

## ASSESSMENT AND TREATMENT OF ACUTE ASTHMA IN CHILDREN

BRADLEY E. CHIPPS, MD, AND KEVIN R. MURPHY, MD

**O**ver the last decade, significant advances in asthma therapy have been made. Yet asthma remains the leading cause of emergency care in children, and hospitalization rates continue to increase. The direct costs of asthma are estimated to exceed 6 billion dollars per annum in the United States alone<sup>1</sup>; 35% to 50% of this expense occurs in the emergency department (ED) and hospital.

In 2002, asthma affected approximately 6.1 million children younger than 18 years of age, with an inner-city prevalence of 8.6%.<sup>2,3</sup> Thus, asthma is a disease that pediatricians can expect to encounter. The ability to effectively treat asthma is therefore essential. This article will discuss the assessment of acute pediatric asthma and we will review recent studies pertaining to its treatment.

### DETERMINING SEVERITY

A reliable estimate of the severity of airway obstruction is difficult to ascertain on clinical grounds. Many signs can characterize a severe episode: accessory muscle activity, a paradoxical pulse >25 mm Hg, a heart rate >130 beats/min, a respiratory rate >25 to 30 breaths/min, a limited ability to speak, a peak expiratory flow (PEF) or forced expiratory volume (FEV<sub>1</sub>) <50% predicted, and an oxygen saturation (SpO<sub>2</sub>) <91% to 92%.<sup>4-6</sup> These symptoms and signs may or may not develop simultaneously, may or may not impair the patient at the same level, and can be present in any combination.

The PEF is measured in the first 150 to 200 milliseconds of the expiratory maneuver and primarily reflects flow from the large airways. This measurement is highly dependent on patient effort and muscle strength. Thus, an inaccurate measurement is possible when PEF is measured during a severe episode. As the severity of airway obstruction increases during an acute asthma attack, residual volume may dramatically increase, reaching values up to 60% to 70% of total lung capacity. This physiologic event can result in initial flow transients that lead to higher PEF than would be expected.<sup>7</sup> The most recent National Heart, Lung, and Blood Institute guidelines suggest that PEF be obtained in the assessment and treatment of acute asthma in children.<sup>4</sup> PEF can be used especially in older children to follow trends and assess response to  $\beta$ -agonists.

### PREDICTIVE SCORING INDEXES

The measurement of the severity of an acute asthma exacerbation is an important guide to treatment and response to therapy. Several asthma scoring systems estimate the degree of airway obstruction in children when standard measurements cannot be performed. These systems combine a number of physical signs such as respiratory rate, inspiratory/expiratory ratio, and accessory muscle use, to form a score that estimates the severity of an acute asthma exacerbation. Smith and Strunk developed a Pulmonary score (PS) for younger children (<6 years), who had little experience with peak flow meters, or children in significant respiratory distress, in whom it is difficult to obtain an accurate peak flow measurement (Table I).<sup>8-10</sup> This measure, based on respiratory rate, wheezing, and accessory muscle use, uses a scoring scale from 0 to 9. When tested in children who present to the ED with mild to severe asthma, the PS correlated well with PEF.

Arterial oxygen saturation may also be used to predict the need for hospital admission. Geelhoed et al<sup>9</sup> found that children presenting with SpO<sub>2</sub> <91% needed hospitalization with a sensitivity of 1.00 and a specificity of 0.84; however, an SpO<sub>2</sub> >96% was needed to predict successful discharge from the ED. It has been suggested that admission to the hospital should be considered in children with a PS >2, PEF <80%, and room air O<sub>2</sub> saturation <95%, 30 to 45 minutes after the last treatment.<sup>10</sup>

Other authors have attempted to develop scoring systems in older children and adults based on response to therapy. Rodrigo and Rodrigo<sup>11</sup> studied 184 patients (age, 18 to

From Capital Allergy and Respiratory Disease Center, Sacramento, California, and Midwest Childrens Chest Physicians, Omaha, Nebraska.

