Introduction

Michael Schatz[1], Amin Antoine Nabih Kazzi[2], Barry Brenner[3], Carlos A. Camargo, Jr.[4], Thomas Corbridge[5], Jerry A. Krishnan[6], Richard Nowak[7], and Gary Rachelefsky[8]

[1]Department of Allergy, Kaiser Permanente Medical Center, San Diego, California; [2]Department of Emergency Medicine, American University of Beirut, Beirut, Lebanon; [3]Department of Emergency Medicine, Case Western Reserve School of Medicine, Cleveland, Ohio; [4]Department of Emergency Medicine and Division of Rheumatology, Allergy and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; [5]Division of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois; [6]Asthma and COPD Center, Department of Medicine, and Department of Health Studies, University of Chicago, Chicago, Illinois; [7]Department of Emergency Medicine, Henry Ford Health System, Detroit, Michigan; and [8]Executive Care Center for Asthma, Allergy, and Respiratory Diseases at the Geffen School of Medicine, University of California Los Angeles, Los Angeles, California

Keywords: asthma exacerbation; acute asthma; emergency department; Expert Panel Report 3; noninvasive positive pressure ventilation; continuous positive airway pressure ventilation; bilevel positive airway pressure ventilation; respiratory failure; intubation; mechanical ventilation; discharge medications; corticosteroids; follow-up care; asthma specialist care

Approximately 22.5 million Americans had asthma in 2005, conferring an estimated financial burden of $19.7 billion in annual health care costs (1). In 2005, nearly 1.8 million patients with asthma were treated in emergency departments (EDs) (2).

An in-depth review of the National Asthma Education and Prevention Program Expert Panel Report 2 guidelines was conducted to identify knowledge gaps in relationship to newer information regarding the appropriate emergency management of patients with severe asthma exacerbations. Knowledge gaps were identified in the following areas: (*1*) use of noninvasive ventilation, (*2*) use of intubation and mechanical ventilation, (*3*) appropriate discharge medications, (*4*) techniques for ensuring proper follow-up after an ED visit, (*5*) asthma education in the ED, (*6*) prehospital emergency treatment, (*7*) use of heliox, (*8*) use of magnesium sulfate, (*9*) use of intravenous β-agonists, (*10*) use of leukotriene modifiers for acute asthma, and (*11*) acute use of inhaled corticosteroids.

A task force of physicians comprised of three members (C.C., G.R., M.S.) of the American Academy of Asthma, Allergy and Immunology; three members (B.B., A.K., R.N) of the American Academy of Emergency Medicine; and three members (T.C., J.K.) of the American Thoracic Society was formed to develop evidence-based recommendations regarding the above topics. Shortly after this task force was formed, plans for updated National Asthma Education and Prevention Program guidelines (Expert Panel Report 3 [EPR3]) were announced. In discussion with the EPR3 panel, it was determined that items 5 to 11 above would be covered in the new EPR3 guidelines and that the current task force would focus on items 1 to 4. It was also determined that this task force report would include a targeted summary of the EPR3 guideline recommendations for the management of asthma in the ED.

The task force conducted a literature search for randomized controlled trials and meta-analyses related to each of the four chosen topics from 1997 to October 2006 (to conform with the dates of the EPR3 review) in the PubMed and Cochrane databases. Keywords were identified for each topic based on MeSH terms, and editorial teams of three members each were assigned to each topic. Each literature review underwent an initial title and abstract review. On determining those articles that were appropriate for review, the full-text article was obtained, and a data summary was developed for each article. The randomized controlled trials and meta-analyses retrieved during the time period of the search (1997–2006) were supplemented by older randomized controlled trials and by observational studies at the discretion of the editorial teams. Summaries of such articles deemed to warrant detailed presentation are included separately in the RESULTS sections.

The body of evidence is discussed in detail for each topic, and the task force provides specific recommendations at the end of each topic discussion. The task force specified the level of evidence used to justify the recommendations being made. The task force used the same system to describe the level of evidence as used by the EPR3 Expert Panel (3), which is described as follows (4):

- Evidence Category A: randomized controlled trials, rich body of data;
- Evidence Category B: randomized controlled trials, limited body of data;
- Evidence Category C: nonrandomized trials and observational studies; and
- Evidence Category D: task force consensus judgment based on clinical experience and other nonsystematic clinical observations.

This system tracks well with the 4-point Grading of Recommendations Assessment, Development and Evaluation (GRADE) quality-of-evidence system (high, moderate, low, and very low) officially recommended by the American Thoracic Society after the initiation of the current project (5).

In addition to specifying the level of evidence supporting a recommendation, the task force categorized the strength of a

---

Abbreviations used: ED, Emergency department; EPR3, Expert Panel Report 3.

This article is part of the Joint Task Force Report: Supplemental Recommendations for the Management and Follow-up of Asthma Exacerbations, an official workshop report of the American Academy of Allergy, Asthma and Immunology (AAAAI), the American Academy of Emergency Medicine (AAEM), and the American Thoracic Society (ATS). It was approved by the AAAAI Board of Directors, January 16, 2008, the AAEM Board of Directors, January 14, 2008, and the ATS Board of Directors, March 13, 2009.

The Joint Task Force Report is copublished in the *Journal of Allergy and Clinical Immunology,* the *Journal of Emergency Medicine,* and the *American Journal of Respiratory and Critical Care Medicine.*

Supported through an unrestricted educational grant to AAAAI and AAEM for publication and dissemination costs from GlaxoSmithKline, which had no input into the task force recommendations.

Correspondence and requests for reprints should be addressed to Michael Schatz, M.D., M.S., Department of Allergy, Kaiser Permanente Medical Center, 7060 Clairemont Mesa Blvd., San Diego, CA 92111.

Proc Am Thorac Soc Vol 6. pp 353–356, 2009
DOI: 10.1513/pats.P09ST1
Internet address: www.atsjournals.org

TABLE 1. NATIONAL ASTHMA EDUCATION AND PREVENTION PROGRAM EPR3 RECOMMENDATIONS

Recommendation 1	Management of Asthma Exacerbations Requiring Urgent Medical Care (e.g., in the urgent care setting or ED) Includes: Oxygen to relieve hypoxemia in moderate or severe exacerbations (evidence not reviewed) SABAs to relieve airflow obstruction, with addition of inhaled ipratropium bromide in severe exacerbations (Evidence Category A) Systemic corticosteroids to decrease airway inflammation in moderate or severe exacerbations or for patients who do not respond promptly and completely to a SABA (Evidence Category A) Conditional: consideration of adjunct treatments, such as intravenous magnesium sulfate or heliox, in severe exacerbations unresponsive to the initial treatments listed above (Evidence Category B) Monitoring response to therapy with serial measurements of lung function (Evidence Category B)
Recommendation 2	Preventing relapse of the exacerbation or recurrence of another exacerbation by providing referral to follow-up asthma care within 1–4 wk; an ED asthma discharge plan with instructions for medications prescribed at discharge and for increasing medications or seeking medical care if asthma worsens; review of inhaler techniques, when possible; and (conditional) consideration of initiating inhaled corticosteroids (Evidence Category B)

Definition of abbreviations: ED = emergency department; SABA = short-acting β-agonist.

TABLE 2. CLINICAL PRACTICE RECOMMENDATIONS: NONINVASIVE VENTILATION

Recommendation 1	Conditional: a trial of NPPV before intubation and mechanical ventilation should be considered in selected patients with acute asthma and respiratory failure (Evidence Category B). Remarks: These would include patients who can tolerate and cooperate with this therapy. NPPV should only be used in these patients provided that the respiratory therapists, nurses, and physicians who are responsible for their care are very familiar with this technology and the patients are in an area where they can be constantly observed and monitored and can receive immediate intubation, if needed.
Recommendation 2	Conditional: pending additional data, specific settings for NPPV should follow the protocol set forth in the article by Soroksky and coworkers (6) (Evidence Category D). Remarks: The protocol of Soroksky and colleagues (6) called for an initial expiratory pressure of 3 cm H_2O that was increased by 1 cm H_2O every 15 minutes to a maximum pressure of 5 cm H_2O. The initial inspiratory pressure was set at 8 cm H_2O and increased by 2 cm H_2O every 15 min to a maximum pressure of 15 cm H_2O or until the respiratory rate was $<$ 25 breaths/min, whichever came first. Settings should be individualized and guided by careful evaluation of clinical response.

Definition of abbreviation: NPPV = noninvasive positive pressure ventilation.

TABLE 3. CLINICAL PRACTICE RECOMMENDATIONS: INTUBATION AND MECHANICAL VENTILATION

Recommendation 1	Criteria for intubation (Evidence Category D) Clinical indications Cardiac arrest Respiratory arrest Altered mental status Progressive exhaustion Silent chest Laboratory indications Severe hypoxia with maximal oxygen delivery Failure to reverse severe respiratory acidosis despite intensive therapy pH $<$ 7.2, carbon dioxide pressure increasing by $>$ 5 mm Hg/h or to $>$ 55–70 mm Hg, or oxygen pressure of $<$ 60 mm Hg
Recommendation 2	Intubation technique (Evidence Category D) There are four choices of technique, each with its own benefits and risks: Nasotracheal intubation Awake orotracheal intubation Orotracheal intubation with sedation Orotracheal intubation with sedation and neuromuscular blockade In general, orotracheal intubation with sedation and neuromuscular blockade are preferred for asthmatic patients in critical respiratory distress. The use of ketamine and propofol might be preferred over other sedative agents.
Recommendation 3	Recommendations for appropriate ventilator settings (Evidence Category D) Control of hyperinflation and auto-PEEP Reduction of respiratory rate might help control hyperinflation. Reduction of tidal volume might help control hyperinflation. An initial set-up of 80 L/min with a decelerating wave form configuration might be appropriate in adults. Shortening of inspiration with a square wave pattern and an inspiratory flow rate of 60 L/min allows greater time for exhalation in each respiratory cycle and might help control hyperinflation. Auto-PEEP and plateau pressure should be followed during mechanical ventilation. Hypercapnia is preferable to hyperinflation. It should not be used in the presence of increased intracranial pressure. An acceptable level of hypercapnia and acidosis is a pH as low as 7.15 and a Pa_{CO_2} of $\leqslant$ 80 mm Hg.
Recommendation 4	Management in the postintubation period (Evidence Category D)

(*Continued*)

TABLE 3. (CONTINUED)

	Verify endotracheal tube placement with a carbon dioxide detector, adequate oximeter readings, and chest radiography. Chest radiography will determine the depth of intubation but not esophageal intubation with the patient breathing "around the tube."
	Postintubation sedation should be provided with a benzodiazepine.
Recommendation 5	Medical management of the intubated asthmatic patient
	Continued treatment with inhaled bronchodilators, such as nebulized albuterol or albuterol administered with a metered-dose inhaler (Evidence Category B)
	Systemic corticosteroid treatment, such as 40 mg of methylprednisolone every 6 hours (Evidence Category B)
	No routine use of heliox once the patient is intubated (Evidence Category D)
Recommendation 6	Prevention and treatment of complications (Evidence Category D)
	Hypoxemia
	Exclude right mainstem intubation (21 cm at incisors)
	Exclude pneumothorax and place pleural drain
	Exclude tube obstruction (kinking, biting of tube, or plugging)
	Exclude pneumonia and other lung disease
	Hypotension
	Exclude pneumothorax but first perform a trial of apnea or hypopnea to decrease intrathoracic pressure unless unequivocal evidence, such as tracheal shift with unilateral breath sounds or subcutaneous emphysema
	Consider tension pneumothorax early. (This is a clinical diagnosis. If lung examination suggests this complication, proceed with a needle thoracostomy followed by a chest tube thoracostomy.)
	Administer fluids
	Measure auto-PEEP and plateau pressure and apply reduction measures
	Exclude other causes, such as myocardial infarction and sepsis
	Cardiac arrest
	A trial of apnea or hypopnea for no more than 30–60 s with external compressions and volume challenge is therapeutic for lung hyperinflation as a cause of cardiac arrest.
	Consider tension pneumothorax early (If lung examination suggests this complication, proceed with a needle thoracostomy followed by a careful chest tube thoracostomy.)

Definition of abbreviations: PEEP = positive end-expiratory pressure.

recommendation. In EPR3, when a clinical practice "is recommended," this indicates a strong recommendation (3). When a clinical practice should or might be "considered" in EPR3, this indicates that the recommendation is less strong or conditional. In the current document, recommendations are categorized as strong or conditional, which is consistent with GRADE and American Thoracic Society recommendations (5).

The EPR3 recommendations are summarized in Table 1, and the recommendations of this task force are summarized in Tables 2–5 (6). The recommendations in these tables are strong recommendations, unless preceded by the term "conditional." The task force recommendations are meant to provide guidance to clinicians who manage acute asthma and are based on the task force's interpretation of the best available data and expert opinion. It is hoped that the EPR3 recommendations combined with those of this task force will improve the care and outcomes for patients who present with asthma exacerbations. Because many of the recommendations are based on only Evidence Category D, we also hope that this report will stimulate additional needed research.

TABLE 4. CLINICAL PRACTICE RECOMMENDATIONS: DISCHARGE MEDICATIONS

Recommendation 1	Conditional: consider IMCSs* in patients who are likely to have difficulty in obtaining or using OCSs after ED discharge. Patients selected for IMCS therapy should be informed of an increased risk of local injection site complications (mostly pain and bruising; Evidence Category B).
Recommendation 2	Conditional: consider a short course of very high-dose ICSs† instead of OCSs after ED discharge in patients with mild forms of acute asthma and who are able to obtain, afford, and use ICSs correctly and/or have difficulty tolerating OCSs (Evidence Category B). Such patients should receive adequate training about how to use ICSs before ED discharge.
Recommendation 3	Recommend initiating daily ICSs‡ (in patients not already receiving daily ICSs) or continuing daily ICSs‡ (in patients already receiving daily ICSs) on ED discharge (in addition to a short course of OCSs)‡ for patients with a history compatible with persistent asthma,§ even between episodes of acute asthma (Evidence Category A). Consider initiating daily ICSs in patients who have experienced an episode of asthma requiring OCSs in the prior 12 months (Evidence Category D).
	Remarks: Patients starting ICSs should receive adequate training about how to use them before ED discharge.
Recommendation 4	Additional studies are needed to evaluate the efficacy and safety of macrolides and leukotriene modifiers in adults with acute asthma after ED discharge before recommendations regarding their use can be made (Evidence Category B; no recommendation).

Definition of abbreviations: ED = emergency department; ICS = inhaled corticosteroid; IMCS = intramuscular corticosteroid; OCS = oral corticosteroid.

* Alphabetical order: betamethasone sodium phosphate, 6 mg, with betamethasone acetate, 6 mg, administered intramuscularly × 1; dexamethasone, 10 mg, administered intramuscularly × 1; methylprednisolone sodium acetate, 80 to 160 mg, administered intramuscularly × 1; or triamcinolone diacetate, 40 mg, administered intramuscularly × 1.

† Budesonide dry powder inhaler, 2,400 to 3,200 μg/d, inhaled in divided doses (2–4 times/d) for 7 to 10 d. Alternative regimens, in alphabetical order with estimated equivalent daily doses, include flunisolide, 4,000 to 5,000 μg/d; fluticasone dry powder inhaler, 1,000 to 1,500 μg/d; mometasone dry powder inhaler, 800 to 1200, μg/d; and triamcinolone acetonide, 3,000 to 4,000 μg/d.

‡ Alphabetical order: daily inhaled budesonide dry powder inhaler, 1,200 μg/d; flunisolide metered-dose inhaler, 2,000 μg/d; fluticasone dry powder inhaler, 500 μg/d; mometasone dry powder inhaler, 400 μg/d; triamcinolone acetonide, 1,500 μg/d, in divided doses (twice per day) for 3 to 4 wk AND prednisone, 40 to 50 mg/d, for 5 to 7 d.

§ Any of the following: prescribed daily controller use; daytime symptoms or use of rescue inhalers (e.g., albuterol) more than twice a week; interference with sleep more than twice a month; activity limitation caused by asthma; exacerbations requiring systemic corticosteroids more than once a year; and airflow obstruction with FEV_1 of less than 80% of predicted value.

TABLE 5. CLINICAL RECOMMENDATIONS: IMPROVING FOLLOW-UP

Recommendation 1	Recommend that all patients with asthma seen in the ED have their chronic asthma characterized by National Asthma Education and Prevention Program guidelines. Chronic severity assessment can be ac complished by determining pre-exacerbation medication use, daytime and nighttime symptoms, history of activity limitation, and history of exacerbations requiring oral corticosteroids. Patients with persistent asthma or recurrent asthma exacerbations need appropriate assessment and asthma expertise that allows for comprehensive care and management (Evidence Category D).
Recommendation 2	Recommend that the appointment to the primary care physician, asthma specialist, or specialized asthma clinic be made before leaving the ED, if possible, and a reminder by telephone should occur several days later (Evidence Category B). Conditional: when indicated, consider providing a transportation voucher for the appointment with the primary care physician, the asthma specialist, or both (Evidence Category B). Recommend that the follow-up visit with the PCP, asthma specialist, or specialized asthma clinic be within 1 week of the ED visit (Evidence Category D). Conditional: consider faxing an ED visit summary to the PCP, asthma specialist, or asthma clinic before the follow-up visit (Evidence Category D).
Recommendation 3	Recommend that elements of the follow-up include optimal controller management, assurance of satis factory inhaler technique, asthma self-monitoring and self-management education, an individualized action plan, trigger identification and avoidance instruction, and arrangement for ongoing follow-up. Such follow-up could occur in the ED itself in a specialized clinic or in the offices of primary care physicians or specialists and could be augmented by telephone contact and home visits (Evidence Category B).
Recommendation 4	Recommend that all patients with severe persistent asthma or a history of prior severe exacerbations requiring hospitalization be referred to an asthma specialist (Evidence Category C) or specialized asthma clinic (Evidence Category B) from the ED. Conditional: consider referral to an asthma specialist or specialized asthma clinic for patients with moderate persistent asthma (Evidence Category D).

Definition of abbreviations: ED = emergency department; PCP = primary care physician.

Author disclosures were obtained by the *Journal of Allergy and Clinical Immunology* (JACI) using questions determined by the American Academy of Allergy, Asthma and Immunology (AAAAI) and JACI. Questions pertained to: employment; financial interests between the author or members of the author's immediate family or household with organizations and commercial interests; research support during the past calendar year; and legal consultation services/expert witness testimony during the past calendar year. Authors were asked to state dollar amounts in ranges of either $< \$10{,}000$ or $\geqslant \$10{,}000$. Authors were not required to disclose other facts that are now requested by *PATS* in conformance with American Thoracic Society policy, including knowledge of any significant financial relationship between the author's institution or employer and relevant commercial interests, and all relationships with tobacco entities.

Disclosure of potential conflict of interest: M.S. has been a consultant for GlaxoSmithKline and has received research support from Aerocrine, Genentech, GlaxoSmithKline, and Merck. A.A.N.K. has declared that he had no conflict of interest. B.B. has declared that he had no conflict of interest. C.A.C., Jr. has been a consultant, speaker, or advisory board member for AstraZeneca, Critical Therapeutics, Dey, Genentech, GlaxoSmithKline, Merck, Novartis, and Schering-Plough and has received research support from the National Institutes of Health, AstraZeneca, Critical Therapeutics, GlaxoSmithKline, Merck, Novartis, and Respironics. T.C. is on the speakers' bureau for GlaxoSmithKline. J. A. Krishnan has declared that he had no conflict of interest. R.N. has declared that he had no conflict of interest. G.R. has been a speaker or advisory board member for AstraZeneca, Schering-Plough, CSL Behring, Merck, and Sanofi Aventis and has provided legal consultation or expert witness testimony on the topic of environmental injuries, mostly mold-related.

Acknowledgment: We thank Kersten Hammond for her editorial assistance and Dr. Holger Schünemann for his valuable suggestions.

References

1. American Lung Association. American Lung Association Asthma in Adults Fact sheet [accessed April 8, 2008]. Available from: http://www.lungusa.org/site/apps/nl/content3.asp?c=dvLUK9O0E&b=2058817&content_id=%7b39966A20-AE3C-4F85-B285-68E23EDC6CA8%7d&notoc=1.
2. Centers for Disease Control and Prevention. National Center for Health Statistics national ambulatory medical care survey, 1992–2005. National Hospital Ambulatory Medical Care Survey, 2005. Atlanta: Centers for Disease Control and Prevention; 2005.
3. Jadad AR, Moher M, Browman GP, Booker L, Sigouin C, Fuentes M, *et al.* Systematic reviews and meta-analyses on treatment of asthma: critical evaluation. *BMJ* 2000;320:537–540.
4. National Asthma Education and Prevention Program Expert Panel Report 3: guidelines for the diagnosis and treatment of asthma. *J Allergy Clin Immunol* 2007;120:S94–S138.
5. Schunemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, *et al.* An official ATS statement: Grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med* 2006;174:605–614.
6. Soroksky A, Stav D, Shpirer I. A pilot prospective, randomized placebo-controlled trial of bilevel positive airway pressure in acute asthma attack. *Chest* 2003;123:1018–1025.

Managing Asthma Exacerbations in the Emergency Department

Summary of the National Asthma Education and Prevention Program Expert Panel Report 3 Guidelines for the Management of Asthma Exacerbations

Carlos A. Camargo, Jr.[1], Gary Rachelefsky[2], and Michael Schatz[3]

[1]Department of Emergency Medicine and Division of Rheumatology, Allergy and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; [2]Executive Care Center for Asthma, Allergy, and Respiratory Diseases at the Geffen School of Medicine, University of California Los Angeles, Los Angeles, California; and [3]Department of Allergy, Kaiser Permanente Medical Center, San Diego, California

Keywords: asthma exacerbation, emergency department, Expert Panel Report 3, acute asthma, respiratory failure

This article summarizes the recommendations regarding the management of asthma exacerbations presented in the Expert Panel Report 3 (EPR3) (1). The evidence supporting these recommendations can be found in the report itself. All of the recommendations in this article are strong recommendations, unless indicated by the term "conditional."

Asthma exacerbations consist of acute or subacute episodes of progressively worsening shortness of breath, coughing, wheezing, and chest tightness or any combination thereof. These episodes differ from poor asthma control in that diurnal variability in airflow, a key marker of poor asthma control, might not change during an exacerbation (2). An important advance in the new National Asthma Education and Prevention Program (NAEPP) EPR3 guidelines (1) is the creation of a chapter devoted to the management of asthma exacerbations. Moreover, the new EPR3 guidelines present different spirometry cut points for assessing the severity of acute asthma (exacerbations) versus chronic asthma. These and other changes underscore the distinction between acute and chronic asthma management.

Two patient populations at particular risk during an asthma exacerbation include patients with one or more risk factors for asthma-related death (Table 1) and infants, who are at greater risk for respiratory failure because of differences in lung anatomy and physiology. The assessment and treatment of young children pose unique challenges, but management of asthma exacerbations in older children is generally similar to that in adults.

Abbreviations used: ED, Emergency department; EMS, emergency medical services; EPR3, Expert Panel Report 3; MDI, metered-dose inhaler; PEF, peak expiratory flow; Sa_{O_2}, arterial oxygen saturation.

This article is part of the Joint Task Force Report: Supplemental Recommendations for the Management and Follow-up of Asthma Exacerbations, an official workshop report of the American Academy of Allergy, Asthma and Immunology (AAAAI), the American Academy of Emergency Medicine (AAEM), and the American Thoracic Society (ATS). It was approved by the AAAAI Board of Directors, January 16, 2008, the AAEM Board of Directors, January 14, 2008, and the ATS Board of Directors, March 13, 2009.

The Joint Task Force Report is copublished in the *Journal of Allergy and Clinical Immunology*, the *Journal of Emergency Medicine*, and the *American Journal of Respiratory and Critical Care Medicine*.

Supported through an unrestricted educational grant to AAAAI and AAEM for publication and dissemination costs from GlaxoSmithKline, which had no input into the task force recommendations.

Reprint requests: Not available.

Proc Am Thorac Soc Vol 6. pp 357–366, 2009
DOI: 10.1513/pats.P09ST2
Internet address: www.atsjournals.org

Early treatment of asthma exacerbations is the best strategy for management. Important elements of early treatment at the patient's home include a written asthma action plan; recognition of early signs and symptoms of worsening; appropriate intensification of therapy by increasing short-acting β-agonists and, in some cases, adding a short course of oral corticosteroids; removal, or withdrawal from an environmental factor contributing to the exacerbation; and prompt communication between the patient and clinician, seeking emergency care for severe manifestations, or both. Despite adherence to optimal chronic asthma care, it is increasingly recognized that some patients will require an urgent office visit or even an emergency department (ED) visit for further asthma care.

CLASSIFYING THE SEVERITY OF ASTHMA EXACERBATIONS

Symptoms of asthma exacerbations include breathlessness, coughing, wheezing, and chest tightness. The signs of asthma exacerbation include agitation, increased respiratory rate, increased pulse rate, and decreased lung function as measured by FEV_1, peak expiratory flow (PEF), Pa_{O_2}, Pa_{CO_2}, and arterial oxygen saturation (Sa_{O_2}). The use of accessory muscles and the inability to talk in sentences or even in phrases might or might not be present, depending on the severity of the exacerbation.

The severity of these symptoms and signs, along with the findings on functional lung assessment, are used to categorize asthma exacerbations as mild, moderate, severe, or life-threatening (Table 2). The primary determinant of severity is percent predicted FEV_1 or PEF. The exacerbation severity determines treatment. Mild exacerbations can usually be managed at home, but more severe exacerbations might require treatment and monitoring in the ED or, in more serious cases, hospital admission.

INITIAL ASSESSMENT OF ASTHMA EXACERBATIONS IN THE ED

Severe exacerbations of asthma are potentially life-threatening and therefore require prompt care, close observation for deterioration, and frequent treatments. Serial measurement of lung function provides an objective measure of improvement. The NAEPP Expert Panel recommends that all clinicians treating asthmatic patients be prepared to treat an asthma exacerbation, recognize the signs and symptoms of severe and life-threatening exacerbations (Table 2), and be familiar with the risk factors for asthma-related death (Table 1). All patients presenting with a reported asthma exacerbation should be evaluated and triaged immediately, with treatment instituted

TABLE 1. RISK FACTORS FOR DEATH FROM ASTHMA (ORIGINALLY PUBLISHED AS FIGURE 5-2A IN THE EPR3 [1])

Asthma history
Previous severe exacerbation (e.g., intubation or ICU admission for asthma)
Two or more hospitalizations for asthma in the past year
Three or more ED visits for asthma in the past year
Hospitalization or ED visit for asthma in the past month
Using > 2 canisters of SABA per month
Difficulty perceiving asthma symptoms or severity of exacerbations
Other risk factors: lack of a written asthma action plan, sensitivity to *Alternaria*
Social history
Low socioeconomic status or inner-city residence
Illicit drug use
Major psychosocial problems
Comorbidities
Cardiovascular disease
Other chronic lung disease
Chronic psychiatric disease

Definition of abbreviations: ED = emergency department; ICU = intensive care unit; SABA, short-acting beta$_2$-agonist.

Sources: Abramson *et al.*, 2001; Greenberger *et al.*, 1993; Hardie *et al.*, 2002; Kallenbach *et al.*, 1993; Kikuchi *et al.*, 1994; O'Hollaren *et al.*, 1991; Rodrigo and Rodrigo, 1993; Strunk and Mrazek, 1986; Suissa *et al.*, 1994.

promptly on determination of a moderate, severe, or life-threatening exacerbation (Figure 1).

While initial treatment is given, the clinician should obtain a brief history and perform a brief physical examination. The clinician should assess lung function (unless patient is in respiratory extremis) and obtain laboratory studies only as needed.

HISTORY

The brief history should include the time of onset; any potential causes of the exacerbation; the severity of symptoms, especially compared with previous exacerbations; and the response to any treatment given before admission to the ED. In addition, the clinician should list all current medications and the time of the last dose (especially for asthma medications), along with the estimated number of previous unscheduled office visits, ED visits, and hospitalizations for asthma, particularly within the preceding year. It is also important to note any previous episodes of serious respiratory insufficiency (e.g., involving loss of consciousness or intubation) and any other potentially complicating illness, particularly pulmonary or cardiac disease or any disease that might be aggravated by systemic corticosteroid therapy, such as diabetes or hypertension.

