Current Trends in Management of Pediatric Asthma

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Though asthma cannot be cured, it can be effectively controlled with existing treatments. Management strategies for acute and chronic asthma often vary substantially within and among medical facilities and practices, often driven by physician preference and familiarity rather than by data. The use of carefully designed care paths can improve quality of care and decrease management costs of acute asthma in both the emergency department and in-patient setting. Using newer β agonists and attention to proper inhalation delivery systems may also improve outcomes and patient satisfaction. Assessment-driven care paths can be safely and effectively administered by respiratory therapists and nurses. The major controversies in the management of chronic asthma center on what to do for the patient who fails to respond to low or moderate doses of inhaled corticosteroids. The addition of a long-acting β agonist or a leukotriene receptor antagonist may be beneficial. *Key words: pediatric, asthma, emergency management, ambulatory care, acute asthma.* [Respir Care 2003;48(3):194–205. © 2003 Daedalus Enterprises]

Introduction

Asthma is defined as reversible obstruction of the airways, characterized by hyperresponsiveness to a variety of stimuli, caused by chronic inflammation. The airway obstruction is reversible, at least in part, and results in recurrent episodes of wheezing, cough, and shortness of breath that resolve either spontaneously or with treatment. The airway inflammation is complex and involves a wide array of inflammatory cells that are resident in the airways (mast cells, macrophages), circulating cells that migrate into the airways (eosinophil, lymphocytes, neutrophils), and the mediators that they produce. Prominent pro-inflammatory substances active in asthma include cytokines (interleukin 4, 5, and 13, RANTES [regulated on activation, normal T expressed and secreted]), leukotrienes, neurokinins, proteases, histamine, and neurotransmitters (acetylcholine). These cells and substances result in airway vascular leak, mucosa edema, smooth muscle hyperplasia and hyperreactivity, mucus hypersecretion, and epithelial cell sloughing and dysfunction. Left unchecked these processes can result in increased collagen deposition in the subepithelial region and fixed airway obstruction (airway remodeling).

The natural history of asthma is currently incompletely understood, but for most patients asthma is a lifelong condition characterized by periods of remission and relapse. Although many patients improve, the disease severity appears to change little over time: disease that starts mild

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tends to stay mild and severe disease tends to stay severe. The effect of long-term treatment on asthma outcome and natural history is not yet established.

In view of the plethora of inflammatory cells and substances involved in the asthmatic airway and the number of target cell types (epithelium, smooth muscle, mucus glands), it is not surprising that asthma management is complex and often requires multiple medications. Moreover, no current treatment results in cure; the disease usually remains controlled while medication is taken but relapses if treatment is stopped. Current treatment strategies recommend anti-inflammatory medications for control and prevention of symptoms, reduction in airway hyperresponsiveness and prevention of airway remodeling. Bronchodilators, which relieve smooth muscle constriction, are used as rescue medication for treatment of acute exacerbations.

The use of currently available medications for asthma, coupled with close medical follow-up, can result in excellent control for the vast majority of patients. However, asthma continues to be a major health problem, resulting in health care costs of over 14 billion dollars per year in the United States. Over half these costs are due to emergency department visits and hospitalizations that are all considered preventable, major treatment failures. There remain a number of controversies around the optimal care of acute and chronic asthma in children. This review focuses on optimal management of the hospitalized pediatric asthma patient, emergency department treatment of the acutely ill child, and ambulatory long-term management of moderate asthma.

In-Patient Asthma

Asthma is the most common discharge diagnosis in children's hospitals nationwide, accounting for 10–30% of all admissions and over 500,000 admissions annually.[1]

The treatment of acute asthma in the hospital is presumed to be fairly straightforward. Although the number of pharmacologic agents for treatment of status asthmaticus is relatively limited, management strategies are inconsistent among and within institutions. Evidence-based practice is often replaced by physician personal experience and preference. Elimination of treatments that add risk and cost but do not improve quality of care should be a primary goal. Status asthmaticus readily lends itself to treatment by standardized clinical pathway.

An in-patient asthma clinical pathway should address a number of issues. Rapid resolution of symptoms and return to normal activities of daily living should be the primary objective. Provision of targeted patient education, identification of risk factors for future asthma exacerbations, determination of severity and control of chronic asthma symptoms, provision of an appropriate asthma action plan, and medical follow-up must be included in the care path. Secondary goals should be to decrease cost of care, typically by reducing overall hospital length of stay (LOS), decreasing resource utilization, and avoiding unnecessary laboratory and radiographic testing.

A relatively small number of studies have reported the results of implementation of asthma clinical pathways. Care path structure, outcome measures, and results vary among the studies; most compared a historical control group (1–2 years before care path use) with the study group treated using the pathway. Such before-and-after designs are susceptible to numerous pitfalls, making evaluation of efficacy difficult. Seasonal differences in asthma severity, unplanned evolution in care practices, alteration in admission criteria, and availability of new treatments can affect outcomes apart from the clinical pathway.

Investigators at an academic children's hospital evaluated an in-patient asthma clinical pathway.[2] The authors hypothesized that implementing best-care practices, documenting variations in care, and improving coordination of care among service providers would result in better care, better short-term outcomes, and facilitation of research. A multidisciplinary team designed the pathway, which included a flow chart outlining suggested doses and frequencies of medications and indications for consultations and diagnostic testing placed in the patient chart. The nurses were responsible for identifying variance from the care path. Data from the first year of the pathway group were compared to the group of patients admitted in the year prior to implementing the pathway. Outcomes measured included hospital LOS, rate of readmission in 14 days, and resource utilization (peak expiratory flow meter use, systemic steroid use, laboratory and radiology studies ordered, pharmacy and respiratory therapy charges). The pathway group ($n = 297$) differed from the control group in that it contained more males and more Asians. There were no significant differences between the groups in any outcome measure, including LOS, steroid use, or total charges. There was lower laboratory and radiology service utilization in the pathway group; cost savings per year would be about $12,000. The lack of effect on LOS was in part attributed to the already relatively short 2-day LOS the pre-care-path group. Most variances related to patient progress through the care path (50% were slower) and physician order variances (27%). The authors concluded that better nurse and physician education and data feedback are needed to more accurately assess the impact of the clinical pathway and that more evaluation of the patient education component of the pathway might prove useful.[2]