Submitted for publication Aug 31, 2004; last revision received Dec 29, 2004; accepted Apr 21, 2005.

Reprint requests: Bradley E. Chipps, MD. E-mail: bchipps@capitalallergy.com.

J Pediatr 2005;147:288-94.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.04.052

CS	Corticosteroids	PEF	Peak expiratory flow
ED	Emergency department	PS	Pulmonary score
IB	Ipratropium bromide	SVN	Small-volume nebulizer
ICS	Inhaled corticosteroids	VHC	Valved holding chamber
MDI	Metered-dose inhaler		

**Table I. Pulmonary index**

Score	Respiratory Rate		Wheezing*	Accessory Muscle Use (Sternocleidomastiod Activity)
	<6 Y	≥6 Y		
0	<30	<20	None	No apparent activity
1	31-45	21-35	Terminal expiration with stethoscope	Questionable increase in activity
2	46-60	36-50	Entire expiration with stethoscope	Increased activity
3	>60	>50	Inspiration and expiration without stethoscope	Maximal activity

From Smith SR, Strunk RC. Acute asthma in the emergency department. Reprinted with permission.<sup>10</sup>

\*If no wheezing due to minimal air exchange, score 3.

**Table II. Predictive index scoring system**

Variable	Score		
	Score 0	Score 1	Score 2
PEF variation at 30 minutes (L/min)	>50	50-20	<20
PEF at 30 minutes (% predicted)	>45	45-35	<35
Accessory muscle use at 30 minutes	0-1	2	3

PEF: Peak expiratory flow.

Table 2 from Rodrigo G, Rodrigo C. A New Index for Early Prediction of Hospitalization in Patients with Acute Asthma. Reprinted with permission.<sup>11</sup>

50 years) who presented to the ED for an acute asthma episode with FEV<sub>1</sub> or PEF <50% predicted. A predictive scoring index was developed (Table II).<sup>11</sup> Each patient received a score between 0 and 2 for each of the three variables; the three scores were added together to obtain a final score (0 to 6). In the analysis sample, 163 patients (89%) were discharged (relapse rate within 7 days was 10%) and 21 patients (11%) were hospitalized. An index score > 4 30 minutes after starting therapy demonstrated a sensitivity of 0.86, a specificity of 0.96, a positive predictive value of 0.75, and a negative predictive value of 0.98 for hospital admission. These data suggest that severity may best be determined by early response (within 30 minutes) to treatment rather than by the patient's initial presentation, a conclusion that has been supported by others.<sup>12</sup>

Characteristics identifying patients at a particular risk for life-threatening deterioration are summarized in Table III. Although there is no single variable that can describe the severity of an acute asthma episode, it appears, however, that a combination of PEF <50% predicted, SpO<sub>2</sub> <91%, and lack of response to initial bronchodilator treatment are the most reliable factors in predicting need for hospitalization and relapse after discharge from the ED.

## TREATMENT

β<sub>2</sub>-adrenergic agonists (β-agonists) are the most effective known bronchodilators and have been the first-line treatment of acute childhood asthma for several decades. In

**Table III. Characteristics identifying patients at particular risk for life threatening deterioration**

- Infants < 1 year old
- Prior history of life-threatening exacerbation
- Less than 10% improvement in PEF in the emergency department
- PEF or FEV<sub>1</sub> <25% of predicted value
- PCO<sub>2</sub> ≥40mm Hg
- Wide daily fluctuations in PEF
- Patient cannot recognize airflow obstruction

children, there are a number of important considerations concerning types of β-agonist, doses, delivery systems, and factors important to positive clinical outcomes.