PHYSICAL EXAMINATION

The objective of the brief physical examination is to assess both the severity of the exacerbation (Table 2) and overall patient status, including level of alertness, fluid status, presence of cyanosis, respiratory distress, and wheezing, although wheezing can be an unreliable indicator of airway obstruction. Any possible complications, such as pneumonia, pneumothorax, or pneumomediastinum, should be identified. Upper airway obstruction, such as that caused by foreign bodies, epiglottitis, organic diseases of the larynx, vocal cord dysfunction, and extrinsic and intrinsic tracheal narrowing, should be ruled out. Clues to the presence of upper airway obstruction as a cause of dyspnea include dysphonia, inspiratory stridor, monophonic wheezing that is loudest over the central airway, normal Pa_{O_2}, and complete resolution of airflow obstruction with intubation. If upper airway obstruction is suspected, the patient should be evaluated by using flow–volume curves and laryngoscopy, either during or after the ED visit, depending on the severity of the obstruction.

ASSESSMENT OF LUNG FUNCTION

In adults and most children older than 5 years, serial measurement of lung function by using either FEV_1 or PEF performed at presentation and again 30 to 60 minutes after initial treatment is very useful in categorizing the severity of the exacerbation and indicating the need for hospitalization. However, in patients experiencing a severe or life-threatening exacerbation with obvious airway compromise and cyanosis, these objective measurements are not recommended at the time of presentation because they provide little additional information and can be very uncomfortable for the patient. In such cases the physical presentation should suffice for initial clinical assessment, and treatment should be initiated promptly. Thus 100% FEV_1 or PEF testing at triage is not a realistic or desirable goal. The optimal percentage of early spirometric testing (e.g., > 80%) will depend on the frequency of very severe exacerbations in a given ED. For the patients who present in respiratory extremis, for whom initial FEV_1 or PEF assessment was not performed, it is important to note that they are likely to benefit from such testing later in the ED visit (e.g., after a few inhaled short-acting β_2-agonist treatments or before hospital admission).

Assessment of lung function is more difficult in children than in adults. No single assessment tool appears to be the best for determining the severity of exacerbation in children (3–11), and in some children neither FEV_1 nor PEF results are obtainable during an exacerbation. In one study only 65% of children aged 5 to 18 years could complete either of these measurements during an exacerbation; among children younger than 5 years, these maneuvers were almost impossible (4).

For this reason, pulse oximetry performed at the time of arrival to the ED and repeated 1 hour after initial treatment is recommended for assessment of lung function in infants and young children. After 1 hour, those children who continue to meet the criteria for a severe exacerbation have a greater than 86% chance of requiring hospitalization, those who meet the criteria for a moderate exacerbation have an 84% chance of requiring hospitalization, and those in whom the second assessment indicates mild exacerbation have only an 18% chance of requiring hospitalization (7).

In infants, assessment of lung function depends more on physical examination than on objective measurement. Use of accessory muscles, inspiratory and expiratory wheezing, paradoxical breathing, cyanosis, and a respiratory rate of greater than 60 breaths/minute all signal serious distress, as does Sa_{O_2} of less than 90%. Because infants are at greater risk of respiratory failure, a lack of response to short-acting β_2-agonist therapy, as evidenced by either physical examination or objective measurements, indicates the need for hospitalization (9). In infants it is particularly important to monitor Sa_{O_2} by means of pulse oximetry because infants' ventilation–perfusion characteristics cause them to become hypoxemic more readily than adults. Sa_{O_2} should be normal for altitude, and a repeat Sa_{O_2} of less than 92% on room air 1 hour after initial treatment is a reliable predictor of the need for hospitalization (10, 12, 13). Use of oral corticosteroids early in the episode is essential but should not substitute for careful assessment by a physician. Most acute wheezing episodes result from viral infections and might be accompanied by fever; antibiotic treatment generally is not required.

LABORATORY STUDIES

Most patients with an asthma exacerbation do not require laboratory studies. If ordered, laboratory studies must not result

TABLE 2. CRITERIA FOR CATEGORIZING THE SEVERITY OF ASTHMA EXACERBATIONS (ORIGINALLY PUBLISHED AS FIGURE 5-3 IN THE EPR3 [1])

	Mild	Moderate	Severe	Subset: Respiratory Arrest Imminent
Symptoms				
Breathlessness	While walking	While at rest (infant—softer, shorter cry, difficulty feeding)	While at rest (infant—stops feeding)	
	Can lie down	Prefers sitting	Sits upright	
Talks in	Sentences	Phrases	Words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
Signs				
Respiratory rate	Increased	Increased	Often > 30/minute	
		Guide to rates of breathing in awake children:		
		Age	Normal rate	
		< 2 mo	< 60/min	
		2–12 mo	< 50/min	
		1–5 yr	< 40/min	
		6–8 yr	< 30/min	
Use of accessory muscles; suprasternal retractions	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Wheeze	Moderate, often only end expiratory	Loud; throughout exhalation	Usually loud; throughout inhalation and exhalation	Absence of wheeze
Pulse/minute	< 100	100–120	> 120	Bradycardia
		Guide to normal pulse rates in children:		
		Age	Normal rate	
		2–12 mo	< 160/min	
		1–2 yr	< 120/min	
		2–8 yr	< 110/min	
Pulsus paradoxus	Absent < 10 mm Hg	May be present 10–25 mm Hg	Often present > 25 mm Hg (adult), 20–40 mm Hg (child)	Absence suggests respiratory muscle fatigue
Functional assessment				
PEF percent predicted or percent personal best	⩾ 70 percent	~ 40–69 percent or response lasts < 2 hours	< 40 percent	< 25 percent (Note: PEF testing may not be needed in very severe attacks)
Pa_{O_2} (on air)	Normal (test not usually necessary)	⩾ 60 mm Hg (test not usually necessary)	< 60 mm Hg: possible cyanosis	
and/or				
P_{CO_2}	< 42 mm Hg (test not usually necessary)	< 42 mm Hg (test not usually necessary)	⩾ 42 mm Hg: possible respiratory failure	
Sa_{O_2} percent (on air) at sea level	> 95 percent (test not usually necessary)	90–95 percent (test not usually necessary)	< 90 percent	
	Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents.			

Definition of abbreviations: Pa_{O_2} = arterial oxygen pressure; P_{CO_2} = partial pressure of carbon dioxide; PEF = peak expiratory flow; Sa_{O_2} = oxygen saturation.

The presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation.

Many of these parameters have not been systematically studied, especially as they correlate with each other. Thus, they serve only as general guides (Cham *et al.*, 2002; Chey *et al.*, 1999; Gorelick *et al.*, 2004b; Karras *et al.*, 2000; Kelly *et al.*, 2002b and 2004; Keogh *et al.*, 2001; McCarren *et al.*, 2000; Rodrigo and Rodrigo 1998b; Rodrigo *et al.*, 2004; Smith *et al.*, 2002).

The emotional impact of asthma symptoms on the patient and family is variable but must be recognized and addressed and can affect approaches to treatment and follow up (Ritz *et al.*, 2000; Strunk and Mrazek 1986; von Leupoldt and Dahme 2005).

in delay of treatment. Laboratory studies are used to detect actual or impending respiratory failure, theophylline toxicity, or conditions that complicate asthma treatment, such as cardiovascular disease, pneumonia, or diabetes. For example, arterial blood gas measurements are helpful for evaluating Pa_{CO_2} in patients with suspected hypoventilation, those in severe distress, or those with FEV_1 or PEF results of 25% or less of predicted value after initial treatment. A complete blood cell count is rarely needed, but might be appropriate in patients with fever or purulent sputum, but clinicians should bear in mind that modest leukocytosis is common in patients with asthma. A chest radiograph is not recommended for routine assessment but should be obtained for patients suspected of having congestive heart failure, pneumothorax, pneumomediastinum, pneumonia, or lobar atelectasis. A baseline electrocardiogram and monitoring of cardiac rhythm are appropriate in patients older than 50 years and in those who have known coexistent heart disease or chronic obstructive pulmonary disease.

TREATMENT OF ASTHMA EXACERBATIONS

Prehospital Management

The Expert Panel recommends that emergency medical services (EMS) providers administer supplemental oxygen and inhaled short-acting bronchodilators to all patients who have signs or symptoms of an asthma exacerbation. EMS providers should have a standing order allowing them to provide albuterol to patients with an asthma exacerbation, which is consistent with

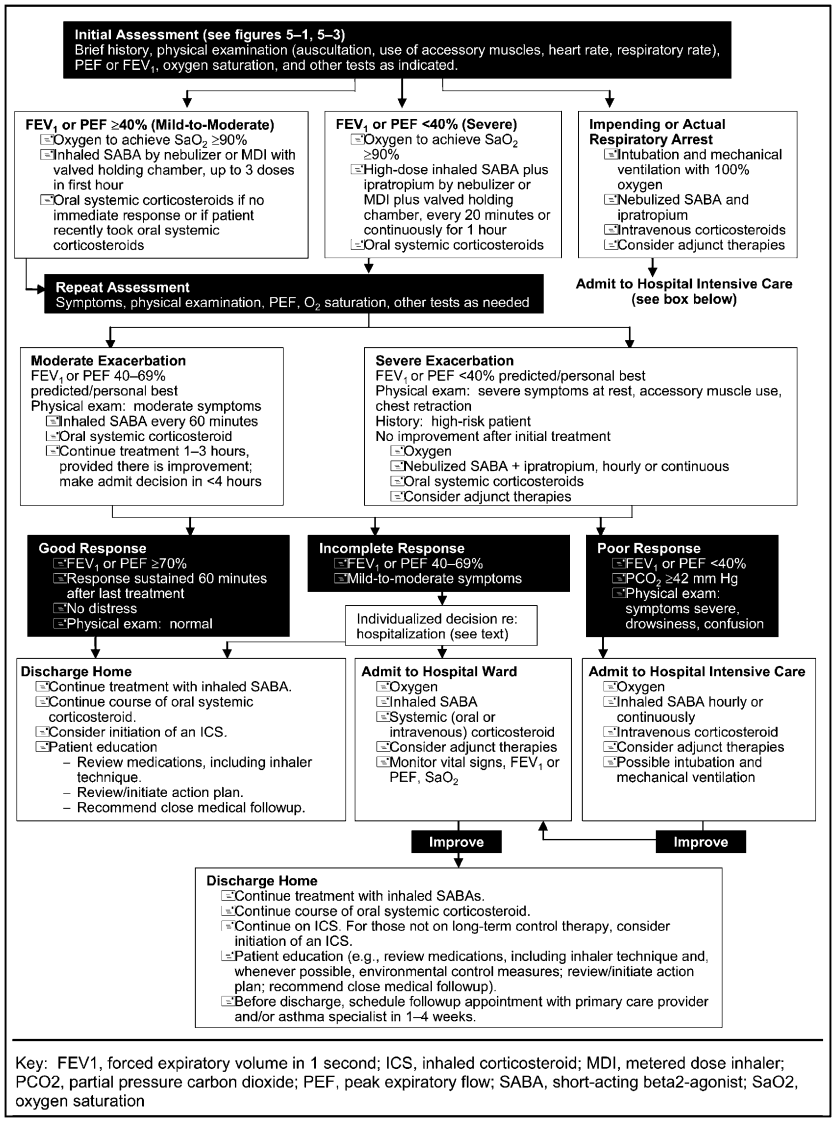


Figure 1. Management of asthma exacerbations: ED- and hospital-based care (originally published as Fig 5-6 in the EPR3 [1]).

their legally authorized scope of practice and with local medical directives. They should also have available a nebulizer, an inhaler plus a spacer/holding chamber, or both for β_2-agonist administration. If β_2-agonist treatment is not possible, subcutaneous epinephrine or terbutaline can also be administered for severe exacerbations (14, 15).

When administering bronchodilator treatment, EMS personnel should not delay patient transport to the hospital. Treatment can be repeated while transporting the patient to a maximum of three bronchodilator treatments during the first hour and then one per hour thereafter. All EMS personnel should receive training in how to respond to the signs and symptoms of severe airway obstruction and impending respiratory failure (16).

ED Management

In the ED, the severity of the asthma exacerbation determines the intensity of treatment and the frequency of patient monitoring. In general, primary treatment (i.e., administration of oxygen, inhaled β_2-agonists, and systemic corticosteroids) is the same for all asthma exacerbations, but the dose and frequency of administration, along with the frequency of patient monitoring, differ depending on the severity of the exacerbation (Figure 1 and Table 3). In addition to these three primary treatments, therapy with inhaled ipratropium bromide or other agents might also be necessary in severe exacerbations.

Oxygen. Administration of oxygen through nasal cannulae or a mask is recommended to maintain Sa_{O_2} at greater than 90% (> 95% in pregnant women and patients with concomitant heart disease). Oxygen saturation should be monitored until a clear response to bronchodilator therapy has occurred.

Inhaled short-acting β_2-agonists. All patients should receive inhaled β_2-agonist treatment because repetitive or continuous administration of these agents is the most effective means of reversing airflow obstruction (Table 3) (17–20). In the ED, three treatments administered every 20 to 30 minutes is a safe strategy for initial therapy. Thereafter, frequency of treatment varies according to patient response (i.e., improvement in airflow obstruction and associated symptoms). About 60% to 70% of patients will respond sufficiently to the initial three doses to be discharged, and most of these will demonstrate a significant response after the first dose (18, 21, 22).

In patients with severe exacerbations (i.e., < 40% of predicted value for either FEV_1 or PEF), continuous administration of β_2-agonists might be more effective than intermittent administration (17). The duration of bronchodilation from short-acting β_2-agonists is not precisely known, but might be significantly shorter than in patients with stable asthma. Because of

TABLE 3. DOSAGES OF DRUGS FOR ASTHMA EXACERBATIONS (ORIGINALLY PUBLISHED AS FIGURE 5-5 IN THE EPR3 [1])

	Dosages		
Medication	Child Dose*	Adult Dose	Comments
Inhaled short-acting beta$_2$-agonists (SABA)			
Albuterol			
Nebulizer solution (0.63 mg/3 ml, 1.25 mg/3 ml, 2.5 mg/3 ml, 5.0 mg/ml)	0.15 mg/kg (minimum dose 2.5 mg) every 20 min for 3 doses then 0.15–0.3 mg/kg up to 10 mg every 1–4 h as needed, or 0.5 mg/kg/h by continuous nebulization.	2.5–5 mg every 20 min for 3 doses, then 2.5–10 mg every 1–4 h as needed, or 10–15 mg/h continuously.	Only selective beta$_2$-agonists are recommended. For optimal delivery, dilute aerosols to minimum of 3 ml at gas flow of 6–8 L/min. Use large volume nebulizers for continuous administration. May mix with ipratropium nebulizer solution.
MDI (90 μg/puff)	4–8 puffs every 20 min for 3 doses, then every 1–4 h inhalation maneuver as needed. Use VHC; add mask in children < 4 yr.	4–8 puffs every 20 min up to 4 h, then every 1–4 h as needed.	In mild-to-moderate exacerbations, MDI plus VHC is as effective as nebulized therapy with appropriate administration technique and coaching by trained personnel.
Bitolterol			
Nebulizer solution (2 mg/ml)	See albuterol dose; thought to be half as potent as albuterol on mg basis.	See albuterol dose.	Has not been studied in severe asthma exacerbations. Do not mix with other drugs.
MDI (370 μg/puff)	See albuterol MDI dose.	See albuterol MDI dose.	Has not been studied in severe asthma exacerbations.
Levalbuterol (R-albuterol)			
Nebulizer solution (0.63 mg/3 ml, 1.25 mg/0.5 ml 1.25 mg/3 ml)	0.075 mg/kg (minimum dose 1.25 mg) every 20 min for 3 doses, then 0.075–0.15 mg/kg up to 5 mg every 1–4 h as needed.	1.25–2.5 mg every 20 min for 3 doses, then 1.25–5 mg every 1–4 h as needed.	Levalbuterol administered in one-half the mg dose of albuterol provides comparable efficacy and safety. Has not been evaluated by continuous nebulization.
MDI (45 μg/puff)	See albuterol MDI dose.	See albuterol MDI dose.	
Pirbuterol			
MDI (200 μg/puff)	See albuterol MDI dose; thought to be half as potent as albuterol on a mg basis.	See albuterol MDI dose.	Has not been studied in severe asthma exacerbations.
Systemic (injected) beta$_2$-agonists			
Epinephrine 1:1,000 (1 mg/ml)	0.01 mg/kg up to 0.3–0.5 mg every 20 min for 3 doses sq.	0.3–0.5 mg every 20 min for 3 doses sq.	No proven advantage of systemic therapy over aerosol.
Terbutaline (1 mg/ml)	0.01 mg/kg every 20 min for 3 doses then every 2–6 h as needed sq.	0.25 mg every 20 min for 3 doses sq.	No proven advantage of systemic therapy over aerosol.
Anticholinergics			
Ipratropium bromide			
Nebulizer solution (0.25 mg/ml)	0.25–0.5 mg every 20 min for 3 doses, then as needed	0.5 mg every 20 min for 3 doses then as needed	May mix in same nebulizer with albuterol. Should not be used as first-line therapy; should be added to SABA therapy for severe exacerbations. The addition of ipratropium has not been shown to provide further benefit once the patient is hospitalized.
MDI (18 μg/puff)	4–8 puffs every 20 min as needed up to 3 h	8 puffs every 20 min as needed up to 3 h	Should use with VHC and face mask for children < 4 yr. Studies have examined ipratropium bromide MDI for up to 3 h.
Ipratropium with albuterol			
Nebulizer solution (each 3-ml vial contains 0.5 mg ipratropium bromide and 2.5 mg albuterol)	1.5 ml every 20 min for 3 doses, then as needed	3 ml every 20 min for 3 doses, then as needed	May be used for up to 3 h in the initial management of severe exacerbations. The addition of ipratropium to albuterol has not been shown to provide further benefit once the patient is hospitalized.
MDI (each puff contains 18 μg ipratropium bromide and 90 μg of albuterol)	4–8 puffs every 20 min as needed up to 3 h	8 puffs every 20 min as needed up to 3 h	Should use with VHC and face mask for children < 4 years.
Systemic corticosteroids			
	(Applies to all three corticosteroids)		
Prednisone	1–2 mg/kg in 2 divided doses (maximum = 60 mg/d) until PEF is 70% of predicted or personal best	40–80 mg/d in 1 or 2 divided doses until PEF reaches 70% of predicted or personal best	For outpatient "burst," use 40–60 mg in single or 2 divided doses for total of 5–10 days in adults (children: 1–2 mg/kg/d maximum 60 mg/d for 3–10 d).
Methylprednisolone			
Prednisolone			

Definition of abbreviations: ED = emergency department; MDI = metered-dose inhaler; PEF = peak expiratory flow; VHC = valved holding chamber.

There is no known advantage for higher doses of corticosteroids in severe asthma exacerbations, nor is there any advantage for intravenous administration over oral therapy provided gastrointestinal transit time or absorption is not impaired.

The total course of systemic corticosteroids for an asthma exacerbation requiring an ED visit of hospitalization may last from 3 to 10 days. For corticosteroid courses of less than 1 week, there is no need to taper the dose. For slightly longer courses (e.g., up to 10 d), there probably is no need to taper, especially if patients are concurrently taking ICSs.

ICSs can be started at any point in the treatment of an asthma exacerbation.

* Children ⩽ 12 years of age.

potential cardiotoxicity, only selective short-acting β-agonists (albuterol, levalbuterol, and pirbuterol) should be administered in high doses.

In patients with milder exacerbations, treatment should consist of high doses (4–12 puffs) of a β_2-agonist administered by trained personnel through a metered-dose inhaler (MDI) with a valved holding chamber or by means of nebulizer therapy. Nebulizer therapy might be preferred for those patients who are unable to cooperate effectively in using an MDI because of their age, agitation, or more severe exacerbations.

Systemic corticosteroids. Systemic corticosteroids are recommended for most patients (Table 3) because they speed the resolution of airflow obstruction and reduce the rate of post-ED relapse (23). In the ED, systemic corticosteroids should be administered to all patients with moderate-to-severe exacerbations and to those who do not respond to initial β_2-agonist therapy.

The Expert Panel recommends oral administration of prednisone, which has been shown to have effects equivalent to those of intravenous methylprednisolone (24, 25) but is less invasive. Supplemental doses should be given to patients who regularly take corticosteroids, even if the exacerbation is mild. In patients with moderate-to-severe exacerbations, early administration of corticosteroid therapy might reduce the likelihood of hospitalization (23).

The Expert Panel agrees that current evidence is insufficient to warrant recommending high-dose inhaled corticosteroids over oral corticosteroids in the ED; more study is needed regarding the use of inhaled corticosteroids for acute treatment (26).

Inhaled ipratropium bromide. The Expert Panel recommends use of inhaled ipratropium bromide for acute treatment in the ED. Multiple high doses (0.5 mg of nebulizer solution or 8 puffs by means of MDI in adults and 0.25–0.5 mg of nebulizer solution or 4–8 puffs by means of MDI in children) should be added to β_2-agonist therapy to increase bronchodilation. The combination of a β_2-agonist and inhaled ipratropium bromide has been shown to reduce hospitalizations, particularly in patients with severe airflow obstruction (27, 28).

Other treatments. Antibiotics are not generally recommended for the treatment of asthma exacerbations because viruses are a much more common cause of exacerbations than bacteria. Thus antibiotics should be reserved for relatively rare cases in which there is strong evidence of a coexistent bacterial infection (e.g., pneumonia or sinusitis). Data on possible benefits of macrolide antibiotics are discussed later in this issue, although their use is still not recommended in the absence of other clinical indications based on currently available data. Aggressive hydration is not recommended for older children and adults but might be appropriate for some infants and young children, who could become dehydrated as a result of increased respiratory rate and decreased oral intake. Fluid status should be assessed before administering hydration therapy. The Expert Panel does not recommend the use of methylxanthines, chest physiotherapy, mucolytics, or sedation.

Repeat Assessment

The Expert Panel recommends that patients with severe exacerbations undergo repeat assessment after the initial dose of inhaled bronchodilator treatment and that all patients, regardless of exacerbation severity, are assessed after three doses of inhaled bronchodilator treatment (i.e., 60–90 min after initiation of therapy). Response to treatment in the ED is a better predictor of the need for hospitalization than the severity of an exacerbation at the time of presentation (3, 5, 7, 9, 29–35). All repeat assessments should include the patient's subjective response to treatment, physical findings, and FEV_1 or PEF results (or arterial blood gas measurements or pulse oximetry in patients with suspected hypoventilation, those who are in severe distress, and those with FEV_1 or PEF results $\leqslant 25\%$ of predicted value; *see* earlier discussion of laboratory studies in INITIAL ASSESSMENT OF ASTHMA EXACERBATIONS IN THE ED).

Impending Respiratory Failure

Although most patients respond well to therapy, a small percentage will show signs of worsening ventilation. Because respiratory failure can progress rapidly and is difficult to reverse, early recognition and treatment are necessary. Signs of impending respiratory failure include an inability to speak, altered mental status, intercostal retraction (29), worsening fatigue, and a Pa_{CO_2} of 42 mm Hg or greater. The Expert Panel recommends that intubation not be delayed once it is deemed necessary.

Because intubation of a severely ill asthmatic patient is difficult and can result in complications, other treatments, such as intravenous magnesium, heliox, and other treatments, are sometimes attempted.

- Intravenous magnesium sulfate has no apparent value in patients with exacerbations of lower severity, but it might be considered (conditional recommendation) in those with life-threatening exacerbations and those whose exacerbations remain severe after 1 hour of intensive conventional treatment (36, 37). The selective use of intravenous magnesium sulfate already has been adopted by many academic EDs (38). The dose is 2 g over 20 minutes in adults and 25 to 75 mg/kg in children (up to a maximum of 2 g).
- Heliox-driven albuterol nebulization can also be considered (conditional recommendation) in these patients (39, 40). Heliox also can be used to quickly decrease the work of breathing. Unfortunately, the heliox literature is complicated by the small number of subjects in most trials and by important methodological differences between trials. For example, some studies have neglected to account for the different effect of heliox versus oxygen on respirable mass (41). A large multicenter study is needed to resolve lingering questions about this promising therapy.
- Intravenous administration of β_2-agonists is a largely unproved treatment (20), and the Expert Panel does not recommend use of intravenous isoproterenol in the treatment of asthma because of the danger of myocardial toxicity. Similarly, there is insufficient evidence to date to recommend the use of leukotriene modifiers (42) or noninvasive ventilation (43) in the treatment of acute asthma.

Intubation

The Expert Panel makes the following recommendations with regard to intubation:

- Patients presenting with apnea or coma should be intubated immediately. Persistent or increasing hypercapnia, exhaustion, and depressed mental status strongly suggest the need for ventilatory support.
- Consultation with or comanagement by a physician expert in ventilator management is essential because ventilation of patients with severe asthma is complicated and risky.
- Because intubation is difficult in asthmatic patients, it should be done semielectively and before respiratory

EMERGENCY DEPARTMENT—ASTHMA DISCHARGE PLAN

Name: _____ was seen by **Dr.**_____ on ___/___/___

- Take your prescribed medications as directed—do not delay!
- Asthma attacks like this one can be prevented with a long-term treatment plan.
- Even when you feel well, you may need daily medicine to keep your asthma in good control and prevent attacks.
- Visit your doctor or other health care provider as soon as you can to discuss how to control your asthma and to develop *your own* action plan.

Your followup appointment with _____ is on: ___/___/___. **Tel:** _____

YOUR MEDICINE FOR THIS ASTHMA ATTACK IS:

Medication	Amount	Doses per day, for # days
Prednisone/prednisolone (oral corticosteroid)		_____ a day for _____ days Take the entire prescription, even when you start to feel better.
Inhaled albuterol		_____ puffs every 4 to 6 hours if you have symptoms, for _____days

YOUR DAILY MEDICINE FOR LONG-TERM CONTROL AND PREVENTING ATTACKS IS:

Medication	Amount	Doses per day
Inhaled corticosteroids		

YOUR QUICK-RELIEF MEDICINE WHEN YOU HAVE SYMPTOMS IS:

Medication	Amount	Number of doses/day
Inhaled albuterol		

ASK YOURSELF 2 TO 3 TIMES PER DAY, EVERY DAY, FOR AT LEAST 1 WEEK:

"How good is my asthma compared to when I left the hospital?"

If you feel much better:	**If you feel better, but still need your quick-relief inhaler often:**	**If you feel about the same:**	**If you feel worse:**
• Take your daily long-term control medicine.	• Take your daily long-term-control medicine. • See your doctor as soon as possible.	• Use your quick-relief inhaler. • Take your daily long-term control medicine. • See your doctor as soon as possible—don't delay.	• Use your quick-relief inhaler. • Take your daily long-term control medicine. • Immediately go to the emergency department or call 9–1–1.

YOUR ASTHMA IS UNDER CONTROL WHEN YOU:

① Can be active daily and sleep through the night.	② Need fewer than 4 doses of quick-relief medicine in a week.	③ Are free of shortness of breath, wheeze, and cough.	④ Achieve an acceptable "peak flow" (discuss with your health care provider).

Figure 2. ED asthma discharge plan (originally published as Fig 5-7 in the EPR3 [1]).

arrest occurs. Once intubation is deemed necessary, it should not be delayed and therefore should be performed in the ED, with the patient transferred to an intensive care unit appropriate to the patient's age.

- Two issues must be considered at the time of intubation. First, intravascular volume should be maintained or replaced because hypotension commonly accompanies the initiation of positive pressure ventilation. In addition, high ventilator pressures, with their associated risks of barotrauma, should be avoided.
- "Permissive hypercapnia" or "controlled hypoventilation" is the recommended ventilator strategy because it provides adequate oxygenation while minimizing airway pressures and the possibility of barotrauma (44–46). However, this strategy is not uniformly successful in critically ill asthmatic patients, and additional therapies are under evaluation.

EDUCATION OF THE ASTHMATIC PATIENT IN THE ED

The Expert Panel acknowledges that more research is needed in this area but, based on currently available information, advises offering a focused patient-education intervention to individuals who present to the ED with an asthma exacerbation. The general points of focus for this intervention are general asthma education, review of inhaler technique, a simple written asthma discharge plan, and referral for follow-up.