McDowell et al published one of the few prospective, controlled trials of an asthma clinical pathway for management of status asthmaticus in children.[3] A multidisci-

plinary team designed an assessment-based pathway that used a unique "Algoform" that combines the treatment algorithm with a form on which to record patient assessments and treatments (Fig. 1). Failure to achieve pre-established advancement or discharge criteria (based on wheezing severity, respiratory rate, accessory muscle use, pulse oximetry, air exchange, and pulmonary function test results) resulted in delivery of an albuterol aerosol and repeated assessment at a pre-set interval. Medication types, doses, and frequency were mandated by the care path. Respiratory therapists and nurses administered treatments, performed assessments, and provided asthma education. Patients were discharged when specific criteria were met while receiving treatments every 6 hours. Patients were assigned (by personnel not involved with or aware of the study) to either the care path group in one hospital division or to a usual-care group assigned to a different in-patient division. The study was adequately powered to detect a 0.5-day difference in LOS. Results of this trial showed that the care path group had an almost 1 day shorter LOS than the usual-care group and received significantly fewer aerosol treatments, with no difference in readmission rate at 72 hours after hospital discharge. This care path also resulted in substantially lower hospital charges, saving over $700 per patient. This care path has been in use for 7 years and has resulted in an average LOS of 1.8 days, with a 0.5% (72 h) readmission rate. In addition, all patients receive a brief asthma risk assessment by the asthma counselor (registered nurse), training in asthma medication use, trigger avoidance, and medical follow-up. All patients also receive an appropriate home asthma action plan that stresses the importance of anti-inflammatory medication appropriate to the patient's disease severity. Since this care path captures all patients admitted for acute asthma, clinical research is facilitated. We have completed several studies comparing efficacy of different drugs and devices on hospital admission and LOS.[4–6]

A study very similar in design to the McDowell report also used a prospective, randomized, controlled design.[7] Similar results were obtained, although the reduction in LOS was less (13 h). Treatment group patients also received less albuterol than those in the control group at all stages of the care path. The authors speculate that trained nurses or respiratory therapists could perform assessments and weaning treatments according to the protocol. This scenario has in fact successfully been accomplished at Rainbow Babies and Children's Hospital in a 10-bed asthma unit staffed by respiratory therapists.[8]

The clinical pathway reported by Kelly et al[9] also used an algorithm design and permitted nurses and respiratory staff to adjust treatment dose and frequency based on patient assessment. This study also described a significant reduction (50%, 1 d) in LOS, and cost reduction. The study compared care path patients to a matched, historical control group. However, there were few enrollees (34) and patients were discharged when receiving aerosols every 4 hours rather than every 6 hours. During the study period 149 children were treated using the clinical pathway, but data are reported only from the randomly selected group of 34; such a small sample size and before-and-after design limit the generalizability of the data. The decrease in LOS may have resulted from the care path directions to discharge when patients required aerosols every 4 hours rather than the more common practice (56% of patients) of discharging patients at a treatment interval of every 6 hours in the pre-care-path group. Although no readmissions occurred, discharging patients while requiring treatments every 4 hours probably shifts considerable morbidity (time lost from school or work, in-home care for the child) to the family. Requiring treatment no more frequently than every 6 hours permits children to return to school and parents to at least a modified work schedule.

Several studies document that asthma care provided by specialists (pulmonologists and allergists) is more cost-effective than that provided by general practitioners.[10,11] An asthma clinical pathway directed by asthma specialists (pulmonologist or allergist) also resulted in a significantly shorter LOS, fewer laboratory tests, lower nursing care costs, and a very low readmission rate (0.02%).[10] The pathway provided guidelines for type and frequency of patient assessment, medication use, laboratory and radiologic testing, patient education, and discharge criteria and planning. Medication dose was left to the discretion of the specialist in charge. Discharge criteria were also specified. Although the results of this study are consistent with the few reported prospective trials and included approximately 1,000 patients, the study suffers from several problems: it was retrospective, used a historical control group, and data were collected from a hospital computer database. It is unclear if decisions about admission, discharge, and accounting practices changed during the 4-year study period.

Summary of In-Patient Asthma Treatment

Properly designed asthma clinical pathways that are implemented in an organized fashion and diligently adhered to can improve patient care, decrease LOS, and save money. The best care path designs specify treatment regimens, are patient-assessment-driven, identify root causes of failure of out-patient management, and provide appropriate and aggressive home treatment plans.

Emergency Department Treatment

Although acute asthma episodes requiring medical attention are considered preventable major treatment failures, asthma exacerbations account for a large proportion of visits to pediatric emergency departments. Primary ther-