## Delivery Systems

Inhaled β-agonists may be delivered via metered-dose inhalers (MDI), which are increasingly used in combination with a valved holding chamber (VHC). The development of VHCs has greatly improved the efficacy of MDIs for young children by creating a reservoir of aerosol that can be inhaled for 3 to 5 seconds after actuation, eliminating the need for hand-breath coordination and for slow, deep inhalation.<sup>13</sup>

An alternative to the MDI is the small-volume nebulizer (SVN). Advantages to SVNs include use at any age, administration while asleep, use of oxygen or helium plus oxygen as driving gas, and variable drug combination (β-agonist, anticholinergic, epinephrine, inhaled corticosteroid).

Extensive literature comparing MDI + VHC with SVN (Table IV) supports the equivalence of the two delivery systems in treating acute asthma.<sup>14-17</sup> However, there is an increasing body of evidence, including a recent meta-analysis, which finds the efficacy of MDI with spacing device superior to that of SVNs, particularly in regard to onset of action, cost-effectiveness, convenience, and reduction of hospitalization.<sup>18-20</sup> In one such study, Rubilar et al<sup>19</sup> studied 123 patients with moderate to severe wheezing seen in the ED. Patients were randomly chosen for treatment by either MDI-VHC or SVN. In the first hour, the MDI-VHC group was given 2 puffs of albuterol every 10 minutes for 5 doses; the SVN group

**Table IV. Summary of Study Design and Results in Studies Comparing Treatments for Acute Childhood Asthma\***

Source, y	Setting	Mean Age (Range), y	No. Subjects, MDI/SVN	Dose Ratio, MDI:SVN	Variables Measured			Results of MDI vs SVN
					Clinical Outcomes	SaO <sub>2</sub>	PFT	
Freelander and Van Asperen	ED	7.6 (3-13)	14/14	1:2	Yes	No	Yes	=
Fuglsand and Pedersen	ED	10.0 (7-14)	21/21	1:1	Yes	No	Yes	Better
Pendergast et al,	ED	4.5 (3-7)	18/9	1:2, 1:4	Yes	No	No	=
Ba et al,	Hospital	11.9 (7-18)	14/13	1:4	Yes	No	Yes	=
Lee et al,	Office	3.2 (0.5 - 6)	16/17	1:3	Yes	Yes	No	=
Kerem et al,	ED	10.3 (6-14)	17/16	1:5	Yes	Yes	Yes	=
Lin et al,	ED/Clinic	10.3 (6 - 14)	56/55	1:6	Yes	Yes	Yes	Better
Parkin et al,	Hospital	3.0 (1-5)	30/30	1:4	Yes	No	No	=
Chou et al,	ED	7.7 (NA)	71/81	NA	Yes	Yes	Yes	= or Better
Williams et al,	ED	10.4 (6-18)	42/18	1:6.9	Yes	Yes	Yes	=
Schuh et al,	ED	9.1 (5-17)	30/30/30 <sup>1</sup>	1:5:10	Yes	Yes	Yes	All =
Mandelberg et al,	ED	1.4 (0.8-4)	23/19	1:6.9	Yes	Yes	No	=
Plain et al,	ED	2.1 (1-5.2)	32/32	1:3	Yes	Yes	No	=

\*MDI indicates metered-dose inhaler, SVN, small-volume nebulizer; SaO<sub>2</sub>, oxyhemoglobin saturation; PFT, pulmonary function tests; NA, not available; and ED, emergency department.

<sup>1</sup>MDI low dose 2 puff MDI high dose 6 - 10 puff MDI (100 mcg albuterol) neb = 0.15 mg/kg albuterol.

received 0.25 mg/kg albuterol every 20 minutes for 3 doses. Patients who did not respond in the first hour received another hour of the same treatment in addition to a dose of intramuscular betamethasone. Success (determined by a clinical score  $\leq 5$ ; range, 0 to 12) after the first hour was 90% in the MDI-VHC group and 71% in the SVN group; after the second hour, success was 100% in the MDI-VHC group and 94% in the SVN group. However, in children younger than 2 years of age, optimal delivery of drug may not be achieved easily when crying.<sup>21</sup>

