

The initial 2 hrs of the study took place in the emergency department under supervision of the primary investigators. All patients were fully monitored with the treatment following a standard protocol. During the next phase of the study (the subsequent 22 hrs), the researchers closely monitored clinical progress on the medical wards. In this phase, four medical teams supervised asthma treatment. Clinical management decisions and changes in medication regimes were the responsibility of the physicians who follow a standard hospital asthma clinical pathway.

In the initial phase of the study, each child was treated according to a standard protocol (16). A prestudy dose of nebulized salbutamol was given, 20 mins after which children were assessed to see whether they met inclusion severity criteria. If the child was assessed as severe on both the clinical scale and by having a pulmonary index score ≥7 (12), a cannula was inserted and a baseline blood sample (2 mL) was drawn for serum potassium and glucose levels.

Each child was given high-dose salbutamol via a nebulizer. The dose of salbutamol was 2.5 mg or 5.0 mg (for <2 yrs or ≥2 yrs, respectively), given with saline to a volume of 4 mL. Doses were given every 20 mins with continuous oxygen at 4 L/min or 6 L/min if the oxygen saturation was <93% in room air. Children remained on oxygen therapy until oxygen saturation was maintained above 93% for 30 mins.

After insertion of the intravenous cannula, 1 mg/kg of methylprednisolone was administered as an intravenous bolus over 3 mins. All children were given three inhaled doses of salbutamol within the first hour of study commencement. Additional treatment consisted of either 15 μg/kg salbutamol or placebo (saline) as an intravenous bolus over 10 mins in combination with either frequent inhaled salbutamol and inhaled placebo (saline) or inhaled ipratropium bromide, depending on randomization allocation. The cannula was flushed with 5–10 mL of saline after the intravenous medication was administered and then it was capped. All inhaled study drugs were administered using the standard nebulizer system available in the emergency department (Hudson mask and Baxter nebulizer at an oxygen flow rate of 6 L/min). Therefore, all children received nebulized salbutamol every 20 mins as baseline therapy, and, in addition, children received one of the following:

- intravenous salbutamol 15 μg/kg (group IS);
- intravenous saline and inhaled ipratropium bromide (250 μg) every 20 mins (group IB);
- intravenous salbutamol 15 μg/kg and inhaled ipratropium bromide (250 μg) every 20 mins (group IS+IB).

The hospital pharmacy was responsible for randomization of all study drugs, which were prepared according to a table of random numbers in syringes and nebulizers under sterile conditions. Only the pharmacist was aware of the numbering code, which was not broken until after completion of the study, or if a serious adverse effect occurred. A 60-mL dose (six 10-mL syringes) was prepared that contained either saline or salbutamol (15 μg/mL) solution with instructions to administer an intravenous dose of 1 mL/kg. Children ≤2 yrs of age had a study pack that contained the intravenous study drug, either intravenous salbutamol or saline in six 10-mL syringes, and the inhaled study drug, salbutamol 2.5 mg with either ipratropium bromide 250 μg or placebo to a total volume of 4 mL in a single ampoule. Children >2 yrs had a study pack that contained the intravenous study drug, which was either salbutamol or saline, in six 10-mL syringes and the inhaled study drug, salbutamol 5 mg with ipratropium bromide 250 μg or placebo. To ensure that contents remained blinded to emergency department staff at all times, both intravenous and inhaled drugs were taken out of the coded packs by a study nurse who was blinded to treatment in a separate preparation room. The treating physician in the acute treatment area was handed six syringes marked for intravenous use to be.

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delivered at a dose of 1 mL/kg and three nebulization vials all made up to a total volume of 4 mL, each marked for nebulization at 20-min intervals.