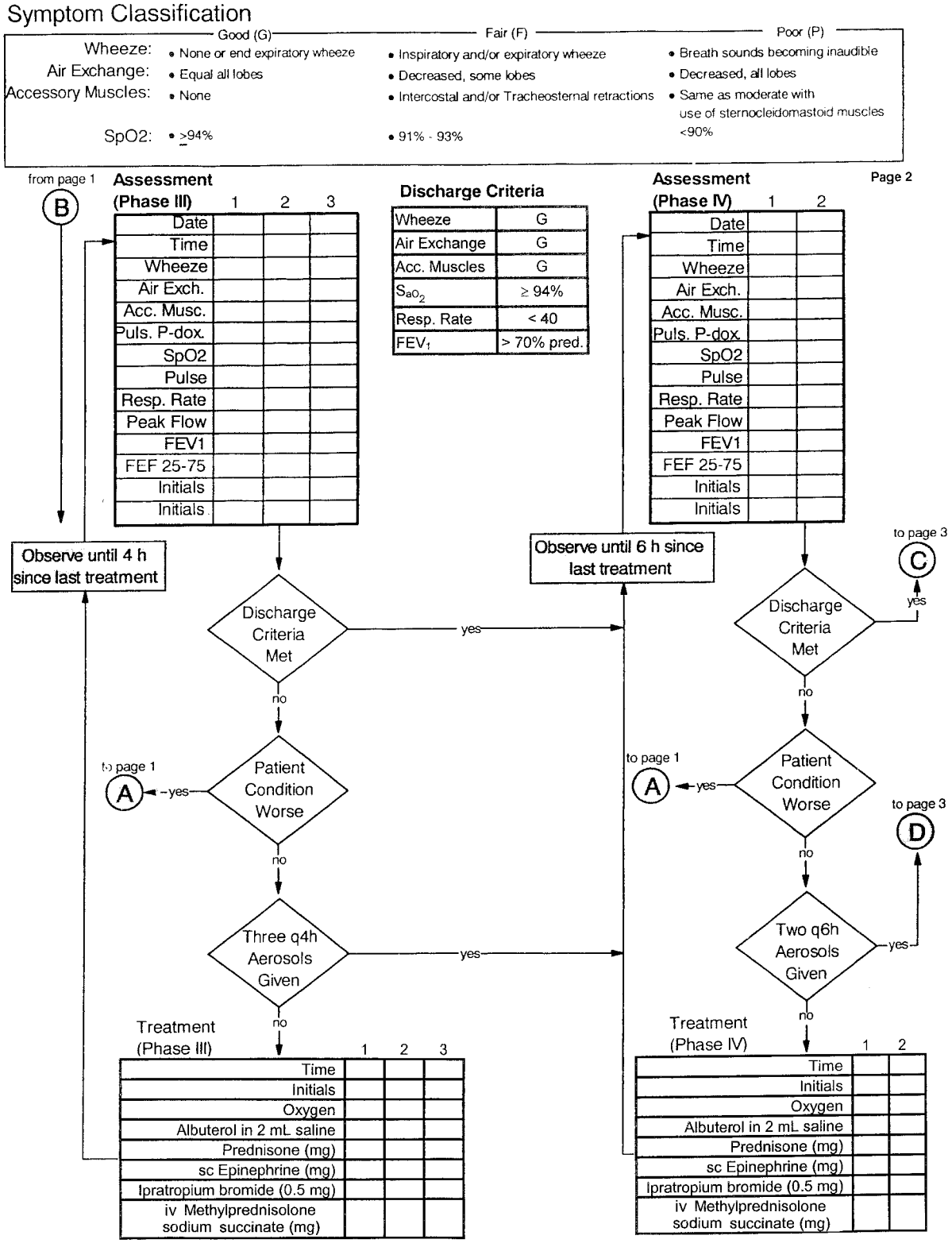


Fig. 1. Asthma Algoform used at Rainbow Babies and Children's Hospital, Cleveland, Ohio. Form includes areas to record patient assessments, algorithm cues, and discharge criteria.

apy for acute asthma is aimed at relief of bronchospasm and initiation of aggressive anti-inflammatory medications.

Children presenting with acute asthma exacerbations demonstrate abrupt onset of a broad spectrum of symptoms, ranging from mild wheezing and cough to increased work of breathing, accessory muscle use, and in most severe cases dyspnea, anxiety, changed mental status, respiratory failure, and cardiorespiratory arrest. Oxygen, inhaled selective β_2 adrenergic agonists, and corticosteroids are the cornerstones of therapy for acute severe asthma. Other therapies, including anticholinergic agents, helium-oxygen mixtures, intravenous magnesium sulfate, and single-isomer levalbuterol, may have clinical benefit in some situations.

Inhaled selective β_2 agonists are the most effective bronchodilators; they offer rapid efficacy, flexibility of dose, and good clinical-effect-to-adverse-effect ratio, so they are the treatment of choice for acute asthma.[12] Albuterol, the most commonly used β agonist, has been demonstrated in numerous controlled trials[13–15] to relieve acute bronchoconstriction. Onset of action is in $<$ 5 min, peak effect in 15 min, and the duration of bronchodilation is 4–6 hours. There are several options in choosing dose, frequency of administration, route of delivery, and delivery device for β_2 agonists in the acute setting.

Rapid sequential nebulization of standard doses of β agonists has been demonstrated to result in bronchodilation and sustained improvement in lung function. Comparison of studies examining the effectiveness of albuterol doses and regimens for acute asthma have often been complicated by multiple factors, including differences in clinical scoring, treatment algorithms, nebulizer devices, and outcome measures. The National Asthma Education and Prevention Program Expert Panel Report 2 recommends initiation of aerosolized albuterol at a dose of 2.5–10 mg every 20 min for at least 1 hour.[16] There are broad differences in the literature regarding optimal albuterol dose and delivery method, with recommended doses ranging from 0.05–0.3 mg/kg to a maximum of 10 mg.[15–18] Although these seem like high doses, $<$ 10% of the dose from a standard nebulizer reaches the lung, even under optimal conditions.[19] Moreover, other factors affect drug deposition in the lower airways, including respiratory rate, minute ventilation, and degree of bronchoconstriction at onset of therapy. Studies employing higher doses of intermittently delivered albuterol have failed to consistently demonstrate significantly greater degrees of improvement in forced expiratory volume in the first second (FEV_1) or clinical scores than doses recommended by the National Asthma Education and Prevention Program.[18,20,21] Studies of continuous albuterol nebulization (10–15 mg/h) have yielded mixed results, though most favor continuous nebulization. Papo et al[21] demonstrated the safety and improved clinical efficacy of a continuous nebulization protocol in patients with impending respiratory failure, although the study was limited by a small number of subjects. Shrestha et al[20] compared high- and low-dose albuterol administered intermittently and continuously in adults with severe acute asthma, demonstrating greater initial improvement in those treated with continuous nebulization. Most studies have demonstrated a lack of clinically important adverse effects during continuous nebulization protocols in severe acute pediatric asthma, suggesting that this mode of delivery is safe, if not necessarily more effective, and may be more convenient for patient and staff.

Small-volume nebulizer (SVN) and metered-dose inhaler (MDI) both effectively deliver β agonists to the lower airways in acute asthma. Both devices require patient cooperation and proper technique to achieve maximum therapeutic benefit—an important factor in the emergency department. The pros and cons of both devices should be considered carefully before choosing a modality that fits the patient population served and the staff available.

The efficacy of SVN therapy depends on the flow generated by the compressor, the nebulizer device, and the dose (as well as volume) of β agonist administered. Although different nebulizers have different flow-particle size relationships, most require flow rates of 6–8 L/min to provide respirable particles in the optimal 1–3 μm diameter range.[19] Valved, air-entrainment-style nebulizers nebulize a substantially larger amount of the dose into respirable-size particles than do conventional nebulizers. Nebulized β agonist should be administered via a tight-fitting face mask or mouthpiece device for optimal benefit. Several studies have demonstrated a significant decrease in amount of medicine received when the face mask or mouthpiece is moved away from the patient by 2 cm.[22,23] Since the nose is an effective particle filter, use of a mouthpiece in all children old enough to use one ($>$ 3 years) should be encouraged.