To help patients recognize and respond to symptoms of asthma, the provider should prepare a simple asthma discharge plan for asthma symptoms and explain it and be sure to include daily treatment plans, as well as plans for how to manage an exacerbation (Figure 2). Because many patients do not use an inhaler correctly, it is important to review inhaler technique with the patient and correct technique errors (Figure 3). Also, refer the patient for a follow-up asthma care appointment with a primary care physician or an asthma specialist within 1 week

Using an inhaler seems simple, but most patients do not use it the right way. When you use your inhaler the wrong way, less medicine gets to your lungs.

For the next few days, read these steps aloud as you do them or ask someone to read them to you. Ask your doctor, nurse, other health care provider, or pharmacist to check how well you are using your inhaler.

Use your inhaler in one of the three ways pictured below. A or B are best, but C can be used if you have trouble with A and B. Your doctor may give you other types of inhalers.

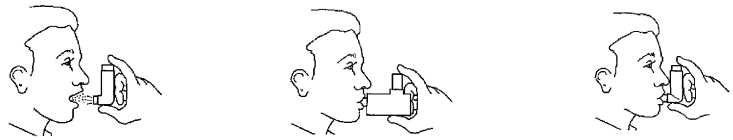
Steps for Using Your Inhaler

Getting ready	1. Take off the cap and shake the inhaler. 2. Breathe out all the way. 3. Hold your inhaler the way your doctor said (A, B, or C below).
Breathe in slowly	4. As you start breathing in slowly through your mouth, press down on the inhaler one time. (If you use a holding chamber, first press down on the inhaler. Within 5 seconds, begin to breathe in slowly.) 5. Keep breathing in slowly, as deeply as you can.
Hold your breath	6. Hold your breath as you count to 10 slowly, if you can. 7. For inhaled quick-relief medicine (short-acting $beta_2$-agonists), wait about 15–30 seconds between puffs. There is no need to wait between puffs for other medicines.

A. Hold inhaler 1 to 2 inches in front of your mouth (about the width of two fingers).

B. Use a spacer/holding chamber. These come in many shapes and can be useful to any patient.

C. Put the inhaler in your mouth. Do not use for steroids.



Clean your inhaler as needed, and know when to replace your inhaler. For instructions, read the package insert or talk to your doctor, other health care provider, or pharmacist.

Figure 3. ED asthma discharge education: how to use your MDI (originally published as Fig 5-7b in the EPR3 [1]).

and encourage the patient's participation in a more formal asthma education program.

PATIENT DISCHARGE

The Expert Panel recommends that patients who demonstrate a rapid response to treatment be observed for 30 to 60 minutes after the most recent dose of bronchodilator therapy to ensure stability of response before discharge to home. In general, patients can be discharged if FEV_1 or PEF results are 70% or more of predicted value or personal best and symptoms are minimal or absent. Patients with an incomplete response to therapy (i.e., FEV_1 or PEF results of 50% to 69% of predicted value or personal best) and with mild symptoms should be assessed on an individual basis, taking into account any risk factors for asthma-related death. Extended treatment or observation in a holding or overnight unit might be appropriate for some patients.

Patients given systemic corticosteroids should be prescribed sufficient medication to continue therapy for 3 to 10 days after discharge. For those patients considered at high risk of nonadherence, intramuscular depot injections might be as effective as oral corticosteroids in preventing relapse (47–49). The need for additional corticosteroid treatment should be assessed at a follow-up visit. Patients who are currently receiving inhaled corticosteroid therapy should continue this treatment while taking systemic corticosteroids. The Expert Panel recommends that clinicians consider (conditional recommendation) initiating inhaled corticosteroids at discharge in patients not already receiving them.

Because an ED visit is often the result of inadequate long-term management of asthma, clinicians should stress the need for regular care in an outpatient setting and ensure that all patients are referred for a follow-up medical appointment. When possible, the ED should schedule such an appointment before discharge to increase the likelihood that the patient will keep the appointment.

A discharge plan is useful to ensure that patients are provided with the necessary medications and taught how to use them, instructed in how to monitor symptoms, given a follow-up appointment, and instructed in a written plan for managing recurrence of airflow obstruction (Figures 2 and 3).

SUMMARY

Most asthma exacerbations require immediate care, close observation for deterioration, frequent treatment, and repeated measurement of lung function. The NAEPP Expert Panel recommends that all clinicians treating asthmatic patients should be prepared to treat an asthma exacerbation, recognize the signs and symptoms of severe and life-threatening exacerbations, and be familiar with the risk factors for asthma-related death. Because infants are at greater risk for respiratory failure, clinicians should also be familiar with special considerations in the assessment and treatment of infants experiencing asthma exacerbations.

All patients presenting with an asthma exacerbation should be evaluated and triaged immediately, with treatment instituted promptly on determination of a moderate, severe, or life-threatening exacerbation. Primary treatment consists of administration of oxygen, inhaled β_2-agonists, and systemic corticosteroids, with the dose and frequency of administration, along with the frequency of patient monitoring, dependent on the severity of the exacerbation.

After treatment and repeat assessment, patients can generally be discharged if FEV_1 or PEF results are 70% or more of predicted value or personal best and symptoms are minimal or absent. Before discharge, patients should be prescribed 3 to 10 days of corticosteroid therapy to reduce the risk of recurrence and provided with a follow-up appointment to evaluate the need for additional corticosteroid treatment. Clinicians should consider (conditional recommendation) initiating inhaled corticosteroids. Patients should also be educated on correct use of the inhaler and should be given a written discharge plan for increasing medications or seeking care in the event of worsening asthma.

Author disclosures were obtained by the *Journal of Allergy and Clinical Immunology* (JACI) using questions determined by the American Academy of Allergy, Asthma and Immunology (AAAAI) and JACI. Questions pertained to: employment; financial interests between the author or members of the author's immediate family or household with organizations and commercial interests; research support during the past calendar year; and legal consultation services/expert witness testimony during the past calendar year. Authors were asked to state dollar amounts in ranges of either $<$ \$10,000 or $\geqslant$ \$10,000. Authors were not required to disclose other facts that are now requested by *PATS* in conformance with American Thoracic Society policy, including knowledge of any significant financial relationship between the author's institution or employer and relevant commercial interests, and all relationships with tobacco entities.

Disclosure of potential conflict of interest: C.A.C., Jr. has been a consultant, speaker, or advisory board member for AstraZeneca, Critical Therapeutics, Dey, Genentech, GlaxoSmithKline, Merck, Novartis, and Schering-Plough and has received research support from the National Institutes of Health, AstraZeneca, Critical Therapeutics, GlaxoSmithKline, Merck, Novartis, and Respironics. G.R. has been a speaker or advisory board member for AstraZeneca, Schering-Plough, CSL Behring, Merck, and Sanofi Aventis and has provided legal consultation or expert witness testimony on the topic of environmental injuries, mostly mold-related. The rest of the authors have declared that they have no conflict of interest. M.S. has been a consultant for GlaxoSmithKline and has received research support from Aerocrine, Genentech, GlaxoSmithKline and Merck.

References

1. US Department of Health and Human Services, National Institute of Health, National Heart, Lung, and Blood Institute. Expert Panel Report 3: guidelines for the diagnosis and management of asthma [Accessed April 8, 2008]. Available from: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.
2. Reddel H, Ware S, Marks G, Salome C, Jenkins C, Woolcock A. Differences between asthma exacerbations and poor asthma control. *Lancet* 1999;353:364–369.
3. Chey T, Jalaludin B, Hanson R, Leeder S. Validation of a predictive model for asthma admission in children: how accurate is it for predicting admissions? *J Clin Epidemiol* 1999;52:1157–1163.
4. Gorelick MH, Stevens MW, Schultz T, Scribano PV. Difficulty in obtaining peak expiratory flow measurements in children with acute asthma. *Pediatr Emerg Care* 2004;20:22–26.
5. Gorelick MH, Stevens MW, Schultz TR, Scribano PV. Performance of a novel clinical score, the Pediatric Asthma Severity Score (PASS), in the evaluation of acute asthma. *Acad Emerg Med* 2004;11:10–18.
6. Keahey L, Bulloch B, Becker AB, Pollack CV Jr, Clark S, Camargo CA Jr. Initial oxygen saturation as a predictor of admission in children presenting to the emergency department with acute asthma. *Ann Emerg Med* 2002;40:300–307.
7. Kelly AM, Kerr D, Powell C. Is severity assessment after 1 hour of treatment better for predicting the need for admission in acute asthma? *Respir Med* 2004;98:777–781.
8. Keogh KA, Macarthur C, Parkin PC, Stephens D, Arseneault R, Tennis O, *et al.* Predictors of hospitalization in children with acute asthma. *J Pediatr* 2001;139:273–277.
9. Smith SR, Baty JD, Hodge D III. Validation of the pulmonary score: an asthma severity score for children. *Acad Emerg Med* 2002;9: 99–104.
10. Sole D, Komatsu MK, Carvalho KV, Naspitz CK. Pulse oximetry in the evaluation of the severity of acute asthma and/or wheezing in children. *J Asthma* 1999;36:327–333.
11. Wright RO, Santucci KA, Jay GD, Steele DW. Evaluation of pre- and posttreatment pulse oximetry in acute childhood asthma. *Acad Emerg Med* 1997;4:114–117.
12. Connett GJ, Lenney W. Use of pulse oximetry in the hospital management of acute asthma in childhood. *Pediatr Pulmonol* 1993;15:345–349.
13. Geelhoed GC, Landau LI, Le Souef PN. Evaluation of Sa_{O_2} as a predictor of outcome in 280 children presenting with acute asthma. *Ann Emerg Med* 1994;23:1236–1241.
14. Sly RM, Badiei B, Faciane J. Comparison of subcutaneous terbutaline with epinephrine in the treatment of asthma in children. *J Allergy Clin Immunol* 1977;59:128–135.
15. Smith PR, Heurich AE, Leffler CT, Henis MM, Lyons HA. A comparative study of subcutaneously administered terbutaline and epinephrine in the treatment of acute bronchial asthma. *Chest* 1977;71:129–134.
16. Workgroup on EMS Management of Asthma Exacerbations. A model protocol for Emergency Medical Services management of asthma exacerbations. *Prehosp Emerg Care* 2006;10:418–429.
17. Camargo CA Jr, Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists in the treatment of acute asthma. *Cochrane Database Syst Rev* 2003;4:CD001115.
18. Karpel JP, Aldrich TK, Prezant DJ, Guguchev K, Gaitan-Salas A, Pathiparti R. Emergency treatment of acute asthma with albuterol metered-dose inhaler plus holding chamber: how often should treatments be administered? *Chest* 1997;112:348–356.
19. McFadden ER Jr. Acute severe asthma. *Am J Respir Crit Care Med* 2003;168:740–759.
20. Travers A, Jones AP, Kelly K, Barker SJ, Camargo CA, Rowe BH. Intravenous beta2-agonists for acute asthma in the emergency department. *Cochrane Database Syst Rev* 2001;2:CD002988.
21. Rodrigo C, Rodrigo G. Therapeutic response patterns to high and cumulative doses of salbutamol in acute severe asthma. *Chest* 1998; 113:593–598.
22. Strauss L, Hejal R, Galan G, Dixon L, McFadden ER Jr. Observations on the effects of aerosolized albuterol in acute asthma. *Am J Respir Crit Care Med* 1997;155:454–458.
23. Rowe BH, Edmonds ML, Spooner CH, Diner B, Camargo CA Jr. Corticosteroid therapy for acute asthma. *Respir Med* 2004;98: 275–284.
24. Harrison BD, Stokes TC, Hart GJ, Vaughan DA, Ali NJ, Robinson AA. Need for intravenous hydrocortisone in addition to oral prednisolone in patients admitted to hospital with severe asthma without ventilatory failure. *Lancet* 1986;1:181–184.
25. Ratto D, Alfaro C, Sipsey J, Glovsky MM, Sharma OP. Are intravenous corticosteroids required in status asthmaticus? *JAMA* 1988;260: 527–529.
26. Edmonds ML, Camargo CA Jr, Pollack CV Jr, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. *Cochrane Database Syst Rev* 2003; (3):CD002308.
27. Plotnick LH, Ducharme FM. Combined inhaled anticholinergics and beta2-agonists for initial treatment of acute asthma in children. *Cochrane Database Syst Rev* 2000; (4):CD000060.
28. Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. *Thorax* 2005;60:740–746. (published erratum appears in *Thorax* 2006;61:274 and *Thorax* 2006;61:458).
29. Cham GW, Tan WP, Earnest A, Soh CH. Clinical predictors of acute respiratory acidosis during exacerbation of asthma and chronic obstructive pulmonary disease. *Eur J Emerg Med* 2002;9:225–232.
30. Karras DJ, Sammon ME, Terregino CA, Lopez BL, Griswold SK, Arnold GK. Clinically meaningful changes in quantitative measures of asthma severity. *Acad Emerg Med* 2000;7:327–334.
31. Kelly AM, Powell C, Kerr D. Patients with a longer duration of symptoms of acute asthma are more likely to require admission to hospital. *Emerg Med (Fremantle)* 2002;14:142–145.
32. McCarren M, Zalenski RJ, McDermott M, Kaur K. Predicting recovery from acute asthma in an emergency diagnostic and treatment unit. *Acad Emerg Med* 2000;7:28–35.
33. Rodrigo GJ. Comparison of inhaled fluticasone with intravenous hydrocortisone in the treatment of adult acute asthma. *Am J Respir Crit Care Med* 2005;171:1231–1236.
34. Rodrigo G, Rodrigo C. Assessment of the patient with acute asthma in the emergency department: a factor analytic study. *Chest* 1993;104: 1325–1328.

35. Rodrigo G, Rodrigo C. Early prediction of poor response in acute asthma patients in the emergency department. *Chest* 1998;114:1016–1021.
36. Cheuk DK, Chau TC, Lee SL. A meta-analysis on intravenous magnesium sulphate for treating acute asthma. *Arch Dis Child* 2005;90:74–77.
37. Rowe BH, Bretzlaff JA, Bourdon C, Bota GW, Camargo CA Jr. Intravenous magnesium sulfate treatment for acute asthma in the emergency department: a systematic review of the literature. *Ann Emerg Med* 2000;36:181–190.
38. Rowe BH, Camargo CA Jr. The use of magnesium sulfate in acute asthma: rapid uptake of evidence in North American emergency departments. *J Allergy Clin Immunol* 2006;117:53–58.
39. Kim IK, Phrampus E, Venkataraman S, Pitetti R, Saville A, Corcoran T, *et al.* Helium/oxygen-driven albuterol nebulization in the treatment of children with moderate to severe asthma exacerbations: a randomized, controlled trial. *Pediatrics* 2005;116:1127–1133.
40. Lee DL, Hsu CW, Lee H, Chang HW, Huang YC. Beneficial effects of albuterol therapy driven by heliox versus by oxygen in severe asthma exacerbation. *Acad Emerg Med* 2005;12:820–827.
41. Hess DR, Acosta FL, Ritz RH, Kacmarek RM, Camargo CA Jr. The effect of heliox on nebulizer function using a beta-agonist bronchodilator. *Chest* 1999;115:184–189.
42. Camargo CA Jr, Smithline HA, Malice MP, Green SA, Reiss TF. A randomized controlled trial of intravenous montelukast in acute asthma. *Am J Respir Crit Care Med* 2003;167:528–533.
43. Ram FS, Wellington S, Rowe BH, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. *Cochrane Database Syst Rev* 2005;1:CD004360.
44. Darioli R, Perret C. Mechanical controlled hypoventilation in status asthmaticus. *Am Rev Respir Dis* 1984;129:385–387.
45. Menitove SM, Goldring RM. Combined ventilator and bicarbonate strategy in the management of status asthmaticus. *Am J Med* 1983;74:898–901.
46. Tuxen DV. Permissive hypercapnic ventilation. *Am J Respir Crit Care Med* 1994;150:870–874.
47. Lahn M, Bijur P, Gallagher EJ. Randomized clinical trial of intramuscular vs oral methylprednisolone in the treatment of asthma exacerbations following discharge from an emergency department. *Chest* 2004;126:362–368.
48. Rowe BH, Edmonds ML, Spooner CH, Camargo CA Jr. Evidence-based treatments for acute asthma. *Respir Care* 2001;46:1380–1391.
49. Schuckman H, DeJulius DP, Blanda M, Gerson LW, DeJulius AJ, Rajaratnam M. Comparison of intramuscular triamcinolone and oral prednisone in the outpatient treatment of acute asthma: a randomized controlled trial. *Ann Emerg Med* 1998;31:333–338.

Noninvasive Ventilation

Richard Nowak[1], Thomas Corbridge[2], and Barry Brenner[3]

[1]Department of Emergency Medicine, Henry Ford Health System, Detroit, Michigan; [2]Division of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois; and [3]Department of Emergency Medicine, Case Western Reserve School of Medicine, Cleveland, Ohio

Keywords: acute asthma; asthma exacerbation; emergency department; noninvasive mechanical ventilation; noninvasive positive pressure ventilation; continuous positive airway pressure ventilation; bilevel positive airway pressure ventilation

Noninvasive positive pressure ventilation (NPPV) offers ventilatory assistance for respiratory failure. There are two principal forms used: continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP). Both provide positive airway pressure during the respiratory cycle, but BiPAP offers pressure in a biphasic manner, with higher pressures during inspiration than expiration. Studies in patients with obstructive lung disease indicate that low-level CPAP offsets the detrimental effects of auto–positive end-expiratory pressure, which are caused by gas trapped in alveoli at end expiration and decrease inspiratory work of breathing (1). The addition of inspiratory pressure support to CPAP (or BiPAP) generally improves tidal volume in proportion to the amount of pressure applied (2). Both CPAP and BiPAP have been used as an alternative to intubation in patients with a variety of respiratory conditions, including congestive heart failure with pulmonary edema and chronic obstructive pulmonary disease (COPD), avoiding the complications associated with endotracheal intubation (3, 4).

In acute exacerbations of COPD, a number of randomized controlled trials have demonstrated that NPPV decreases respiratory rate, dyspnea, Pa_{CO_2}, hospital length of stay, rates of intubation, and mortality (3). Asthma exacerbations are similar to COPD exacerbations in that increased airway obstruction and dynamic hyperinflation impair ventilatory efforts, potentially leading to respiratory muscle fatigue. However, there is a paucity of randomized controlled trials on the use of NPPV in asthma. Still, positive results have been reported in a limited number of case reports, case series, or uncontrolled studies with both CPAP and BiPAP (5–12). In these reports the experience with NPPV in patients with acute severe asthma has been encouraging, but its specific use in the treatment of acute asthma remains poorly defined. The goal of this review is to critically evaluate the body of literature relating to the use of NPPV and resultant outcomes in patients with severe asthma exacerbations. The authors combine evidence-based data with expert opinion to provide guidance on this controversial topic.

METHODS

Two sets of keywords were selected for the systematic literature review. The first set included the terms *acute asthma*, *acute severe asthma*, *acute bronchospasm*, *acute reactive airways disease*, *asthma exacerbation*, *emergency asthma*, and *status asthmaticus*. The second set of keywords included the following terms: *airway pressure ventilation*, *bilevel positive airway pressure ventilation (BiPAP)*, *continuous positive airway pressure ventilation (CPAP)*, *intermittent positive-pressure ventilation*, *nasal ventilation*, *noninvasive mechanical ventilation*, *noninvasive positive pressure ventilation*, *NIPPV*, *NPPV*, *noninvasive ventilatory support*, *noninvasive ventilation*, *NIV*, *positive pressure ventilation*, *pressure-controlled ventilation*, *ventilation support*, and *volume-controlled ventilation*. Additional details of the methodology for all literature reviews in this supplement are provided in the introduction to this issue (13). The task force specified the level of evidence used to justify the recommendations being made, and the system used to describe the level of evidence is also defined in the introduction to this issue.

RESULTS

The literature search produced eight randomized controlled trials and three meta-analyses. Two of these randomized controlled trials were deemed appropriate for this review, and two meta-analyses were considered relevant. One of the randomized trials (14) was included in one of the meta-analyses (15).

Randomized Controlled Trials

Soroksky *et al.* (14) reported on a randomized, placebo-controlled study that compared conventional asthma treatment plus 3 hours of therapeutic BiPAP (n = 15) with conventional treatment plus sham BiPAP (n = 15) in patients aged 18 to 50 years with acute asthma presenting to the emergency department. The protocol called for an initial expiratory pressure of 3 cm H_2O that was increased by 1 cm H_2O every 15 minutes to a maximum pressure of 5 cm H_2O. The initial inspiratory pressure was set at 8 cm H_2O and increased by 2 cm H_2O every 15 minutes to a maximum pressure of 15 cm H_2O or until the respiratory rate was less than 25 breaths/minute, whichever came first. Patients were eligible to be enrolled in the study if they had an FEV_1 of less than 60% of predicted value, a respiratory rate of greater than 30 breaths/minute, at least a 1-year history of asthma, and a current asthma attack duration of less than 7 days. Intervention effectiveness was measured based on improvement in lung function test results defined as an increase of at least 50% in FEV_1 compared with the baseline value on hospital admission or an increase in FEV_1 to greater than 60% of predicted value. Secondary end points included need for hospitalization and occurrence of respiratory failure with need for mechanical ventilation. BiPAP improved lung function test results. Eighty

Abbreviations used: BiPAP, Bilevel positive airway pressure; CAS, Clinical Asthma Score; COPD, Chronic obstructive pulmonary disease; CPAP, Continuous positive airway pressure; NPPV, Noninvasive positive pressure ventilation.

This article is part of the Joint Task Force Report: Supplemental Recommendations for the Management and Follow-up of Asthma Exacerbations, an official workshop report of the American Academy of Allergy, Asthma and Immunology (AAAAI), the American Academy of Emergency Medicine (AAEM), and the American Thoracic Society (ATS). It was approved by the AAAAI Board of Directors, January 16, 2008, the AAEM Board of Directors, January 14, 2008, and the ATS Board of Directors, March 13, 2009.

The Joint Task Force Report is copublished in the *Journal of Allergy and Clinical Immunology*, the *Journal of Emergency Medicine*, and the *American Journal of Respiratory and Critical Care Medicine*.

Supported through an unrestricted educational grant to AAAAI and AAEM for publication and dissemination costs from GlaxoSmithKline, which had no input into the task force recommendations.

Reprint requests: Richard M. Nowak, M.D., Department of Emergency Medicine, Henry Ford Health System, 2799 West Grand Blvd., Detroit, MI 48202.

Proc Am Thorac Soc Vol 6. pp 367–370, 2009
DOI: 10.1513/pats.P09ST3
Internet address: www.atsjournals.org

percent of patients in the BiPAP group reached predetermined primary end points compared with 20% of control patients. The mean increase in FEV_1 was 53.5% ± 23.4% with BiPAP compared with 28.5% ± 22.6% in the conventional treatment group ($P = 0.0006$). Hospitalization was required in 17.6% of the BiPAP group versus 62.5% of control group ($P = 0.0134$). Based on these findings, the researchers concluded that the addition of BiPAP to conventional treatment improves lung function and reduces the need for hospitalization in patients with severe acute asthma exacerbations.

Thill *et al.* (16) tested the hypothesis that BiPaP improves respiratory function in children with lower airway obstruction in a prospective, randomized, crossover study. Lower airway obstruction was defined as increased work of breathing, wheezing, dyspnea, and a Clinical Asthma Score (CAS) of greater than 3. A total of 20 children (mean age, 48 mo; range, 2 mo to 14 yr) with acute lower airway obstruction were randomized to receive either 2 hours of noninvasive ventilation with a nasal mask followed by crossover to 2 hours of standard therapy (group 1) or 2 hours of standard therapy followed by 2 hours of noninvasive ventilation (group 2). The primary end point of this study was the efficacy of BiPAP, as demonstrated by a change in respiratory rate, CAS, and assessment of gas exchange. All patients received supplemental oxygen with the high-flow Venturi mask system with fraction of inspired oxygen titrated, inhaled β_2-agonists, and intravenous corticosteroids. The study demonstrated the following results: (*1*) BiPAP was associated with a decrease in respiratory rate for all patients after 2 hours compared with baseline values (49.5 ± 13.9 versus 32.0 ± 6.2 breaths/min, $P < 0.01$); (*2*) BiPAP was associated with lower total CASs (2.1 ± 1.0 versus 5.4 ± 1.2, $P < 0.0001$); (*3*) BiPAP was associated with lower scores for individual components of accessory muscle use, wheezing, and dyspnea (all $P < 0.01$); (*4*) discontinuation of BiPAP in group 1 at the 2-hour crossover time point was associated with an increase in respiratory rate and total CAS by the 4-hour data collection time point; (*5*) BiPAP was not associated with significant differences in oxygen saturation or transcutaneous CO_2 measurement; and (*6*) the delivered oxygen concentration needed to maintain oxygen saturations of 90% or greater was lower when patients were receiving BiPAP (0.57 versus 0.38, $P < 0.0001$). Based on these results, the researchers concluded that BiPAP can be an effective treatment for children with acute lower airway obstruction.

Meta-Analyses

Keenan and Brake (17) undertook a meta-analysis to determine the level of evidence available in the literature to support the use of NPPV in various causes of acute respiratory failure. A systematic review of the literature was done using a Medline search, review of personal files, and review of bibliographies of relevant articles for randomized controlled trials, controlled trials, and clinical trials. Numerous studies were identified, but most were in the form of case reports or case series. Seven randomized controlled trials were identified in the meta-analysis that supported the use of NPPV in patients with severe exacerbation of COPD. An additional single randomized controlled trial and three case series were identified in the meta-analysis that provided evidence supporting the use of NPPV in patients with a severe asthma exacerbation. Additional studies were identified that evaluated the use of NPPV in patients with pneumonia, adult respiratory distress syndrome, and cardiogenic pulmonary edema. The authors found that numerous studies described the use of NPPV, but most were in the form of case reports or case series. The authors concluded that there is some evidence for benefit in patients with COPD, but there is currently a lack of randomized controlled trial data and therefore insufficient evidence to support the use of NPPV in acute respiratory failure of other causes.

Ram *et al.* (15) analyzed the literature to determine the efficacy of various types of NPPV in adults with severe acute asthma in comparison with usual medical care with respect to mortality, tracheal intubation, changes in blood gases, and hospital length of stay. Of 11 identified trials, 10 were excluded, leaving only the trial by Soroksky *et al.* (14) discussed above. Ram *et al.* (15) concluded that the results of Soroksky *et al.* (14) are promising but that large, randomized controlled trials are needed to determine the role of NPPV in status asthmaticus. One point noted by Ram *et al.* (15) is that attempts to mask NPPV treatment are possible, as demonstrated in the study by Soroksky *et al.* (14), and this masking should be encouraged in future studies to reduce bias in the study outcomes.

Other Studies

Shivaram *et al.* (5) studied the effects of CPAP on 21 asthmatic patients and 19 control subjects. The fractional inspiratory time, a marker of diaphragm fatigue, was significantly reduced, with the best sensation of comfort in asthmatic patients occurring at a mean of 5.3 cm H_2O CPAP. The authors concluded that low-to-medium levels of CPAP assist inspiratory muscles, thereby decreasing the potential for fatigue. CPAP reduces the magnitude of the inspiratory effort during spontaneous breathing by overcoming detrimental effects of auto–positive end-expiratory pressure. At higher levels of CPAP, beneficial effects might be offset by decreased expiratory flow rates and an increase in lung hyperinflation.

In a separate study Shivaram *et al.* (6) studied the effects of 5 and 7.5 cm H_2O CPAP on 21 acutely ill asthmatic patients. Six control subjects were fitted with sham CPAP at ambient pressure. Application of either level of CPAP reduced respiratory rate and dyspnea without adverse effects on gas exchange, expiratory airflow, or hemodynamics.

Meduri *et al.* (7) evaluated the effects of BiPAP in an uncontrolled study of 17 patients with acute severe asthma and ventilatory failure. Therapy was initiated with CPAP (4 ± 2 cm H_2O) and inspiratory pressure support (14 ± 5 cm H_2O), and the mean peak inspiratory pressure required to achieve target goals (respiratory rate < 25 breaths/min and exhaled tidal volume > 7 ml/kg) was 18 ± 5 cm H_2O. BiPAP-treated patients demonstrated rapid improvements in gas exchange abnormalities. Two patients were subsequently intubated for worsening hypercapnia. All patients survived. In a separate report Meduri *et al.* (8) reported that within a larger group with respiratory failure, all 5 of a subset with acute severe asthma and respiratory failure improved with CPAP, and only 1 required intubation and mechanical ventilation.