All children entered into the study were monitored with continuous oximetry, electrocardiograph, respiratory rate measured by the attending nursing staff every 15 mins, blood pressure at the beginning and end of phase one, and peak expiratory flow at each assessment in children over the age of 7 yrs. At 1 hr, a blood sample was taken from the arm without the cannula to allow potassium and glucose testing. Each child was also assessed before commencement of the study and at 1 and 2 hrs into the study using the clinical assessment scale and the pulmonary index score. All potential adverse effects were recorded at each assessment. For salbutamol, these included tachycardia >200 beats per minute, premature ventricular contractions, palpitations, muscle tremor, agitation, headache, dizziness, insomnia, hyperglycemia, nausea, and vomiting. For ipratropium bromide, these included, dryness of the mouth, throat irritation, cough, ocular disturbance, and urinary disturbance. The research assistants were trained to evaluate and record any adverse effects caused by drug treatment at each clinical assessment.

The next phase of the study commenced at 2 hrs and finished at 24 hrs. The child’s clinical progress was monitored at 4, 8, 12, and 24 hrs, with clinical side effects of the study drugs recorded at each assessment. Inhaled salbutamol therapy during phase two was in accordance with the hospital’s asthma clinical pathway using high-dose salbutamol administered first continuously, then every 30 mins, then at 1, 2, and 3 hrs, depending on clinical state. When children were ready to start hourly nebulization, they were transferred to the ward. The frequency of inhaled salbutamol treatment needed in the medical ward was assessed from the clinical assessment scale and the pulmonary index and administered by the medical team physician, who was blinded to study treatment. The research assistants followed all patients to discharge.

A child was withdrawn from the study if he or she suffered significant clinical deterioration at any time during the study. Any child with persistent tachycardia, defined as a heart rate of ≥200 beats/min sustained for a minimum period of 5 mins, or with significant anticholinergic effects was also withdrawn.

To assess the effectiveness of blinding, the physicians who administered the intravenous solution were surveyed and asked whether they thought they had given salbutamol or saline at the time of the bolus infusion.

The primary outcomes for this study were as follows:

- Mean recovery time of each group (time from randomization to when patients no longer needed nebulized therapy of a given frequency).
- Mean discharge time from the emergency department and hospital. Patients are discharged from the emergency department on reaching hourly nebulized salbutamol treatment, and from the hospital on reaching nebulized salbutamol treatment every 3 hrs.

Other outcomes of interest were:

- clinical signs indicative of moderate to severe (15) asthma 2 hrs after randomization (a pulmonary index score (17) was also calculated from this data);
- number of patients experiencing salbutamol or ipratropium related side effects; and
- means of the quantitative variables (respiratory rate, pulse rate, plasma potassium, plasma glucose).

Differences in time to cessation of high-frequency nebulizer therapy and time to discharge between the three study groups was assessed using one-way analysis of variance. Because the age of the child is an influencing factor for outcome, it was considered as a covariant in analysis. The mean age of each group was incorporated into the statistical methods to be adjusted for in comparison of mean recovery time and mean discharge time. Confidence intervals and differences between means of continuous data and significance levels were calculated by the Student’s t-test and the Newman-Keul’s procedure. We used a chi-square test and Fisher’s exact test to compare treatment effects of categorical variables. Data were entered into a customized Access 97 database (Microsoft, Redmond, WA) and statistical analyses was carried out using Minitab Release 12 (Minitab, State College, PA) and SAS version 6.12 (SAS Institute, Cary, NC).

Analysis was by intention to treat, although there were no deviations from protocol. No children were withdrawn from the study and no children were lost to follow-up.

**RESULTS**

A total of 270 children presented to the emergency department with severe acute asthma during the period of active recruitment, with 77 patients meeting the inclusion criteria of whom 55 had parents who consented to their participation in the study. A total of 21 children were allocated intravenous salbutamol therapy (group IS), 19 were allocated ipratropium bromide (group IB), and 15 were allocated ipratropium bromide and intravenous salbutamol (group IS+IB), (Fig. 1). The patients ranged in age from 1 to 14 yrs (mean age 6.4 yrs in group IS, 6.0 yrs in group IB, and 6.1 yrs in group IS+IB). Baseline demographics and clinical characteristics of all three groups were similar (Table 1). The duration of the asthma attack before emergency department presentation was similar in all three groups (mean 22.3 hrs in group IS, 20.4 hrs in group IB, and 16.2 hrs in group IS+IB).