### Medications And Doses

Medications available for aerosol therapy include racemic albuterol (a 50:50 mixture of [R]- and [S]-albuterol) and levalbuterol (the pure [R]-enantiomer). Levalbuterol is 100-fold more potent in  $\beta_2$ -receptor binding than (S)-albuterol and is primarily responsible for the bronchodilating effects of the racemic compound. Levalbuterol is available in unit dose vials of 0.31 mg, 0.63 mg, and 1.25 mg. The racemic mixture is available in a solution of 5 mg/mL or unit dose vials. It has been suggested that the total dose of racemic albuterol required to maximally bronchodilate adult patients with an asthma exacerbation is between 5 and 10 mg.<sup>22</sup> There does not appear to be any advantage in giving quantities larger than 10 mg once pulmonary function approaches discharge criteria as judged by PEF measurement.<sup>23</sup> A similar prospective, randomized study is needed to define optimal dosing in children.

Recently, Carl et al<sup>24</sup> studied 547 patients (age, 1 to 18 years) with acute asthma presenting to the ED. Every 20 minutes, patients received either 2.5 mg racemic albuterol

or 1.25 mg levalbuterol via nebulizer, until they either met discharge criteria or reached a maximum of six treatments within 2 hours, at which point they were admitted. Patients who did not meet the discharge criteria after the first treatment were given 2 mg/kg per day of oral prednisone (maximum, 60 mg). In the racemic albuterol group, 122 patients (45%) required hospitalization, whereas a significantly lower number of patients in the levalbuterol group (101 patients or 36%) were admitted. The relative risk of admission in the racemic albuterol group compared with the levalbuterol group was 1.25 (95% CI, 1.01 to 1.51,  $P = .04$ ). However, children who reported frequent use of racemic albuterol before coming to the ED were almost twice as likely to be hospitalized as patients with little or no previous albuterol use. Similarly, in another study, adult patients who presented to the ED with high serum levels of the (S)-enantiomer had the poorest response to ED treatment.<sup>25</sup> These studies suggest that repeated doses of racemic albuterol may be associated with more severe bronchospasm, increased airway hyperreactivity, and blunted bronchodilator responses caused by tachyphylaxis. Before recommending that all patients be treated only with levalbuterol, more data are required, especially because of its significant cost.

Parenteral  $\beta$ -agonist (epinephrine or terbutaline sulfate), administered by subcutaneous injection, is primarily indicated for bronchodilation associated with a systemic anaphylactic reaction (for example, to food, insect sting, and allergy immunotherapy).<sup>26</sup> The recommended dose of aqueous epinephrine is 0.01 mg/kg to a maximum of 0.3 mg in children; terbutaline is recommended at 10 to 12  $\mu$ g/kg.<sup>27</sup> The long-acting  $\beta$ -agonist formoterol, however, has an onset of

action similar to albuterol, and 4.5  $\mu\text{g}$  was found to be as effective as 180  $\mu\text{g}$  of albuterol for acute asthma when delivered via MDI.<sup>28</sup> This drug is being investigated in the treatment of acute asthma.