Patrick *et al.* (9) reported on 2 patients with acute severe asthma (1 with a Pa_{CO_2} of 73 mm Hg and a pH of 7.17) requiring immediate therapy and treated with proportional assist ventilation. Neither patient was intubated, and both were later discharged from the hospital. These authors concluded that proportional assisted ventilation is useful in patients with respiratory failure, including acute asthma.

Fernandez *et al.* (10) in 2001 reported a retrospective trial of 22 patients, detailing their clinical experience with the use of CPAP in patients with acute asthma admitted to their intensive care unit. They concluded that CPAP was a suitable method for improving alveolar ventilation and could decrease the need for intubation in a selected group of patients with severe acute asthma.

In a retrospective study published in 2005, Carroll and Schramm (11) reviewed the treatment of status asthmaticus with BiPAP in 5 children. They found that BiPAP was well tolerated and that there was improvement in respiratory rate ($P = 0.03$) and modified pulmonary index scores ($P = 0.03$) after the initiation of BiPAP.

Finally, Beers *et al*. (12) recently evaluated 83 pediatric patients with status asthmaticus to examine the safety, tolerance, and benefit of BiPAP used with β_2-agonist therapy. Of the 77% (73/83) who tolerated BiPAP, 77% showed an average respiratory rate decrease of 23.6%. Improved oxygen saturation (average of 6.6%) was experienced by 88%. Furthermore, 22% (16/73) of the patients started on BiPAP in the emergency department avoided designated admission to the pediatric intensive care unit. BiPAP was found to be well tolerated and safe in these patients and provided benefits when used as an adjunct treatment.

DISCUSSION

As reviewed above, retrospective studies, case series, and subgroup analyses of larger studies in patients with respiratory failure have shown that patients with acute severe asthma have improved with treatment with NPPV. In our search of the literature for recent controlled trials and meta-analyses, four studies were identified that were believed to be relevant to the current review of the use of NPPV in patients with severe asthma exacerbations. Two of the studies were randomized controlled trials, and two were meta-analyses. The two randomized controlled studies examined two different clinical aspects of the use of NPPV: (*1*) the effects of BiPAP on respiratory function in children with lower airway obstruction and (*2*) the use of nasal bilevel pressure ventilation combined with conventional treatment in adults.

In both studies the outcomes supported the use of NPPV in the treatment of an acute exacerbation of asthma. In the study by Thill *et al*. (16) of children with lower airway obstruction, there was an improvement in respiratory rate and clinical signs of asthma with the use of BiPAP, although oxygen saturation did not change with the addition of BiPAP. This was the first prospective study of BiPAP in children, and it demonstrated that BiPAP was feasible and resulted in both clinically and statistically significant improvements in asthma symptoms. Although patient compliance with BiPAP might be more difficult to achieve in very young patients, these authors were able to demonstrate successful use of BiPAP in children as young as 2 months of age. In the study by Soroksky *et al*. (14), adults treated with nasal bilevel pressure ventilation had improved lung function and less need for hospitalization.

The two meta-analyses that were examined also reported results that were supportive of the use of NPPV in the treatment of respiratory failure. The two meta-analyses studied the use of NPPV in adults with acute asthma (15) and the use of CPAP in various types of respiratory failure with a limited number of asthmatic patients (17). The former meta-analysis only found that the Soroksky *et al*. (14) study met their criteria for review. The second meta-analysis demonstrated benefit in severe acute exacerbations of COPD in multiple randomized controlled trials but found much less evidence in patients with severe asthma attacks. The conclusions from the meta-analyses regarding asthma are limited by a lack of randomized controlled trial data because much of the information about patient response to NPPV in severe asthma exacerbations comes from case reports, which are subject to selection bias and other biases that might affect the conclusions. Nonetheless, limited controlled data suggest that NPPV might be useful in the treatment of severe asthma exacerbations.

SUMMARY OF RECOMMENDATIONS

Overall, the current systematic review of the literature suggests that NPPV might be a useful adjunct in the treatment of severe asthma exacerbations. However, despite these encouraging reports, the data from randomized prospective controlled trials currently available are minimal. Thus although no definitive conclusion about the role of NPPV in the treatment of severe acute asthma can be made from the literature search, the following recommendations are provided by the authors given the current knowledge regarding NPPV and acute asthma.

1. Conditional: a trial of NPPV before intubation and mechanical ventilation should be considered in selected patients with acute asthma and respiratory failure (Evidence Category B). These would include patients who can tolerate and cooperate with this therapy. NPPV should only be used in these patients provided that the respiratory therapists, nurses, and physicians who are responsible for their care are very familiar with this technology and the patients are in an area where they can be constantly observed and monitored and can receive immediate intubation, if needed.

Given the minimal complications reported to date with NPPV use in patients with acute severe asthma and the potential ability to avoid intubation and mechanical ventilation for some of these patients, this seems to be a reasonable approach until further clinical trials are reported.

2. Conditional: pending additional data, specific settings should follow the protocol set forth in the article by Soroksky *et al*. (14) (Evidence Category D). Settings should be individualized and guided by careful evaluation of clinical response.

Author disclosures were obtained by the *Journal of Allergy and Clinical Immunology* (JACI) using questions determined by the American Academy of Allergy, Asthma and Immunology (AAAAI) and JACI. Questions pertained to: employment; financial interests between the author or members of the author's immediate family or household with organizations and commercial interests; research support during the past calendar year; and legal consultation services/expert witness testimony during the past calendar year. Authors were asked to state dollar amounts in ranges of either $<$ \$10,000 or $\geq$ \$10,000. Authors were not required to disclose other facts that are now requested by *PATS* in conformance with American Thoracic Society policy, including knowledge of any significant financial relationship between the author's institution or employer and relevant commercial interests, and all relationships with tobacco entities.

Disclosure of potential conflict of interest: R.N. has declared that he has no conflict of interest. T.C. is on the speakers' bureau for GlaxoSmithKline. B.B. has declared that he has no conflict of interest.

References

1. Appendini L, Patessio A, Zanaboni S, Carone M, Gukov B, Donner CF, *et al.* Physiologic effects of positive end-expiratory pressure and mask support during exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1994;149:1069–1076.
2. Meyer TJ, Hill NS. Noninvasive positive pressure ventilation to treat respiratory failure. *Ann Intern Med* 1994;120:760–770.
3. Mehta S, Hill N. Noninvasive ventilation. State of the Art. *Am J Respir Crit Care Med* 2001;163:540–577.
4. Yosefy C, Hay E, Ben-Barak A, Derazon H, Magen E, Reisin L, *et al.* BiPAP ventilation as assistance for patients presenting with respiratory distress in the department of emergency medicine. *Am J Respir Med* 2003;2:343–347.
5. Shivaram U, Donath J, Khan FA, Juliano J. Effects of continuous positive airway pressure in acute asthma. *Respiration* 1987;52:157–162.
6. Shivaram U, Miro AM, Cash ME, Finch PJ, Heurich AE, Kamholz SL. Cardiopulmonary responses to continuous positive airway pressure in acute asthma. *J Crit Care* 1993;8:87–92.
7. Meduri GU, Cook TR, Turner RE, Cohen M, Leeper KV. Noninvasive positive pressure ventilation in status asthmaticus. *Chest* 1996;110:767–774.
8. Meduri GU, Turner RE, Abou-Shala N, Wunderink R, Tolley E. Noninvasive positive pressure ventilation via face mask. First-line

intervention in patients with acute hypoxemic respiratory failure. *Chest* 1996;109:179–193.
9. Patrick W, Webster K, Ludwig L, Roberts D, Wiebe P, Younes M. Noninvsive positive-pressure ventilation in acute respiratory distress without prior chronic respiratory failure. *Am J Respir Crit Care Med* 1996;153:1005–1011.
10. Fernandez MM, Villagra A, Blanch L, Fernandez R. Non-invasive mechanical ventilation in status asthmaticus. *Intensive Care Med* 2002;27:486–492.
11. Carroll CL, Schramm CM. Noninvasive positive pressure ventilation for the treatment of status asthmaticus in children. *Ann Allergy Asthma Immunol* 2006;96:454–459.
12. Beers SL, Abrama TJ, Bracken A, Wiebe RA. Bilevel positive airway pressure in the treatment of status asthmaticus in pediatrics. *Am J Emerg Med* 2007;25:6–9.
13. Schatz M, Kazzi AAN, Brenner B, Camargo Jr CA, Corbridge T, Krishnan JA, Nowak R, Rachelefsky G. Introduction. *Proc Am Thorac Soc* 2009;6:353–356.
14. Soroksky A, Stav D, Shpirer I. A pilot prospective, randomized placebo-controlled trial of bilevel positive airway pressure in acute asthma attack. *Chest* 2003;123:1018–1025.
15. Ram FS, Wellington SR, Rowe B, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. *Cochrane Database Syst Rev* 2005;3:CD004360.
16. Thill PJ, McGuire JK, Baden HP, Green TP, Checchia PA. Noninvasive positive-pressure ventilation in children with lower airway obstruction. *Pediatr Crit Care Med* 2004;5:337–342. (published erratum appears in Pediatr Crit Care Med 2004;5:590.)
17. Keenan SP, Brake D. An evidence-based approach to noninvasive ventilation in acute respiratory failure. *Crit Care Clin* 1998;14:359–372.

Intubation and Mechanical Ventilation of the Asthmatic Patient in Respiratory Failure

Barry Brenner[1], Thomas Corbridge[2], and Antoine Kazzi[3]

[1]Department of Emergency Medicine, Case Western Reserve School of Medicine, Cleveland, Ohio; [2]Division of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois; and [3]Department of Emergency Medicine, American University of Beirut, Beirut, Lebanon

Keywords: acute asthma; asthma exacerbation; emergency department; mechanical ventilation; respiratory failure; respiratory arrest; intubation; orotracheal intubation; nasotracheal intubation

There are approximately 2 million emergency department visits for acute asthma per year with 12 million people reporting having had asthma "attacks" in the past year (1). Approximately 2% to 20% of admissions to intensive care units (ICUs) are attributed to severe asthma, with intubation and mechanical ventilation deemed necessary in up to one third in the ICU (2) and mortality rates in patients receiving intubation from 10% to 20% in this patient population (3).

The onset of acute asthma symptoms ranges from hours to weeks. Type I acute asthma, also known as slow-onset asthma, often presents as a gradual deterioration of the clinical scenario, which is superimposed on a background of chronic and poorly controlled asthma. Type II acute asthma, or rapid-onset asthma, tends to be more dangerous and frequently presents with sudden narrowing of the airways (4).

This article reviews the recent evidence-based data regarding the indications, techniques, and complications of intubation and mechanical ventilation in the treatment of acute asthma in the emergency department (ED). It also discusses possible strategies for preventing the need for intubation in patients with severe exacerbations who are not responding to conventional therapy. Finally, this article provides practical management recommendations in this clinical setting.

METHODS

Three sets of keywords were used for the systematic literature review. The first set included the terms *acute asthma*, *acute severe asthma*, *acute bronchospasm*, *acute reactive airways disease*, *asthma exacerbation*, *emergency asthma*, and *status asthmaticus*. The second set of keywords included the following terms: *mechanical ventilation*, *mechanical ventilator*, *invasive ventilation*, *mechanical ventilatory support*, *continuous mandatory ventilation (CMV)*, *assist-control ventilation*, *synchronized intermittent mandatory ventilation (SIMV)*, *intermittent positive-pressure ventilation*, and *complications of mechanical ventilation*. The third set of keywords included the following terms: *hypercapnea*, *hypercapnia*, *hypopnea*, *hypercapnic*, *respiratory failure*, *respiratory insufficiency*, *respiratory arrest*, *arrest*, *hypoventilation*, *hypoxemia*, *intubation*, *endotracheal intubation*, *oral intubation*, *orotracheal intubation*, *nasal intubation*, *nasotracheal intubation*, *intratracheal intubation*, *respiratory acidosis*, *fatal*, and *life-threatening*. Additional details of the methodology for all literature reviews in this issue are provided in the introduction to this issue (5). The task force specified the level of evidence used to justify the recommendations being made, and the system used to describe the level of evidence is also defined in the introduction to this issue.

RESULTS

The search for the topic of *intubation* produced 41 randomized controlled trials (RCTs) and 6 meta-analyses. Five RCTs were deemed appropriate for this review. The search for the topic of *mechanical ventilation* revealed 5 RCTs and 4 meta-analyses. None of these RCTs or meta-analyses was deemed appropriate for this review because they did not deal specifically with mechanical ventilation of asthmatic patients or effects of mechanical ventilation on airway function.

RCTs

Groeben *et al.* (6) conducted a study on 10 asthmatic patients (2 women and 8 men) to assess the effect on lung function of awake fiberoptic intubation after lidocaine or dyclonine inhalation with or without pretreatment with salbutamol. Baseline FEV_1 was recorded, and inhalational challenge with histamine was administered to confirm bronchial hyperreactivity. There were 3 hypotheses: (*1*) awake tracheal intubation during topical anesthesia leads to a decrease in FEV_1; (*2*) there is no difference in the response to awake tracheal intubation when either lidocaine or dyclonine are used for topical anesthesia; and (*3*) pretreatment with salbutamol attenuates the response to awake tracheal intubation and eliminates possible minor differences in the response after topical anesthesia with either lidocaine or dyclonine. On 4 different days in a randomized double-blind fashion, the volunteers inhaled either dyclonine or lidocaine with or without salbutamol pretreatment. FEV_1 did not change significantly from baseline values with lidocaine inhalation versus placebo (4.43 ± 0.67 versus 4.29 ± 0.72 L) or dyclonine inhalation compared with placebo (4.53 ± 0.63 versus 4.42 ± 0.80 L); however, salbutamol slightly but significantly increased FEV_1 in the treatment group receiving lidocaine compared with the placebo group (4.45 ± 0.76 versus 4.71 ± 0.61 L, $P = 0.0034$) and with the treatment group receiving dyclonine versus the placebo group (4.48 ± 0.62 versus 4.71 ± 0.61 L, $P = 0.0121$). After awake intubation, FEV_1 decreased significantly with lidocaine topical anesthesia (4.29 ± 0.72 to

Abbreviations used: ABG, Arterial blood gas; ED, Emergency department; ICU, Intensive care unit; MDI, Metered-dose inhaler; PEEP, Positive end-expiratory pressure; Pplat, Plateau pressure; RCT, Randomized controlled trial; Rrs, Respiratory system resistance; Vei, Volume at end-inspiration.

This article is part of the Joint Task Force Report: Supplemental Recommendations for the Management and Follow-up of Asthma Exacerbations, an official workshop report of the American Academy of Allergy, Asthma and Immunology (AAAAI), the American Academy of Emergency Medicine (AAEM), and the American Thoracic Society (ATS). It was approved by the AAAAI Board of Directors, January 16, 2008, the AAEM Board of Directors, January 14, 2008, and the ATS Board of Directors, March 13, 2009.

The Joint Task Force Report is copublished in the *Journal of Allergy and Clinical Immunology*, the Journal of *Emergency Medicine,* and the *American Journal of Respiratory and Critical Care Medicine*.

Supported through an unrestricted educational grant to AAAAI and AAEM for publication and dissemination costs from GlaxoSmithKline, which had no input into the task force recommendations.

Reprint requests: Barry Brenner, M.D., Ph.D., Professor of Emergency Medicine, Professor of Medicine, Program Director, Department of Emergency Medicine, University Hospitals, Case Medical Center, 11100 Euclid Ave., Cleveland OH 44106.

Proc Am Thorac Soc Vol 6. pp 371–379, 2009
DOI: 10.1513/pats.P09ST4
Internet address: www.atsjournals.org

2.86 ± 0.87 L) and decreased to an even greater degree with dyclonine (4.24 ± 0.80 to 2.20 ± 0.67 L, $P < 0.0001$). The decrease in FEV_1 was significantly attenuated by salbutamol, both in the lidocaine group (4.72 ± 0.62 to 3.37 ± 1.03 L, $P = 0.0011$) and in the dyclonine group (4.73 ± 0.62 to 2.74 ± 0.98 L, $P = 0.0003$). The study concluded combined treatment with lidocaine and salbutamol can be recommended for awake intubation; however, bronchial hyperreactivity might be a contraindication to the use of dyclonine.

A study by Conti *et al.* (7) was conducted to evaluate the effects of the last-generation opioid alfentanil on respiratory system mechanics in a group of American Society of Anesthesiology classification I nonasthmatic patients ventilated mechanically during general anesthesia. A total of 20 patients (10 men and 10 women) were randomized into 2 groups. Group A received alfentanil at 15 μg/kg, and group B received alfentanil at a dose of 30 μg/kg. Respiratory mechanics variables were obtained at baseline and after 3, 10, and 15 minutes. There were no statistically significant differences in respiratory mechanics variables after administration of alfentanil. The various components of respiratory system resistance (Rrs) were all within the standard limits for intubated patients and showed no variations after alfentanil administration. Furthermore, there were no other respiratory or hemodynamic side effects recorded during the study or surgical procedure, and no respiratory adverse effect was reported after intravenous alfentanil administration. Although opioids are believed to have a bronchoconstrictor effect, alfentanil did not appear to cause bronchoconstriction when administered intravenously to nonasthmatic patients; additional data are required to demonstrate safety in asthmatic patients.

Scalfaro *et al.* (8) tested the hypothesis that the preanesthetic administration of inhaled salbutamol would prevent the Rrs increase after tracheal intubation during sevoflurane-induced anesthesia in asthmatic children. Nineteen patients were randomly assigned to receive either salbutamol or placebo. When patients inhaled 3% sevoflurane in a mixture of 50% nitrous oxide in oxygen, there was no difference in ventilation variables and respiratory mechanics in patients pretreated with salbutamol or placebo. Mean Rrs was similar between groups; however, there was a significant difference in percentage change between the groups and the number of patients experiencing increased Rrs after tracheal intubation. With salbutamol, the Rrs decreased by a mean of 6.0% (95% CI, −25.2% to +13.2%) compared with a 17.7% mean decrease with placebo (95% CI, 4.4% to 30.9%; $P = 0.04$). A significantly larger proportion of patients in the placebo group manifested increased Rrs after tracheal intubation in comparison with pretreated patients (91% versus 46%, $P = 0.03$). The researchers concluded that salbutamol prevented increases in Rrs in asthmatic children having their tracheas intubated during sevoflurane induction. These data suggest that a preanesthetic treatment with salbutamol is useful in asthmatic children to protect against an increase in Rrs after tracheal intubation.

Maslow *et al.* (9) compared respiratory response during intubation after administration of intravenous lidocaine with that after inhaled albuterol in a group of patients with asthma scheduled for elective surgery requiring general anesthesia and tracheal intubation. These authors reported that inhaled albuterol blunted the airway response to tracheal intubation in asthmatic patients, whereas intravenous lidocaine did not. A total of 60 patients were randomized to receive 1.5 mg/kg intravenous lidocaine or placebo, which was administered 3 minutes before intubation. Fifty additional patients were randomized to receive 4 puffs of inhaled albuterol or placebo, which was administered 15 to 20 minutes before intubation. All patients were premedicated with midazolam and had anesthesia induced with propofol. The lidocaine and placebo groups were not different in terms of peak lower pulmonary resistance before isoflurane administration (8.2 versus 7.6 cm H_2O/L/s) or frequency of airway response to intubation (lidocaine: 6 of 30 versus placebo: 5 of 27). In contrast, the albuterol group had lower peak lower pulmonary resistance (5.3 versus 8.9 cm H_2O/L/s, $P < 0.05$) and a lower frequency of airway response (1 of 25 versus 8 of 23, $P < 0.05$) than the placebo group. Thus pretreatment with lidocaine administration did not blunt the intubation-induced bronchospasm compared with placebo, but pretreatment with albuterol did appear to blunt the hyperactive airway response.

Wu *et al.* (10) studied the efficacy of fenoterol and ipratropium in treating asthmatic patients with intraoperative bronchospasm. Sixteen asthmatic patients were enrolled in the study, all with a minimum 3-year history of clinically diagnosed asthma, regular treatment with β-adrenergic agents, and increased Rrs after intubation. They were randomized to receive either 10 puffs of fenoterol or 10 puffs of ipratropium through a metered-dose inhaler (MDI) with a spacer 5 minutes after intubation. All patients had an Rrs value at least 2 SDs greater than the previously established mean value, which confirmed the presence of hyperreactive airways. Rrs 30 minutes after treatment represented a 58% (SD, 6) decrease from 5 minutes after intubation (pretreatment) for fenoterol compared with 17% (SD, 5) for ipratropium. The percentage decrease in Rrs for patients in the fenoterol group was significantly greater than that for patients in the ipratropium group at all times ($P < 0.05$). The authors concluded that patients with a history of asthma were at high risk of having an exaggerated response to tracheal intubation and that fenoterol was effective in reducing Rrs after tracheal intubation in asthmatic subjects.

Other Studies

A study was conducted by Tobin (11) to determine the incidence, risk factors, and outcome of barotrauma in a cohort of mechanically ventilated patients. A total of 5,183 patients were studied, and barotrauma was present in 154 (2.9%) patients. Eighty percent of patients who had barotrauma did so within the first 3 days of mechanical ventilation. The incidence varied according to the reason for mechanical ventilation; 6% had asthma. The study found that patients with and without barotrauma did not differ in any ventilator parameter; however, patients with underlying lung diseases, such as adult respiratory distress syndrome and asthma, are more likely to have barotrauma with mechanical ventilation.

Behbehani *et al.* (12) conducted a retrospective cohort study over a 10-year period of all asthmatic patients receiving mechanical ventilation at 2 centers in Vancouver to determine the incidence of acute myopathy and examine predictors of development. The authors reported there was a high incidence of acute myopathy when neuromuscular blocking agents were used for near-fatal asthma. The development of myopathy was significantly associated with the duration of muscle relaxation, with an odds ratio of 2.1 (95% CI, 1.4–3.2) with each additional day of muscle relaxation. It was noted that the dose and type of corticosteroid were not significantly associated with myopathy in a multiple logistic regression analysis.

DISCUSSION

The ED task force identified 7 key areas for discussion from the review of the literature and their clinical experience:

1. prevention of intubation,
2. criteria for intubation,

3. recommendations for intubation technique,
4. recommendations for appropriate ventilator settings,
5. management in the immediate postintubation period,
6. medical management of asthma in the ventilated patient, and
7. prevention and treatment of complications.

Prevention of Intubation

The decision to intubate a patient in the ED is multifactorial and must be weighed carefully. Studies have shown that most asthmatic patients are able to be treated without intubation. Braman and Kaemmerlen (13) reported that of 2,094 patients admitted for asthma over a 10-year period, 80 were admitted to the ICU, and only 24 required mechanical ventilation. Mountain and Sahn (14) studied patients with hypercapnia and noted that only 5 of 61 patients required intubation.

Prevention of intubation is an important goal in the treatment of severe acute asthma because mortality rates range from 10% to 20% in patients requiring intubation (3). Patients with severe asthma exacerbations often respond to first- and second-line therapies, such as β_2-adrenergic agonist use, corticosteroids, anticholinergic agents, magnesium, aminophylline, and systemic catecholamines. However, there are times when patients with severe acute asthma do not respond to first- or second-line therapies, and special therapies might be necessary for the possible prevention of intubation (Table 1) (15). Noninvasive ventilation is discussed in a separate article.

Criteria for Intubation

Clinical. There are 4 indications for intubation, including (*1*) cardiac arrest, (*2*) respiratory arrest or profound bradypnea, (*3*) physical exhaustion, and (*4*) altered sensorium, such as lethargy or agitation, interfering with oxygen delivery or anti-asthma therapy. For example, a patient who repeatedly pulls off his or her oxygen mask and states "I cannot breathe" might require intubation (Table 2) (16).

Clinical judgment must determine whether intubation is appropriate in the setting of physical exhaustion and altered mental status. In the past, respiratory acidosis or an increasing Pa_{CO_2} was considered an indication for intubation; however, a systematic review of the literature by Leatherman (17) determined that intubation might not be necessary for a successful outcome in most asthmatic patients with hypercarbia. Intubation is indicated with a progressively increasing Pa_{CO_2} that is unresponsive to therapy and possibly associated with a change in mental status; however, a high Pa_{CO_2} alone might not be an indication for intubation, provided the patient has no change in mental status and does not appear to be exhausted.

Arterial blood gases. In general, it is not necessary to obtain arterial blood gases (ABGs) for asthmatic patients presenting to the ED with bronchospasm. ABGs are usually obtained for patients who are refractory to therapy. The literature suggests the following ABG results are indications for intubation and mechanical ventilation: pH less than 7.2, carbon dioxide pressure increasing by more than 5 mm Hg/h or greater than 55 to 70 mm Hg, or oxygen pressure less than 60 mm Hg on 100% oxygen delivered through a mask.

In addition to the above clinical and laboratory indications for intubation, additional factors that might need to be taken into consideration include a respiratory rate of greater than 40 breaths/minute, silent chest despite respiratory effort, complicating barotrauma, or unresolving lactic acidosis (18). Corbridge and Hall (19) and Zimmerman *et al.* (20) have emphasized that observation of a patient's clinical condition and course might be more valuable than laboratory testing.

TABLE 1. ALTERNATIVE THERAPIES FOR POSSIBLE PREVENTION OF INTUBATION

Heliox
Ketamine
Glucagon
Leukotriene inhibitors
Nebulized clonidine
Nitroglycerin
Nebulized calcium channel blockers
Nebulized lidocaine
External chest compression

Modified with permission from Panacek and Pollack (15).

Intubation Technique

Once the decision to intubate the patient has been made, the appropriate method for achieving intubation is controversial. There are 4 methods of intubation, including awake nasotracheal intubation, awake orotracheal intubation, orotracheal intubation with sedation, or orotracheal intubation with sedation and neuromuscular blocks (Table 3).

Although there are advantages to nasal intubation, such as more rapid preparation and less need for sedation, oral endotracheal intubation is generally preferred for patients in critical respiratory distress. Asthmatic patients are more likely to have nasal polyps and sinus pathology that complicate nasotracheal intubation (21). In addition, oral intubation allows the use of an endotracheal tube of a larger diameter, facilitating secretion removal and bronchoscopy, if needed (21).

Because even minor manipulation of the airway during intubation can elicit laryngospasm and worsen bronchospasm, the airway should be established by experienced personnel. Atropine can be administered initially to attenuate the vagal reflexes that lead to these responses, and lidocaine can be used for topical anesthesia, as mentioned above.

Sedation can make intubation easier to achieve. Intubation with a rapid sequence of sedation and muscle paralysis is preferred, although some advocate awake intubation because of concern for the potential for apnea with sedation (22). Although there might be some concern about sedating a patient who is in respiratory distress, once intubation is planned, there is no contraindication to sedation (23).

Ketamine is one option to consider for preintubation sedation. It stimulates the release of catecholamines and might have a direct relaxation effect on bronchial smooth muscle, leading to bronchodilation (24, 25). This, in turn, allows for easier ventilation in the peri-intubation period. Side effects associated with ketamine include hypersecretion, hypotension and hypertension, arrhythmias, and hallucinations, and its use is contraindicated in patients with ischemic heart disease, hypertension, preeclampsia, and increased intracranial pressure.