The relative clinical effects of administering β agonists via nebulizer versus via MDI with valved holding chamber has been the subject of many studies. Most data demonstrate that MDI with holding chamber is of equal clinical efficacy to SVN in relieving symptoms and improving pulmonary function in children experiencing both mild and more severe acute asthma exacerbations. Schuh et al[24] demonstrated in mild acute asthma that 2 puffs (100 mg/puff) of albuterol from an MDI with spacer was as effective as higher doses delivered either via MDI or via nebulizer (600–1,000 μg). Studies comparing nebulizer to MDI with spacer in acute severe asthma have also demonstrated therapeutic equivalency of the 2 methods.[24–27] Fewer adverse effects[27] typically occur with MDI, since the total body burden of the drug is substantially less than with SVN. Parents often prefer MDI with holding chamber, although some patients prefer the nebulizer. Careful supervision of patient technique and monitoring of response

to therapy should be done with either modality. Patients who refuse to wear the mask of the nebulizer or holding chamber, or who cry during administration, are unlikely to respond well to therapy, as drug delivery to the lower airways is negligible under these conditions.[28,29]

A relatively new option for treatment of acute asthma is single-isomer R-albuterol (levalbuterol), the enantiomer responsible for the bronchodilating and systemic activity of the racemate.[30] Levalbuterol can currently be administered only with an SVN, but an MDI version should be available in the next year or two. Levalbuterol may be safer and more effective than the racemic drug, since some in vitro and in vivo data suggest that the S-isomer may not be inert. S-albuterol has been associated with small increases in bronchoconstrictive response to methacholine in guinea pigs,[31] and repeated dosing with racemic albuterol has resulted in increased inflammation[32] and increased airway responsiveness to allergen.[33] In vitro cellular data suggests S-albuterol may cause airway hyperreactivity or bronchoconstriction.[34] S-albuterol may produce such anti-therapeutic effects by increasing intracellular calcium levels and inhibiting adenyl cyclase, increasing pulmonary microvascular permeability, and directly enhancing airway hyperresponsiveness.[34–36] When moderate-to-severe asthma was treated with levalbuterol, a greater degree of bronchodilation at lower comparable doses of racemic albuterol was observed.[37] In an emergency department study a significantly lower rate of hospitalization[6] was observed among children treated with levalbuterol than among those receiving an equivalent dose of racemic albuterol containing equal amounts of R-isomer. Although more confirmatory studies are needed, emerging clinical evidence supports the in vitro and animal model observations that S-albuterol may have an anti-therapeutic effect when delivered with levalbuterol.

The role of high-dose inhaled steroids (eg, 2 mg fluticasone) in acute asthma therapy remains controversial. Most data suggest administration of oral or intravenous steroid is superior to inhaled corticosteroid (ICS) in acute severe asthma.[38–40] Adding high-dose ICS to typical emergency department treatment with β agonist and oral corticosteroid may decrease hospitalization rate and rate of relapse following discharge.[41,42] The mechanism of action of high-dose inhaled steroids in the treatment of acute asthma is poorly understood but may involve decreasing vasodilation and vascular leak from mucosal vessels. The onset of action appears to be within 1–2 hours or certainly within the typical emergency department observation period. In patients receiving long-term inhaled steroids and who exhibit mild symptom increases, increasing inhaled steroid dose has been demonstrated to be effective in attenuating some exacerbations,[43] although other researchers have failed to demonstrate this effect.[44]

A number of steroid dose regimens and preparations have been recommended for treatment of acute asthma. Oral prednisone and methylprednisolone are rapidly absorbed and are the most commonly used agents. The limiting factors include gastrointestinal tolerance and bad taste, which may affect patient adherence. The standard dose of methylprednisolone is 2–4 mg/kg/d divided every 6 hours, with a maximum single intravenous dose of 125 mg. Use of oral doses $>$ 2 mg/kg (60 mg total) are probably not necessary and risk increased incidence of transient hypokalemia, hyperglycemia, and mental status changes.

The optimal schedule or duration of systemic corticosteroid therapy for acute exacerbations has not been well described. The usual course of prednisone or methylprednisolone lasts 5–7 days and results in significant decreases in the number of submucosal inflammatory cells such as eosinophils, mast cells, basophils, and neutrophils.[45] Qureshi et al[46] compared a 2-dose regimen of oral dexamethasone with a standard 5-day oral prednisone course for preventing relapse after acute asthma exacerbation in children. Similar clinical improvement, with possibly lower incidence of adverse effects, was found with the shorter dexamethasone course. Although there were some important design flaws in that study, dexamethasone may be preferable because of its low cost and potential to improve patient compliance.

Summary of Emergency Department Treatment

Emergency department care of acute asthma should consist of rapid, sequential administration of albuterol, either at 20-min intervals or (especially for the sickest patients) continuously at a dose of 10 mg/h.

Use of SVN or MDI with valved holding chamber to administer albuterol results in similar degrees of improvement, and selection of device depends on patient and staff preference and experience. Strict attention to appropriate technique is necessary for maximum benefit. Levalbuterol may provide an advantage in reducing the need for hospital admission, compared to racemic albuterol use, but at present levalbuterol can only be delivered via SVN. Further studies are needed to determine if levalbuterol is more cost-effective than racemic albuterol for treating acute asthma. All patients who fail to improve substantially after a single albuterol treatment should receive systemic corticosteroids. There are no data to support the use of doses higher than 2 mg/kg (60 mg maximum), and a 1 mg/kg dose may have fewer adverse effects without compromise of efficacy. Moreover, use of dexamethasone for 2 days may be as efficacious as 5 days of prednisone, with better patient compliance.

Ambulatory Care

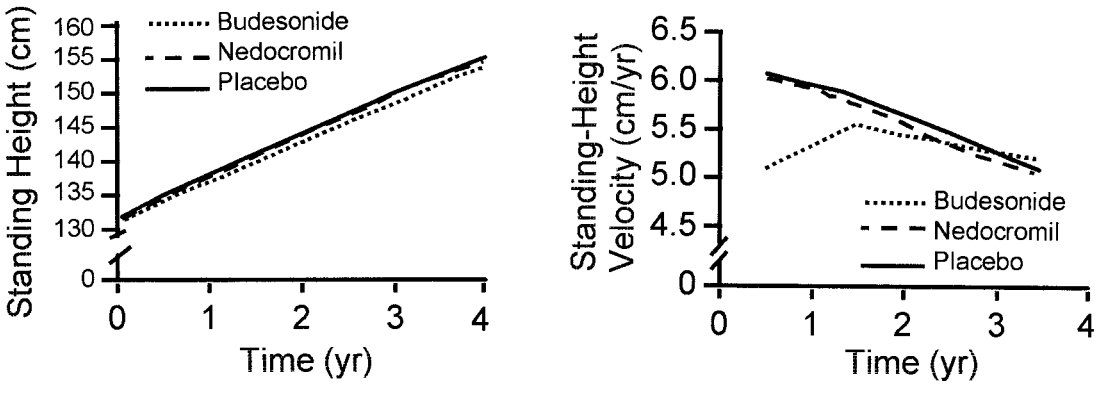
Primary emphasis for the management of chronic asthma is on symptom control, trigger avoidance, and prevention of irreversible consequences of disease. The symptoms of asthma can be controlled, but asthma cannot be cured. Discontinuation of anti-inflammatory medications results within weeks in recurrence of symptoms, loss of pulmonary function, and increased airway responsiveness. Therefore, finding an effective, safe, long-term treatment regimen for children with asthma is of paramount importance.