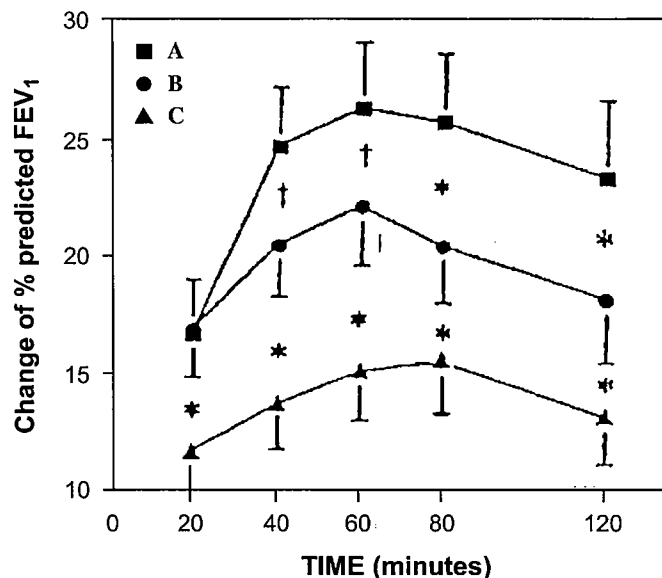
## ANTICHOLINERGICS

Recent data have shown that the addition of ipratropium bromide (IB) to  $\beta$ -agonists improves outcomes in acute pediatric asthma. IB is available as an MDI (18  $\mu\text{g}$  per puff) and as a solution (200  $\mu\text{g}/\text{mL}$ ) in unit dose vials of 500  $\mu\text{g}$ .

Schuh et al<sup>29</sup> reported the outcome of 120 children (age, 5 to 17) with severe asthma ( $\text{FEV}_1 < 50\%$ ) in a three-arm, randomized study. Three groups all received 0.15 mg/kg (0.03 mL/kg) of nebulized albuterol every 20 minutes for 3 doses. In addition, group A received 250  $\mu\text{g}$  of IB every 20 minutes, whereas group B received 250  $\mu\text{g}$  of IP in the initial dose only. Group C did not receive IB (Figure 1). None of the patients received corticosteroid or other additional form of bronchodilator therapy. Group A showed the greatest improvement in  $\text{FEV}_1$ , with an increase of 27% after three doses, whereas  $\text{FEV}_1$  in group B increased by 22% and in group C by 15% (Figure 1). There was no statistical difference in side effects or hospitalization rate among the three groups, except in patients with severe asthma (initial  $\text{FEV}_1 < 30\%$ ), where the hospitalization rate was 27% for group A, 56% for group B, and 83% for group C. This study was not powered for admission rate but rather dose and efficacy.

Qureshi et al<sup>30</sup> reported similar results in a randomized, double-blinded, placebo-controlled study of 434 children (age, 2 to 18 years) presenting with an acute asthma exacerbation. In the group receiving albuterol (2.5 mg) plus IB (250  $\mu\text{g}$ ), 27.4% were admitted to the hospital compared with 36.5% in the group receiving albuterol only. As in the Schuh study, effects were more evident in children with severe asthma (PEF  $< 50\%$ , asthma score 12 to 15, with maximum score of 15), where 37.5% of patients receiving albuterol + IB were admitted compared with 52.6% of the control group. There was no significant decrease in admission rates in patients with mild to moderate/acute asthma.

Some studies have found that there is no significant difference between albuterol + IB and albuterol alone. In a report by Ducharme and Davis,<sup>31</sup> a group of 298 children (age, 3 to 17 years) with mild to moderate acute asthma were given 250  $\mu\text{g}$  of IB every 30 minutes in addition to low-dose or high-dose albuterol. There was no significant difference in either group for respiratory resistance, symptoms, hospital admission, or ED relapse. No additional benefit is derived in hospitalized patients who are treated with 250  $\mu\text{g}$  IB added to frequency dosed albuterol.<sup>32,33</sup> However, when patients are stratified according to disease severity, IB, though less effective in patients with mild to moderate asthma, significantly improves symptoms and reduces hospitalization rates in some patients with severe disease, especially when a multiple dose protocol is used.