TABLE 2. CONSENSUS INDICATORS FOR INTUBATION (16)

Clinical
Cardiac arrest
Respiratory arrest
Altered sensorium
Progressive exhaustion
Silent chest
Laboratory
Severe hypoxemia with maximal oxygen delivery
Failure to reverse severe respiratory acidosis despite intensive therapy

TABLE 3. BENEFITS/RISKS OF INTUBATION METHODOLOGY

Method of Intubation	Benefits/Risks	Contraindications
Nasotracheal	Benefits	Nasal polyps
	Minimal need for sedation	Coagulation disorder
	Rapidity of preparation	Thrombocytopenia
	Greater postintubation comfort for awake patient	Abnormal nasal anatomy
	Maintenance of semiupright posture	
	Maintenance of spontaneous respiration	
	Decreased likelihood of aspiration	
	Risks	
	Epistaxis	
	Purulent sinusitis	
Orotracheal	Benefits	
	Larger-sized endotracheal tube	
	Direct visualization	
	Relative ease of obtaining pharyngeal anesthesia	
	Risks	
	Oral or tracheal trauma	
	Esophageal intubation	
	Vocal cord injury	
	Aspiration	
Awake orotracheal	Benefits	
	Avoid rendering patient apneic	
	Risks	
	Oral or tracheal trauma	
	Esophageal intubation	
	Vocal cord injury	
	Aspiration	
	Patient might be unable to tolerate the procedure	
	Coughing reflex can be triggered	
Orotracheal with sedation	Benefits	
	Rapid procedure, less traumatic than awake	
	Intubation might be easier to accomplish	
	Risks	
	Oral or tracheal trauma	
	Esophageal intubation	
	Vocal cord injury	
	Aspirationtrun -1	
	Hypotension caused by excessive sedation	
	Opioids might cause bronchospasm	
Orotracheal with neuromuscular blockade	Benefits	
	Increases the ease of intubation by reducing muscular resistance	
	Eliminates the risk of coughing	
	Might provide superior control during intubation compared with sedation alone (Baumgarten, *Can J Anaesth* 1988;35:5–11)	
	Risks	
	Few, rarely serious	
	Side effects of neuromuscular blocking agents	
	Sedation is necessary in addition to neuromuscular blockade	
	Airway loss caused by inability to intubate, ventilate, or both	

Propofol (2 mg/kg administered intravenously over 2 min) is an excellent alternative to ketamine to achieve sedation in the peri-intubation period, particularly in the hypertensive patient. Propofol is a short-acting agent with bronchodilatory effects that allows for rapid awakening (24). It does not cause hyperkalemia, except during rare cases of propofol infusion syndrome associated with high-dose use. Features of this syndrome include hyperlipidemia, hepatomegaly, hyperkalemia, rhabdomyolysis, severe metabolic acidosis, renal failure, and cardiovascular collapse (26). A short-acting and rapid-onset benzodiazepine, such as midazolam, can also be used for patient sedation. Opioids, such as morphine sulfate, are not used in asthmatic patients for intubation because of the potential for histamine release, nausea and vomiting, and hypotension, and although the clinical significance of histamine release is doubtful in this setting, its other side effects preclude routine use (21).

In addition to ketamine or propofol, succinylcholine or a competitive neuromuscular blocking agent can be used for muscle paralysis (27). Succinylcholine offers the advantage of a rapid onset and short duration of action. Some authorities prefer a nondepolarizing agent, such as vecuronium, because succinylcholine causes a greater histamine release, which could theoretically worsen bronchospasm. On the other hand, the clinical significance of histamine release in this setting is once again doubtful (16). However, the increase in potassium levels caused by succinylcholine might cause severe cardiac arrhythmias if the patient has hyperkalemia from respiratory acidosis. Vecuronium does not carry the risk of hyperkalemia but produces a longer duration of paralysis (28). Before inducing muscle paralysis, the physician should be sure that the patient can be ventilated and intubated, particularly with a longer-acting agent, such as vecuronium. This might be difficult to ascertain because of the severe bronchospasm preventing ventilation by means of bag valve mask. Facial features of patients and preintubation assessments (dentures, loose teeth, and Mallampati score) might provide important clues to the success of intubation.

In summary, rapid-sequence induction can be safely achieved in most patients by using 1.0 to 1.5 mg/kg ketamine administered intravenously and 1.0 to 1.5 mg/kg succinylcholine administered

by means of intravenous push or 2 mg/kg propofol administered intravenously over 2 minutes with succinylcholine (23). Propofol is preferred over ketamine for patients with hypertension, and succinylcholine should be avoided in patients with hyperkalemia.

Recommendations for Appropriate Ventilator Settings

When an asthmatic patient is ventilated, severe hyperinflation can result from breath stacking, placing the patient at risk for hypotension and barotrauma (29). It is essential to recognize, measure, and control hyperinflation and auto–positive end-expiratory pressure (PEEP) to ensure a good outcome in the intubated asthmatic patient (30).

Auto-PEEP occurs when diminished expiratory flow causes incomplete emptying of alveolar gas. As end-expiratory lung volume increases, so does end-inspiratory volume for a given tidal volume predisposing to lung hyperinflation (30, 31). There are 3 ventilator strategies that can be used to reduce hyperinflation and auto-PEEP in the intubated asthmatic patient: (*1*) reduction of the respiratory rate, (*2*) reduction of tidal volume, and (*3*) shortening of inspiration by increasing inspiratory flow to allow greater time for exhalation with each respiratory cycle. Changes in respiratory rate have the greatest effect on hyperinflation and auto-PEEP. In most intubated asthmatic patients, an inspiratory flow with decelerating waveform configuration is reasonable during the initial setup if inspiratory time is not excessively long. However, if one is unable to reduce the respiratory rate enough for reduction of hyperinflation and auto-PEEP to acceptable levels (10–15 cm H_2O, *see below*), inspiratory time can be shortened to allow for a proportionately longer time for exhalation per respiratory duty cycle by increasing the inspiratory flow rate. Reduction of tidal volume is appropriate; however, it is limited by its progressive effect on the dead-space fraction. Increasing pressure limitation to 100 cm H_2O might be necessary so that patient receives the full tidal volume. The use of a square wave-flow pattern and increasing flow rate shortens inspiratory time and might be appropriate because it does not represent a significant danger for barotrauma and should reduce auto-PEEP and hyperinflation (30, 31). One concern regarding the use of high flow rates is that the patient's respiratory rate might increase in response to high flows, particularly during assist-control ventilation, thereby decreasing expiratory time and worsening auto-PEEP (32).

Decreasing respiratory rate can cause hypercapnia. Fortunately, hypercapnia is often well tolerated, even with arterial Pa_{CO_2} values as high as 90 mm Hg, and in selected, critically ill patients it might be safer to accept hypercapnia than to overventilate to a normal Pa_{CO_2} at the cost of critical hyperinflation. Anoxic brain injury and severe myocardial dysfunction are contraindications to permissive hypercapnia because of the potential for hypercapnia to dilate cerebral vessels, constrict pulmonary vessels, and decrease myocardial contractility (33). In patients with mild-to-moderate myocardial dysfunction, the clinician must balance the benefits of decreasing lung hyperinflation with the potential adverse effects of hypercapnia.

Determining the severity of lung hyperinflation is central to assessing patients and adjusting ventilator settings. Several methods have been proposed to assess lung inflation, including the measurement of exhaled gases and the volume at end-inspiration (Vei) (34). This volume is determined by collecting expired gas from total lung capacity to functional residual capacity during 40 to 60 seconds of apnea. A Vei of greater than 20 ml/kg correlates with barotrauma; however, Vei might underestimate air trapping if there are slowly emptying lung units. This measure requires staff training and patient paralysis and is not performed in routine ICU practice.

In common practice 2 relatively easy-to-measure pressures are used as surrogate markers of lung inflation: auto-PEEP and plateau pressure (Pplat). Auto-PEEP is an estimate of the lowest average alveolar pressure achieved during the respiratory cycle. It is obtained by measuring airway-opening pressure during an end-expiratory hold maneuver. The presence of expiratory gas flow at the beginning of inspiration (which can be detected by means of auscultation or flow tracings) also suggests auto-PEEP. Auto-PEEP can underestimate the severity of hyperinflation when there is poor communication between the alveoli and the airway opening (35).

Pplat (or lung distension pressure) estimates average end-inspiratory alveolar pressure. Pplat is affected by the entire respiratory system, including lung parenchyma, the chest wall, and the abdomen. It is determined by temporarily stopping flow at end-inspiration during a single delivered breath.

Accurate measurements of Pplat and auto-PEEP require patient-ventilator synchrony and absence of patient effort. Paralysis is generally not required. Unfortunately, neither auto-PEEP nor Pplat have been validated as a predictor of complications of mechanical ventilation. Still, many experts agree that complications are rare when Pplat is less than 30 cm H_2O and auto-PEEP is less than 15 cm H_2O (36).

Ventilator-applied PEEP is not recommended in sedated and paralyzed patients because it increases lung volume if used excessively. However, use of low levels of ventilator-set PEEP (e.g., 5 cm H_2O) in spontaneously breathing patients decreases the inspiratory work of breathing by decreasing the pressure gradient required to overcome auto-PEEP without worsening lung inflation (11).

Table 4 (31) lists appropriate initial ventilator settings for the intubated asthmatic patient.

Management in the Immediate Postintubation Period

Sedation. Effective sedation improves patient comfort, decreases oxygen consumption and carbon dioxide production, and allows synchronism between the patient and the ventilator (37). Sedation also prevents the risk of an awakening patient becoming combative, self-extubating, or triggering auto-PEEP because of a rapid respiratory rate (31). Benzodiazepines are commonly used for this purpose, but other agents are used as well. Propofol is a useful sedating agent because it can be titrated to provide deep sedation and has bronchodilating properties (37). However, propofol can lead to seizures, hypertriglyceridemia, and increased carbon dioxide production when used long-term (37). High doses of propofol should be avoided to minimize the risk of propofol infusion syndrome (26). To provide the best combination of amnesia, sedation, analgesia, and suppression of respiratory drive, a narcotic, such as fentanyl or alfentanil, should be added to either propofol or a benzodiazepine, such as lorazepam (37).

After intubation, inhaled anesthetic agents might be useful because of their potent direct bronchodilatory effect and their ability to decrease airway responsiveness (37, 38). The benefits of the use of these agents must be balanced against the risk of inducing myocardial depression and arrhythmias (37) and the logistical problems associated with their use (31).

TABLE 4. INITIAL VENTILATOR SETTINGS FOR THE INTUBATED ASTHMATIC PATIENT (31)

Controlled mechanical ventilation at 10 breaths/min
Tidal volume at 7–8 ml/kg (ideal body weight)
Peak inspiratory flow at 60 L/min (constant flow) or 80–90 L/min (decelerating flow)
Fraction of inspired oxygen at 1.0

Neuromuscular blockade. Continuing neuromuscular blockade during mechanical ventilation might reduce the risk for barotrauma, avoids coughing and dyssynchronous breathing, and allows the respiratory muscles to rest (37). In this regard cisatracurium is a good choice because it is essentially free of cardiovascular effects, does not release histamine, and does not rely on hepatic and renal function for clearance.

Because paralytic agents can cause a myopathy, particularly when used concomitantly with corticosteroids, neuromuscular blockade after intubation is recommended only for patients who do not have adequate relaxation with deep sedation alone to allow for a passive response to the ventilator (31). Neuromuscular blockade should be limited, when possible, to less than 24 hours to avoid an associated myopathy, particularly because deep sedation is generally all that is required by that time (30). Full resolution of the myopathy generally occurs, although the recovery time might be prolonged (31).

Heliox. Heliox is a mixture of oxygen and helium that decreases airway resistance by reducing airflow turbulence in the bronchial passages. The results of studies on the benefits of the use of heliox are conflicting, but there might be some benefit to its use in patients with severe asthma before intubation as a means of avoiding intubation. There is currently insufficient evidence to support the use of heliox in intubated patients.

Medical Management of Asthma in the Intubated Patient

Systemic corticosteroids. Because bronchospasm continues after intubation, inhaled bronchodilators and systemic corticosteroids should be continued (30). Systemic corticosteroids are the gold standard of treatment in intubated asthmatic patients. Manser *et al.* (39) conducted a systematic review of the literature and determined that 40 mg every 6 hours of methylprednisolone (or equivalent) is appropriate, and higher doses do not appear more efficacious.

Inhaled β-agonists. Inhaled β-agonists are also indicated; however, the most effective dosing is debated. The literature shows that delivery of sufficient puffs of β-agonists through an MDI using a well-designed reservoir system is cost-effective and has proved to be as effective as using a nebulizer in intubated asthmatic patients (40). Table 5 (31) summarizes guidelines for the use of MDIs and nebulizers in mechanically ventilated patients.

Other bronchodilators. The clinical benefits of intravenous theophylline in intubated patients are unknown, but outcomes in hospitalized asthmatic patients in general do not appear to improve with intravenous theophylline (Expert Panel Report 3).

Prevention and Treatment of Complications

Intubation-induced bronchospasm. It is well known that tracheal intubation increases airway resistance in patients with bronchial hyperreactivity (41). It is, however, unknown to what extent reflex bronchoconstriction in asthmatic patients occurs after awake tracheal intubation. Four studies addressed these issues.

Groeben *et al.* (6) (*see* RESULTS) determined that dyclonine inhalation might be contraindicated in patients with bronchial hyperreactivity, given the greater than 50% decrease in FEV_1 in the asthmatic patients they studied. Furthermore, they found the decrease in FEV_1 was significantly mitigated (35%) by administration of lidocaine for topical anesthesia, and salbutamol pretreatment might have provided additional attenuation. Therefore they recommended combined pretreatment with lidocaine and salbutamol for awake intubation in patients with acute asthma.

In an attempt to better understand the ability of intravenous lidocaine to prevent intubation-induced bronchospasm, Maslow *et al.* (9) (*see* RESULTS) found inhaled albuterol blunted the airway response to tracheal intubation in asthmatic patients,

TABLE 5. GUIDELINES FOR THE USE OF MDIs AND NEBULIZERS IN MECHANICALLY VENTILATED PATIENTS (31)

MDI Technique	Nebulizer Technique
Ensure tidal volume > 500 ml in adults during assisted ventilation	Place the drug solution in the nebulizer using a fill volume (2–6 ml) that ensures the greatest aerosol-generating efficacy*
Aim for an inspiratory time (excluding the inspiratory pause) of > 0.3 of total breath duration	Place the nebulizer in the inspiratory line at least 30 cm from the ventilator wye†
Ensure that the ventilator breath is synchronized with the patient's inspiration	Ensure an airflow of 6–8 L/min through the nebulizer‡
Shake the MDI vigorously	Ensure adequate tidal volume (> 500 ml in adults); attempt to use duty cycle > 0.3, if possible
Place the canister in the actuator of a cylindrical spacer situated in the inspiratory limb of the ventilator circuit§	Adjust minute volume to compensate for additional airflow through the nebulizer, if required
Actuate the MDI to synchronize with the precise onset of inspiration by the ventilator¶	Turn off flow-by or continuous-flow mode on ventilator
Allow a breath hold at the end of inspiration for 3–5 seconds‖	
Allow passive exhalation	Observe nebulizer for adequate aerosol generation throughout use
Repeat actuation after 20–30 seconds the until total dose is delivered**	Disconnect nebulizer when all medication is nebulized or when no more aerosol is being produced
	Reconnect ventilator circuit and return to original ventilator settings

* The volume of solution placed in the nebulizer (i.e., the fill volume) that achieves maximal efficiency varies among nebulizers.

† Bypassing the humidifier has been suggested as a means of improving aerosol delivery in mechanically ventilated patients. However, administration of dry gas might lead to drying of the airway mucosa; therefore administration with humidified gas is preferred for routine bronchodilatory therapy. This is the description of airway lines leading from the patient.

‡ The nebulizer can be operated continuously or only during inspiration; the latter method is more efficient. Some ventilators provide inspiratory gas flow to the nebulizer; alternatively, the nebulizer can be powered by continuous gas flow from an external source.

§ With MDIs, it is preferable to use a spacer that remains in the ventilator circuit to avoid disconnecting the ventilator circuit for each treatment. Although bypassing the humidifier can increase aerosol delivery, it prolongs each treatment and requires disconnecting the ventilator circuit.

¶ In ambulatory patients with an MDI placed near the mouth, actuation is recommended briefly after initiation of inspiratory airflow. In mechanically ventilated patients using an MDI and spacer combination, actuation should be synchronized with the onset of inspiration.

‖ The effect of a postinspiratory breath hold has not been evaluated in mechanically ventilated patients.

** The manufacturer recommends repeating the dose after 1 minute. However, MDI actuation within 20 to 30 seconds after the prior dose does not compromise drug delivery.

whereas intravenous lidocaine did not. Hence intravenous lidocaine cannot be recommended as a means of preventing intubation-induced bronchospasm.

Scalfaro *et al*. (8) (*see* RESULTS) investigated the protective effect of an inhaled β_2-adrenergic agonist in the setting of increased Rrs in children having their tracheas intubated and showed that in children with mild-to-moderate asthma, a preanesthetic treatment with inhaled salbutamol can prevent the increase of Rrs, as evidenced by a 6.0% decrease in Rrs with salbutamol treatment.

One additional study assessed medication effects on total Rrs. Wu *et al*. (10) (*see* RESULTS) investigated the effects of a β-agonist and cholinergic antagonist on postintubation total Rrs in asthmatic patients who experienced an increase in resistance after tracheal intubation and concluded that fenoterol can reduce Rrs after tracheal intubation in asthmatic patients.

Overall, one can therefore conclude from these studies that (*1*) airway resistance does increase in response to intubation and (*2*) pretreatment with bronchodilators appears to be useful in decreasing or preventing this complication of intubation in patients with hyperreactive airways.

Persistent or worsening hypoxemia. Persistent or worsening hypoxemia during mechanical ventilation suggests the development of a complication of mechanical ventilation. Complications such as right main stem intubation (proper endotracheal tube placement is generally 21 cm at the incisors in a woman and 23 cm in a man), pneumothorax, endotracheal tube displacement, endotracheal tube blockage, leakage of air around the endotracheal tube, gastric distention decreasing respiratory system compliance, mechanical malfunction of the ventilatory apparatus, aspiration, and progressive bronchospasm can all contribute to hypoxemia and must be addressed individually as appropriate. In addition, appropriate settings for mechanical ventilation (*see below*), treatment of recurrent or persistent bronchospasm, nasogastric tube placement to decompress the stomach, and frequent reassessment of the patient to determine the cause of hypoxemia and the response to interventions are critical.

Hypotension. Hypotension is another common complication that can develop after intubation. During periods of asthma exacerbations, patients typically have decreased oral intake and faster respiratory rates, both of which contribute to a negative fluid balance. This relative or actual dehydration can contribute directly to hypotension. Hypotension can also result from complications related directly to mechanical ventilation. The increase in intrathoracic pressure caused by mechanical ventilation leads to decreased systemic venous return, potentially leading to a decrease in cardiac output. These effects of ventilation can be avoided by preventing complications that increase intrathoracic pressure, such as hyperinflation, gastric distention, and tension pneumothorax. Lastly, medications used for sedation or medical management can cause hypotension. For example, the general anesthetic isoflurane improved Pa_{CO_2} in pediatric patients but caused hypotension severe enough to require vasopressor support in 8 of the 10 children studied (42).

A fluid bolus is an immediate measure that is useful for managing hypotension (unless there are contraindications to a fluid bolus, such as concurrent pulmonary edema). Decreasing the respiratory rate and adjusting the ventilatory cycle to allow for a shorter inspiratory cycle and longer expiratory cycle are typical strategies for avoiding complications caused by lung hyperinflation (*see* the discussion on ventilatory settings). In critical hypotension (defined as a decrease in systolic blood pressure to < 90 mm Hg or a reduction of > 40 mm Hg from baseline value), a trial of hypopnea (2–3 breaths/min) or apnea in a preoxygenated patient for 30 to 60 seconds can be both diagnostic and therapeutic for lung hyperinflation. Critical hypotension for which a reversible cause cannot be immediately found is an indication for epinephrine.

Cardiac arrest. Cardiac arrest can occur as a result of critical lung hyperinflation by (*1*) decreasing preload to the right ventricle, (*2*) increasing pericardial pressure and tamponade physiology, (*3*) increasing total pulmonary vascular resistance and right ventricular strain, and (*4*) predisposing to tension pneumothorax. A trial of apnea or hypopnea for no more than 30 to 60 seconds, external chest compressions, volume challenge, and epinephrine are indicated for cardiac arrest presenting as pulseless electrical activity.

Tension pneumothorax is a clinical diagnosis. If lung examination suggests this complication (e.g., tracheal shift with unilateral breath sounds or subcutaneous emphysema), proceed with needle thoracostomy followed by careful chest tube thoracostomy. Note that if the hyperinflated lung is punctured inadvertently, this could produce a rush of air similar to releasing a tension pneumothorax but result in ineffective ventilation. Note further that patients with tension pneumothorax might respond initially to a trial of apnea or hypopnea.

Other causes of cardiac arrest include hypoxemia, acidemia, electrolyte abnormalities (including lethal hyperkalemia if succinylcholine was used for intubation of a patient with respiratory acidosis), myocardial ischemia (particularly if high-dose β-agonists were used systemically), and endotracheal tube displacement, kinking, or plugging. Use of illicit drugs, such as heroin or crack cocaine, should also be considered.

Barotrauma. Increased morbidity and mortality are associated with barotrauma (43–46). The issue of development of barotrauma in relation to airway pressure, PEEP, and tidal volume is controversial. Amato *et al*. (47) reported that the use of small tidal volumes and PEEP titrated to lung mechanics reduced the frequency of barotrauma in patients with acute respiratory distress syndrome. Conversely, Weg *et al*. (48) found no relationship between the development of barotrauma and high airways pressures or high tidal volumes in patients with acute respiratory distress syndrome.

As noted above (11), patients with underlying lung diseases, such as acute respiratory distress syndrome and asthma, are more likely to experience barotrauma with mechanical ventilation.

A case-control analysis showed increased mortality rates in patients with barotrauma (51.4% versus 39.2%, $P = 0.04$) and prolonged ICU stay (14 ± 13.6 days in patients with barotrauma versus 10.9 ± 11.4 days in patients without barotrauma, $P = 0.04$). In asthmatic patients Tuxen and Lane (34) have demonstrated that a Vei of greater than 20 ml/kg correlates with barotrauma (*see above*).

Myopathy. Acute muscle weakness after mechanical ventilation has been shown to be secondary to acute myopathy (49). The pathogenesis of muscle injury has been linked to corticosteroids and neuromuscular blocking agents, such as pancuronium, vecuronium, and atracurium (50). As noted above, Behbehani *et al*. (12) reported that there was a high incidence of acute myopathy when neuromuscular blocking agents were used for near-fatal asthma, but corticosteroids were not independently associated with myopathy in their study.

Extubation. Because patients often have prolonged hold times in the ED while waiting for critical care beds, weaning and extubation have become germane to emergency medicine. Weaning and extubation criteria have not been validated for patients with acute asthma. One approach is to perform a spontaneous breathing trial in an awake patient once Pa_{CO_2} normalizes, airway resistance is less than 20 cm H_2O, auto-PEEP is less than 10 cm H_2O, and neuromuscular weakness has not been identified. Extubation should proceed in a timely

manner to avoid complications of mechanical ventilation, including endotracheal tube–induced bronchospasm. After extubation, observation in an ICU is recommended for an additional 12 to 24 hours. During this time, the focus can switch to safe transfer to the ward and outpatient management.

SUMMARY OF RECOMMENDATIONS (ALL STRONG)

1. Criteria for intubation (Evidence Category D)
   - Clinical indications
     - — Cardiac arrest
     - — Respiratory arrest
     - — Altered mental status
     - — Progressive exhaustion
     - — Silent chest
   - Laboratory indications
     - — Severe hypoxia with maximal oxygen delivery
     - — Failure to reverse severe respiratory acidosis despite intensive therapy
     - — pH < 7.2, carbon dioxide pressure increasing by more than 5 mm Hg/h or greater than 55 to 70 mm Hg, or oxygen pressure of less than 60 mm Hg
2. Intubation technique (Evidence Category D)
   - There are 4 choices of technique, each with its own benefits and risks:
     - — nasotracheal intubation,
     - — awake orotracheal intubation,
     - — orotracheal intubation with sedation, and
     - — orotracheal intubation with sedation and neuromuscular blockade.
   - In general, orotracheal intubation with sedation and neuromuscular blockade are preferred for asthmatic patients in critical respiratory distress.
   - The use of ketamine and propofol might be preferred over other sedative agents. Pretreatment with bronchodilators might reduce airway bronchospasm associated with tracheal intubation in patients with nonacute asthma requiring intubation. Patients with acute asthma almost invariably would have received bronchodilation before intubation unless presenting in arrest or near arrest.
3. Recommendations for appropriate ventilator settings (Evidence Category D)
   - Control of hyperinflation and auto-PEEP
     - — Reduction of respiratory rate might help control hyperinflation.
     - — Reduction of tidal volume might help control hyperinflation.
     - — An initial set-up of 80 L/min with a decelerating waveform configuration might be appropriate in adults.
     - — Shortening of inspiration with a square wave pattern and an inspiratory flow rate of 60 L/min allows greater time for exhalation in each respiratory cycle and might help control hyperinflation.
     - — Auto-PEEP and Pplat should be followed during mechanical ventilation.
   - Hypercapnia is preferable to hyperinflation.
     - — Hypercapnia should not be used in the presence of increased intracranial pressure.
     - — An acceptable level of hypercapnia and acidosis is a pH as low as 7.15 and a Pa_{CO_2} of up to 80 mm Hg.
4. Management in the postintubation period (Evidence Category D)
   - Verify endotracheal tube placement with a carbon dioxide detector, adequate oximeter readings, and chest radiography. Chest radiography will determine the depth of intubation but not esophageal intubation with the patient breathing "around the tube."
   - Postintubation sedation should be provided with a benzodiazepine.
5. Medical management of the intubated asthmatic patient
   - Continued treatment with inhaled bronchodilators, such as nebulized albuterol or albuterol administered with an MDI (Evidence Category B)
   - Systemic corticosteroid treatment, such as 40 mg of methylprednisolone every 6 hours (Evidence Category B)
   - No routine use of heliox once the patient is intubated (Evidence Category D)
6. Prevention and treatment of complications (Evidence Category D)
   - Hypoxemia
     - — Exclude right mainstem intubation (21 cm at incisors)
     - — Exclude pneumothorax and place pleural drain
     - — Tube obstruction (kinking, biting of tube, or plugging)
     - — Exclude pneumonia and other lung disease
   - Hypotension
     - — Consider pneumothorax early but first perform a trial of apnea or hypopnea to decrease intrathoracic pressure unless there is unequivocal evidence of pneumothorax, such as tracheal shift with unilateral breath sounds or subcutaneous emphysema
     - — Tension pneumothorax is a clinical diagnosis. If a lung examination suggests this complication, proceed with a needle thoracostomy followed by a chest tube thoracostomy.
     - — Fluids
     - — Measure auto-PEEP and Pplat and apply reduction measures
     - — Exclude other causes, such as myocardial infarction and sepsis
   - Cardiac arrest
     - — A trial of apnea or hypopnea for no more than 30 to 60 seconds with external compressions and volume challenge is therapeutic for lung hyperinflation as a cause of cardiac arrest.
     - — Consider tension pneumothorax early. If lung examination suggests this complication, proceed with a needle thoracostomy followed by a careful chest tube thoracostomy.

Author disclosures were obtained by the *Journal of Allergy and Clinical Immunology* (JACI) using questions determined by the American Academy of Allergy, Asthma and Immunology (AAAAI) and JACI. Questions pertained to: employment; financial interests between the author or members of the author's immediate family or household with organizations and commercial interests; research support during the past calendar year; and legal consultation services/expert witness testimony during the past calendar year. Authors were asked to state

dollar amounts in ranges of either $< \$10{,}000$ or $\geqslant \$10{,}000$. Authors were not required to disclose other facts that are now requested by *PATS* in conformance with American Thoracic Society policy, including knowledge of any significant financial relationship between the author's institution or employer and relevant commercial interests, and all relationships with tobacco entities.

Disclosure of potential conflict of interest: B.B. has declared that he has no conflict of interest. T.C. is on the speakers' bureau for GlaxoSmithKline. A.K. has declared that he has no conflict of interest.