Although demonstrating efficacy of asthma treatments may be accomplished using a number of measures, deciding what constitutes effectiveness is less straightforward. Most clinical trials of new asthma medications or comparison studies choose some measure of pulmonary function (eg, morning peak expiratory flow or FEV_1) as the primary outcome, and secondary outcomes include change in symptom scores, rescue medication use, time to first exacerbation, and quality-of-life measures. More recently, emphasis has also been on measuring change in airway hyperresponsiveness (using methacholine or adenosine challenge) and other measures of airway inflammation, such as exhaled nitric oxide, peripheral blood, bronchoalveolar lavage fluid, or induced sputum eosinophil count, or serum levels of eosinophil or mast cell proteases.[47,48] These somewhat indirect markers of inflammation are sometimes correlated with airway mucosal biopsy findings, which is the accepted standard for measuring airway remodeling and inflammation. Since airway inflammation is a complex process involving multiple cells types and numerous mediators, it is difficult to ascribe the pathophysiology of asthma to one or a few cell types or mediators. For instance, much emphasis has been placed on the role of the eosinophil in asthmatic airway inflammation. The airway mucosa in most asthmatics typically has a predominant eosinophilic infiltrate. Eosinophil products, such as eosinophil cationic protein and leukotrienes, are known to cause epithelial cell damage, mucosal edema, smooth muscle constriction, and mucus secretion. Reduction in circulating and airway eosinophils is often used as an indicator of treatment efficacy. However, recent trials with anti-interleukin 5, which greatly reduces airway eosinophils, did not result in improved asthma symptom control or airway hyperresponsiveness.[49] The large number of inflammatory mediators and redundancy in effect of these substances will probably necessitate a broad-based approach to controlling inflammation, improving asthma symptom control, and preventing disease progression.

The most effective anti-inflammatory medication currently available for chronic persistent asthma is ICS. At low doses ICS is safe and effective for the vast majority of patients. ICS improves symptom control, decreases acute exacerbations, and decreases airway hyperresponsiveness. In addition, low-dose ICS (200 μg/d of fluticasone or 400 μg/d of budesonide) appears to be safe.[50–52] At low dose there is no significant effect on long-term linear growth or adrenal suppression. However, with higher doses the risk of adverse effects due to systemic absorption increases.[53,54] Although many ICS preparations, such as fluticasone or budesonide, are either poorly absorbed from the gastrointestinal tract or metabolized to inactive forms (or both), much of the ICS dose is absorbed systemically through the respiratory epithelium.[55]

An important challenge in managing pediatric asthma is what to do with the child who has moderate persistent asthma and has failed to achieve adequate asthma control with low-dose ICS. Current choices for management include increasing the ICS dose or adding a nonsteroidal medication to the regimen, such as a leukotriene receptor antagonist (LTRA), a long-acting β agonist (LABA), or even theophylline. The optimum choice remains controversial, and there are as yet incomplete data on which to make a decision.

Increasing the ICS dose as a management strategy assumes that there is a dose-dependent effect on disease control. Several studies provide data that there is indeed improved pulmonary function, symptom control, prevention of acute exacerbations, and reduced airway hyperresponsiveness with higher doses of ICS.[56–58] But some studies have not demonstrated such an effect, and the differences may be due to the type of outcomes measured or the stimulus used to induce asthma symptoms.[59,60] In all cases, however, the dose-response curve appears to flatten at relatively low doses of ICS. There is little evidence to support doses higher than 800 μg of budesonide or beclomethasone or 400 μg per day of fluticasone in improving pulmonary function or decreasing airway hyperresponsiveness.[61] Higher doses are likely to result in substantial suppression of cortisol secretion, without meaningful further improvement in asthma control. Some of the difficulty in measuring dose-response to ICS comes from the interindividual variability in response. In several studies, 25–40% of individuals treated with low to moderate doses of ICS failed to show significant improvement in FEV_1.[62–64] These patients may either be refractory to the effects of ICS or require higher doses. Other markers of disease activity or airway inflammation, such as exhaled nitric oxide or sputum eosinophilia, are not yet standardized in interpretation.[47] It has been suggested that it may be possible to predict the response to ICS using baseline markers of pulmonary function and markers of inflammation. Patients with lower baseline FEV_1, greater airway hyperresponsiveness (as measured by methacholine challenge), or higher levels of exhaled nitric oxide may be more likely to respond to low to moderate doses of ICS.[65] However, further studies on larger numbers of patients are needed to confirm these results.



	Number of Patients Remaining In Study			
Budesonide	308	294	293	289
Nedocromil	309	303	293	284
Placebo	414	400	392	386

	Number of Patients Remaining In Study			
Budesonide	294	286	288	275
Nedocromil	303	291	278	266
Placebo	400	388	379	370

Fig. 2. Effects of long-term budesonide use on linear growth in children with mild-to-moderate asthma. Children in the budesonide group were approximately 1 cm shorter at the end of the 4-year follow-up period (left panel). Growth velocity was slower in the first year of study, but returned to the same rate as that of the nedocromil and placebo groups afterwards (right panel). (Adapted from Reference 51.)

Data from the Childhood Asthma Management Project (CAMP) indicate that a budesonide dose of 400 μg per day, administered over a 4-year period, did not result in significant long-term suppression of linear growth.[51] Most of the growth suppression occurs in the first several months of steroid administration and is related to a decrease in growth rate (Fig. 2). Beyond the first year of administration there is no further significant reduction in linear growth, and growth rate returns to normal. Similar results were reported by Agertoft and Pederson.[50] In a group of 141 children who were treated with a mean dose of 400 μg/d budesonide for 4–9 years, there was no significant reduction in the final adult height attained (based on predicted values from mid-parental height). However, there may be greater reductions in growth rate with higher doses of ICS.[66] Based on current data, to minimize risks to growth and other systemic adverse effects in children, keeping the ICS dose in the low range (Table 1) is paramount. Therefore, unless all other treatment options with a better safety profile are exhausted, the ICS dose should be kept low.