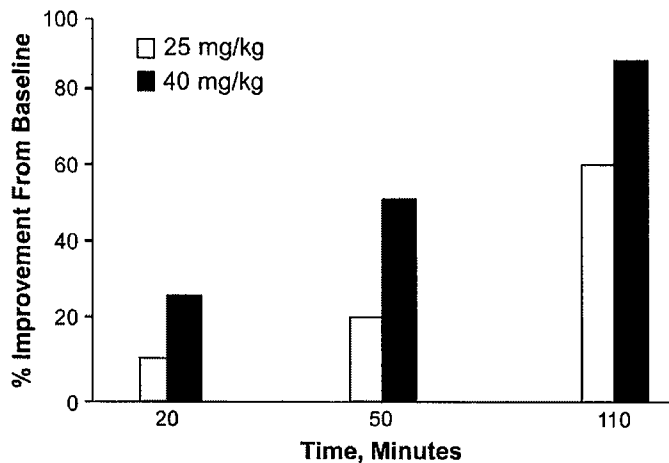


**Figure 1.** Mean difference ( $\pm$ SEM) from baseline of percentage of predicted  $\text{FEV}_1$  with time in group A (three ipratropium doses), group B (one ipratropium dose), and group C (no ipratropium). Repeated-measures analysis of variance:  $P = .0001$  \* $P < .01$ . † $P < .05$ .

## CORTICOSTEROIDS

Extensive data demonstrate that the use of systemic corticosteroids (CS) in the treatment of acute asthma has a beneficial effect. The most commonly used agents are oral prednisone and methylprednisolone (intravenous or intramuscular). Oral prednisone is recommended at 2 mg/kg per day (60 mg maximum) for 5 to 10 days. Oral dexamethasone (DEX 0.6 mg/kg per day max 16 mg for 2 days) has been compared with prednisone (Pred. 2 mg/kg per day 60 mg max for 5 days) in children 2 to 18 years of age with acute asthma in the ED. The primary outcome was need to return for acute care: There was no difference in relapse rates at 10 days DEX (7.4%) and Pred. (6.9%). The prednisone group had higher incidence of vomiting in the ED (3% vs 0.3%), nonadherence to protocol (4% vs 0.4%), and more missed school days (19.5% vs 13.5%).<sup>34</sup> Methylprednisolone is recommended at 2 to 4 mg/kg divided into 3 or 4 doses per day, with a maximum single dose of 125 mg. Higher doses are not thought to offer additional benefit and may be associated with increased side effects. Studies have shown that intravenous, intramuscular, and oral administrations produce equal effects.<sup>35,36</sup> The clinical effects of corticosteroids occur at 1 to 3 hours and maximal effects at 4 to 8 hours. Intervention with CS incorporated into the early stages of emergency department treatment, in most studies,<sup>37-40</sup> though not all,<sup>41,42</sup> led to reduced hospital admissions.

There is little evidence that inhaled corticosteroids (ICS) are effective in the treatment of pediatric acute asthma, regardless of severity. Although most data indicate that systemic CS are superior to ICS in treating asthma exacerbations,<sup>43-45</sup> some studies did not reach this conclusion.<sup>46,47</sup> When therapy combining ICS and systemic CS is used,



**Figure 2.** Comparison of percent improvement of PEF from baseline with low- and high-dose intravenous magnesium sulphate. Reprinted with permission. <sup>47-53</sup> 2000

American Medical Association All rights reserved  
 studies yield mixed results.<sup>48-50</sup> Overall, without further data, ICSs appear to play a marginal role in treating severe acute asthma. Though ICS may be effective in treating mild asthma symptoms in children at home, systemic CS should be used in moderate to severe exacerbations.

### LEUKOTRIENE RECEPTOR ANTAGONISTS

There are two available leukotriene receptor antagonists: zafirlukast and montelukast. To date, no published studies have examined the efficacy of leukotriene receptor antagonists in acute childhood asthma. However, in a placebo-controlled study of adults with acute asthma, Camargo et al<sup>51</sup> found that the addition of montelukast to standard therapy causes rapid benefit. In this study, patients were randomly assigned to receive either 7 mg IV montelukast, 14 mg IV montelukast, or intravenous placebo in addition to aerosol  $\beta$ -agonist and ICS. Over the first 20 minutes, there was no difference in the response between the 7 mg and 14 mg groups. The montelukast-treated groups had a significant improvement in FEV<sub>1</sub> with an increase of 14.8% predicted FEV<sub>1</sub> versus 3.6% predicted in the placebo group over a period of 2 hours.