References

1. Environmental Protection Agency. Asthma Facts. Available from: http://www.epa.gov/asthma/pdfs/asthma_fact_sheet_en.pdf.
2. McFadden ER Jr. Acute severe asthma. *Am J Respir Crit Care Med* 2003;168:740–759.
3. Shapiro JM. Intensive care management of status asthmaticus. *Chest* 2001;120:1439–1441.
4. Carroll N, Carello S, Cooke C, James A. Airway structure and inflammatory cells in fatal attacks of asthma. *Eur Respir J* 1996;9: 709–715.
5. Schatz M, Kazzi AAN, Brenner B, Camargo Jr CA, Corbridge T, Krishnan JA, Nowak R, Rachelefsky G. Introduction. *Proc Am Thorac Soc* 2009.
6. Groeben H, Schlicht M, Stieglitz S, Pavlakovic G, Peters J. Both local anesthetics and salbutamol pretreatment affect reflex bronchoconstriction in volunteers with asthma undergoing awake fiberoptic intubation. *Anesthesiology* 2002;97:1445–1450.
7. Conti G, De Cosmo G, Bocci MG, Antonelli M, Ferro G, Costa R, *et al.* Alfentanil does not increase resistance of the respiratory system in ASA I patients ventilated mechanically during general anesthesia. *Can J Anaesth* 2002;49:718–723.
8. Scalfaro P, Sly PD, Sims C, Habre W. Salbutamol prevents the increase of respiratory resistance caused by tracheal intubation during sevoflurane anesthesia in asthmatic children. *Anesth Analg* 2001;93:898–902.
9. Maslow AD, Regan MM, Israel E, Darvish A, Mehrez M, Boughton R, *et al.* Inhaled albuterol, but not intravenous lidocaine, protects against intubation-induced bronchoconstriction in asthma. *Anesthesiology* 2000;93:1198–1204.
10. Wu RS, Wu KC, Wong TK, Tsai YH, Cheng RK, Bishop MJ, *et al.* Effects of fenoterol and ipratropium on respiratory resistance of asthmatics after tracheal intubation. *Br J Anaesth* 2000;84:358–362.
11. Tobin MJ. Advances in mechanical ventilation. *N Engl J Med* 2001;344: 1986–1996.
12. Behbehani NA, Al-Mane F, D'yachkova Y, Pare P, FitzGerald JM. Myopathy following mechanical ventilation for acute severe asthma: the role of muscle relaxants and corticosteroids. *Chest* 1999;115:1627–1631.
13. Braman SS, Kaemmerlen JT. Intensive care of status asthmaticus: a 10-year experience. *JAMA* 1990;264:366–368.
14. Mountain RD, Sahn SA. Acid-base disturbances in acute asthma. *Chest* 1990;98:651–655.
15. Panacek EA, Pollack CV Jr. Medical management of severe acute asthma. In: Brenner B, editor. Emergency asthma. New York: Marcel Dekker; 1999.
16. Kohn MS. Intubation of the asthma patient. *Clin Allergy Immunol* 1999; 13:419–428.
17. Leatherman J. Life-threatening asthma. *Clin Chest Med* 1994;15:453–479.
18. Hall JB, Wood LDH. Management of the critically ill asthmatic patient. *Med Clin North Am* 1990;74:779–796.
19. Corbridge TC, Hall JB. The assessment and management of adults with status asthmaticus. *Am J Respir Crit Care Med* 1995;151:1296–1316.
20. Zimmerman JL, Dellinger RP, Shah AN, Taylor RW. Endotracheal intubation and mechanical ventilation in severe asthma. *Crit Care Med* 1993;21:1727–1730.
21. Madison JM, Irwin RS. Respiratory failure part III: status asthmaticus. In: Irwin RS, Rippe JM, editors. Irwin & Rippe's intensive care medicine, 5th ed. Philadelphia: Lippincot Williams & Wilkins; 2003. pp. 509–511.
22. Bellomo R, McLaughlin P, Tai E, Parkin G. Asthma requiring mechanical ventilation: a low morbidity approach. *Chest* 1994;105:891–896.
23. Nee PA, Benger J, Walls RM. Airway management. *Emerg Med J* 2008; 25:98–102.
24. Brown RH, Wagner EM. Mechanisms of bronchoprotection by anesthetic induction agents: propofol versus ketamine. *Anesthesiology* 1999;90:822–828.
25. L'Hommedieu CS, Arens JJ. The use of ketamine for the emergency intubation of patients with status asthmaticus. *Ann Emerg Med* 1987; 16:568–571.
26. Kam PC, Cardone B. Propofol infusion syndrome. *Anaesthesiology* 2007; 62:690–701.
27. El-Orbany MI, Joseh NJ, Salem MR, Klowden AJ. The neuromuscular effects and tracheal intubation conditions after small doses of succinylcholine. *Anesth Analg* 2004;98:1680–1685.
28. Saitoh Y, Kaneda K, Murakawa M. Onset of vecuronium-induced neuromuscular block after a long priming interval. *J Anesth* 2002; 16:102–107.
29. Lougheed MD, Fisher T, O'Donnell DE. Dynamic hyperinflation during bronchoconstriction in asthma: implications for symptom perception. *Chest* 2006;130:1072–1081.
30. Reddy VG. Auto-PEEP: how to detect and how to prevent—a review. *Middle East J Anaesthesiol* 2005;18:293–312.
31. Mayo P, Radeos MS. The severe asthmatic: intubated and difficult to ventilate. In: Brenner B, editor. Emergency asthma. New York: Marcel-Dekker; 1999. pp. 469–487.
32. Corne S, Gillespie D, Roberts D, Younes M. Effect of inspiratory flow rate on respiratory rare in intubated patients. *Am J Respir Crit Care Med* 1997;156:304–308.
33. Tuxen DV. Permissive hypercapnic ventilation. *Am J Respir Crit Care Med* 1994;150:870–874.
34. Tuxen DV, Lane S. The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe air-flow obstruction. *Am Rev Respir Dis* 1987;136:872–879.
35. Leatherman JW, Ravenscraft SA. Low measured auto-positive end-expiratory pressure during mechanical ventilation of patients with severe asthma: hidden auto-positive end-expiratory pressure. *Crit Care Med* 1996;24:541–546.
36. Corbridge T, Corbridge S. Severe asthma exacerbation. In: Fink M, Abraham E, Vincent JL, Kochanek PM, editors. Textbook of critical care, 5th ed. Philadelphia: Elsevier Saunders; 2005. pp. 587–597.
37. Papiris S, Kotanidou A, Malagari K, Roussos C. Clinical review: severe asthma. *Crit Care* 2002;6:30–44.
38. Adams BK, Cydulka RK. Asthma evaluation and management. *Emerg Med Clin North Am* 2003;21:315–330.
39. Manser R, Reid D, Abramson M. Corticosteroids for acute severe asthma in hospitalised patients. *Cochrane Database Syst Rev* 2001;1: CD001740.
40. Dhand R, Tobin MJ. Inhaled bronchodilator therapy in mechanically ventilated patients. *Am J Respir Crit Care Med* 1997;156:3–10.
41. Silvanus MT, Groeben H, Peters J. Corticosteroids and inhaled salbutamol in patients with reversible airway obstruction markedly decrease the incidence of bronchospasm after tracheal intubation. *Anesthesiology* 2004;100:1052–1057.
42. Shankar V, Churchwell KB, Deshpande JK. Isoflurane therapy for severe refractory status asthmaticus in children. *Intensive Care Med* 2006;32:927–933.
43. Oddo M, Feihl F, Schaller MD, Perret C. Management of mechanical ventilation in acute severe asthma: practical aspects. *Intensive Care Med* 2006;32:501–510.
44. Boussarsar M, Thierry G, Jaber S, Roudot-Thoraval F, Lemaire F, Brochard L. Relationship between ventilatory settings and barotraumas in the acute respiratory distress syndrome. *Intensive Care Med* 2002;28:406–413.
45. Shin MS, Gammon RB. Pulmonary barotraumas in mechanical ventilation: patterns and risk factors. *Chest* 1992;102:568–572.
46. Williams TJ, Tuxen DV, Scheinkestel CD, Czarny D, Bowes G. Risk factors for the morbidity in mechanically ventilated patients with acute severe asthma. *Am Rev Respir Dis* 1992;146:607–615.
47. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, *et al.* Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998;338:347–354.
48. Weg JG, Anzueto A, Balk RA, Wiedemann HP, Pattishall EN, Schork MA, *et al.* The relation of pneumothorax and other air leaks to mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998;338:341–346.
49. Douglass JA, Tuxen DV, Horne M, Scheinkestel CD, Weinmann M, Czarny D, *et al.* Myopathy in severe asthma. *Am Rev Respir Dis* 1992; 146:517–519.
50. Williams TJ, O'Hehir RE, Czarny D, Horne M, Bowes G. Acute myopathy in severe acute asthma treated with intravenously administered corticosteroids. *Am Rev Respir Dis* 1988;137:460–463.

Anti-inflammatory Treatment after Discharge Home from the Emergency Department in Adults with Acute Asthma

Jerry A. Krishnan[1], Richard Nowak[2], Steven Q. Davis[3], and Michael Schatz[4]

[1]Asthma and COPD Center, Department of Medicine, and Department of Health Studies, University of Chicago, Chicago, Illinois; [2]Department of Emergency Medicine, Henry Ford Health System, Detroit, Michigan; [3]Texas Pulmonary and Critical Care Consultants, PA, Fort Worth, Texas; and [4]Department of Allergy, Kaiser Permanente Medical Center, San Diego, California

Keywords: asthma exacerbation; acute asthma; emergency department; discharge medications; corticosteroids; leukotriene modifiers

Airway inflammation from respiratory infections or exposure to allergens, irritants, or both leads to increased airflow obstruction and respiratory symptoms in patients with acute asthma. Anti-inflammatory therapy with systemic corticosteroids (CSs) is therefore a cornerstone of the management of patients with acute asthma, particularly those presenting to the emergency department (ED) (1, 2). After initial management in the ED, most patients improve sufficiently to be discharged home with instructions to complete a short course of daily oral corticosteroids (OCSs) and short-acting inhaled bronchodilators as needed for symptom relief. Unfortunately, up to one third of patients who initially respond to therapy relapse within the first 3 to 4 weeks after ED discharge (e.g., require treatment escalation, urgent care or ED visits, or hospitalizations for asthma) (3, 4). The propensity of many patients to relapse after ED discharge has led to a number of randomized clinical trials evaluating alternative outpatient anti-inflammatory treatment strategies in this population, including the use of inhaled corticosteroids (ICSs), intramuscular corticosteroids (IMCSs), and noncorticosteroid anti-inflammatory regimens.

The objective of this systematic review is to synthesize the results of randomized clinical trials in adults with acute asthma, comparing alternative outpatient anti-inflammatory treatment strategies to reduce the risk of relapse after discharge home from the ED. More specifically, this systematic review examined the following anti-inflammatory treatment options in adults after ED discharge: (*1*) IMCSs versus OCSs, (*2*) ICSs versus OCSs, (*3*) combination of ICSs plus OCSs versus OCSs alone, and (*4*) noncorticosteroid anti-inflammatory agents (macrolide antibiotics and leukotriene modifiers) in addition to systemic corticosteroids. This report updates previously published systematic reviews in acute asthma (5–7) with subsequently published studies and provides a single document summarizing this body of literature for easy use by clinicians.

METHODS

The following keywords and combinations were used for the search: asthma exacerbation + discharge + medication; acute asthma + discharge medication; asthma + emergency department + discharge medication; asthma + emergency + department + adherence; and severe + asthma + adherence + emergency + department.

Additional details of the methodology for all literature reviews in this supplement are provided in the introduction to this supplement (8). The task force specified the level of evidence used to justify the recommendations being made, and the system used to describe the level of evidence is also defined in the introduction to this supplement.

RESULTS

The literature search identified 37 clinical randomized controlled trials (RCTs) and 5 meta-analyses potentially relevant to the study questions. After excluding noneligible studies, 5 RCTs were identified comparing IMCSs with OCSs; 1 meta-analysis of 7 trials comparing ICSs with OCSs, 2 of which were specifically in adults; 1 meta-analysis of 3 trials comparing ICSs plus OCSs versus OCSs alone; and 2 RCTs of noncorticosteroid anti-inflammatory agents.

IMCSs versus OCS

There are 5 randomized, placebo-controlled clinical trials comparing IMCSs with OCSs in a total of 599 adults with acute asthma (Table 1) (4, 9–12). All 5 trials used a double-dummy design (IMCS plus oral placebo versus intramuscular placebo plus OCS) to keep patients and investigators masked to treatment assignment. These studies compared a single dose of various formulations of IMCSs with a 5- to 8-day course of OCSs and assessed outcomes over a 5- to 21-day period. Rates of study completion were high, ranging from 89% to 100%. Overall, there were no significant differences in symptoms, lung function parameters, or rates of relapse between the 2 treatment groups. Some studies, however, reported a higher rate of complications at the injection sites (e.g., pain or bruising) in patients who received IMCSs. For example, in the study by Lahn *et al*. (12), mean pain scores (3.3/10 versus 1.9/10, $P < 0.05$) and rates of bruising (8% versus 0%, $P < 0.05$) were significantly higher in the IMCS group compared with those in the OCS group at the follow-up visit. Taken together, these studies suggest that IMCSs represent a similarly effective regimen in preventing relapse after ED discharge compared with several days' therapy with OCSs.

Abbreviations used: ED, Emergency department; ICS, Inhaled corticosteroid; IMCS, Intramuscular corticosteroid; OCS, Oral corticosteroid; RCT, Randomized clinical trial.

This article is part of the Joint Task Force Report: Supplemental Recommendations for the Management and Follow-up of Asthma Exacerbations, an official workshop report of the American Academy of Allergy, Asthma and Immunology (AAAAI), the American Academy of Emergency Medicine (AAEM), and the American Thoracic Society (ATS). It was approved by the AAAAI Board of Directors, January 16, 2008, the AAEM Board of Directors, January 14, 2008, and the ATS Board of Directors, March 13, 2009.

The Joint Task Force Report is copublished in the *Journal of Allergy and Clinical Immunology*, the *Journal of Emergency Medicine*, and the *American Journal of Respiratory and Critical Care Medicine*.

Supported through an unrestricted educational grant to AAAAI and AAEM for publication and dissemination costs from GlaxoSmithKline, which had no input into the task force recommendations.

Reprint requests: Jerry A. Krishnan, M.D., Ph.D., Associate Professor of Medicine and Epidemiology, Director, Asthma and COPD Center, Section of Pulmonary & Critical Care Medicine, University of Chicago, 5841 S. Maryland Ave, MC 6076, Room M644, Chicago, IL 60637. E-mail: jkrishna@medicine.bsd.uchicago.edu.

Proc Am Thorac Soc Vol 6. pp 380–385, 2009
DOI: 10.1513/pats.P09ST5
Internet address: www.atsjournals.org

TABLE 1. RANDOMIZED CLINICAL TRIALS COMPARING IMCSs WITH OCSs AFTER ED DISCHARGE (TOTAL N = 599 PARTICIPANTS)

Reference	Study Design*	Treatment Groups†	Country	Age (*yr*)	No. (%)‡	Follow-up (*d*)§	Relapse (%)‖
Hoffman and Fiel, 1988 (9)	RCT, double-dummy	Methylprednisolone sodium acetate, 80 mg IM, vs methylprednisolone, 32 mg BID PO with an 8-d taper	United States	15–55	16/18 (89)	5-7	20.0% vs 0%, P = NS
Lee *et al.*, 1992 (10)	RCT, double-dummy	Dexamethasone, 10 mg IM, vs dexamethasone, 1.5 mg BID PO with an 8-day taper, vs double placebo (IM and PO)	Taiwan	16–60	52/52 (100)	7	5.9% vs 6.2%, P = NS
Shuckman *et al.*, 1998 (11)	RCT, double-dummy	Triamcinolone diacetate, 40 mg IM, vs prednisone, 40 mg/d PO × 5 d	United States	18–50	154/168 (92)	7	9.0% vs 14.5%, P = NS
Chan *et al.*, 2001 (4)	RCT, double-dummy	Betamethasone sodium phosphate, 6 mg, + betamethasone acetate, 6 mg IM, vs prednisone, 50 mg/d PO × 7 d	Canada	>18	159/171 (93)	21	36.8% vs 31.0%, P = NS
Lahn *et al.*, 2004 (12)	RCT, double-dummy	Methylprednisolone acetate, 160 mg IM, vs methylprednisolone, 32 mg PO with an 8-d taper	United States	18–45	180/190 (95)	21	18.5% vs 22.7%, P = NS

Definition of abbreviations: BID = twice daily; ED = emergency department; IM = intramuscularly; IMCSs = intramuscular corticosteroids; NS = not significant; OCSs = oral corticosteroids; PO = by mouth; RCT = randomized clinical trial.

* Double-dummy refers to use of a placebo in both treatment groups.

† Corticosteroid treatment groups.

‡ Study completion rate: numbers (percentages) of participants who completed versus enrolled in the study are shown.

§ Follow-up period during which outcomes were compared between treatment groups.

‖ Relapse during the follow-up period in the IMCS versus OCS groups, as defined in individual studies (e.g., need for treatment intensification, ED visit, or hospitalization).

ICSs versus OCSs

For more information, *see* Table 2 (13, 14). A meta-analysis by Edmonds *et al.* (7) evaluated the results of 7 trials comparing ICSs with OCSs in patients with acute asthma. In this meta-analysis 4 trials focused on pediatric populations and 1 study focused on patients presenting to their primary care physicians' offices. The remaining 2 trials, in a total of 269 adults, compared high-dose ICSs with OCSs for 7 to 10 days, using a double-dummy design, in adults with acute asthma discharged from the ED after initial therapy (13, 14). Rates of study completion were high (96% [13] and 89% [14]), and there were no significant differences in relapse or other outcomes, including need for rescue medications, improvements in lung function, asthma symptoms, and quality of life. The low relapse rates in the control groups (7% at 7 d [13] and 12% at 10 d [14]), together with lung function measurements on ED discharge (FEV_1 of 64% of predicted value [13] and peak expiratory flow of 407 L/min [14]), suggest that participants in this study had mild or moderate forms of acute asthma. There were also no significant differences in outcomes when analysis included all patients (adults and children) across the 7 trials (7).

Combination of ICSs Plus OCSs versus OCSs Alone

For more information, *see* Table 3 (15–17). Edmonds *et al.* (5) performed a meta-analysis of 3 trials (total n = 912 adults) that investigated the efficacy of combining ICSs and OCSs versus use of OCSs alone in patients discharged from the ED after initial treatment for acute asthma (15–17). Only 2 of these studies have been published (15, 16). Moderate-to-high doses of ICSs combined with 5- to 7-day courses of oral prednisone at 40 to 50 mg/day were compared with oral prednisone alone, and outcomes were assessed up to 20 to 24 days after ED discharge. The study by Rowe *et al.* (15), which had the highest follow-up rate (97%) and the highest overall relapse rate (19%) of all 3 studies, reported a significant reduction in the risk of relapse in patients assigned combination therapy versus an OCS alone (12.8% versus 24.5%, P = 0.049). In contrast, no significant differences in relapse rates by treatment group were reported in the other 2

TABLE 2. RANDOMIZED CLINICAL TRIALS COMPARING ICSs VERSUS OCSs AFTER ED DISCHARGE (TOTAL N = 269 PARTICIPANTS)

Reference	Study Design*	Treatment Groups†	Country	Age (*yr*)	No. (%)‡	Follow-up (*d*)§	Relapse (%)‖
Nana *et al.*, 1998 (13)	RCT, double-dummy	Budesonide DPI, 1,600 μg BID × 7 d, vs prednisolone, 40 mg/d with a 7-d taper	Thailand	16–50	81/84 (96)	7	11.9% vs 7.1%, P = NS
Fitzgerald *et al.*, 2000 (14)	RCT, double-dummy	Budesonide DPI, 600 μg QID × 7–10 d, vs prednisone, 40 mg/d × 7–10 d	Canada	15–50	151/185 (82)	10	10% vs 11.8%, P = NS

Definition of abbreviations: BID = twice daily; DPI = dry powder inhaler; ED = emergency department; NS = not significant; OCSs = oral corticosteroids; QID = 4 times daily; RCT = randomized clinical trial.

* Double-dummy refers to use of a placebo in both treatment groups.

† Corticosteroid treatment groups.

‡ Study completion rate: numbers (percentages) of participants who completed versus enrolled in the study are shown.

§ Follow-up period during which outcomes were compared between treatment groups.

‖ Relapse during the follow-up period in the ICS versus OCS groups, as defined in individual studies (e.g., need for treatment intensification, ED visit, or hospitalization).

TABLE 3. RANDOMIZED CLINICAL TRIALS COMPARING ICSs PLUS OCSs VERSUS OCSs ALONE AFTER ED DISCHARGE (TOTAL N = 912 PARTICIPANTS)

Reference	Study Design*	Treatment Groups†	Country	Age (*yr*)	No. (%)‡	Follow-up (*d*)§	Relapse (%)‖
Rowe *et al.*, 1999 (15)	RCT, double-dummy	Budesonide DPI, 800 μg BID × 3 wk, + prednisone, 50 mg/d PO × 7 d, vs prednisone, 50 mg/d PO × 7 d	Canada	18–60	186/191 (97)	21	12.8% vs 24.5%, $P = 0.049$
Brenner *et al.*, 2000 (16)	RCT, double-dummy	Flunisolide MDI, 1,000 μg BID × 24 d, + prednisone, 40 mg/d PO × 5 d, vs prednisone, 40 mg/d PO × 5 d	United States	18–50	73/104 (70)	24	7.8% vs 7.5%, P = NS
Camargo, 2000 (17)	RCT, double-dummy	Fluticasone Diskhaler, 250 μg BID × 20 d, + prednisone, 50 mg/d PO × 5 d, vs prednisone, 50 mg/d PO × 5 d	United States	12–54	517/617 (84)	20	9.7% vs 12.0%, P = NS

Definition of abbreviations: BID = twice daily; DPI = dry powder inhaler; ED = emergency department; NS = not significant; OCSs = oral corticosteroids; PO = by mouth; RCT = randomized clinical trial.

* Double-dummy refers to use of a placebo in both treatment groups.

† Corticosteroid treatment groups.

‡ Study completion rate: numbers (percentages) of participants who completed versus enrolled in the study are shown.

§ Follow-up period during which outcomes were compared between treatment groups.

‖ Relapse during the follow-up period in the ICS plus OCS versus OCS groups, as defined in individual studies (e.g., need for treatment intensification, ED visit, or hospitalization).

studies. When data were pooled across all 3 studies, there was a nonsignificant trend toward a reduction in relapse rates with combination therapy (odds ratio for relapse with combination therapy versus OCS alone, 0.68; 95% CI, 0.46–1.02). There were no significant differences in other pooled outcomes between treatment groups, including lung function, use of β-agonists, asthma symptoms, or adverse effects of ICSs (e.g., hoarseness or sore throat).

Noncorticosteroid Anti-inflammatory Agents

For more information, *see* Table 4 (3, 18). Johnston and other Telithromycin in Acute Exacerbations of Asthma investigators (18) conducted a multicenter, double-blind, placebo-controlled clinical trial to compare the efficacy and safety of telithromycin (800 mg/d), a macrolide, in 278 adults with acute asthma presenting to the urgent care clinic, ED, or hospital. Findings indicate a significantly greater improvement in asthma symptoms in the telithromycin group compared with the placebo group during the 10-day treatment period (−0.3 points [0- to 6-point scale], $P = 0.004$). Benefits were also noted in other outcomes during the treatment period, including a greater improvement in FEV_1 (0.63 versus 0.34 L, $P = 0.001$). Interestingly, results were similar in patients with and without laboratory evidence of infection with atypical bacteria at enrollment. However, differences in lung function disappeared by the end of the 42-day follow-up period, and relapse rates were very low and similar in both treatment groups (1.5% each). Nausea was significantly more common in the telithromycin-treated versus placebo-treated patients (5.3% versus 0%, $P = 0.01$), but other adverse events were uncommon and similar across treatment groups.

In a multicenter study Silverman *et al.* (3) evaluated the effects of adding zafirlukast, an oral leukotriene receptor antagonist, or placebo to a standardized regimen of systemic corticosteroids and an inhaled β_2-agonist in 546 participants. Study participants were given a single oral dose of zafirlukast (160 mg or 20 mg) or placebo in the ED. Patients who were discharged from the ED (86% of all study participants) were enrolled in an outpatient phase and randomly assigned to continue treatment with 20 mg of zafirlukast twice daily or placebo by mouth for 28 days (in addition to other asthma medications). The zafirlukast group had a significantly lower 28-day relapse rate (primary outcome) compared with the placebo group (23.6% versus 28.9%, $P = 0.047$), better lung function (FEV_1 of 2.49 versus 2.27 L), lower mean daytime symptom scores (0.82 versus 1.01), less frequent β-agonist use (3.3 versus 4.1 puffs/d, $P < 0.01$), and fewer disruptions of daily activities (20% versus 26%, $P = 0.02$). Adverse events were uncommon and similar between the treatment groups, including increases in alanine aminotransferase levels (1% versus 2%, P = not significant).

TABLE 4. RANDOMIZED CLINICAL TRIALS EVALUATING NONCORTICOSTEROID TREATMENTS AFTER ED DISCHARGE

Reference	Study Design	Treatment Groups	Country	Age (*yr*)	No. (%)*	Follow-up (*d*)†	Relapse (%)‡
Johnston *et al.*, 2006 (18)	RCT, double-blind	Telithromycin, 800 mg/d PO, vs placebo, PO × 10 d	Multiple	18–55	231/278 (83)	42	1.5% vs 1.5%, P = NS
Silverman *et al.*, 2004 (3)	RCT, double-blind	Zafirlukast, 160 mg or 20 mg PO × 1 and then 20 mg PO BID, vs placebo PO × 28 d	United States	12–65	457/546 (84)§	28	23.6% vs 28.9%, $P = 0.047$

Definition of abbreviations: BID = twice daily; ED = emergency department; NS = not significant; PO = by mouth; RCT = randomized clinical trial.

* Study completion rate: numbers (percentages) of participants who completed versus enrolled in the study are shown.

† Follow-up period during which outcomes were compared between treatment groups.

‡ Relapse rates in the treatment versus placebo groups, as defined in individual studies (e.g., need for treatment intensification, ED visit, or hospitalization).

§ Six hundred forty-one patients were initially enrolled in the ED; 549 were eligible and enrolled in the outpatient (post-ED discharge) phase.

DISCUSSION

The main findings of this systematic review of clinical trials in adults with acute asthma after ED discharge are as follows: (*1*) IMCS regimens appear to be as effective as OCS regimens in preventing relapse (total n = 599 participants); (*2*) in patients with mild-to-moderate acute asthma, ICS and OCS regimens are similarly effective in preventing relapse (total n = 269 participants); (*3*) there was a nonsignificant trend suggesting that combination therapy with ICSs and OCSs might be more effective than an OCS alone in preventing relapse (total n = 912 participants); and (*4*) additional studies are needed to examine the safety and efficacy of initiating macrolide antibiotics (in the absence of infection) and leukotriene modifiers after an episode of acute asthma.

Several studies have documented a link between low rates of patient adherence to asthma therapy and poorly controlled asthma, including increased risk of ED visits or hospitalizations for acute asthma (19, 20). Nonadherence to systemic corticosteroid treatment is even common immediately after ED or hospital discharge (21–23). A single intramuscular dose of a long-acting (depot or repository) corticosteroid achieves a prolonged anti-inflammatory effect and might therefore be superior to discharging patients with an OCS regimen (which depends on patients to fill prescriptions and then use them appropriately). However, findings from this systematic review failed to detect differences in relapse rates or other efficacy outcomes between patients treated with IMCSs and OCSs, and 1 study found higher rates of injection-site pain and bruising with IMCSs. The available data are based on studies comparing IMCSs versus OCSs provided at ED discharge (not a prescription for an OCS), suggesting that the study designs might have underestimated the benefits of depot IMCSs that would be observed in clinical practice. Also, the studies were not designed as equivalency trials and therefore enrolled too few patients in any single study (range, 18–190 patients) to exclude the possibility of a small but clinically important reduction in the rate of relapse with IMCSs. Nevertheless, findings from studies to date suggest that IMCSs offer an attractive alternative in selected patients who are likely to have difficulty in obtaining or using an OCS after ED discharge.

There are ample data from clinical trials to support the use of ICSs in chronic asthma (2, 24). Results of this review suggest that adults with mild or moderate acute asthma discharged from the ED with ICSs or OCSs have similar short-term ($\leqslant$ 10 d) outcomes. However, because these studies were not designed as equivalency studies, it is not possible to exclude clinically important differences in relapse rates between ICS and OCS regimens after discharge. Also, ICSs are more costly and difficult for patients to use compared with OCSs. Therefore we recommend using ICSs instead of OCSs only in patients with milder forms of acute asthma who are able to obtain, afford, and use ICSs appropriately; have difficulty tolerating OCSs because of adverse effects (e.g., hyperglycemia or sleep disturbance); or both.