A second option for improving asthma control without raising the ICS dose is to add a LABA. β agonists are not considered anti-inflammatory agents, although they do have salutary effects on the asthmatic airway that are not directly related to their bronchodilatory properties. For instance, β agonists may increase ciliary beat frequency and also may stabilize mast cell granules and impair release of histamine.[12] There are 2 available LABAs in widespread clinical use: salmeterol and formoterol. These drugs differ in structure and pharmacology. Salmeterol has a long aliphatic side chain that may allow it to detach and reattach repeatedly to the β receptor, although there may be other mechanisms as well. Formoterol, a full agonist, is lipophilic and may reside in the membrane lipid bilayer in a reservoir that slowly diffuses to receptor sites.[67] Since formoterol is also available in the aqueous phase, it can reach receptors rapidly. As a result, formoterol, unlike salmeterol, has a rapid onset of action as well as a long (up to 12 h) duration of action. Salmeterol, a partial agonist, has a similar duration of action, but significant bronchodilation takes up to 20 min. There is little doubt that LABAs work in children, producing bronchodilation and protection from exercise-induced symptoms. However, the improvement in FEV_1 seen with long-term administration of salmeterol is small ($\leq$ 5%), and the duration of protection from exercise-induced asthma decreases after the second week of treatment.[68] The important issue about which there is still limited data is whether the addition of a LABA to ICS improves asthma control, compared to increasing the ICS dose. In addition it would be important to determine if the addition of a LABA would allow reducing the ICS dose without loss of asthma control.

LABAs appear to have some steroid-sparing effect that occurs via as yet incompletely described mechanisms. One possibility is that LABAs enhance translocation of steroid receptors to the nucleus.[69] There are substantial data demonstrating that the addition of a LABA to low-to-moderate dose ICS improves asthma control in adults,[70–72] but comparable data for children are lacking. There are studies demonstrating the efficacy of a combination of ICS and LABA in pediatric patients, but little or no data showing a steroid-sparing effect.[73,74] A well-designed study performed by Verberne et al compared the administration of low-dose beclomethasone (400 μg/d administered via dry-powder inhaler) and high-dose (800 μg/d) and low-dose beclomethasone plus salmeterol for 1 year.[66] There was no significant difference between the groups in any measure of pulmonary function or airway reactivity. There was a trend toward a rebound increase in airway hyperrespon-

Table 1.

Usual Doses for Long-Term-Control Medications

Medication	Dosage Form	Adult Dose	Child Dose*
Inhaled Corticosteroids *(See Estimated Comparative Daily Doses for Inhaled Corticosteroids.)*			
Systemic Corticosteroids *(Applies to all three corticosteroids.)*			
Methylprednisolone	2, 4, 8, 16, 32 mg tablets	• 7.5–60 mg daily in a single dose in a.m. or qod as needed for control • Short-course "burst" to achieve control: 40–60 mg per day as single or 2 divided doses for 3–10 days	• 0.25–2 mg/kg daily in single dose in a.m. or qod as needed for control • Short-course "burst": 1–2 mg/kg/day, maximum 60 mg/day for 3–10 days
Prednisolone	5 mg tablets, 5 mg/5 mL, 15 mg/5 mL		
Prednisone	1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/mL, 5 mg/5 mL		
Long-Acting Inhaled β_2-Agonists *(Should not be used for symptom relief or for exacerbations. Use with inhaled corticosteroids.)*			
Salmeterol	MDI 21 mcg/puff	2 puffs q 12 hours	1–2 puffs q 12 hours
	DPI 50 mcg/blister	1 blister q 12 hours	1 blister q 12 hours
Formoterol	DPI 12 mcg/single-use capsule	1 capsule q 12 hours	1 capsule q 12 hours
Combined Medication			
Fluticasone/Salmeterol	DPI 100, 250, or 500 mcg/50 mcg	1 inhalation bid; dose depends on severity of asthma	1 inhalation bid; dose depends on severity of asthma
Cromolyn and Nedocromil			
Cromolyn	MDI 1 mg/puff	2–4 puffs tid-qid	1–2 puffs tid-qid
	Nebulizer 20 mg/ampule	1 ampule tid-qid	1 ampule tid-qid
Nedocromil	MDI 1.75 mg/puff	2–4 puffs bid-qid	1–2 puffs bid-qid
Leukotriene Modifiers			
Montelukast	4 or 5 mg chewable tablet	10 mg qhs	4 mg qhs (2–5 y)
	10 mg tablet		5 mg qhs (6–14 y)
Zafirlukast	10 or 20 mg tablet	40 mg daily (20 mg tablet bid)	20 mg daily (7–11 y) (10 mg tablet bid)
Zileuton	300 or 600 mg tablet	2,400 mg daily (give tablets qid)	
Methylxanthines *(Serum monitoring is important [serum concentration of 5–15 mcg/mL at steady state]).*			
Theophylline	Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day up to 300 mg max; usual max 800 mg/day	Starting dose 10 mg/kg/day; usual max: • < 1 year of age: 0.2 (age in weeks) + 5 = mg/kg/day • ≥ 1 year of age: 16 mg/kg/day

Estimated Comparative Daily Doses for Inhaled Corticosteroids

Drug	Low Daily Dose		Medium Daily Dose		High Daily Dose	
	Adult	Child*	Adult	Child*	Adult	Child*
Beclomethasone CFC 42 or 84 mcg/puff	168–504 mcg	84–336 mcg	504–840 mcg	336–672 mcg	> 840 mcg	> 672 mcg
Beclomethasone HFA 40 or 80 mcg/puff	80–240 mcg	80–160 mcg	240–480 mcg	160–320 mcg	> 480 mcg	> 320 mcg
Budesonide DPI 200 mcg/inhalation	200–600 mcg	200–400 mcg	600–1,200 mcg	400–800 mcg	> 1,200 mcg	> 800 mcg
Inhalation suspension for nebulization (child dose)	—	0.5 mg	—	1.0 mg	—	2.0 mg
Flunisolide 250 mcg/puff	500–1,000 mcg	500–750 mcg	1,000–2,000 mcg	1,000–1,250 mcg	> 2,000 mcg	> 1,250 mcg
Fluticasone						
MDI: 44, 110, or 220 mcg/puff	88–264 mcg	88–176 mg	264–660 mcg	176–440 mcg	> 660 mcg	> 440 mcg
DPI: 50, 100, or 250 mcg/inhalation	100–300 mcg	100–200 mcg	300–600 mcg	200–400 mcg	> 600 mcg	> 400 mcg
Triamcinolone acetonide 100 mcg/puff	400–1,000 mcg	400–800 mcg	1,000–2,000 mcg	800–1,200 mcg	> 2,000 mcg	> 1,200 mcg

MDI = metered-dose inhaler
DPI = dry-powder inhaler
CFC = chlorofluorocarbon
HFA = hydrofluoroalkane
*Children ≤ 12 years of age.
(Adapted from Reference 16.)

siveness in the group receiving ICS plus LABA. Growth rate declined in all groups, with the greatest effect seen in the group receiving the highest dose of beclomethasone. Possible mechanisms for the lack of effect in children include higher baseline pulmonary function and different metabolism of ICS and LABA. Further studies are needed to determine if the same salutary asthma control effect from ICS plus LABA seen in adult patients occurs in children.