Time taken from the start of the study to each step down in the frequency of nebulized salbutamol therapy (recovery time) is shown in Table 2. Recovery time to cessation of salbutamol every 30 mins was 2.0 hrs for group IS, 3.2 hrs for group IB, and 1.9 hrs for group IS+IB, although the differences were not statistically significant. Time to cessation nebulizer therapy every 90 min was 10.2 hrs for group IS and 12.5 hrs for group IS+IB, compared with 26.4 hrs for group IB (p = .02). Time to nebulization every 2 hrs was 17.1 hrs for group IS and 16.2 hrs for group IS+IB, compared with 32.8 hrs for group IB (p = .008). The addition of ipratropium bromide to intravenous salbutamol (group IS+IB) showed no significant differences between recovery times compared with group IS. Groups IS and IS+IB demonstrated significantly shorter recovery times compared with group IB for 90- and 120-min nebulization cessation times (Table 2).

Overall, children in group IS were ready for discharge from the hospital 28.0 hrs earlier than those children in group IB (48.3 hrs vs. 76.3 hrs, p = .005). The discharge time between groups remained significant after adjusting for age differences between groups (p = .013) (Table 2).

The need for supplemental oxygen therapy was similar in all three groups until 12 hrs postrandomization. The need for supplemental oxygen therapy at 12 hrs postrandomization was 9.5% (2/21) for the IS group and 20% (3/15) for the IS+IB group, compared with 59% (11/19) for the IB group, differences between the groups being statistically significant (p = .0003). This meant that earlier weaning of supplemental oxygen therapy occurred in those children who received intravenous salbutamol rather than ipratropium alone.

Analysis of mean plasma glucose concentrations at 1 and 2 hrs showed rises in glucose of between 1.7 and 3.8 mmol/L, which, although statistically significant, is not clinically significant (Table 3). Falls in plasma potassium were also statistically but not clinically significant for two of the three groups.
No adverse effects or significant side effects were documented in any of the children in this study. Of the 51 physician guesses as to whether the patient received salbutamol or saline, 27 (53%) guessed correctly, consistent with chance, given that two of the three groups received salbutamol (IS and IS+IB), and as would happen with effective blinding. Twenty-five physicians (49%) guessed correctly as to whether the patient received ipratropium bromide or saline, again consistent with chance.

**DISCUSSION**

We have shown in a preliminary study that the early use of intravenous salbutamol in initial therapy for severe asthma leads to earlier clinical improvement resulting in earlier discharge from the emergency department (14). Recent studies have also shown that initial use of frequent inhaled ipratropium bromide early in asthma management may improve outcome for children with severe asthma (12, 13). Regimes using frequent-dose ipratropium bromide show improved pulmonary function of children with severe asthma (10, 12, 13). These therapies are potentially beneficial to children with severe asthma. It is clear from our current study that a better clinical outcome is achieved in those children administered intravenous salbutamol early in the treatment of severe asthma compared with those administered ipratropium bromide. Discharge from the emergency department occurred 3.7 hrs earlier and from the hospital 28 hrs earlier in those receiving intravenous salbutamol. This data support the hypothesis that, if treatment in severe asthma is delivered early, it can overcome the pathophysiology that renders airways unresponsive to bronchodilation. There also appeared to be no additional advantage to adding ipratropium bromide to intravenous salbutamol in the children studied.