Observational studies suggest that ICS treatment (compared with no ICS treatment) might reduce acute asthma relapse rates after ED discharge by about 50% (20, 25–26). Many RCTs show that ICSs reduce exacerbations in patients with persistent asthma (24). Results of this review (with $>$ 900 total participants), however, only found a trend toward a lower relapse rate when high-dose ICSs (versus placebo) are added to a 5- to 7-day OCS regimen. Thus the available evidence is insufficient to recommend combination corticosteroid therapy in all adults with acute asthma after ED discharge but does not rule out a clinically important benefit either, including a long-term benefit in reducing exacerbations (24). A number of studies have documented low rates of ICS prescription at ED discharge in this population (16% to 24%) (27–29), even in patients with evidence of poorly controlled asthma (e.g., a history of ED visits). Because national asthma guidelines recommend daily ICSs in patients with persistent asthma (2, 30), based on their documented efficacy in such patients, we recommend discharging patients with daily ICSs (in addition to a short course of an OCS) when there is evidence of persistent asthma between episodes of acute asthma. Based on current guidelines (30), discharging patients with a daily ICS regimen in addition to a short course of an OCS should also be considered in patients with an exacerbation requiring OCSs in the prior 12 months. Because poor inhaler technique is common in patients presenting with acute asthma, all patients prescribed ICSs should receive adequate training before ED discharge (31–33).

The antibacterial effects of macrolide antibiotics are well known, particularly against atypical bacteria, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. There is increasing awareness, however, that macrolides also possess separate immunomodulatory effects that could suppress airway inflammation and might be the basis for clinical benefits observed in patients with cystic fibrosis and diffuse panbronchiolitis (34). There are now promising data (from 1 trial [18]), suggesting that a 10-day course of telithromycin, a macrolide antibiotic, initiated during acute asthma might improve symptom control and lung function. However, these effects were temporary and disappeared after treatment discontinuation, and no benefit on the risk of relapse was observed. Moreover, the U.S. Food and Drug Administration recently added a "black box" warning regarding an increased risk of serious and possibly fatal hepatotoxicity after use of telithromycin (35). Thus although promising, additional studies are needed about the role of macrolide antibiotics in acute asthma, and until then, we recommend against the use of macrolide antibiotics in the absence of other clinical indications (e.g., concomitant community-acquired pneumonia).

Cysteinyl leukotrienes, potent mediators of airway inflammation and bronchoconstriction in patients with chronic asthma, can be further increased during episodes of acute asthma (36, 37). Results of a single trial (3) suggest that a 28-day course of the leukotriene receptor antagonist zafirlukast might significantly reduce relapse rates and improve lung function and symptoms when initiated in the ED and continued after ED discharge. As with macrolide antibiotics, these results are promising, and additional studies are needed to confirm the safety and efficacy of initiating leukotriene modifiers during and after acute asthma.

SUMMARY OF RECOMMENDATIONS

1. Conditional: consider IMCSs* in patients who are likely to have difficulty in obtaining or using OCSs after ED discharge. Patients selected for IMCS therapy should be informed of an increased risk of local injection site

---

* In alphabetical order: betamethasone sodium phosphate, 6 mg, with betamethasone acetate, 6 mg, administered intramuscularly $\times$1; dexamethasone, 10 mg, administered intramuscularly $\times$1; methylprednisolone sodium acetate, 80 to 160 mg, administered intramuscularly $\times$1; or triamcinolone diacetate, 40 mg, administered intramuscularly $\times$1.

† Budesonide dry powder inhaler, 2,400 to 3,200 μg/d, inhaled in divided doses (2–4 times a day) for 7 to 10 days. Alternative regimens, in alphabetical order, with estimated equivalent daily dose (29) include flunisolide, 4,000 to 5,000 μg/d; fluticasone dry powder inhaler, 1,000 to 1,500 μg/d; mometasone dry powder inhaler, 800 to 1,200 μg/d; triamcinolone acetonide, 3,000 to 4,000 μg/d.

complications (mostly pain or bruising) (Evidence Category B).

2. Conditional: consider a short course of a very high-dose ICS[†] instead of an OCS after ED discharge in patients with mild forms of acute asthma who are able to obtain, afford, and use ICSs correctly; have difficulty tolerating OCSs; or both (Evidence Category B). Such patients should receive adequate training about how to use ICSs before ED discharge.
3. Strong: recommend initiating daily ICSs[‡] (in patients not already receiving a daily ICS) or continuing daily ICSs[‡] (in patients already receiving a daily ICS) on ED discharge (in addition to a short course of an OCS)[‡] for patients with a history compatible with persistent asthma,[§] even between episodes of acute asthma (Evidence Category A). Conditional: consider initiating daily ICSs in patients who have required OCSs for an asthma exacerbation in the prior 12 months (Evidence Category D). Patients starting ICSs should receive adequate training about how to use them before ED discharge.
4. Additional studies are needed to evaluate the efficacy and safety of macrolides and leukotriene modifiers in adults with acute asthma after ED discharge before recommendations regarding their use can be made (Evidence Category B, no recommendation).

Author disclosures were obtained by the *Journal of Allergy and Clinical Immunology* (JACI) using questions determined by the American Academy of Allergy, Asthma and Immunology (AAAAI) and JACI. Questions pertained to: employment; financial interests between the author or members of the author's immediate family or household with organizations and commercial interests; research support during the past calendar year; and legal consultation services/expert witness testimony during the past calendar year. Authors were asked to state dollar amounts in ranges of either $<$ \$10,000 or $\geq$ \$10,000. Authors were not required to disclose other facts that are now requested by *PATS* in conformance with American Thoracic Society policy, including knowledge of any significant financial relationship between the author's institution or employer and relevant commercial interests, and all relationships with tobacco entities.

Disclosure of potential conflict of interest: J.A.K. has declared that he has no conflict of interest. R.N. has declared that he has no conflict of interest. S.Q.D. has declared that he has no conflict of interest. M.S. has been a consultant for GlaxoSmithKline and has received research support from Aerocrine, Genentech, GlaxoSmithKline, and Merck.

References

1. Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma. *Cochrane Database Syst Rev* 2001;1:CD000195.
2. National Asthma Education Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007 [Accessed May 30, 2009]. Available from: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.
3. Silverman RA, Nowak RM, Korenblat PE, Skobeloff E, Chen Y, Bonuccelli CM, *et al.* Zafirlukast treatment for acute asthma. *Chest* 2004;126:1480–1489.
4. Chan JS, Cowie RL, Lazarenko GC, Little C, Scott S, Ford GT. Comparison of intramuscular betamethasone and oral prednisone in the prevention of relapse of acute asthma. *Can Respir J* 2001;8:147–152.
5. Edmonds ML, Camargo CA, Saunders LD, Brenner BE, Rowe BH. Inhaled steroids in acute asthma following emergency department discharge. *Cochrane Database Syst Rev* 2000; (3):CD002316.
6. Rowe BH, Edmonds ML, Spooner CH, Diner B, Camargo CA Jr. Corticosteroid therapy for acute asthma. *Respir Med* 2004;98:275–294.
7. Edmonds ML, Camargo CA Jr, Brenner BE, Rowe BH. Replacement of oral corticosteroids with inhaled corticosteroids in the treatment of acute asthma following emergency department discharge: a meta-analysis. *Chest* 2002;21:1798–1805.
8. Schatz M, Kazzi AAN, Brenner B, Camargo Jr CA, Corbridge T, Krishnan JA, Nowak R, Rachelefsky G. Introduction. *Proc Am Thorac Soc* 2009;6:353–356.
9. Hoffman IB, Fiel SB. Oral vs repository corticosteroid therapy in acute asthma. *Chest* 1988;93:11–13.
10. Lee CH, Lee CJ, Lan RS, Tsai YH, Chiang YC, Wang WJ, *et al.* Repository dexamethasone in the treatment of acute bronchial asthma. *Changgeng Yi Xue Za Zhi* 1993;16:25–29.
11. Shuckman H, DeJulius DP, Blanda M, Gerson L, DeJulius A, Rajaratnam M. Comparison of intramuscular tramcionlone and oral prednisone in the outpatient treatment of acute asthma: a randomized controlled trial. *Ann Emerg Med* 1998;31:333–338.
12. Lahn M, Bijur P, Gallagher EJ. Randomized clinical trial of intramuscular vs oral methylprednisolone in the treatment of asthma exacerbations following discharge from an emergency department. *Chest* 2004;126:362–368.
13. Nana A, Youngchaiyud P, Charoenratanakul S, Boe J, Lofdahl CG, Selroos O, *et al.* High-dose inhaled budesonide may substitute for oral therapy after an acute asthma attack. *J Asthma* 1998;35:647–655.
14. Fitzgerald JM, Shragge D, Haddon J, Jennings B, Lee J, Bai T, *et al.* A randomized, controlled trial of high dose, inhaled budesonide versus oral prednisone in patients discharged from the emergency department following an acute asthma exacerbation. *Can Respir J* 2000;7:61–67.
15. Rowe BH, Bota GW, Fabris L, Therrien SA, Milner RA, Jacono J. Inhaled budesonide in addition to oral corticosteroids to prevent asthma relapse following discharge from the emergency department: a randomized clinical trial. *JAMA* 1999;281:2119–2126.
16. Brenner BE, Chavda KK, Camargo CA Jr. Randomized trial of inhaled flunisolide versus placebo among asthmatic patients discharged from the emergency department. *Ann Emerg Med* 2000;36:417–426.
17. Camargo C Jr. on behalf of the MARC investigators. Randomized trial of medium dose flunisolide vs. placebo after an emergency department visit for acute asthma. Presented at: American Academy of Allergy. Asthma & Immunology 56th Annual Meeting: San Diego, 2000.
18. Johnston SL, Blasi F, Black MB, Martin RJ, Farrell DJ, Nieman RB, *et al.* The effect of telithromycin in acute exacerbations of asthma. *N Engl J Med* 2006;354:1589–1600.
19. Williams LK, Pladevall M, Xi H, Peterson EL, Joseph C, Lafata JE, *et al.* Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. *J Allergy Clin Immunol* 2004; 114:1288–1293.
20. Camargo CA, Ramanchandran S, Ryskina KL, Lewis BE, Legorreta AP. Association between common asthma therapies and recurrent asthma exacerbations in children enrolled in a state Medicaid plan. *Am J Health Syst Pharm* 2007;64:1054–1061.
21. Butler K, Cooper WO. Adherence of pediatric asthma patients with oral corticosteroid prescriptions following emergency department visit or hospitalization. *Pediatr Emerg Care* 2004;20:730–735.
22. Krishnan JA, Riekert KA, McCoy JV, Stewart DY, Schmidt S, Chanmugam A, *et al.* Corticosteroid use after hospital discharge among high-risk adults with asthma. *Am J Respir Crit Care Med* 2004; 170:1281–1285.
23. Cooper WO, Hickman GB. Corticosteroid prescription filling for children covered by Medicaid following an emergency department visit or hospitalization for asthma. *Arch Pediatr Adolesc Med* 2001; 155:1111–1115.
24. Adams N, Bestall J, Jones PW. Budesonide versus placebo for chronic asthma in children and adults. *Cochrane Database Syst Rev* 1999;4:CD003274.
25. Smith MJ, Rascati KL, McWilliams BC. Inhaled anti-inflammatory pharmacotherapy and subsequent hospitalizations and emergency department visits among patients with asthma in the Texas Medicaid program. *Ann Allergy Asthma Immunol* 2004;92:40–46.
26. Sin DD, Man SFP. Low-dose inhaled corticosteroid therapy and risk of emergency department visits for asthma. *Arch Intern Med* 2002;162: 1591–1595.

[‡] In alphabetical order: daily inhaled budesonide dry powder inhaler, 1,200 μg/d; flunisolide metered-dose inhaler, 2,000 μg/d; fluticasone dry powder inhaler, 500 μg/d; mometasone dry powder inhaler, 400 μg/d; triamcinolone acetonide, 1500 μg/d, in divided doses (twice per day) for 3 to 4 weeks AND prednisone, 40 to 50 mg/d, for 5 to 7 days.

[§] Any of the following: prescribed daily controller use; daytime symptoms or use of rescue inhalers (e.g., albuterol) more than twice a week; interference with sleep more than twice a month; activity limitation caused by asthma; exacerbations requiring systemic corticosteroids more than once a year; or airflow obstruction with FEV1 less than 80% of predicted value.

27. Salerno EL, Wolf S, Troy P, Horowitz S, Banever A, Metersky M, *et al.* Discharge patterns of patients with asthma from the emergency department: a retrospective review. *Conn Med* 2005;69:621–627.
28. Scarfone RJ, Zorc JJ, Angsuco CJ. Emergency physicians' prescribing of asthma controller medications. *Pediatrics* 2006;117:821–827.
29. Cydulka RK, Tamayo-Sarver JH, Wolf C, Herrick E, Gress S. Inadequate follow-up controller medications among patients with asthma who visit the emergency department. *Ann Emerg Med* 2005; 46:316–322.
30. National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the diagnosis and management of asthma [Accessed May 30, 2009]. Available from: http://www.nhlbi.nih.gov/guidelines/asthma/index.htm.
31. Shrestha M, Parupia H, Andrews B, Kim SW, Martin MS, Park DI, *et al.* Metered-dose inhaler technique of patients in an urban ED: prevalence of incorrect technique and attempt at education. *Am J Emerg Med* 1996;14:380–384.
32. Numata Y, Bourbeau J, Ernst P, Duquette G, Schwarzman K. Teaching time for metered-dose inhalers in the emergency setting. *Chest* 2002; 122:498–504.
33. Paasche-Orlow MK, Riekert KA, Bilderback A, Chanmugam A, Hilll P, Rand CS, *et al.* Tailored education may reduce health literacy disparities in asthma self-management. *Am J Respir Crit Care Med* 2005;172:980–986.
34. Healy DP. Macrolide immunomodulation of chronic respiratory diseases. *Curr Infect Dis Rep* 2007;9:7–13.
35. US Food and Drug Administration. Telithromycin (marketed as Ketek) information [Accessed May 30, 2009]. Available from: http://www.fda.gov/cder/drug/infopage/telithromycin/default.htm.
36. Weiss JW, Drazen JM, Coles N, McFadden ER Jr, Weller PF, Corey EJ, *et al.* Bronchoconstrictor effects of leukotriene C in humans. *Science* 1982;216:196–198.
37. Taylor GW, Taylor I, Black P, Maltby NH, Turner N, Fuller RW, *et al.* Urinary leukotriene E4 after antigen challenge and in acute asthma and allergic rhinitis. *Lancet* 1989;1:584–588.

Follow-up after Acute Asthma Episodes
What Improves Future Outcomes?

Michael Schatz[1], Gary Rachelefsky[2], and Jerry A. Krishnan[3]

[1]Department of Allergy, Kaiser Permanente Medical Center, San Diego, California; [2]Executive Care Center for Asthma, Allergy, and Respiratory Diseases at the Geffen School of Medicine, University of California Los Angeles, Los Angeles, California; and [3]Asthma and COPD Center, Department of Medicine, and Department of Health Studies, University of Chicago, Chicago, Illinois

Keywords: acute asthma; asthma exacerbation; emergency department; follow-up care; allergist care; pulmonologist care; asthma specialist care

Emergency departments (EDs) are commonly used for the acute and chronic management needs of patients with asthma in the United States and account for nearly 2 million visits each year (1–5). Traditionally, the role of emergency physicians in caring for patients with acute asthma has been to provide emergency treatment and then to suggest follow-up visits with the primary care provider for ongoing preventive care. However, rates of follow-up with primary care providers are often low (6).

Effective and timely outpatient care of asthma can prevent adverse asthma outcomes, specifically ED visits and hospitalizations (7, 8). For example, Ford *et al.* (7) assessed the effect of an asthma education program on African American and white adults with asthma and found patients who received an asthma education intervention demonstrated a decrease in ED visits after the education intervention versus patients who did not receive the educational intervention, with the most significant period of improvement observed in the first 4 months of receiving the educational intervention program. A case-control study on children ages 0 to 14 years was conducted to identify outpatient management practices associated with increased or decreased risk of adverse outcomes. It was noted that patients with written asthma management plans were half as likely to have a hospitalization or an ED visit as those who lacked a plan (9).

The current systematic review is an attempt to identify effective strategies for patient follow-up after an asthma exacerbation that lead to improved clinical outcomes and decreased rates of subsequent exacerbations. Studies in both children and adults are included. Although follow-up after an asthma ED visit was the specific subject of the review, studies that report follow-up interventions after an asthma hospitalization that could be used after an ED visit are also included. The goal is to formulate specific follow-up management recommendations based on this review.

METHODS

Two sets of keywords were selected for the systematic literature review. The first set included the following terms: *emergency asthma*; *status asthmaticus*; *acute asthma*; *severe asthma*; and *asthma exacerbation*. The second set of keywords included the following terms: *allergist care*; *asthma specialist*; *discharge planning*; *discharge instructions*; *follow-up care*; *follow-up*; *long-term asthma care*; *patient care planning*; *preventative healthcare*; *preventative care*; *preventative health maintenance*; *primary health care provider*; *pulmonologist care*; *respiratory specialist care*; and *specialist care*. Additional details of the methodology for all literature reviews in this supplement are provided in the introduction to this issue (10). The task force specified the level of evidence used to justify the recommendations being made, and the system used to describe the level of evidence is also defined in the introduction to this issue.

RESULTS

The literature search produced 25 randomized controlled trials and 6 meta-analyses. Ten randomized controlled trials were deemed relevant for this review, with none of the meta-analyses considered relevant. The relevant randomized controlled trials and other articles deemed important by the editorial team were organized by themes.

Achieving the Follow-up Appointment

Randomized controlled trials. Four studies have tested interventions to improve follow-up with primary care physicians after ED visits (Table 1) (11–14). One studied adults only (11), 1 studied children and adults (12), and 2 studied children only (13, 14). The studies by Baren *et al.* (11, 12) used free prednisone, transportation vouchers, and appointment reminder telephone calls in 1 study (11) and actually scheduled the appointment before discharge in the other (12). The interventions improved follow-up in both studies. Factors associated with improved follow-up in the first study (11) were identified to be a prior relationship with a primary care provider, older patient age, regular access to transportation for scheduled medical care, black race, and lack of health insurance coverage. Although follow-up improved, the intervention in the second study (12) was not associated with improved outcomes, such as proportion of patients with relapse events; subsequent urgent care visits, ED visits, or hospitalizations; reported activity limitation; or use of asthma controllers.

The 2 studies in children by Smith *et al.* (13, 14) tested monetary incentives and coaching, either by telephone (13) or in the ED (14), to enhance follow-up. The largest study (13), which used telephone coaching on days 2 and 5 after the ED visit, was associated with an increased likelihood of follow-up and reduced symptoms. The smaller study (14), which used asthma coaching in the ED but not telephone coaching, was not

Abbreviations used: ED, Emergency department.

This article is part of the Joint Task Force Report: Supplemental Recommendations for the Management and Follow-up of Asthma Exacerbations, an official workshop report of the American Academy of Allergy, Asthma and Immunology (AAAAI), the American Academy of Emergency Medicine (AAEM), and the American Thoracic Society (ATS). It was approved by the AAAAI Board of Directors, January 16, 2008, the AAEM Board of Directors, January 14, 2008, and the ATS Board of Directors, March 13, 2009.

The Joint Task Force Report is copublished in the *Journal of Allergy and Clinical Immunology*, the *Journal of Emergency Medicine*, and the *American Journal of Respiratory and Critical Care Medicine*.

Supported through an unrestricted educational grant to AAAAI and AAEM for publication and dissemination costs from GlaxoSmithKline, which had no input into the task force recommendations.

Reprint requests: Michael Schatz, M.D., M.S., Department of Allergy, Kaiser Permanente Medical Center, 7060 Clairemont Mesa Blvd., San Diego, CA 92111.

Proc Am Thorac Soc Vol 6. pp 386–393, 2009
DOI: 10.1513/pats.P09ST6
Internet address: www.atsjournals.org

TABLE 1. RANDOMIZED CONTROLLED TRIALS ADDRESSING ACHIEVING THE FOLLOW-UP APPOINTMENT

Reference	Country	Age (*yr*)	No. of Subjects (Intervention/ Control Groups)	Intervention	Results: Primary Outcome	Other Results
Baren *et al.*, 2001 (11)	United States	22.4–39.8	95/83	Five-day course of 50 mg of prednisolone daily Taxicab vouchers Asthma information card Written instructions Appointment reminder telephone call in 48 h	Asthma follow-up with PCP within 4 wk of index ED visit more common in intervention group (RR, 1.6; 95% CI, 1.1–2.4)	Study intervention was inexpensive (3-part intervention approximately $15 per patient).
Baren *et al.*, 2006 (12)	United States	2–54	126 (a); 132 (b)/ 126 (c)	Free prednisone (a and b) Transportation vouchers (a and b) Telephone reminder for appointment (a) Scheduling of appointment before discharge (b)	Follow-up higher in group b (65%) vs group a (48%) or group c (42%) ($P = 0.002$)	There was no improvement in long-term clinical and functional outcomes in group b (better follow-up) compared with groups a or c.
Smith *et al.*, 2004 (13)	United States	Parents of children 2–12	263/264	Telephone coaching on days 2 and 5 after ED visit Coaching addresses recommendations for and benefits of follow-up, barriers to follow-up Monetary incentive ($15) for achieving follow-up	Intervention group more likely to attend asthma planning visit within 15 d of ED visit (35.7%) than control group (18.9%; $P < 0.0001$)	Greater decrease in asthma symptoms was seen in the first 2 wk in the intervention vs control groups. The proportions of children with asthma planning visits and acute asthma care visits during the 16-d to 6-mo period were similar for both groups.
Smith *et al.*, 2006 (14)	United States	Parents of children 2–12	50/42	Asthma coaching in the ED, including discussing the importance and advantages of seeking follow-up care with the child's PCP, discussing barriers to such care, and discussing strategies for overcoming those barriers Fifteen dollar monetary incentive for completing the follow-up visit	No significant differences between groups in verified follow-up PCP visits (intervention group, 22.0% [95% CI, 11.5% to 36.0%]; control group, 23.8% [95% CI, 12.0% to 39.4%])	

Definition of abbreviations: ED = emergency department; PCP = primary care physician.

associated with increased verified follow-up. It is of interest that of the visits of patients who reported having follow-up in that study, only 37% could be verified by medical record review.

Other studies. Sin *et al.* (15) conducted a relevant non-randomized controlled trial in Edmonton, Alberta, Canada, in which patients were allocated to the intervention group during certain weeks and to the usual care group during other weeks. The intervention consisted of a study coordinator offering to make the follow-up appointment directly with the patient's primary care physician on behalf of the patient and a reminder call 1 or 2 days before the scheduled follow-up visit. Patients in the intervention group (n = 63) were significantly more likely ($P \leq 0.003$) to make at least 1 follow-up visit in the first month, 3 months, and 6 months after the ED visit compared with patients in the usual care group (n = 62). However, similar to the above results, there were no significant differences between groups in mean asthma control scores or the occurrence of subsequent asthma-related ED visits or hospitalizations during the first 1, 3, 6, or 12 months after the index ED visit.

Asthma Education after an Asthma Exacerbation

Three studies tested various educational models for their effect after an asthma ED visit or hospitalization (Table 2) (16–18). The information provided in all 3 programs dealt with reinforcing treatment recommendations, optimizing inhaler technique, and self-management education. Two studies in children, one testing a telephone education session (16) and the other testing an enhanced nurse education visit (18), reported improved outcomes, ranging from increased likelihood of using preventer medication and written action plans in one study (16) to reduced emergency hospital care and greater patient satisfaction in the other (18). In contrast, a study in adults and children (17), which used a facilitated follow-up visit, optimization of medical therapy, a tailored self-management plan, and a home visit to identify triggers, was not associated with subsequent reduced urgent care visits. However, 39% of the intervention patients did not comply with post-ED visit activities in that study.

Comprehensive Follow-up Interventions

Three studies described trials of comprehensive follow-up interventions in adults or children (Table 3) (19–21). Outcomes evaluated in all 3 studies were also comprehensive, including medical utilization and quality-of-life parameters. The intervention in the study by Castro *et al.* (19) used a multifaceted approach consisting of 7 key elements: (*1*) nurse's suggestion of simplification or consolidation of the patient's medical regimen to the primary physician (based on National Asthma Education and Prevention Program II guidance); (*2*) daily completion of an asthma care flow sheet; (*3*) asthma education in accordance with patient education, cultural beliefs, and motivation; (*4*) psychosocial support and screening for professional counseling;

TABLE 2. RANDOMIZED CONTROLLED TRIALS ADDRESSING ASTHMA EDUCATION AFTER AN ED VISIT

Reference	Country	Age	No. of Subjects (Intervention/ Control Groups)	Intervention	Results: Primary Outcome	Other Results
Khan *et al.*, 2004 (16)	Australia	Parents of children ages 1–15 yr discharged from ED with asthma	136/130	Asthma educator provides telephone consultation Teach patient empowerment, use family/social system theory, reinforce recommendations Provide written educational materials with facts on use of spacer device, management and prevention of exercise-induced asthma, questions to ask and information to share with physician on follow-up	Symptom improvement (days of wheezing and doses of reliever) similar between groups	Intervention patients were more likely than control subjects to possess a written action plan.
Ng *et al.*, 2006 (18)	China	Children ages 2–15 yr	55/45	Nurse visit 1–2 d after hospital admission providing written and verbal education and an asthma diary Enhanced program included a predischarge nurse session, a video, and a 1-wk postdischarge follow-up nurse telephone call	Intervention group less likely than control subjects to experience asthma ED visits ($P = 0.004$) or hospitalizations ($P = 0.004$)	Intervention group demonstrated improved compliance and satisfaction with care.
Brown *et al.*, 2006 (17)	United States	80 adults/ 110 children	117/122	Facilitated primary care physician and nurse educator visit Optimizing medical therapy Asthma self-management education Tailored asthma self-management plan Home visit to identify triggers and reinforce education	There were no significant differences between groups in the occurrence of an urgent asthma visit, which occurred in 23.1% of the intervention group and 31.1% of the usual care group (HR, 0.79; 95% CI, 0.48-1.29).	Subgroup analysis suggested greater (but still not significant) benefit in children (HR, 0.62; 95% CI, 0.33-1.19) than adults (HR, 1.08; 95% CI, 0.50-2.33). It should be noted that 39% of the patients assigned to the intervention group did not comply with any of the post-ED activities.

Definition of abbreviations: ED = emergency department; HR = hazard ratio.

(*5*) individualized asthma self-management plans; (*6*) social service professional consultations for discharge planning facilitation; and (*7*) outpatient follow-up through telephone contact, home visits, and follow-up appointments with the primary care physician. The intervention group in this study experienced fewer readmissions, less missed work and school, and lower health care costs.

The study by Gorelick *et al*. (20) was a randomized, 3-arm, single-blind trial. The first arm received standard care, which included patient education, a written care plan, and instructions to follow up with the primary care provider within 7 days. In addition to the above, the second arm received assistance with scheduling follow-up. The third arm received all of the above, plus enrollment in a case management system, which included up to 6 home visits and several telephone calls during the 6-month follow-up period. There were no differences between groups in subsequent ED visits, quality of life, or controller use, although the latter 2 improved in all groups.

The intervention in the study by Teach *et al*. (21) was a single follow-up visit to a clinic located physically in the ED. The visit focused on 3 domains: (*1*) asthma self-monitoring and management, including an individualized action plan, device teaching, controller medications, and symptom and/or peak flow self-monitoring; (*2*) environmental modification and trigger control; and (*3*) linkages and referral to ongoing primary care, including sending reports of the clinic visits to each child's primary care physician and scheduling a follow-up appointment with the primary care physician. The intervention group experienced significantly fewer unscheduled visits, demonstrated more inhaled corticosteroid use, and reported better quality of life compared with the control group.