Theophylline has also been used as an add-on medication for the treatment of chronic moderate asthma. The effect of theophylline is less substantial than that observed with the addition of a LABA, but clinically meaningful improvement has been reported.[75] Since the dose of theophylline used is low, the risk of adverse effects is also low. Adding theophylline is usually substantially less expensive than higher-dose ICS or adding an LTRA.

Lastly, the addition of an LTRA to low-dose ICS should be considered. Based on the pharmacology of the drug and the pathophysiology occurring in the airways, LTRA would be predicted to benefit asthma control when combined with ICS.[76] ICS does not appear to have a significant direct effect in reducing the synthesis or release of leukotriene, so the combination of an LTRA with ICS would be expected to be an excellent choice for managing moderate asthma that fails to respond to treatment with ICS alone. Several studies of adult asthmatics demonstrate such an effect. In a study of 642 adults randomized to receive either montelukast (an LTRA) or placebo in addition to inhaled beclomethasone, the group treated with beclomethasone had significantly better FEV_1, morning peak expiratory flow, and daytime symptom score, and fewer nocturnal awakenings.[77] In addition, there was a trend toward fewer asthma attacks in the group receiving montelukast. In another trial, 226 adult asthmatics who required at least moderate doses of ICS were randomized to receive either placebo or 10 mg of montelukast, and attempts were made to taper the ICS dose every 2 weeks.[78] Significantly more patients treated with montelukast were able to taper the steroid dose than those receiving placebo (47% vs 30%, $p = 0.046$). A study with 279 children ages 6–14 years examined the effect on FEV_1 and β agonist use of adding montelukast (5 mg/d) or placebo to 200 μg budesonide twice a day.[79] The group that received montelukast had a modestly better mean percentage FEV_1 increase above baseline (4.6% vs 3.3%, $p < 0.001$) than the placebo group. The average number of β agonist puffs per day was lower (1.65 vs 3.01 puffs/d) in the montelukast group ($p < 0.001$). These data suggest that LTRA complements ICS and improves control of chronic asthma, although the effects are relatively modest. The lack of a more substantial effect may reflect lack of sensitivity to LTRA in some patients, either because of rapid deactivation of the drug or because in some patients leukotrienes are not the prominent inflammatory mediators.

Summary of Ambulatory Care

For the asthmatic patient who remains inadequately controlled with low-dose ICS, the most appropriate management strategy is to attempt to keep the ICS dose low and to use a second (nonsteroidal) drug to control symptoms. In older children and adolescents, adding a LABA is probably the best approach and is supported by a number of clinical trials. Although the data are sparse, the combination of low-dose inhaled steroids and a LABA could be considered in younger children. However, adding an LTRA (montelukast) is also a reasonable option. Increasing the ICS dose should be reserved for the patient who fails to respond to the previously mentioned combination therapies. Attempts should be made at regular intervals to taper the ICS dose to the lowest effective level. Importantly, for any patient who fails to respond to aggressive medical management, other factors should be considered, such as poor adherence to the treatment regimen or complicating disorders such as gastroesophageal reflux, sinusitis, and exposure to allergens and irritants.

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Discussion

Wagener: You discussed anti-inflammatory therapy. Why do you think we do not use montelukast as first-line therapy for mild, persistent, or moderate asthma, given some suggestions that it's associated with better patient adherence?

Kercsmar: I think there is some suggestion of better patient adherence with a once-a-day oral drug than with multiple inhalations, although I've seen some data that would suggest that it's not all that much better. But I think the major reason to not use montelukast—and why I don't like to use it as monotherapy—is that it's almost too targeted of an anti-inflammatory. Though leukotrienes are probably very important in airway inflammation, they are not the most important mediator for all patients and are not the only inflammatory mediator involved in asthma. So I think it's too targeted. Though it's hard to get good published data, I think that the clinical experience has also been that probably somewhere between 40% and maybe even 50% of the patients who are treated with an LTRA don't respond. Also a number of patients, maybe 25%, don't respond to low-dose ICS either.[1,2] My argument against using LTRA (and probably why the National Heart, Lung, and Blood Institute's guidelines don't recommend it as first-line therapy) is that its effect is not as great in almost any outcome measure and that the ICS effect is better. Just because we *can* get the patient to take some

thing, does that mean that we *should*? That is, is something better than nothing? I'm not convinced that leaving other aspects of inflammation uncontrolled (when using an LTRA) is necessarily in the patient's best interest.

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Anderson: You mentioned theophylline and its role with the in-patient or in the intensive care unit (ICU). What's your current opinion on the use of theophylline?

Kercsmar: Theophylline is one of my all-time favorite drugs. It has this very interesting track record: like the mythical Phoenix it rises out of the ashes every few years when someone discovers that it's anti-inflammatory or has some other beneficial property, and then it crashes and burns when a new drug comes along and shoots it out of the sky. But I think theophylline has a place in a couple of venues. If you're on a desert island and it's the only bronchodilator you have, it's a great drug for chronic asthma. If you don't have any β agonists, it's not a bad acute bronchodilator. But if you have a selective β agonist and some steroids, it's blown out of the water. If cost is a concern, if you add low-dose theophylline to ICS, you get improved control of symptoms, including nocturnal symptoms, and improved pulmonary function, similar to adding a LABA, but for a lot less money. Also, if you can use a lower ICS dose, it keeps the cost down.

The other place it can be used is in the ICU, but there I think you give it on top of optimal β agonist use (corticosteroids and anticholinergics) and you probably give it for different reasons. The data are sparse as far as efficacy in the ICU. There are a couple of studies that say it helps,[1] but I think their conclusions might be a little misguided, though hopeful. But you give it because of its effect on respiratory muscles, such as increasing diaphragmatic contraction, preventing diaphragmatic fatigue, and acting as a respiratory stimulant, and maybe because it adds a little bit of anti-inflammatory action. In the ICU, where you can monitor things, is it worth a try? Absolutely. Might it add a little benefit to those patients? Yes, but I'm not sure that it's a miracle cure in the ICU.

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Rotta: You mentioned the role of ipratropium bromide in association with β agonists in the treatment of acute asthma exacerbation. In light of the studies on the combination treatment (using ipratropium bromide and albuterol in the first hour of treatment of patients with acute exacerbation in the emergency room) resulting in functional improvement,[1] and decreasing cost of care and the need for hospital admission,[2,3] how does this combination of drugs fit in your algorithm at your institution? Also, would you comment on the role of continuous albuterol in caring for more severe asthma?

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Kercsmar: I think ipratropium's major role is in the emergency department, and patients in our emergency department do get ipratropium. I think the data in the pediatric studies are pretty good to argue that it probably does decrease hospital admissions, and its effect is probably most pronounced in the patients who come in with the most bronchial constriction. Once those patients are admitted to the hospital, however, I think that its effectiveness is minimal.