### MAGNESIUM SULFATE

Magnesium sulfate (MgSO<sub>4</sub>) has been shown to inhibit smooth muscle contraction, decrease histamine release from mast cells, and inhibit acetylcholine release from cholinergic nerve endings. Normal serum levels range from 1.5 to 2.2 mg/dL whereas at 4 to 6 mg/dL it stimulates bronchodilation. Levels of 12 to 15 mg/dL are associated with respiratory failure, cardiac arrhythmia, and death.

Ciarallo et al<sup>52</sup> studied the effects of both low- and high-dose MgSO<sub>4</sub> treatments. 31 patients (age, 6 to 18 years), with PEF <60% predicted after receiving three  $\beta$ -agonist treatments, were given 2 mg/kg methylprednisolone followed by either 25 mg/kg MgSO<sub>4</sub> or placebo. Patients were followed

over 120 minutes. All patients in the control group were admitted compared with 73% of the treatment group.

In their second study,<sup>53</sup> a higher dose of 40 mg/kg MgSO<sub>4</sub> was given as adjunctive therapy to patients presenting to the ED with PEF <70% predicted. All patients had been treated with  $\beta$ -agonists, anticholinergic drugs, and corticosteroids. Initial improvement occurred within 20 minutes and continued up to 110 minutes. The difference between the low- and high-dose studies are summarized in Figure 2. However, not all studies in children have shown beneficial effects with MgSO<sub>4</sub>. For example, a dose of 75 mg/kg (maximum, 2.5 g) MgSO<sub>4</sub> in addition to  $\beta$ -agonist and intravenous methylprednisolone did not change the pulmonary index in children compared with control subjects.<sup>54</sup> There appears to be no consistent positive response to MgSO<sub>4</sub> when doses from 25 to 75 mg/kg are given. This does not rule out individual patients deriving benefit, so MgSO<sub>4</sub> may be tried when respiratory failure is impending.

### METHYLYXANTHINE

Intravenous methylxanthine, a bronchodilator, was first used in the treatment of acute asthma in 1937 and has continued to be used for asthma. Theophylline was commonly used to treat patients hospitalized with asthma exacerbations until numerous studies in the 1990s revealed that theophylline added no benefit to treatment with  $\beta$ -agonists and corticosteroids.<sup>55-57</sup> Routine use of theophylline is no longer advocated although it has been shown to have adjunctive benefit in select patients with impending respiratory failure.<sup>58-60</sup>

### OXYGEN AND HELIUM-OXYGEN MIXTURES

Hypoxemia during an acute asthma exacerbation is secondary to ventilation/perfusion mismatch, which may be accentuated by  $\beta$ -agonist treatment. Hypoxemia may be corrected with administration of low-flow oxygen (28%). This level of supplemental oxygen has been shown to be safer than 100% oxygen, especially in adults with more severe airway obstruction who are at risk for CO<sub>2</sub> retention.<sup>61</sup>

Helium-oxygen mixtures (Heliox) are available in concentrations of 80% helium/20% oxygen and 70% helium/30% oxygen. Heliox mixtures have a low density compared with air (the 80/20 mixture is approximately one-third the density of air). Heliox, however, is a temporary measure to reduce respiratory resistive work and forestall muscle fatigue until airways obstruction improves with conventional therapy. Some studies have found heliox minimally effective,<sup>62</sup> whereas others have not.<sup>63</sup>

Heliox may also be effective as the driving gas for nebulized bronchodilators. The low density of helium improves the deposition of aerosolized particles in the airways, which can lead to a more rapid response to treatment and more significant improvement in airway function.<sup>64</sup> However, this intervention is expensive and may not benefit the majority of patients.