Asthma Specialist Follow-up

Randomized controlled trials. No recent randomized clinical trials addressing outcomes achieved by specialist follow-up after an ED were identified. Two older randomized controlled trials have been reported that evaluated asthma hospitalizations in previously hospitalized patients who were managed by asthma specialists compared with patients receiving usual care. Mayo *et al*. (8) studied 104 adult asthmatic patients previously admitted for asthma. Forty-seven were randomly assigned to an intensive outpatient treatment program in the chest clinic, and 57 continued to receive their previous outpatient care. Intervention patients required one third the number of admissions per patient ($P < 0.004$) compared with those receiving usual care.

Hughes *et al*. (22) studied 95 children and adolescents who had been admitted with a diagnosis of asthma in the prior 5 years. Forty-seven intervention patients were followed by 1 pediatric respirologist, and 48 patients continued to receive regular care from a family physician or pediatrician. Interven-

TABLE 3. RANDOMIZED CONTROLLED TRIALS ADDRESSING COMPREHENSIVE FOLLOW-UP INTERVENTIONS

Reference	Country	Age	No. of Subjects (Intervention/ Control Group)	Intervention	Results: Primary Outcome	Other Results
Castro *et al.*, 2003 (19)	United States	18–65 yr	50/46	Nurse-focused intervention Simplify medication regimen Have patient complete "asthma care flow sheet" daily Asthma education with patient education considering patient cultural beliefs/motivation Psychosocial support/screening for counseling Asthma self-management plan Discharge planning/facilitation with social services Outpatient follow-up through telephone contact, home visits, and follow-up appointments with PCP	Sixty percent reduction in total readmissions in intervention group ($P = 0.04$)	Intervention group experienced less missed work and school and lower health care costs.
Gorelick *et al.*, 2006 (20)	United States	24 mo to 18 yr	95 (a); 81 (b) /99(c)	Copy of ED chart and letter with recommendations faxed to PCP office (a and b) Telephone call reminders/ assistance with making follow-up appointment (a and b) Case manager enrollment, including home visits, telephone calls, environmental assessments, personalized care plan, asthma education, and referral to community services (b)	No difference between treatment groups in subsequent ED visit for asthma (group a, 39.2%; group b, 35.8%; group c, 38.4%)	No difference between intervention group and usual care group in quality of life or controller use, although the latter improved substantially in both groups.
Teach *et al.*, 2006 (21)	United States	12 mo to 17 yr	219/218	Single follow-up visit to clinic in ED Visit focused on asthma self-monitoring and management, environmental modifications and trigger control, and linkages and referrals to ongoing care	Intervention group had significantly fewer unscheduled visits for asthma care during follow-up (1.39 vs 2.34; RR, 0.60; 95% CI, 0.46–0.77).	Intervention group demonstrated more inhaled corticosteroid use and reported better quality of life.

Definition of abbreviations: ED = emergency department; PCP = primary care physician; RR = relative risk.

tion subjects had less school absenteeism than control subjects (10.7 versus 16.0 days, $P = 0.04$), but there were no significant differences in the rates of hospitalizations or ED visits during the study year. However, fewer days were spent in the hospital by the intervention patients admitted compared with the control patients (3.7 versus 11.2 days, $P = 0.02$).

Other studies. Two nonrandomized (alternate assignment) controlled intervention studies have shown reduced ED visits in patients with prior emergency asthma care who were followed by allergists compared with patients followed by generalists. Zeiger *et al.* (23) reported on pediatric and adult patients presenting to the ED with acute asthma who were alternately assigned to receive a facilitated referral and follow-up in the allergy clinic (intervention group, n = 149) or continued outpatient management from generalist physicians (control group, n = 160). Compared with the control group, the intervention group noted an almost 50% reduction in asthma ED relapses over the next 6 months ($P = 0.017$).

Kelly *et al.* (24) described 80 children with a history of 2 or more ED visits or at least 1 hospitalization for asthma in the previous year. Patients assigned (based on alternating assignment) to the intervention group (n = 38) were managed in a tertiary care pediatric allergy clinic, and patients assigned to the control group (n = 40) received care from their primary care providers. Compared with intervention patients, control patients were more than twice as likely ($P = 0.04$) to require a hospitalization and 40% more likely to have an ED visit ($P = 0.04$) after adjusting for preintervention history.

DISCUSSION

The systematic literature review revealed no meta-analyses but several randomized controlled trials on the subject of follow-up in patients treated in the ED or hospital for an asthma exacerbation. It is assumed that appropriate follow-up is essential to optimize outcomes after acute asthma. The knowl-

edge gaps lie in identifying and implementing the most effective methodology for achieving successful follow-up and documentation of the effect follow-up has on clinical, functional, and economic patient outcomes in this clinical setting.

Studies published earlier than the starting point chosen for the current review (January 1997) have shown a relationship between improved outcomes and regular outpatient follow-up. Mayo *et al*. (8) found that the use of an intensive educational program in addition to a dynamic medical regimen decreased hospital use in adult asthmatic patients who had required repeat readmissions for acute asthma exacerbations in the past. Another study demonstrated a reduction in the cost of asthma care when using an educational intervention and regular outpatient follow-up visits, showing the mean total cost of care decreasing from $43,066.00 to $4,914.00 ($P < 0.001$) (25).

Achieving the Follow-up Appointment

Baren *et al*. (11) (*see* RESULTS and Table 1) identified certain characteristics that were associated with primary care provider follow-up. They determined that providing medication, transportation vouchers, and a telephone reminder to make an appointment increased the likelihood that discharged patients with asthma would obtain a follow-up visit with the primary care physician.

Smith *et al*. (13, 14) (*see* RESULTS and Table 1) conducted 2 studies in children from low-income families, testing interventions to improve the rate of follow-up with primary care providers after acute asthma visits in the ED. The studies found that ED or telephone coaching and a modest monetary incentive were not able to overcome many barriers to follow-up because only 22% to 36% of intervention patients in these studies received follow-up care. Telephone coaching after the ED visit appeared to significantly increase the chance of follow-up (13), whereas coaching in the ED did not (14). Although telephone coaching and a monetary incentive achieved improved follow-up in the first 15 days, there was no difference in asthma planning visits from 16 days to 6 months after the ED visit, and there were no differences in long-term asthma morbidity in the intervention and control groups during the 6-month follow-up period (13).

The 2006 study by Baren *et al*. (12) (*see* RESULTS and Table 1) found that an intervention that includes transportation vouchers, appointment assistance, and free medication significantly increased the likelihood that discharged asthmatic patients will obtain primary care follow-up. However, as in the Smith *et al*. study (13), there were no improvements in long-term clinical or functional outcomes.

The study by Gorelick *et al*. (20) also did not show improved outcomes with an intensive primary care linkage and care management program compared with usual care. However, in that study both groups improved substantially regarding quality of life and controller use, and usual care in that study consisted of important interventions in the ED, including showing an educational video, teaching proper peak flow monitor and inhaler technique, and providing an individualized action plan. Finally, the nonrandomized controlled trial by Sin *et al*. (15) showed that making follow-up appointments for patients increased the likelihood of. patients having such follow-up primary care visits, but there was no demonstrable improvement in subsequent asthma control or reduction in exacerbations in intervention patients.

These studies suggest that interventions such as telephone reminders, transportation vouchers, and monetary incentives can increase the likelihood of follow-up appointments after an ED visit. However, these appointments did not substantially improve asthma outcomes. This suggests that the content of the follow-up appointments might have been inadequate for these higher-risk patients.

Elements of Successful Follow-up Appointments

Studies have documented that the following factors, which could be addressed at a follow-up appointment, are related to an increased risk of asthma ED visits or hospitalizations: inadequate asthma knowledge (26–28); not having an action plan (9, 26–30); incorrect use of metered-dose inhalers (31); adverse environmental exposures, especially regarding environmental tobacco smoke (32–34) and mites (9, 35–37); and adverse psychosocial circumstances (35, 38–40). This review focuses on studies that have tested various comprehensive or nonpharmacologic interventions to improve patient self-management. The evidence supporting discharge medications is reviewed in another article in this issue (41).

Education

At a meeting of the Emergency Department Demonstration Program and Centers for Disease Control and Prevention projects, preliminary recommendations for providing asthma education after an ED visit were discussed (42). These were the recommendations based on the experience of select EDs across the country that had an opportunity to provide asthma education to patients with asthma coming to the EDs (42):

- Simplify educational messages and take into consideration patient culture and educational level, making the message primarily visual.
- Use a multifaceted, automated system for follow-up appointments with reminders, incentives, and positive feedback.
- Focus on basic elements of asthma education with key messages:
  - — need for regular follow-up care with a primary care physician or asthma specialist and
  - — need to understand difference between controller and rescue medications and use.

Khan *et al*. (16) (*see* RESULTS and Table 1) tested the hypothesis that asthma education by telephone after an ED visit would achieve several outcomes and found that the children in the intervention group were more likely to possess a written asthma action plan than those in the control group after 6 months of follow-up and that the intervention group was more likely to use the plan often and occasionally. This could be clinically important because possession of action plans has been shown in the past to reduce the likelihood of asthma ED visits and hospitalizations (9, 26–30).

Similarly, Ng *et al*. (18) showed that an intensive education program in children improved outcomes, including reduced subsequent ED visits and hospitalizations, and improved compliance and satisfaction with care. The intensive education intervention included written information with cartoon figures, a video that delivered trigger avoidance and medication compliance messages, a 30-minute teaching session that included inhalation technique and self-monitoring, and a follow-up telephone session to answer questions. Some of this education was completed before the patient left the hospital. In contrast, a single education visit after an ED visit had no effect on subsequent urgent care visits in the study by Brown *et al*. (17), but 39% of the intervention patients did not comply with the post-ED intervention. No matter how effective an educational

program, it must be administered in a way that patients will take advantage of it.

The need for effective, simple, yet multifaceted education after an ED visit and the recommendations for providing such education have face validity. Two of the above studies do indeed show improved outcomes from educational interventions in this setting. Moreover, education has been an important part of effective multifaceted interventions for patients after acute asthma (*see below*).

Other Elements

Castro *et al*. (19) (*see* RESULTS and Table 1) hypothesized that there would be a benefit from a nurse-focused intervention in asthmatic patients with a history of frequent health care use. The study found that a multifaceted approach decreased the readmission rate in the intervention group, with a 69% reduction in total hospital days. In addition, the intervention group experienced cost savings of $2,220 per patient ($P = 0.03$). Similarly, Teach *et al*. (21) showed that a visit to an ED-based, specialized asthma follow-up clinic could improve several types of outcomes in a high-morbidity pediatric population. A multidimensional approach (*see* Table 1) led to fewer unscheduled visits, improved controller use, and improved quality of life in the intervention group. Compliance with the follow-up visit was high in this setting. These 2 comprehensive approaches led to improved outcomes of importance to patients and society in general.

The scope of this review did not include provider education to improve asthma outcomes. However, improved knowledge and clinical skill in physicians managing patients during and after an ED visit would be expected to improve asthma outcomes in their patients. Macias *et al*. (43) described an educational intervention for ED physicians that led to sustained ($>$ 6 mo) improved ability to diagnose asthma and use standardized acute and chronic asthma severity classifications. Boychuk *et al*. (44) reported the results of a multipronged approach in Hawaii that included asthma education for ED staff and community-based health care providers in which the proportion of patients using controller medications and possessing a written action plan increased substantially after intervention. Although the best methods of providing education to providers who manage patients during and after an asthma ED visit have not been identified and data showing a definitive relationship between provider education and reduced subsequent asthma ED visits are lacking, more attention to the role of provider education in improving asthma outcomes in high-risk patients is probably warranted.

Asthma Specialist Follow-up

No recent randomized clinical trials addressing outcomes achieved by means of specialist follow-up after an ED visit were identified. As summarized above, earlier randomized and nonrandomized clinical trials suggest that follow-up with asthma specialists reduces subsequent asthma exacerbations (8, 23, 24). Several observational studies have also reported reduced ED visits, hospitalizations, or both in patients managed by asthma specialists compared with patients managed by generalists (45–51). Such studies have also reported fewer symptoms, less β-agonist use, improved quality of life, and higher patient satisfaction in patients followed by asthma specialists (48, 52–54).

CONCLUSION

The existing interventional and observational data suggest several conclusions. A follow-up visit can be facilitated by financial and cognitive assistance at and immediately after an ED visit. An alternative approach is a telephone consultation that can at least increase the possession of action plans. However, a visit alone does not ensure improved outcomes. An effective visit includes addressing multiple aspects of asthma care, including educational, environmental, pharmacologic, and psychosocial factors. Presumably, patient self-assessment and provider supervision must be ongoing to achieve maximal and persistent benefits. Follow-up with an asthma specialist or a specialized asthma clinic appears to be more likely to reduce subsequent emergency hospital care than follow-up with a primary care provider.

SUMMARY OF RECOMMENDATIONS

In the attempt to improve the effectiveness of patient follow-up after an asthma ED visit, the following recommendations were developed by the current authors and are based on the current available evidence and expert consensus.

1. Strong: recommend that all patients with asthma seen in the ED have their chronic asthma characterized by National Asthma Education and Prevention Program guidelines. Chronic severity assessment can be accomplished by determining pre-exacerbation medication use, daytime and nighttime symptoms, history of activity limitation, and history of exacerbations requiring oral corticosteroids (Table 4) (55). Patients with persistent asthma or recurrent asthma exacerbations need appropriate assessment and asthma expertise that allows for comprehensive care and management (Evidence Category D).
2. Strong: recommend that the appointment to the primary care physician, asthma specialist, or specialized asthma clinic be made before leaving the ED, if possible, and a reminder by telephone should occur several days later (Evidence Category B). Conditional: when indicated, consider providing a transportation voucher for the appointment with the primary care physician, asthma specialist, or both (Evidence Category B). Strong: recommend that the follow-up visit with the primary care physician, asthma specialist, or specialized asthma clinic be within 1 week of the ED visit (Evidence Category D). Conditional: consider faxing an ED visit summary to the primary care physician, asthma specialist, or asthma clinic before the follow-up visit (Evidence Category D).
3. Strong: recommend that elements of the follow-up visit include optimal controller management, assurance of satisfactory inhaler technique, asthma self-monitoring and self-management education, an individualized action plan, trigger identification and avoidance instruction, and arrangement for ongoing follow-up. Such follow-up could occur in the ED itself in a specialized clinic or in the offices of primary care physicians or specialists and could

TABLE 4. CHARACTERISTICS OF PATIENTS WITH PERSISTENT ASTHMA (55)

Any of the following (before the current exacerbation):
Regular controller use
Symptoms or rescue therapy use more than twice a week
Interference with sleep more than twice a month
Activity limitation caused by asthma
Exacerbations requiring oral corticosteroids more than once in past year

be augmented with telephone contact and home visits (Evidence Category B).

4. Strong: recommend that all patients with severe persistent asthma or a history of prior severe exacerbations requiring hospitalization be referred to an asthma specialist (Evidence Category C) or specialized asthma clinic (Evidence Category B) from the ED. Conditional: consider referral to an asthma specialist or specialized asthma clinic for patients with moderate persistent asthma (Evidence Category D).

Author disclosures were obtained by the *Journal of Allergy and Clinical Immunology* (JACI) using questions determined by the American Academy of Allergy, Asthma and Immunology (AAAAI) and JACI. Questions pertained to: employment; financial interests between the author or members of the author's immediate family or household with organizations and commercial interests; research support during the past calendar year; and legal consultation services/expert witness testimony during the past calendar year. Authors were asked to state dollar amounts in ranges of either $< \$10{,}000$ or $\geqslant \$10{,}000$. Authors were not required to disclose other facts that are now requested by *PATS* in conformance with American Thoracic Society policy, including knowledge of any significant financial relationship between the author's institution or employer and relevant commercial interests, and all relationships with tobacco entities.

Disclosure of potential conflict of interest: M.S. has been a consultant for GlaxoSmithKline and has received research support from Aerocrine, Genentech, GlaxoSmithKline, and Merck. G.R. has been a speaker or advisory board member for AstraZeneca, Schering-Plough, CSL Behring, Merck, and Sanofi Aventis and has provided legal consultation or expert witness testimony on the topic of environmental injuries, mostly mold-related. J.A.K. has declared that he has no conflict of interest.

References

1. American Lung Association Epidemiology and Statistic Unit Research and Program Services. Trends in asthma morbidity and mortality [Accessed July 9, 2007]. Available from: http://www.lungusa.org/atf/cf/%7B7A8D42C2-FCCA-4604–8ADE-7F5D5E762256%7D/ASTHMA1.PDF.
2. Centers for Disease Control. National Center for Health Statistics: asthma [Accessed July 9, 2007]. Available from: http://www.cdc.gov/nchs/fastats/asthma.htm.
3. Wissow LS, Gittelsohn AM, Szklo M, Starfield B, Mussman M. Poverty, race, and hospitalization for childhood asthma. *Am J Public Health* 1988;78:777–782.
4. Robison JI, Rogers MA, Carlson JJ, Mavis BE, Stachnik T, Stoffelmayr B, *et al.* Effects of a 6-month incentive-based exercise program on adherence and work capacity. *Med Sci Sports Exerc* 1992;24:85–93.
5. Haas JS, Cleary PD, Guadagnoli E, Fanta C, Epstein AM. The impact of socioeconomic status on the intensity of ambulatory treatment and health outcomes after hospital discharge for adults with asthma. *J Gen Intern Med* 1994;9:121–126.
6. Leickly FE, Wade SL, Crain E, Kruszon-Moran D, Wright EC, Evans R. Self-reported adherence, managing behavior and barriers to care after an emergency department visit by inner city children with asthma. *Pediatrics* 1998;101:e8.
7. Ford ME, Havstad SL, Tilley BC, Bolton MB. Health outcomes among African American and Caucasian adults following a randomized trial of an asthma education program. *Ethn Health* 1997;2:329–339.
8. Mayo PH, Richman J, Harris HW. Results of a program to reduce admissions for adult asthma. *Ann Intern Med* 1990;112:864–871.
9. Lieu TA, Quesenberry CP Jr, Capra AM, Sorel ME, Martin KE, Mendoza GR. Outpatient management practices associated with reduced risk of pediatric asthma hospitalization and emergency department visits. *Pediatrics* 1997;100:334–341.
10. Schatz M, Kazzi AAN, Brenner B, Camargo Jr CA, Corbridge T, Krishnan JA, Nowak R, Rachelefsky G. Introduction. *Proc Am Thorac Soc* 2009;6:353–356.
11. Baren JM, Shofer FS, Ivey B, Reinhard S, DeGeus J, Stahmer SA, *et al.* A randomized, controlled trial of a simple emergency department intervention to improve the rate of primary care follow-up for patients with acute asthma exacerbations. *Ann Emerg Med* 2001;38:115–122.
12. Baren JM, Boudreaux ED, Brenner BE, Cydulka RK, Rowe BH, Clark S, *et al.* Randomized controlled trial of emergency department interventions to improve primary care follow-up for patients with acute asthma. *Chest* 2006;129:257–265.
13. Smith SR, Jaffe DM, Fisher EB Jr, Trinkaus KM, Highstein G, Strunk RC. Improving follow-up for children with asthma after an acute Emergency Department visit. *J Pediatr* 2004;145:772–777.
14. Smith SR, Jaffe DM, Highstein G, Fisher EB, Trinkaus KM, Strunk RC. Asthma coaching in the pediatric emergency department. *Acad Emerg Med* 2006;13:835–839.
15. Sin DD, Bell NR, Man SFP. Effects of increasing primary care access on process of care and health outcomes among patients with asthma who frequent emergency departments. *Am J Med* 2004;117:479–483.
16. Khan MS, O'Meara M, Stevermuer TL, Henry RL. Randomized controlled trial of asthma education after discharge from an emergency department. *J Paediatr Child Health* 2004;40:674–677.
17. Brown MD, Reeves MJ, Meyerson K, Korzeniewski SJ. Randomized trial of a comprehensive asthma education program after an emergency department visit. *Ann Allergy Asthma Immunol* 2006;97:44–51.
18. Ng DK, Chow PY, Lai WP, Chan KC, And BL, So HY. Effect of a structured education program on hospitalized asthmatic children: a randomized controlled study. *Pediatr Int* 2006;48:158–162.
19. Castro M, Zimmermann NA, Crocker S, Bradley J, Leven C, Schechtman KB. Asthma intervention program prevents readmissions in high healthcare users. *Am J Respir Crit Care Med* 2003;168:1095–1099.
20. Gorelick MH, Meurer JR, Walsh-Kelly CM, Brousseau DC, Grabowski L, Cohn J, *et al.* Emergency department allies: a controlled trial of two emergency department-based follow-up interventions to improve asthma outcomes in children. *Pediatrics* 2006;117:S127–S134.
21. Teach SJ, Crain EF, Quint DM, Hylan ML, Joseph JG. Improved asthma outcomes in a high-morbidity pediatric population. *Arch Pediatr Adolesc Med* 2006;160:535–541.
22. Hughes DM, McLeod M, Garner B, Goldbloom RB. Controlled trial of a home and ambulatory program for asthmatic children. *Pediatrics* 1991;87:54–61.
23. Zeiger RS, Heller S, Mellon MH, Wald J, Falkoff R, Schatz M. Facilitated referral to asthma specialist reduces relapses in asthma emergency room visits. *J Allergy Clin Immunol* 1991;87:1160–1168.
24. Kelly CS, Morrow AL, Shukts J, Nakas N, Strope GL, Adelman RD. Outcomes evaluation of a comprehensive intervention program for asthmatic children enrolled in Medicaid. *Pediatrics* 2000;105:1029–1035.
25. Doan T, Grammer LC, Yarnold PR, Greenberger PA, Patterson R. An intervention program to reduce the hospitalization cost of asthmatic patients requiring intubation. *Ann Allergy Asthma Immunol* 1996;76:513–518.
26. Wasilewski Y, Clark NM, Evans D, Levison MJ, Levin B, Mellins RB. Factors associated with emergency department visits by children with asthma: implications for health education. *Am J Public Health* 1996;86:1410–1415.
27. Cowie RL, Revitt S, Underwood MF, Field SK. The effect of a peak flow-based action plan in the prevention of exacerbations of asthma. *Chest* 1997;112:1534–1538.
28. Adams RJ, Smith BJ, Ruffin RE. Factors associated with hospital admissions and repeat emergency department visits for adults with asthma. *Thorax* 2000;55:566–573.
29. Palmer LJ, Valinsky L, Pikora T, Landau LI. Do regular check ups and preventive drug use reduce asthma severity in school children. *Aust Fam Phys* 2004;33:573–576.
30. Debley JS, Redding GJ, Critchlow CW. Impact of adolescence and gender on asthma hospitalization: a population-based birth cohort study. *Pediatr Pulmonol* 2004;38:443–450.
31. Dalcin PTR, Piovesan DM, Kang S, Fernandes AK, Franciscatto E, Millan T, *et al.* Factors associated with emergency department visits due to asthma. *Braz J Med Biol Res* 2004;37:1331–1338.
32. Gaspar AP, Morais-Almeida MA, Pires GC, Prates SR, Camara RA, Godinho NM, *et al.* Risk factors for asthma admissions in children. *Allergy Asthma Proc* 2002;23:295–301.
33. Maziak W, von Mutius E, Keil U, Hirsch T, Leupold W, Rzehak P, *et al.* Predictors of health care utilization of children with asthma in the community. *Pediatr Allergy Immunol* 2004;15:166–171.
34. Eisner MD, Klein J, Hammond SK, Koren G, Lactao G, Iribarren C. Directly measured second hand smoke exposure and asthma health outcomes. *Thorax* 2005;60:814–821.
35. Rand CS, Butz AM, Kolodner K, Huss K, Eggleston P, Malveaux F. Emergency department visits by urban African American children with asthma. *J Allergy Clin Immunol* 1999;105:83–90.

36. Johnston NW, Johnston SL, Duncan JM, Greene JM, Kebadze T, Keith PK, *et al.* The September epidemic of asthma exacerbations in children: a search for etiology. *J Allergy Clin Immunol* 2005;115:132–138.
37. Wever-Hess J, Kouwenberg JM, Duiverman EJ, Hermans J, Wever AMJ. Risk factors for exacerbations and hospital admissions in asthma of early childhood. *Pediatr Pulmonol* 2000;29:250–256.
38. TenBrinke A, Ouwerkerk ME, Zwindeman AH, Spinhover P, Bel EH. Psychopathology in patents seen with severe asthma is associated with increased health care utilization. *Am J Respir Crit Care Med* 2001;163: 1093–1096.
39. Eisner MD, Katz PP, Lactao G, Iribarren C. Impact of depressive symptoms on adult asthma outcomes. *Ann Allergy Asthma Immunol* 2005;94:566–574.
40. Bartlett SJ, Kolodner K, Butz AM, Eggleston P, Malveaux FJ, Rand CS. Maternal depressive symptoms and emergency department use among inner-city children with asthma. *Arch Pediatr Adolesc Med* 2001;155:347–353.
41. Krishnan JA, Nowak R, Davis SQ, Schatz M. Anti-inflammatory treatment after discharge home from the emergency department in adults with acute asthma. *Proc Am Thorac Soc* 2009;6:380–385.
42. Rachelefsky GS, Stone A, Kennedy S. Doing the most to insure the least ED visits: asthma experts consider preliminary project findings. *Pediatrics* 2006;117:S159–S166.
43. Macias CG, Caviness AC, Sockrider M, Brooks E, Kronfol R, Bartholomew LK, *et al.* The effect of acute and chronic asthma severity on pediatric department utilization. *Pediatrics* 2006;117:S86–S95.
44. Boychuk RB, DeMesa CJ, Kiyabu KM, Yamamoto F, Yamamoto LG, Sanderson R, *et al.* Change in approach and delivery of medical care in children with asthma: results from a multicenter emergency department educational asthma management program. *Pediatrics* 2006;117:S145–S151.
45. Sperber K, Ibrahim H, Hoffman B, Eisenmesser B, Hsu H, Corn B. Effectiveness of a specialized asthma clinic in reducing asthma morbidity in an inner-city minority population. *J Asthma* 1995;32:335–343.
46. Westley CR, Spiecher B, Starr L, Simons P, Sanders B, Marsh W, *et al.* Cost effectiveness of an allergy consultation in the management of asthma. *Allergy Asthma Proc* 1997;18:15–18.
47. Vollmer WM, O'Hollaren M, Ettinger KM, Stibolt T, Wilkins J, Buist AS, *et al.* Specialty differences in the management of asthma. *Arch Intern Med* 1997;157:1201–1208.
48. Schatz M, Cook EF, Nakahiro R, Pettiti D. Inhaled corticosteroids and allergy specialty care reduce emergency hospital use for asthma. *J Allergy Clin Immunol* 2003;111:503–508.
49. Schatz M, Zeiger R, Mosen D, Apter AJ, Vollmer WM, Stibolt TB, *et al.* Improved asthma outcomes from allergy specialist care; a population-based cross-sectional analysis. *J Allergy Clin Immunol* 2005;116:1307–1313.
50. Moore CM, Ahmed I, Mouallem R, May W, Ehlayel M, Sorensen RU. Care of asthma: allergy clinic versus emergency room. *Ann Allergy Asthma Immunol* 1997;78:373–380.
51. Erickson S, Tolstykh I, Selby JV, Mendoza G, Iribarren C, Eisner MD. The impact of allergy and pulmonary specialist care on emergency asthma utilization in a large managed care organization. *Health Serv Res* 2005;40:1443–1464.
52. Diette GB, Wu AW, Skinner EA, Markson L, Clark RD, McDonald RC, *et al.* Treatment patterns among adult patients with asthma: factors associated with overuse of inhaled beta-agonists and under-use of inhaled corticosteroids. *Arch Intern Med* 1999;159:2697–2704.
53. Vilar ME, Reddy BM, Silverman BA, Bassett CW, Rao YA, Chiaramonte LT, *et al.* Superior clinical outcomes of inner city asthma patients treated in an allergy clinic. *Ann Allergy Asthma Immunol* 2000;84: 299–303.
54. Kanter LJ, Siegel CJ, Snyder CF, Pelletier EM, Buchner DA, Goss TF. Impact of respiratory symptoms on health-related quality of life and medical resource utilization of patients treated by allergy specialists and primary care providers. *Ann Allergy Asthma Immunol* 2002;89: 139–147.
55. US Department of Health and Human Services, National Institute of Health, National Heart, Lung, and Blood Institute. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma [Accessed November 20, 2007]. Available from: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.