One of our faculty members, Dan Craven, did a very nice study (using our in-patient care pathway), adding ipratropium to albuterol in the in-patient setting, and showed that it did *not* add any benefit.[1] There was no decrease in the LOS and no shortening of the progression through our care path. There were no *adverse* affects, but we could not demonstrate any *benefit* in the hospital setting. I think what happens is you cull out all the good ipratropium responders in the emergency department, and they all get better and go home. The patients who get admitted to the hospital are refractory to ipratropium. Then again, many of these patients are refractory to almost everything we throw at them, and they're the ones who get better in *spite* of us rather than *because* of us. So the major role of ipratropium is in the emergency department.

Why do we add it in that intensification package? Because I'm sure there is the occasional patient who will be a responder to ipratropium, and we'll try it. Plus, when we have a patient who is just getting worse, we really have limited things that we can do for him. We have not dissected our intensification package, by the way, to decide which components are necessary; that's on Tim Myers's list of things to do. In the hospital setting ipratropium probably doesn't add much; it's worth a try, but you shouldn't persist with it, because for most patients there's no added benefit. For acutely ill patients in the emergency department or ICU the data sug-

gest that continuous nebulization of albuterol may be better than giving intermittent aerosols. And it appears to be safe. It's probably what should be done, but it probably should be done in a controlled fashion with careful monitoring so you're not giving patients massive doses of albuterol by just opening a nebulizer cup, dumping in straight albuterol, and then refilling it every 5–10 minutes. You need to titrate and limit the dose (approximately 15 mg/h) to avoid adverse effects.

REFERENCE

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Cheifetz: My question concerns the use of helium-oxygen mixture [heliox] in the delivery of albuterol or levalbuterol. There is a growing body of evidence in the medical literature that indicates that if you use heliox to deliver albuterol in the emergency department setting, the beneficial effects of the albuterol might be enhanced.[1,2] Do you have any thoughts on this?

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Kercsmar: I think that we probably need more data. The studies you mentioned indicate that it may add some benefit.[1] If you have the equipment, the proper nebulizers, and the proper calibration you may be able to use heliox and get a little better deposition in the airways. I think that the problem with β agonists for treating asthma is that they can only do so much. They're not going to affect many components of the profound airway inflammation in acute and severe asthma. Also, there are probably lots of spare β receptors in the airway, and we're probably already giving patients way more β agonist than we need to achieve maximum bronchodilator effect, and all we do is add a lot of adverse effect.

I'm not convinced how much more improvement we can get in the emergency department setting with heliox-driven aerosols; maybe some, particularly in areas of small-airway obstruction that are not being reached with conventional nebulization. You may also decrease work of breathing while the patient is inhaling heliox, which would spare them a little fatigue and allow them to get better a little faster. So I think that there may be a number of salutary benefits of using heliox in an acute care setting. The delivery of aerosols probably makes more sense than just using it for patients to breathe. It's a nice bridge therapy, but most of the data show that when you turn the heliox off, the patient is right back where he started.[2] I think we probably need a few more trials in children and with using the proper equipment.

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Black: It's clear from your presentation that we've got some incredible drugs for treating asthma—very, very effective. I think the next frontier in asthma treatment is going to be in education and patient compliance. The vast majority of asthma exacerbations we see in our emergency department are in people who are very poor at keeping up with their medication regimen. I think the dry powder inhalers have helped a lot because they're compact and easy to use, and it seems that the delivery of the medication may be a little more effective. But it also seems to me that we need a *major* focus on education, patient compliance, and ease of medication delivery.

Kercsmar: I couldn't agree with you more. Some studies indicate that most patients know a lot about asthma,[1] and the longer they've had it the more they know about it, but if you ask them how to manage a certain asthma scenario, they're terrible; they can't translate their knowledge into behavior. We have wonderful drugs for treating asthma, and if we developed no new asthma treatments and just got patients to adhere to their asthma prescriptions, we could control the vast majority of asthma much better than we do now. But the patients just do not, cannot, or will not take the prescribed medications, in part because we ask them to do a lot, and they have a lot of misconceptions about what will and will not work.

REFERENCE

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Salyer: We have put some of your practices in place in an in-patient, protocol-driven, geographically isolated asthma unit, and our initial experience was very positive, so I congratulate you on the great work you and Tim Myers have done. I think the need for education applies not just to patients but to hospital staff as well. There is *enormous* variability in how respiratory therapists and others administer nebulized medications. What did you do to standardize the way clinicians administer these medications in the hospital?

Kercsmar: I can tell you what we're *supposed* to do, and I will tell you that sometimes even that breaks down, but we are serious about educating patients and staff. We have the luxury of a 10-bed asthma unit that is staffed by well-trained, dedicated therapists and nurses. We have a nurse who meets with all the patients and has a few simple goals: make sure they have their medication when they go home, try to help upgrade their treatment plan, and make sure they know how to *use* their medications when they go home. So they go home with all their drugs and devices and have been shown how to use them.

The general rule is that anyone over 3 years of age should receive their nebulized medications with a mouthpiece. We would like them to have monitored therapy if they're using a mask, the mask has to go on the face, and the mask has to be tight fitting on the face, and we don't want tubing waved in front of their noses. I think it's adhered to quite well in the asthma unit.

The emergency department sometimes is a little less strict in following the procedure, I think, because of time and staffing constraints. There are no respiratory therapists in our emergency department. Every patient is given a valved holding chamber when they go home, is shown how to use it, and is asked to demonstrate proper use to the therapist or nurse who is educating the patient.

Myers: The profession of respiratory care has embraced the use of protocols and has published a lot of things in the literature showing the advantages of using protocols in the emergency room, in-patient setting, and other settings.[1–6] But a lot of people struggle with getting protocols up and running. What are your recommendations as to how to successfully implement protocols?

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Kercsmar: I think that when you develop protocols, you must do so with a multidisciplinary team, because everyone who's going to be involved in delivering care needs to have a say in the protocol's development, and you have to try to reach consensus. Another thing you absolutely need is buy-in from the institution's administration to support the infrastructure needed to implement those protocols. You also need data to show what works and what doesn't and to disseminate those data to the protocol users—that usually means the physicians who will be admitting patients or sending patients to the emergency department. You must convince them that what you are doing works and that it is not removing control from what they do but rather enhancing the care of their patients. That often takes a lot of public speaking, cajoling, and arm-twisting, but I think that if you have a track record and have some data and have good administrative support, it can be done. Those are the key strategies that have allowed us to be successful with our care path, and that, hopefully, will be emulated elsewhere.