We have studied a small subset of children with acute severe asthma, all of whom were hospitalized. These are clearly children who are resistant to inhaled therapy in the emergency department and, therefore, would be a group that was likely to respond to intravenous therapy. If this therapy is administered before these children reach a nonresponsive phase of their acute asthma, then a more rapid clinical response should occur. Our data show this to be the case in children we have studied, this effect due, in part, to the fact that a single-dose intravenous salbutamol bolus provides rapid delivery of a very effective bronchodilator, uninfluenced by the patients respiratory status.

The response to inhaled bronchodilators in asthma may vary in an individual

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**Figure 1. Trial profile.** IV, intravenous; IS, intravenous salbutamol; IB, ipratropium bromide.

**Table 1. Baseline characteristics of patients**

<table>
<thead>
<tr>
<th>Patients' characteristics</th>
<th>IS (n = 21)</th>
<th>IB (n = 19)</th>
<th>IS+IB (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>6.4 (2.5)</td>
<td>6.0 (2.2)</td>
<td>6.1 (3.2)</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.21 (0.24)</td>
<td>1.27 (0.21)</td>
<td>1.18 (0.27)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>21.0 (7.3 )</td>
<td>21.8 (7.4 )</td>
<td>20.9 (11.1)</td>
</tr>
<tr>
<td>Duration of present attack, hrs&lt;sup&gt;b&lt;/sup&gt;</td>
<td>14.0 (7.50–36.0)</td>
<td>18.0 (12.0–24.0)</td>
<td>12.0 (9.5–20.0)</td>
</tr>
<tr>
<td>ED visits past 2 yrs&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (0–2.5)</td>
<td>0 (0–1.0)</td>
<td>0 (0–1.0)</td>
</tr>
<tr>
<td>Base pulmonary index score&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9 (8.0–11.0)</td>
<td>10 (9.0–11.0)</td>
<td>10 (8.0–10.0)</td>
</tr>
<tr>
<td>Number of patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15 (71)</td>
<td>14 (74)</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (29)</td>
<td>5 (26)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Atopic</td>
<td>7 (33)</td>
<td>8 (42)</td>
<td>9 (60)</td>
</tr>
<tr>
<td>Pulmonary index score ≥7</td>
<td>21 (100)</td>
<td>19 (100)</td>
<td>15 (100)</td>
</tr>
</tbody>
</table>

IS, intravenous salbutamol; IB, ipratropium bromide; ED, emergency department.

<sup>a</sup>Mean (SD); <sup>b</sup>median (interquartile range).
in relation to the severity of airway obstruction, with severe obstruction associated with little response (18). Our data supports the notion that, in severe acute asthma, many children are in a nonresponsive phase, during which inhaled bronchodilators may be ineffective (19). The use of nebulized ipratropium bromide in severe asthma, although effective in improving pulmonary function in children with severe asthma when combined with conventional nebulized salbutamol therapy (9, 12, 13), produces a clinical response that occurs over a more prolonged period of time. During this time, the child may develop nonresponsive asthma, caused by progressive airway obstruction resulting, in part, from bronchial wall edema and mucus plugging (7), which may prevent the access of inhaled drugs. As a result, overall hospital stay for these children may be significantly longer, as demonstrated in this study.

A concern of past studies that have evaluated treatments for asthma has been a lack of consistent treatment (20). Throughout this study, an asthma clinical pathway was used, thus ensuring consistency in management of patients in all groups. In addition, a standard clinical assessment scale and pulmonary index were used to titrate treatment, in particular the frequency of nebulized salbutamol. The pulmonary index (17) is a score that is both sensitive (100%) and specific (67%), and has been shown to be a predictor of the need for hospital admission (when a cutoff for pulmonary index score of at least 7 is used), this correlating well with clinically severe asthma. Thus, it is likely that our findings reflect real differences in outcome between treatment groups. Our peak flow data are incomplete, as peak flow is often not obtainable in untrained children younger than 7 yrs and in very sick children of all ages. Peak flow is also subject to titration effect, i.e., by more frequent nebulization a child can have a similar peak flow value to one who is on a less frequent nebulization schedule.

Oxygen was titrated to maintain a SaO2 above 93%, so oxygen need rather than SaO2 was the variable indicating desaturation in this study. The importance of supplemental oxygen therapy to correct the hypoxia caused by severe asthma has been highlighted in many studies and suggested as a common reason for hospitalization of children (21). Hypoxia can therefore be considered a useful measure of disease severity and an indication, once oxygen therapy ceased, of readiness for discharge from the hospital (20–22). The majority of children who received intravenous salbutamol had their oxygen therapy ceased at 12 hrs postrandomization, compared with only 59% receiving ipratropium bromide alone. This earlier reduction in oxygen therapy is consistent with the more rapid clinical improvement seen in those children who received intravenous salbutamol, resulting in these groups being ready for discharge home earlier.

It is possible that more frequent or higher-dose ipratropium bromide may have provided greater clinical benefit. At the time of this study, three doses of inhaled ipratropium bromide 250 μg were considered appropriate therapy. Recent evidence supporting the use of higher dosing regimes of ipratropium bromide combined with high-dose salbutamol has demonstrated safety and some

**Table 3. Serum biochemistry**

<table>
<thead>
<tr>
<th>Time to cessation of high-frequency nebulization</th>
<th>IS (n = 21)</th>
<th>IB (n = 19)</th>
<th>IS + IB (n = 15)</th>
<th>Mean Difference (95% CI)</th>
<th>Mean Difference (95% CI)</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nebulization every 30 mins, hrs</td>
<td>2.0 (0.5)</td>
<td>3.2 (1.0)</td>
<td>1.9 (0.5)</td>
<td>1.3 (–0.8 to 3.6)</td>
<td>2 (1.2)</td>
<td>3 (–1.0 to 3.6)</td>
</tr>
<tr>
<td>Nebulization every 60 mins, hrs</td>
<td>4.0 (1.0)</td>
<td>7.7 (2.5)</td>
<td>5.0 (1.6)</td>
<td>2.7 (–3.3 to 8.7)</td>
<td>0.4 (1.8 to 9.1)</td>
<td>3.7 (16.2)</td>
</tr>
<tr>
<td>Nebulization every 90 mins, hrs</td>
<td>10.2 (1.6)</td>
<td>26.4 (5.1)</td>
<td>12.5 (2.3)</td>
<td>13.9 (2.3 to 25.5)</td>
<td>0.02 (5.1 to 27.4)</td>
<td>0.07 (–8.1 to 3.6)</td>
</tr>
<tr>
<td>Nebulization every 120 mins, hrs</td>
<td>17.1 (2.9)</td>
<td>32.8 (5.1)</td>
<td>16.2 (2.5)</td>
<td>16.6 (4.8 to 28.4)</td>
<td>0.008 (3.6 to 27.8)</td>
<td>0.1 (–6.9 to 8.7)</td>
</tr>
<tr>
<td>Nebulization every 180 mins, hrs</td>
<td>26.6 (3.6)</td>
<td>49.6 (6.4)</td>
<td>31.8 (8.6)</td>
<td>17.7 (–4.7 to 29.7)</td>
<td>1 (7.9 to 38.1)</td>
<td>0.2 (–24.8 to 14.2)</td>
</tr>
<tr>
<td>Time to discharge from hospital, hrs</td>
<td>48.3 (3.8)</td>
<td>76.3 (8.2)</td>
<td>57.6 (12.0)</td>
<td>18.7 (–10.4 to 48.0)</td>
<td>2 (9.4 to 46.7)</td>
<td>0.05 (–35.0 to 16.0)</td>
</tr>
</tbody>
</table>

IS, intravenous salbutamol; IB, ipratropium bromide; CI, confidence interval.

*p < .05; **p < .005. Mean (SD).
We advocate the early use of a single-dose intravenous salbutamol bolus, particularly if the initial response to bronchodilators (salbutamol and ipratropium) is poor.

REFERENCES